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Research Article

Design And Evaluation Of Teneligliptin Tablet

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ABSTRACT

Background : Excessive workload, stress, and, genetic disorders are the main reason for the increasing prevalence of Type II diabetes in India. Teneligliptin, is a potent Dipeptidyl peptidase (DPP-4) inhibitor that exerts its action in Type II diabetes mellitus. Teneligliptin mainly acts by increasing insulin levels and decreasing glucagon levels in the circulation in a glucose-dependent manner. It offers sufficient glycemic control in a period of 12 weeks ad is also tolerable by renal-impaired patients.
Methods: Six formulations of teneligliptin tablets were prepared by using different ratios of MCC, maize starch, HPMC, HPC, aerosol, and magnesium stearate. The prepared tablets were evaluated in terms of friability, hardness, disintegration, and dissolution rate profile
Results: Out of all six formulations, F4 reflects better tablet characteristics as compared to the rest five formulations
Conclusions: F4 turns out to be the best formulation of the present study and can be used for commercial production.

Keyword : Teneligliptin, Diabetes mellitus, glycemic control, disintegration, formulation, insulin, glucagon

INTRODUCTION

In today's world when everyone is running with fast pace, keeping ourselves fit and taking a balanced diet is overlooked. It leads to several health problems and diseases. Diabetes mellitus is one of them; it may prove fatal if not being taken care of properly.[1] Diabetes mellitus is a group of disorders mainly characterized by hyperglycemia due to insufficient insulin production or release. If not treated timely, it leads to organ damage, dysfunction and ultimately organ failure. [2] Diabetes was first discovered by Egyptians about 3000 years ago and was characterized by weight loss and polyuria. The Greek physician Aertaeus coined the term "diabetes mellitus".[3,4] Diabetes mellitus is mainly divided into two subtypes: Type I, also known as insulin dependent diabetes mellitus (IDDM) and Type II, also known as non-insulin dependent diabetes mellitus. Type I DM mainly results as an autoimmune reaction to proteins of islets of langerhans of pancreas while type II DM occurs due to combination of genetic factors which impairs insulin secretion.[5] According to a survey done by IDF (International Diabetes Federation), more than 80 million people will be suffering from diabetes by 2025.[6] Type II diabetes mellitus is continuously expanding global health problem. Individuals with Type II DM are at higher risk for both microvascular complications such as retinopathy and nephropathy and macrovascular complications such as cardiovascular comorbidities.[7] Over 90% cases of diabetes mellitus are of Type II DM.[8] Teneligliptin is a newly developed Dipeptidyl peptidase-4 inhibitor mainly used in the treatment of Type II DM. Incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released mainly from the enteroendocrine cells and enhance insulin secretion. These incretin hormones are rapidly inactivated by DPP-4 and hence, DPP-4 inhibitors increase the level of GLP-1 and GIP by inhibiting the enzymatic activity of DPP-4.[9] Teneligliptin belongs to class 3 DPP-4 inhibitors which bind to additional site of S2 and produce more extensive DPP-4 inhibition.[10] Teneligliptin consists of rigidly "J" shaped structure formed by five rings, out of which four rings are strongly connected to DPP-4 and hence provides strongest binding to DPP-4 as compared to other gliptins.[11] This present study explains the formulation and evaluation of Teneligliptin tablet for the management of Type II DM.

MATERIALS AND METHODS

Materials

Teneligliptin was procured from Ami Life Sciences Pvt Ltd. Gujarat. HPMC, HPC, Starch, magnesium stearate, and aerosol were procured from Rankem Laboratories Pvt Ltd. All other chemical reagents were of analytical grade. All the materials were used as received.

Methods

Identification of Pure drug

Identification of Teneligliptin was done by UV-spectrophotometry and was compared with the reference spectrum of drug.

