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Formulation and Evaluation of Bilayered Matrix Tablets of Antidiabetic Drugs for the Control of Diabetes

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ABSTRACT

The objective of present study was to prepare and characterize Bilayer tablet formulation containing Metformin in extended release matrix form and teneligliptin in immediate release form for the treatment of diabetes mellitus. Different formulations containing Metformin and teneligliptin were prepared by direct compression method. Influence of hydrophilic carrier, hydrophobic polymer on drug release was studied. Immediate release layer of teneligliptin was optimized using different super disintegrants. All formulations were evaluated for percentage drug release. Results confirmed that Bilayer tablet formulation containing extended release of Metformin and immediate release of teneligliptin HCl could be used for the treatment of diabetes.

KEYWORDS: Diabetes, Bilayer Tablet, Immediate Release, Extended Release

INTRODUCTION

Type 2 diabetes mellitus is a heterogeneous disorder characterized by multiple defects in the pancreatic β-cell, liver, and peripheral tissues such as skeletal muscle and adipose tissue.[1] Combination therapy has various advantages over monotherapy such as problem of dose-dependent side effects is minimized. a low dose combination of two different agent reduces the dose related risk, the addition of agent may counteract some deleterious effects of the other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dose of individual component of the combined tablet.[2, 3]

Metformin is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60% with relatively short plasma half-life of 1.5-4.5 h. [4, 5] Teneligliptin is a potent and selective inhibitor of dipeptidyl peptidase-IV (DPP-4), orally active, that improves glycemic control in patients with type 2 diabetes (T2DM) primarily by enhancing pancreatic (α and β) islet function. Thus Teneligliptin has been shown both to improve insulin secretion and to suppress the inappropriate glucagon secretion seen in patients with T2DM. Teneligliptin reduces HbA1c when given as monotherapy, without weight gain and with minimal hypoglycemia, or in combination with the most commonly prescribed classes of oral hypoglycemic drugs. [6, 7]

The combination of Metformin and Teneligliptin offers advantages when compared to currently used combinations with additive efficacy and complimentary mechanisms of action, since it does not increase the risk of hypoglycemia and does not promote weight gain. Therefore, by specifically combining these agents in a single tablet, there is considerable potential to achieve better blood glucose control and to improve compliance to therapy [8, 9]. The objective of present study was to formulate and evaluation of Bilayer matrix tablet containing Metformin in extended release matrix tablet form by using HPMCK4M and guar gum by direct compression method and teneligliptin in immediate release form By using super disintegrants (Crospovidone and Avicel pH 102) for the treatment of diabetes mellitus.

MATERIALS AND METHODS

Materials: Metformin and Teneligliptin obtained as gift sample from Tristar Formulation Pvt Ltd, and Pure Chem Pvt. Ltd., Gujarat., Crosspovidone, Avicel pH (102) other excipients and solvent use were of analytical grade.

Infrared Spectrum: The scanning was done using KBr dispersion pellets. About 1 mg of powdered drug mixed with approximately 100 mg of KBr (spectroscopic grade) in a glass mortar. The mixture was compressed into transparent drotes with special designed moisture free atmosphere and IR spectra were obtained on IR spectrophotometer. The scanning was done between 4000-400 cm^{-1}. The spectra so obtained were compared with reported in official compendia. [10]

Formulation Preparation [11-13]

Preparation of Immediate Release Layer of Teneligliptin (TF1–TF4): Immediate release layer of Teneligliptin was prepared by direct compression method. Teneligliptin, crospovidone, avicel pH-102, and lactose were accurately weighed and passed through sieve number 40. All the above ingredients as shown in Table 1 were mixed in a polybag. Talc and magnesium stearate were added after passing through sieve number 40 and mixed properly.

Preparation of Controlled Release Layer of Metformin HCl Formulated with HPMC K4M (MF5–MF8): Controlled release layer of metformin HCl containing HPMC K4M was prepared by direct compression method. Metformin HCl, HPMC K4M, PVP K30, and dicalcium phosphate were passed through sieve number 40. All the above ingredients were mixed in a polybag. Talc and magnesium stearate were added after passing through sieve number 40 and mixed properly.

Preparation of Controlled Release Layer of Metformin HCl Formulated with Guar Gum (MFF9–MFF13): Metformin HCl granules containing guar gum were prepared by wet granulation technique by adding PVP K 30 dissolved in distilled water as a granulating fluid. Required quantities of metformin HCl, guar gum, and dicalcium phosphate were passed through sieve number 40 and were mixed thoroughly and a sufficient volume of granulating fluid was added slowly. After enough cohesiveness was obtained, the mass was passed through sieve number 12. The obtained granules were dried at 50 ºC in hot air oven till a constant weight was obtained (until dry). The dried granules were then passed through after passing through sieve number 40 and mixed properly.

Procedure: Optimization process is done for immediate release layer in order to select the composition to form a multilayered tablet. The first layer consists of immediate release and the second layer consists of controlled release. The first layer was placed in the die cavity which consists of immediate release layer and punched with low compression force and then the second layer was placed in the die cavity which consists of controlled release layer and allowed for punching and finally barrier layer containing 35 mg of ethyl cellulose was placed in the die cavity and compressed with maximum compression force in order to obtain multilayered tablets by using 12 mm punches of SAIMACHSMD16 station tablet compression machine with an average hardness of 6– 8 kg/cm^2. Prior to compression, the granules were evaluated for several tests.