Fabrication of Tablets

Wet granulation technique

The required quantity of different excipients along with the drug except magnesium stearate, aerosil were weighed accurately and were moved into the Rapid Mixer Granulator (RMG) where the mass is

mixed for half an hour. This step remains the same for all six formulations. The varying concentration of binders such as HPMC, HPC was added by dissolving them in hot water which leads to the agglomeration of wet mass. This wet mass was converted to granules of different sizes with the help of RMG. Granules were transferred to a fluidized bed dryer where they were dried for approx. 30 minutes at 37^{o}C temperature. The granules further moved into multi-mill for size reduction. In the multi mill, granules were passed from 0.5mm sieve and then in sieve shaker form sieve no. 30. Magnesium stearate and aerosol were then added and the granules were mixed properly in RMG for 15 minutes. At last, the granules were transferred into the blender for final blending. After the completion of blending, the granules were compressed into tablets.[12-15] The composition of six different formulations is given in Table 1

Table 1: List Of Materials And Quantities For Formulation F1 To F6

SNo.	Ingredients of tablet in mg	F1	F2	F3	F4	F5	F6
1	Teneligliptin	20	20	20	20	20	20
2	MCC	220.5	197	168	198	160.5	193
3	Maize starch	50	48	46.5	46	48	50
4	HPMC	1.5	2.0	2.5	3.0	3.5	4.0
5	HPC	25	-	30	-	35	-
6	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5
7	Magnesium state	1.5	1.5	1.5	1.5	1.5	1.5
8	Purified water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
	Total Weight	**270**	**270**	**270**	**270**	**270**	**270**

Characterization of tablets

Preformulation studies:

Once the granules formulated, the tablet characteristics has been determined with the evaluation of physiochemical properties of blend. There are various methods has been utilized in the formulation process which may affect the characteristics of the blend formulated. [16, 17]

Angle of Repose (θ)

It was determined using the funnel method. The accurately weighed granules were taken in a funnel, and granules were allowed to flow from the tip of the funnel. The diameter of powder heap surface and height of powder pile was determined. [18, 19] The angle of repose was calculated using the following formula:

$$\boldsymbol{\theta} = \mathbf{tan}{-}\mathbf{1}\boldsymbol{h}/\boldsymbol{r}$$

Where,

$\boldsymbol{\theta}$ is the angle of repose

h is height of pile of powder

r is the radius of the horizontal surface

Limits of angle of repose as per I.P is given in Table 2

Table 2: **Limits of Angle of repose according to I.P.**

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

Bulk Density (D_b)

It is characterized as the complete weight/mass of the powder isolate by the mass volume of the powder. It was basically determined by moving the gauge powder into the estimating chamber and its underlying volume was noted. [20] It was calculated using the formula:

$$"Db = M/V_b"$$

Where,
M is the weight/mass of the powder
$v_b$is the bulk volume of the powder

Tapped Density (D_t)

It is defined as the total weight/mass of the powder divided by the volume of powder after tapping. It was calculated by transferring the gauged quantity of powder inside quantify cylinder and then measuring cylinder was tapped until the volume remains unchanged or the difference was less than 2%.[9] It was calculated using the formula:

$$Dt = M/V_t$$

Where,
M is the weight/mass of the powder
V_t is the tapped volume of the powder

Carr's Index (compressibility index)

Carr's Index also known as compressibility index is used regularly to determine the flowability of the powder. If the compressibility index reflects a value of more than 25 then the flow of powder is said to be poor and if the value is below 15 then it reflects good flowability.[18] It is estimated by using the following formula:

$$\% \textbf{ Compressibility} = (Tapped\ Density – Bulk\ Density)) \times 100/Tapped Density$$

Limit for Carr's index according to I.P is given in Table 3

Table 3: Limit for Carr's index according to I.P.

Carr's index	Type of flow
5-15	Excellent (free flowing granules)
12-16	Good (free flowing powdered granules)
18-21	Fair (powdered granules)
23-35	Poor (Fluid cohesive powder)
33-38	Very poor (Fluid cohesive powder)
>40	Extremely poor (cohesive powder)

Hausner's Ratio

It also tell about the flowability of the powder indirectly or it is an index of ease of powder flow. If its value is around 1.25 then it reflects a good powder stream. One can use the equation below to find out Hausner's ratio. [18]

$$HausnerRatio = Dt/Db$$

Where,
Db = Bulk density of the powder
Dt = Tapped density of the powder

Post-compression Parameters:
General Appearance

General appearance should consist of a number of parameters like size, shape, odor, taste, texture, and identifying marks.[21]

Size and Shape

Various shapes and size of tablets are existing in the market. The shape and size of the tablets differ from each other according to the dies used during the manufacturing process. The size of the tablet is calculated using a vernier caliper and the thickness should vary only in the limit of ±5% with standard value.[22]

Hardness

The physical strength and hardness of the tablet are necessary to maintain so that it can easily bear the shock and stress during manufacturing, packaging, transportation and handling by the patient. The considerable strength of the tablet is hard to attain due to specific processes and excipients used in manufacturing. The maximum value for the tablet hardness should be kept in the lower range for ease of disintegration. The hardness of the tablet can be checked with the help of hardness tester such as Monsanto Hardness tester and Pfizer hardness tester. 5 tablets were randomly selected from the prepared batches and hardness was determined using Monsanto type hardness tester.[23]

Friability

Friability test is done to check the strength of tablets during transit. To attain friability within the range is a key challenge for a formulator because maybe the processes used for its casting are liable for the increment of its friability value. It is very essential parameter that must be checked and the resulting value should lie in the range of (0.1-1%). It was measured by using Roche friabilator. Six tablets were taken and placed into the friabilator where they are subjected to rolling and free fall for 4 min at 25 RPM.[24,25] It was calculated with the help of the following formula:

$$Friability = [W1 - W2/W1] \times 100$$

Where,
W1= Weight of tablets before the test.
W2= Weight of tablets after the test.

Weight Variation

20 tablets were randomly selected and weighed accurately; the average weight of the tablets was calculated. The individual weight of the tablet was then measured and the % variation in the comparison should lie inside the acceptable range.[26] It is calculated with the help of this formula:

$$PercentageDiviation = (Individualweight - Averageweight / Averageweight) \times 100$$

Standard Limits for Weight Variation as per I.P. is given in Table 4

Table 4: Standard Limits for Weight Variation as per I.P.

Sr. No.	Average weight of Tablet (mg)	Maximum Percentage difference allowed
1	80	10
2	250	7.5
3	>250	5

Dissolution Test

Dissolution test is performed to check the drug release from the formulation so that we can compare the in-vitro release with in-vivo release. This test was performed using Lab India DS-8000 apparatus USP method II using water as solvent having 50 RPM at the temperature of 37^{o}C. 10ml of sample were taken after 5 min of intervals and it is equilibrated with fresh volume of medium which were analyzed using UV spectrophotometer (Shimadzu) and also with HPLC (waters e2695).[27,28] Parameters and conditions for Dissolution Study is given in Table 5.

Table 5: Parameters and conditions for Dissolution Study.

Parameters	Conditions
Dissolution Media	900ml of purified water
Temperature	37±0.5^{o}C
RPM	50
Λ_{max}	253nm

Disintegration Test

The process of breakdown of a tablet into smaller particles is called disintegration. In vitro disintegration time was calculated using lab India DT-1000 apparatus. The apparatus consists of 6 glass tube that are 3 inches long, open from the top, and in the bottom of the tubes there is a mesh of size 10. To evaluate the disintegration time each tube was filled with one tablet, and to pass this parameter every tablet should pass the 10 mesh size in a specified time. [29, 30]

RESULTS AND DISCUSSION

Calibration curve of Teneligliptin

Calibration curve of Teneligliptin was made using water as a solvent which follows beer's lambert law. Teneligliptin standard curve was drawn through pleasing absorbance at 244nm and the values were taken at different concentration of drug which follows the beer's law. Teneligliptin Calibration curve in purified water is given in Table 6.

Table 6. Teneligliptin Calibration curve in purified water

Sr.no	Concentration µg/ml	Absorbance
1	0	0
2	10	0.1983
3	20	0.3889
4	30	0.5933
5	40	0.7877
6	50	0.9975

Standard curve for Teneligliptin is given in Fig 1.