Table 1: Composition of Immediate Release Layer Formulations of Teneligliptin

Formulation code	**TF1**	**TF2**	**TF3**	**TF4**
Teneligliptin (mg)	20	20	20	20
Crospovidone (mg)	1.5	2.25	3	3.75
Avicel pH 102 (mg)	2.15	2.15	2.15	2.15
Lactose	54.35	53.60	52.85	52.10
Magnesium Stearate(mg)	1	1	1	1
Talc(mg)	1	1	1	1

Table 2: Composition of Bilayered Matrix release layer formulations

Composition of Immediate release formulation				
Formulation code	**MF5**	**MF6**	**MF7**	**MF8**
Teneligliptin mg)	20	20	20	20
Crospovidone (mg)	3	3	3	3
Avicel pH 102 (mg)	2.15	2.15	2.15	2.15
Lactose	52.85	52.85	52.85	52.85
Magnesium Stearate(mg)	1	1	1	1
Talc(mg)	1	1	1	1
Controlled release layer				
Metformin\	500	500	500	500
HPMCK4M(mg)	55	70	115.5	122
Guar gum(mg)	-	-	-	-
PVP K30 (mg)	27	27	27	27

Di-calcium phosphate(mg)	80	65	19.5	13
Magnesium Stearate(mg)	04	04	04	04
Talc(mg)	04	04	04	04
Distill water(mg)	q.s.	q.s.	q.s.	q.s.

Table 3: Composition of Bilayered Matrix release layer formulations

Composition of Immediate release formulation					
Formulation code	**MFF9**	**MFF10**	**MFF11**	**MFF12**	**MFF13**
Teneligliptin (mg)	20	20	20	20	20
Crospovidone (mg)	3	3	3	3	3
Avicel pH 102 (mg)	2.15	2.15	2.15	2.15	2.15
Lactose	52.85	52.85	52.85	52.85	52.85
Magnesium Stearate (mg)	1	1	1	1	1
Talc(mg)	1	1	1	1	1
Controlled release layer					
Metformin	500	500	500	500	500
HPMCK4M (mg)	-	-	-	-	-
Guar gum (mg)	35.5	79.5	117.5	148	117.5
PVP K30 (mg)	12	12	12	14	12
Di-calcium phosphate (mg)	114.5	71	32.5	-	32.5
Magnesium Stearate (mg)	04	04	04	04	04
Talc(mg)	04	04	04	04	04
Distill water (mg)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Barrier layer (mg) Stearic acid	35				

Precompression Parameters

Angle of Repose: Angle of repose was calculated by formula:-

$$\tan \theta = h/r$$

Where, h = height of the powder heap

r = radius of the powder heap

θ = angle of repose

Determination of Bulk Density and Tapped Density: The bulk density and the tapped density were calculated using the following formulae.

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

Hausner's Ratio: It is the ratio of tapped density and bulk density.

$$\text{Hausner's Ratio} = \text{Tapped density/Bulk Density}$$

Compressibility Index: Compressibility index is calculated by:

$$\text{Compressibility index (\%)} = D_f - D_o / D_f \times 100$$

Where, D_o = Bulk density

D_f = Tapped density

Post-compression Parameters

Thickness: The thickness of the tablets was determined using Vernier calipers. Three tablets from each type of formulation were used and average values were calculated. [14]

Uniformity in Weight: The pharmacopoeial limits for deviation for tablets of more than 250 mg are ± 5%. The average percentage deviation for all tablet formulations was found to be within the specified limits and hence all formulations complied with the test for weight variation. [15]

Uniformity of Drug Content: Five tablets of each type of formulation were weighed and crushed in mortar and 900 mg of this powder, which is equivalent to 30 mg of Metformin and Teneligliptin, was weighed accurately and dissolved in 100 ml phosphate buffer pH7.4. This was the stock solution from which 1ml sample was withdrawn and diluted to 10 ml with distilled water. The absorbance was measured at wavelength 249 nm using double beam UV-Visible spectrophotometer. [16, 17]

Hardness: For each type of formulation, the hardness values for 3 tablets were determined using Monsanto hardness tester. [18]

Friability: Percentage friability was calculated by using the formula: [19]

$$\text{\% Friability} = \text{Initial weight of the tablets} - \text{Final weight of the tablets/Initial weight of the tablets X 100}$$

Disintegration Study: The disintegration ratio (% disintegrated) was calculated by the following equation. [20]

$$\text{\% disintegrated} = W_i - W_t / W_i \times 100$$

Where, Wt is the weight of tested DCMT sampled at time t and W_i is the initial weight of DCMT.

Before the test was carried out the initial weight were noted down. The tablets were disintegrated for the 2Hrs, 4Hrs, 6Hrs, and 8Hrs for the study of penetration of the dissolution media. The test was carried out in the 0.1 N HCl and pH 6.8 phosphate buffer. After each reading the final weight of the tablet was obtained. Using the initial and final weight of the tablet % disintegration was calculated for the 2Hrs, 4Hrs, 6Hrs and 8Hrs.

***In-vitro* Dissolution Studies:** The in-vitro dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. Dissolution media was 0.1 N HCl for first 2 hrs and phosphate buffer pH 6.8 for remaining hrs and temperature was maintained at 37±0.5 °C. A 5ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 249 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated. [21]

Mathematical Modelling of Drug Release Profile: Investigation for the drug release from the metformin and teneligliptin controlled release matrix tablets was done by studying the release data with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to Korsmeyer Peppas model. [22]

Stability: The selected formulations TF3, MF8 and MFF13 were tested for stability under the conditions of 45ºC and 75% RH and refrigerator conditions for one month. [23, 24, 25]

RESULTS AND DISCUSSION

Infrared Spectrum: The IR spectrum of the obtained sample was done acc. to the procedure mention in material and method and complied with IR spectra of sample drug show similar characteristic peaks. Figure 1 shows the IR spectra of sample drug.

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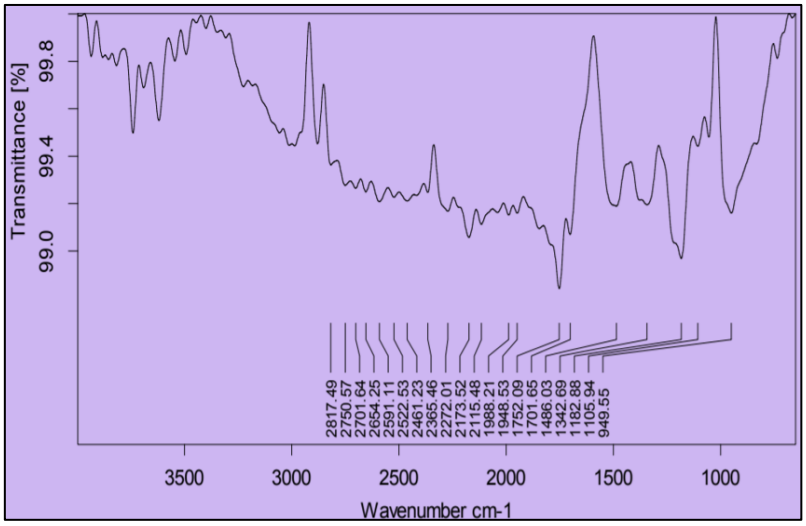

Figure 1: FTIR spectra of pure metformin hydrochloride

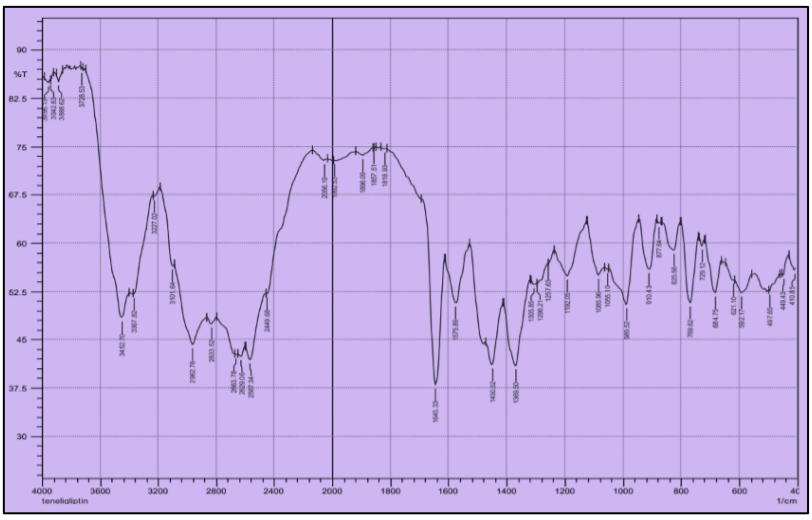

Figure 2: FTIR spectra of pure teneligliptin

FTIR spectrum showed characteristic peaks and bands which are representing the presence of functional groups which help in the identification of drug. FTIR spectrum of Metformin was showing characteristics peaks at 3492.57, 3225.09, 2817.49, 2750.57, 2654.25, 1743 and 1691 cm^{-1} which are indicating, O-H stretching, N-H stretching (1 amine), =CH stretching, C-H_2 stretching, O-H stretching (Carboxylic group), C=O stretching (1˚Carboxylic acid) and C=O stretching (lactone group), respectively. Teneligliptin showed characteristics peaks at 3367.82, 3049.56, 2885, 1635.69, 725.26 cm^{-1} which are indicating, O-H stretching, -CH_2 stretching (1 amine), CH_2 asymmetric stretching, C-C binding with aromatic ring stretching, C-OH stretching (lactone group), respectively. These bending and stretching in FTIR spectrum expressed the structure of Metformin and teneligliptin and presence of functional groups in the drug moiety which would be responsible for the characteristics of the drug and it would also act as a helping tool for the identification of metformin and teneligliptin.

Evaluation Of Pre-Compression Parameter:

Angle of repose (Ɵ): The values obtained for angle of repose for all (TF1-TF4) formulations are tabulated in Table 4. The values were found to be in the range from and 22°.21- 25°.12. The values obtained for angle of repose for all (MF5-MF8) formulations are tabulated in Table 5. The values were found to be in the range from and 23°.56- 26°.67. The values obtained for angle of repose for all (MFF9-MFF13) formulations are tabulated in Table 6. The values were found to be in the range from and 24°.17- 25°.78. This indicates good flow property of the granules.

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2) Hausner's ratio: The values obtained for Hausner's ratio for all (TF1-TF4) formulations are in Table 4. Hausner's ratio value ranges between 1.132 - 1.543 indicating that the granules have the required flow property for compression. The values obtained for Hausner's ratio for all (MF5-MF8) formulations are in Table 5. Hausner's ratio value ranges between 1.189 - 1.247 indicating that the granules have the required flow property for compression. The values obtained for Hausner's ratio for all (MFF9-MFF13) formulations are in Table 6. Hausner's ratio value ranges between 1.185 - 1.533 indicating that the granules have the required flow property for compression.