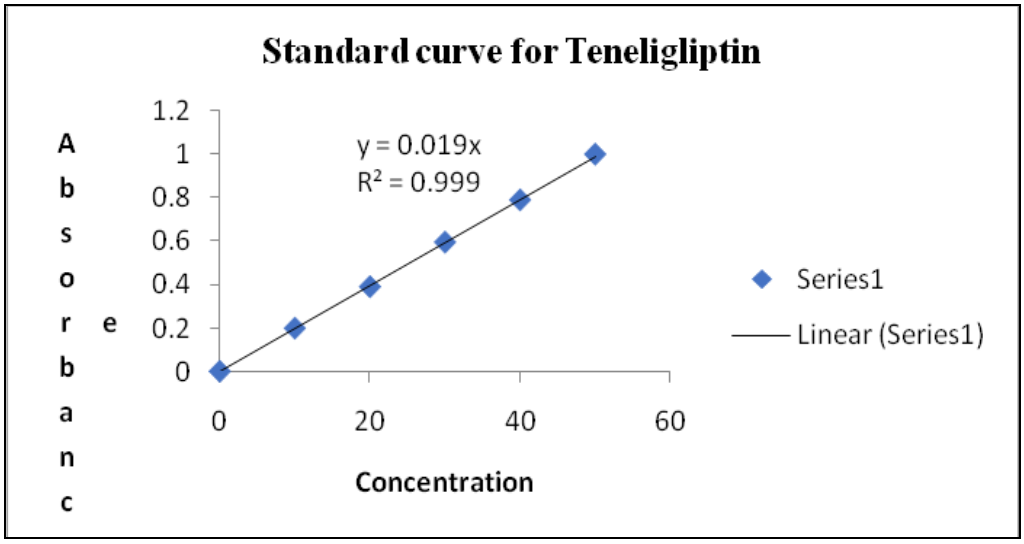

Fig 1. Standard curve for Teneligliptin

Preformulation studies

The drug and excipients were mixed together and checked for "bulk density, tapped density, Carr's index, Hausner ratio". Then it shows different value which is mentioned below. Preformulation parameters of powder blend is given in Table 7.

Table 7: Preformulation Parameters Of Powder Blend

Formulations	Bulk density(gm/ml)	Tapped density(gm/ml)	Angle of repose	Hausner ratio	Carr's index
F1	0.528	0.616	26.78	1.17	14.28
F2	0.669	0.778	27.12	1.16	14.01
F3	0.684	0.825	26.06	1.21	17.09
F4	0.563	0.638	25.19	1.24	11.75
F5	0.705	0.862	28.69	1.13	18.21
F6	0.631	0.716	24.63	1.14	11.87

The value depicts in the table angle of repose in the range of 24°63'-28°69' and the values of Hausner ratio and Carr's index were found to be in range of 1.13-1.24 and 11.75-18.21 respectively. From this it clearly shows that formulation F4 had good flow properties in all above six formulations.

Post-formulation parameters

The post formulation parameters are given in Table 8.

Table 8: Post formulation parameters of tablet

No	Formulations	Thickness (mm)	Diameter (mm)	Weight Variation (mg)	Hardness (K_p[kgf])	Friability (%)	Disintegration time (min)
1	F1	3.47	9.43	272.45	2.2	0.66	3:44
2	F2	3.51	9.44	268.37	2.9	0.63	3:47
3	F3	3.54	9.42	270.98	2.8	0.57	4:46
4	F4	3.52	9.45	270.61	3.2	0.59	5:30
5	F5	3.55	9.42	267.28	2.6	0.38	5:55
6	F6	3.56	9.41	267.52	2.7	0.73	6:13

The table 8 depicts the value of thickness which is in the range of 3.47-3.56mm and its diameter were in the range of 9.41-9.45mm and the average weight of the tablet were in the range of 267.28-272.45mm, hardness of the tablet which is in the range of 2.2-3.2(K_p[kgf]). And its friability was less than 1% for all the six formulations and the time taken to break down into small pieces of tablet were in the range of 3:44-6:13 min.