Tapped Density: The values obtained for tapped density for all (TF1-TF4) formulations are in Table 4. Tapped Density value ranges between 0.74 - 0.81 indicating that the granules have the required flow property for compression. The values obtained for tapped density for all (MF5-MF8) formulations are in Table 5. Tapped Density value ranges between 0.75 - 0.91 indicating that the granules have the required flow property for compression. The values obtained for tapped density for all (MFF9-MFF13) formulations are in Table 6. Tapped Density value ranges between 0.79 - 0.89 indicating that the granules have the required flow property for compression.

Bulk Density: The values obtained for Bulk Density for all (TF1-TF4) formulations are in Table 4. Bulk Density value ranges between 0.48 - 0.67 indicating that the granules have the required flow property for compression. The values obtained for Bulk Density for all (MF5-MF8) formulations are in Table 5. Bulk Density value ranges between 0.44 - 0.71 indicating that the granules have the required flow property for compression. The values obtained for Bulk Density for all (MFF9-MFF13) formulations are in Table 6. Bulk Density value ranges between 0.49 - 0.75 indicating that the granules have the required flow property for compression.

Compressibility index: The values obtained for compressibility index for all (TF1-TF4) formulations are tabulated in Table 4 Compressibility index value ranges between 14.34% - 16.97% indicating that the granules have the required flow property for compression. The values obtained for compressibility index for all (MF5-MF8) formulations are tabulated in Table 5. Compressibility index value ranges between 14.32% - 16.34% indicating that the granules have the required flow property for compression. The values obtained for compressibility index for all (MFF9-MFF13) formulations are tabulated in Table 6 Compressibility index value ranges between 14.32% - 16.34% indicating that the granules have the required flow property for compression.

Table 4: Precompression parameter of granules (TF1-TF4)

Formulation Code	*Angle of repose*	*Hausner ratio*	*Tapped density*	*Bulk Density*
TF1	*25°.12 ± 0.12*	*1.132 ± 0.05*	*0.74± 0.03*	*0.56 ± 0.01*
TF 2	*22°.21 ± 0.11*	*1.156 ± 0.05*	*0.75± 0.02*	*0.61 ± 0.02*
TF3	*23°.87 ± 0.10*	*1.543 ± 0.06*	*0.81± 0.02*	*0.48 ± 0.02*
TF 4	*24°.78 ± 0.12*	*1.332 ± 0.04*	*0.76± 0.03*	*0.67 ± 0.01*

Table 5: Precompression parameter of granules (MF5-MF8)

Formulation Code	*Angle of repose*	*Hausner ratio*	*Tapped density*	*Bulk Density*
MF5	*26°.67 ± 0.13*	*1.247± 0.05*	*0.75± 0.03*	*0.71± 0.01*
MF6	*23°.56 ± 0.12*	*1.191± 0.03*	*0.81± 0.02*	*0.53± 0.02*
MF7	*24°.32 ± 0.11*	*1.245± 0.04*	*0.83± 0.03*	*0.44± 0.03*
MF8	*25°.90 ± 0.12*	*1.189± 0.04*	*0.91± 0.02*	*0.71± 0.01*

Table 6: Precompression parameter of granules (MFF9-MFF13)

Formulation Code	*Angle of repose*	*Hausner ratio*	*Tapped density*	*Bulk Density*
MFF9	*24°.64± 0.11*	*1.189± 0.05*	*0.83± 0.02*	*0.75± 0.03*
MFF10	*25°.21± 0.14*	*1.185± 0.03*	*0.86± 0.02*	*0.49± 0.02*
MFF11	*25°.78± 0.12*	*1.256± 0.04*	*0.81± 0.03*	*0.67± 0.03*
MFF12	*24°.17± 0.13*	*1.465± 0.05*	*0.79± 0.04*	*0.73± 0.01*
MFF13	*25°.78± 0.12*	*1.533± 0.04*	*0.89± 0.03*	*0.70± 0.03*

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Evaluation Of Post-Compression Parameter

Thickness of tablets: All the formulations were evaluated for their thickness using "Vernier callipers" as per procedure in methodology section and the results are shown in table 7. The average thickness for all the formulations (TF1-TF4, MF5-MF8 and MFF9-MFF13) was found in the range of 3.12-4.99, 3.22-421, 3.15-4.75 mm respectively which is within the allowed limit of deviation i.e. 5% of the standard value.

Hardness: Hardness test was performed by "Monsanto hardness tester". All the formulations (TF1-TF4, MF5-MF8 and MFF9-MFF13) have an average hardness in between 4.3 to 5.3, 4.2 to 5.3, 4.9 to 5.2 kg/cm^2 respectively. This ensures good handling characteristics of all formulation batches.

Friability: The average percentage friability for all the formulations was found in between 0.121% to 0.198%, which is found within the pharmacopoeial limit (i.e. less than 1%). So, the maximum friability was 0.121% observed for TF3 and the minimum friability 0.198% observed for MF6.

Weight Variation The weight variation for all formulations (TF1-TF4, MF5-MF8 and MFF9-MFF13) were found in the range of 81 to 84 mg, 751 to 754, 750 to 755 results were dissipated in table 7. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits (<5%). The weights of all the tablets were found to be uniform with low standard deviation values.

Drug content: The percentage of the drug content for formulation TF1 to TF4 was found to be between 95.23% w/w and 96.19% w/w. The percentage of the drug content for formulation MF5 to MF8 was found to be between 95.78%w/w and 97.32%w/w. The percentage of the drug content for formulation MFF9 to MFF13 was found to be between 95.39 % w/w and 98.82 % w/w. The results were shown in **table 7**.

Disintegration Test: The disintegration time for Batch TF1-MFF13 ranged from 45-60 Minutes (Table 7).

Table 7: Post-compression parameters results

Formulation	*Thickness (mm)± SD*	*Weight variation (mg)*	*Drug content (%)*	*Hardness (kg/cm^2)*	*Friability (%)*	*Disintegration time (Min)*
TF1	*3.34 ±0.12*	*82 ± 5*	*96.09 ± 0.15*	*4.3 ± 0.11*	*0.127± 0.02*	*09.03 ± 0.12*
TF 2	*3.12 ±0.11*	*81 ± 5*	*95.23 ± 0.14*	*4.4 ± 0.11*	*0.143± 0.01*	*08.45± 0.11*
TF 3	*4.56 ±0.12*	*84 ± 5*	*96.19 ± 0.15*	*5.1 ± 0.12*	*0.121± 0.1*	*09.18± 0.12*
TF 4	*4.99 ±0.14*	*83 ± 5*	*95.56 ± 0.14*	*5.3 ± 0.12*	*0.123± 0.1*	*8.17± 0.10*
MF5	*3.22 ±0.12*	*752 ± 5*	*95.99 ± 0.13*	*4.7 ± 0.14*	*0.156± 0.2*	*53.3 ± 1.13*
MF6	*3.45 ±0.12*	*751 ± 5*	*97.32 ± 0.15*	*4.2 ± 0.12*	*0.198± 0.2*	*54.7± 1.11*
MF7	*3.89 ±0.11*	*757 ± 5*	*95.78 ± 0.11*	*4.7 ± 0.14*	*0.145± 0.1*	*55.9± 1.15*
MF8	*4.21 ±0.12*	*754 ± 5*	*95.94 ± 0.11*	*5.3 ± 0.12*	*0.165± 0.1*	*54.1± 1.12*
MFF9	*4.75 ±0.14*	*755 ± 5*	*96.19 ± 0.15*	*5.2 ± 0.13*	*0.167± 0.1*	*49.8± 1.12*
MFF10	*3.15 ±0.13*	*752 ± 5*	*95.39 ± 0.14*	*5.1 ± 0.12*	*0.145± 0.2*	*48.3 ± 1.15*
MFF11	*4.67 ±0.13*	*751 ± 5*	*97.09 ± 0.15*	*4.9 ± 0.13*	*0.156± 0.1*	*54.9± 1.11*
MFF12	*4.05 ±0.12*	*750 ± 5*	*95.98 ± 0.13*	*5.1 ± 0.12*	*0.178± 0.1*	*55.7± 1.14*
MFF13	*4.25 ±0.11*	*751 ± 5*	*99.82 ± 0.15*	*5.1 ± 0.11*	*0.165± 0.2*	*53.5± 1.12*

***In-vitro* drug release study:** The *in-vitro* release of metformin and teneligliptin, from prepared matrix tablets formulations was mainly affected by dissolution medium, concentration of chitosan, concentration of HPMC-K4M and concentration of Gaur gum. *The in-vitro* release of metformin and teneligliptin form prepared matrix tablets also depends on swelling behaviour of the tablets, higher the tablet swells comparative the lesser amount of drug release. The *in-vitro* release study was performed in 0.1 N HCl for initial first 2 hrs, and then the medium was replaced by phosphate buffer pH 6.8) and study was continued for 12 hour.

The *in-vitro* release of metformin and teneligliptin, were higher in first 6-7 hours in all formulations. After 1 hour, approximately 10.29%- 22.34% of metformin and teneligliptin, from tablets containing only release retardant polymer has been released. Initially amount of drug release was higher but after 6-7hrs drug release was retarded. Formulation MFF13 do not contains any crosslinking agent, so almost all drugs was released at the end of 12 hrs. Formulation TF3, MF8, and MFF13 containing lower concentration of HPMC-K4M and Gaur gum showed almost all drug release within 120 min, 8 hrs, and 12 hrs respectively. Thus, these formulations

were not considered as good formulation as the maximum amount of drug was released before desire period of time i.e. 12 hrs. The ionic interaction between crosslinking agents and negatively charged polymers was greatly reduced at this pH 6.8 and forms a loose network with increase porous surface which allows great part of dissolution media. Formulation TF3, MF8 and MFF13 containing highest concentration of HPMC K4 and Gaur gum respectively prolong the release of Metformin and teneligliptin to 12 hrs which might be due to the fact that the self-assembled poly electrolyte complexes film was formed on the surface of cross linking agent-polymer based system.