Dissolution data

Cumulative percentage of drug dissolve for F1, F2, F3, F4, F5, F6 is given in **Fig 2** and discussed in **Table 9.**

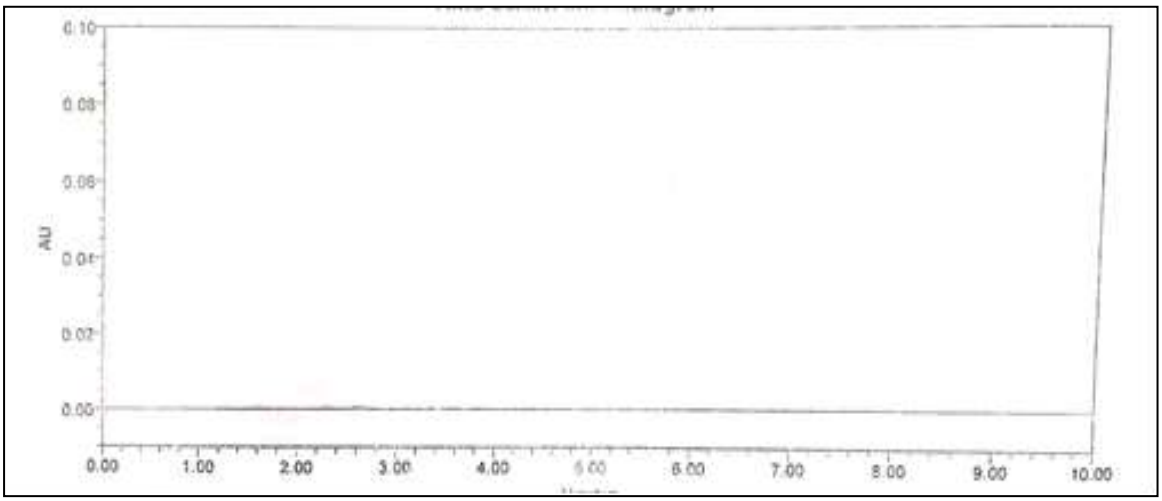

Fig 2: Cumulative percentage of drug dissolve for F1, F2, F3, F4, F5, F6

Table 9: Cumulative percentage of drug dissolve for F1, F2, F3, F4, F5, F6

Time (min)	F1	F2	F3	F4	F5	F6
5	7.89	8.57	8.21	9.95	9.36	10.95
10	19.37	20.35	18.87	20.99	19.25	23.49
15	38.19	34.23	39.56	37.19	40.48	39.01
20	45.40	49.62	51.06	54.08	59.63	53.16
25	70.23	73.03	76.81	78.04	78.29	71.07
30	93.46	91.28	94.16	98.08	92.23	89.33

The graph above illustrate the dissolution data for different batches as F1,F2,F3,F4,F5,F6 which is drawn through putting time on x-axis (mins) and % dissolved at y- axis. In all the batches above F4 has the maximum cumulative percentage release of drug in 30 mins.Chromatogram of blank is given in **Fig 3.**

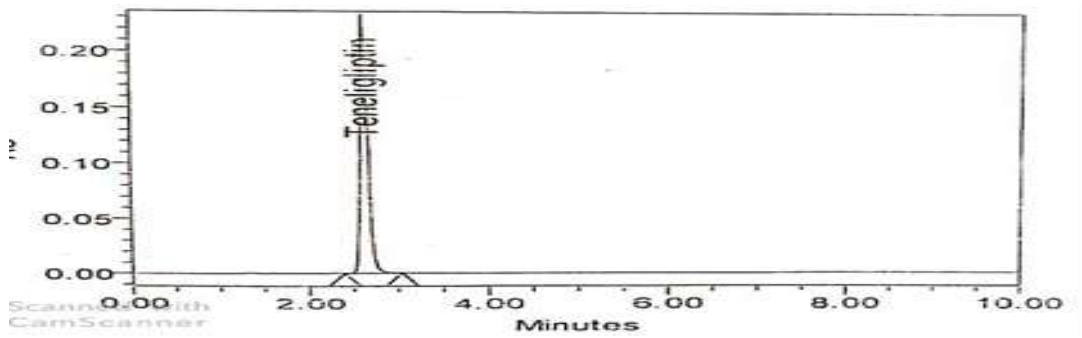

Fig 3: Chromatogram of blank

Chromatogram of working standard and prepared formulation of Teneligliptin is given in **Fig 4.**