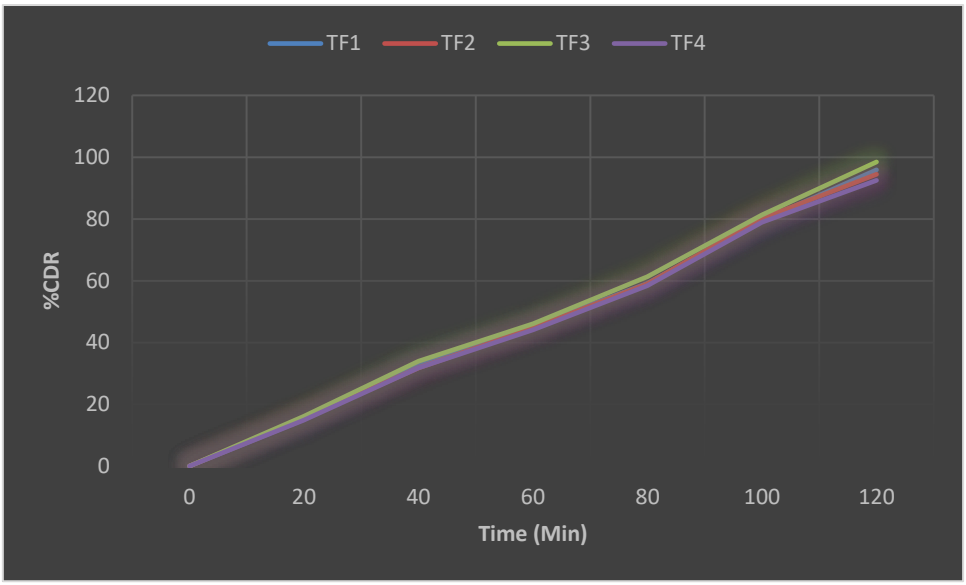

Figure 3: In-vitro drug release (TF1-TF3)

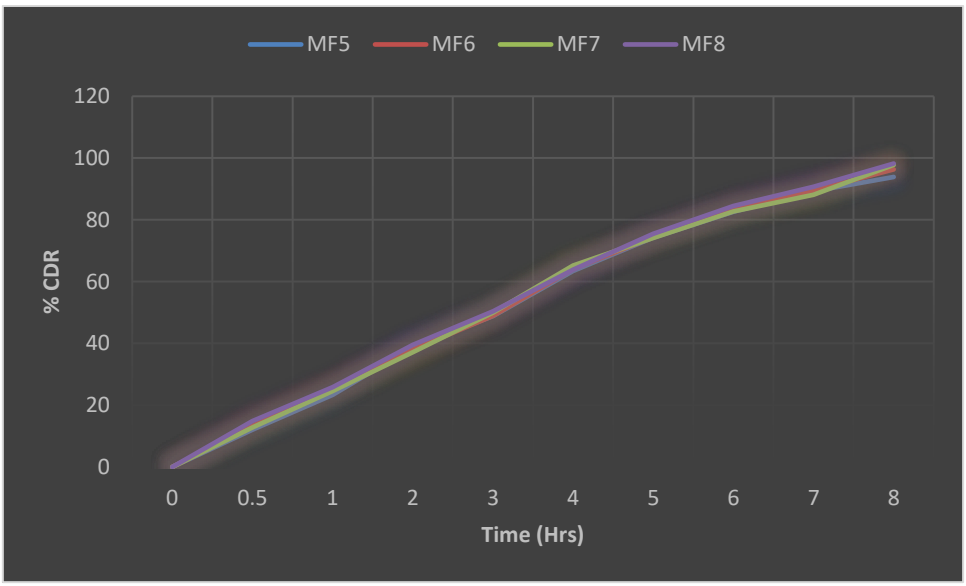

Figure 4: In-vitro drug release (MF5-MF8)

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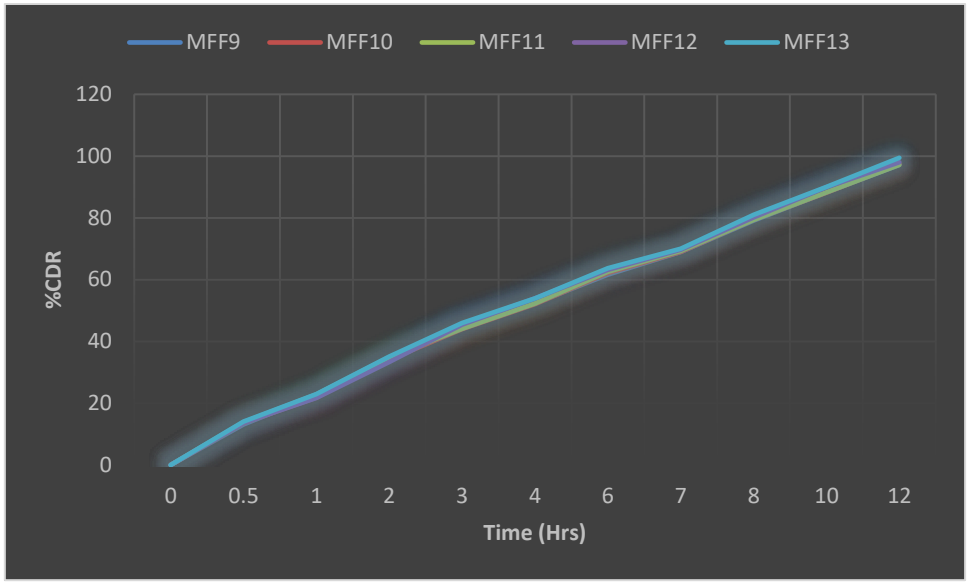

Figure 5: In-vitro drug release (MFF9-MFF13)

Release kinetic studies: The *in-vitro* drug release data of all formulations were analysed for determining kinetics of drug release. The obtained data were fitted to zero order kinetics, first order kinetics and Higuchi model. The highest correlation coefficient (r^2) obtained from these method gives an idea about model best fitted to the release data. From the results of kinetic studies, the examination of correlation coefficient "r" indicated that the drug release followed first order release kinetics. It was found that the value of "r" for first order ranged from 0.981-0.992, which is near to 1 when compared to Higuchi square root ranged from 0.892-0.958 and zero order ranged from 0.895-0.969. So, it was understood to be following first order release pattern followed by all formulations. Further, to understand the drug release mechanism, the data were fitted into Korsmeyer Peppas exponential model Mt / Ma = Ktn. Where Mt / Ma is the fraction of drug released after time 't' and 'k' is kinetic constant and 'n' release exponent which characterizes the drug transport mechanism. The release exponent (n) ranges in between 0.483-0.7911. For all the formulations TF3, MF8, MFF13 the values for 'n' ranged above 0.89 which indicates that all the formulations followed non-fickian release mechanism. The relative complexity of the prepared formulations may indicate that the drug release mechanism was possibly controlled by the combination of diffusion and erosion.

Table 8: Release exponent values and release constant value for different formulations

Batch no.	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
TF3	0.9294	0.9543	0.9456	0.9965	0.594
MF8	0.9543	0.9342	0.9768	0.9545	0.597
MFF13	0.9345	0.9432	0.9987	0.9656	0.578

Stability Studies: Based on the results of *in-vitro* drug release two best formulations TF3, MF8 and MFF13 were selected for three-month stability studies at 25ºC/60% RH. The stability studies were conducted according to the method described in section four. The selected formulations were evaluated for physical appearance, hardness, friability, and drug content. The results showed that there was no significant change in physical appearance, hardness, friability, drug content throughout the study period. Three months of stability studies revealed that; there was no any significant degradation of the drug. Thus, prepared formulations were physically and chemically stable. The result of stability studies was tabulated in **table 9**.

Table 9: Stability Study of TF3, MF8 and MFF13

Formulation	Initial	1 month	2 months	3 months
TF3				
Hardness kg/cm^2	5.1 ± 0.12	5.1 ± 0.12	5.0 ± 0.12	5.0 ± 0.12
Friability %	0.122	0.121	0.120	0.119
Drug content %	96.34 ± 0.15	96.19 ± 0.15	96.05 ± 0.15	95.98 ± 0.15
MF8				
Hardness kg/cm^2	5.2 ± 0.12	5. ± 0.12	5.2 ± 0.12	5.1 ± 0.12
Friability%	0.167	0.165	0.164	0.163
Drug content%	96.04 ± 0.15	95.94 ± 0.15	95.67 ± 0.15	95.49 ± 0.15
MFF13				
Hardness kg/cm^2	5.1 ± 0.12	5.1 ± 0.12	5.0 ± 0.12	4.9 ± 0.12
Friability%	0.166	0.165	0.165	0.164
Drug content%	96.82 ± 0.15	96.65 ± 0.15	96.18 ± 0.15	95.98 ± 0.15

CONCLUSION

In the present work, studies were undertaken for the design and development of oral controlled release matrix tablets of anti-diabetic drug metformin and teneligliptin. Controlled release drug delivery systems have received much attention in the past two decades with numerous technologically sophisticated products on the marketplace. The best formulations TF3, MF8 and MFF13 were subjected to 3 months stability studies and results showed there was no significant change in the hardness, friability, drug content. Thus, it was found that prepared tablets were physico-chemically stable throughout stability period. Thus, it can be summarized that the stable matrix tablet dosage form of Metformin and teneligliptin has been developed for controlled release in the treatment of Diabetes.