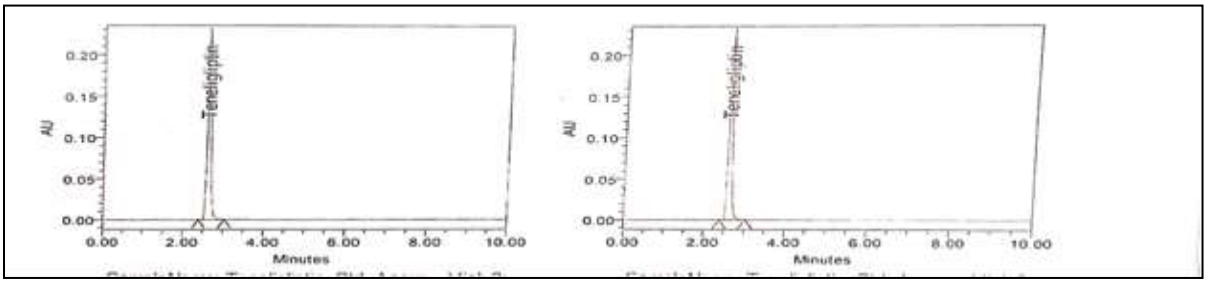

Fig 4: Chromatogram of working standard and prepared formulation of Teneligliptin

IR spectrum analysis

The IR spectrum confers its chemical structure 1-(3-Methyl-1-Phenyl-1H-Pyrazol-5-yl)-4-[(3S,5S)-5-(1,3Thiazolidine-3-Carboxy)Pyrrolidin-3-yl] Piperazine. IR spectrum is given in Fig 5.

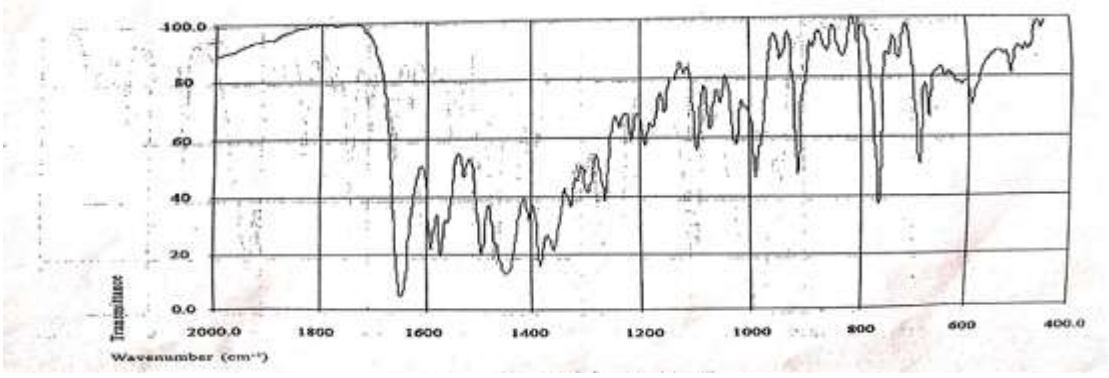

Fig 5: IR spectrum of Teneligliptin Tablet

CONCLUSION

According to this study, the drug and the different type of formulations results in the formation of Teneligliptin tablet with acceptable results for the treatment of type II diabetes. Above all the formulations represent the adequate results in hardness, friability, disintegration time, weight variation studies and in-vitro dissolution studies. Various excipients used for filler, diluents, lubricant, and disintegrant pick up the tablet quality as well as its release from the formulation. Wet granulation proves the best method for the formulation and F4 proves the best formulation in this study.

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