REFERENCES

1. Rang HP, Dale MM, Ritter JM, Moore PK. Rang and Dale's pharmacology. 6th Edn. Elsevier; 2007. [Google Scholar]
2. Giuseppe D, Sibilla A, Teresa S. Pioglitazone And Metformin Fixed-Dose Combination In Type 2 Diabetes Mellitus: An Evidence-Based Review Of Its Place In Therapy, Department of Internal Medicine and Therapeutics, University of Pavia, Italy. 2007:189–198. [Google Scholar]
3. Hemalatha S, Srikanth P, Mounica Sai G. Formulation and evaluation of bilayered tablets containing immediate release layer of Glimepiride complexed with Mangifera indica gum and sustained release layer containing Metformin HCl by using HPMC as release retardant. International Journal of Pharmaceutical and Clinical Research. 2017; 9(6): 455-461.
4. Basavaraj KN, Mhase SR, Manvi FV. Preparation and Evaluation of Biphasic Release Tablet Formulation for the Treatment of Diabetes Mellitus. Int J Novel Drug Deliv Tech. 2011;1(1) [Google Scholar]
5. Abdul S, Poddar S.S. A flexible technology for modified release of drugs: Multi layered tablets. Journal of Control Release. 2004;42(2):393–405. doi: 10.1016/j.jconrel.2004.03.034. [DOI] [PubMed] [Google Scholar]
6. Chaudhari PD, Chaudhari, Yeola GS, Barhate NS. Melt Granulation Technique: A Review. Pharmainfo.net. 2006;85(3):123–131. [Google Scholar]
7. Guarino E, Nigi L, Patti A, Fondelli C, Dotta F. Combination therapy with Metformin plus Vildagliptin in type 2 diabetes mellitus. Expert Opinion in Pharmacotherapy. 2012; 13(9): 1377-1384.
8. Shaikh AR, Ahmed BARK, Ibrahim M. A validated stability indicating RP-HPLC method for simultaneous estimation of Metformin and Teneligliptin in bulk and pharmaceutical dosage form. International Journal of Pharmaceutical Sciences and Research. 2018; 9(4): 1705-1712.
9. Patil M, Jani HD, Khoja SS, Pirani NA, Khoja S. A review on chemistry and pharmacological activity of Metformin hydrochloride and Teneligliptin hydrobromide hydrate in combined dosage form. Pharma Tutor. 2017; 5(3); 24-30.
10. Anil Kumar Ch, Sreekanth J, Raghunandhan N. Formulation and evaluation of sustained release bilayered tablets of Metformin HCl and Glimepiride. International Journal of Pharmacy and Biological Sciences. 2013; 3(4): 1-9.
11. Deepak P, Sufiyan A, Shastry VM, Tabrej M, Lalit T. Analytical method development and validation for the simultaneous estimation of Metformin and Teneligliptin by RP-HPLC in bulk and tablet dosage forms. Journal of Pharmacy Research. 2017; 11(6): 676-681.
12. Thamma NK, Kota CM, Sreenivasulu R, Raju NSV, Reddy V. Novel RP-HPLC Method for the estimation of Metformin Hydrochloride in pharmaceutical dosage forms. International Journal of Science Innovations and Discoveries. 2011; 1(3): 395-421.
13. Kokare V, Nagras MA, Patwardhan SK. Bioanalytical method development of Metformin co-administered with Ocimum Sanctum for potential bioenhancer Activity. International Journal of Pharmaceutical Sciences and Research. 2015; 6(5): 2056-2065.

14. Rohan D. Deshpande, D. V. Gowda 1, Nawaz Mahammed and Deepak N. Maramwar ,Bi-Layer Tablets - An Emerging Trend: A Review, International Journal of Pharmaceutical sciences and research, 2011, Vol. 2(10), 2534-2544.
15. Mogili Vijaya Krishna, T. Venkateswara Rao, "Formulation and Evaluation of Multilayered Tablets of Metformin, Telmisartan and Glipizide for the Combination Therapy of Diabetes and Hypertension, World Journal of Pharmacy and Pharmaceutical Sciences, Volume 3, Issue 11, 1116-1135.
16. Wanjari MM, There AW, Tajne MR, Umathe Rapid and Simple RP-HPLC Method for the Estimation of Metformin in Rat Plasma. Indian Journal of Pharmaceutical Sciences. 2008; 70(2): 198-202.
17. Gao X, Christensen M, Burghen GA, Velasquez-Mieyer P, Moore KT, Donahue SR, Reeves RA, Turner KC. Pharmacokinetics of Metformin in pediatric type 2 diabetic and healthy adult subjects. Clinical Pharmacology & Therapeutics. 2003; 73(2): 46-53.
18. Manish Patil, Harsha D Jani, Suleman S Khoja, Narmin A Pirani, Shamim S Khoja, "A Review on chemistry and pharmacological activity of metformin hydrochloride and teneligliptin hydrobromide hydrate in combined dosage form", Vol. 5, Issue 3, magazine.pharmatutor.org, Pg no: 24-30.
19. Nisharani Ranpise, Preeti Jamkar, Harshada Langote, "Do Fixed Dose Combinations Play an Important Role in the Management of Coexistent Type Two Diabetes Mellitus and Hypertension?", Indian Journal of Pharmaceutical Education and Research, Vol 49, Issue 3, Jul-Sep, 2015, 190-199.
20. Patel H., Shah v., Upadhyay u., "New Pharmaceutical Excipient in Solid Dosage Forms-A Review", International Journal of Pharmacy and Life Sciences, 2011; 2 (8): 1006-1019.
21. Venkateswara Rao. S, Rodhay. G & Padmalatha. K, "Design and evaluation of mouth dissolving tablets of telmisartan by using different super disintegrants", Indo American Journal of Pharmaceutical Research, 2017, Vol 7 Issue 09, 2017. ISSN NO: 2231-6876
22. Sri Harsha Tella & Marc S Rendell, DPP-4 inhibitors: focus on safety Expert Opin. Drug Saf. (2014) 14(1)
23. Piyush Agarwal, Chhavi Jindal, Vinayak Sapakal, "Efficacy and Safety of Teneligliptin in Indian Patients with Inadequately Controlled Type 2 Diabetes Mellitus: A Randomized, Double-blind Study", Indian Journal of Endocrinology and Metabolism, Volume 22, Issue 1, January-February 2018.
24. Chandra Narayan Gupta, Vijay Raghavan, Sukanta Sen, Sanjay Kothari, Role of teneligliptin in rural India as add-on third drug in patients with type 2 diabetes mellitus, International Journal of Advances in Medicine, April 2017; 4 Edition, Issue 2: Pg. No. :-401-405.
25. Modi Foram P., Patel Priyal R., Formulation, Optimization & Evaluation of Fixed Dose Combination Moisture Barrier Film Coated Bilayer Tablet of Artesunate & Amodiaquine Hydrochloride, International Journal of PharmTech Research CODEN (USA): IJPRIF, Vol.3, Issue No.4, Oct-Dec 2011, Pg. No.: 2124-2134.

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