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Research Article

Formulation and Evaluation of Teneligliptine Pellet

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ABSTRACT
The present study is an attempt to formulate and evaluate Teneligliptin hydrobromide hydrate pellets. Teneligliptin is a potent, selective DPP-4 inhibitor, which is believed to exert its actions in diabetes mellitus patients. Teneligliptin increases insulin release and decreases glucagon levels in the circulation in a glucose dependent manner. The Teneligliptin pellets were prepared by using blend of MCC, Lactose, Crospovidone and PVP K-30. Pellet formulation was optimized for formulation parameters (concentration of Crosspovidone and PVP K-30) using 3^2 factorial design. FTIR studies showed absence of chemical interaction between the drug and polymer. The pellets were prepared and evaluated in terms of bulk density, tapped density, angle of repose and in-vitro release study. In-vitro release of drug was compared with in-vitro release of drug from marketed formulation (Dynaglipt Tablet).

Keywords: Teneligliptin, Diabetes mellitus, Pellets, extrusion – spheronization.

INTRODUCTION

Pelletization can be defined as an agglomeration (size-enlargement) process that converts fine powders or particles of bulk drugs and excipients into small, free-flowing, more or less spherical units, called pellets. This technique is used to produce pellets of uniform size with high drug loading capacity and also prevent segregation and dust. The size of pellets range from 0.5 to 2.0 mm. The four processing steps in the extrusion and pelletization are mixing, extrusion, spheronisation, and drying. Accurately weighed all the excipients. All excipients were dry mixed and water was added in such a quantity so as to form the damp mass.

Teneligliptin[4,5,6] is a antidibetic drug which is a potent, reversible and selective inhibitor of the enzyme DPP-4(Dipeptidyl peptidase 4) which is involved in the inactivation of the incretin hormones (glucagon-like peptide-1) (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These incretin hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Teneligliptin binds to DPP-4 in a reversible manner and thus leads to an increase and a prolongation of active incretin levels.Teneligliptin, glucose dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homoeostasis. Currently, teneligliptin tablets are available on market. Here, an attempt is made to prepare pellets of teneligliptin.

MATERIALS AND METHOD

Materials

Teneligliptin hydrobromide hydrate was provided as gift sample by Precise Chemipharma Pvt. Ltd, Navi Mumbai, Maharashtra. The other exipents such as, MCC (Avicel PH-101), Lactose, Crospovidone, and polyvinyl pyrrolidone K-30 (PVP K-30), were purchased from Loba chemicals.

Method

UV spetrophotometric methods for Teneligliptin[7,8]

Preparation of 0.1N HCl

8.5 ml of hydrochloric acid was diluted to 1000 ml with water to get 0.1 N HCl.

Determination of λmax

U.V spectrum of teneligliptin was carried out in 0.1 N HCl Accurately weighed quantity of 10 mg Teneligliptin hydrobromide hydrate (THH) was transferred to 100.0ml volumetric flask, added 30ml of 0.1 N HCl and ultrasonicated for 10 minutes, volume was then made up to the mark with 0.1N HCl (100 µg/ml). The standard stock solution was diluted with 0.1 N HCl to obtain final concentration of 20 µg/ml of THH. The solution was then scanned in spectrum mode, from 400 nm to 200 nm, in 1.0 cm cell against 0.1 N HCl as blank.

Calibration curve

Accurately weighed quantity of 10 mg Teneligliptin hydrobromide hydrate (THH) was transferred to 100.0ml volumetric flask, 30ml of 0.1 N HCl and ultrasonicated for 10 minutes, volume was then made up to the mark with 0.1 N HCl(100 µg/ml). From standard stock solution aliquot portions 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 ml were diluted individually to 10.0 ml with 0.1 N HCl (concentration 5, 10, 20, 30, 40 and 50 µg/ml, respectively). Absorbances of diluted solutions were measured at 242.0 nm against 0.1 N HCl as blank.

Fourier Transform Infra-Red (FTIR) spectrum

The powder sample of Teneligliptin was kept in dryer for making it moisture free. The dry powder of Teneligliptin was mixed and triturated with dry potassium bromide. This mixture was placed in DRS assembly sample holder. The

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Table 1: Formulation of blank pellet.

Batch No	Mcc (gm)	Lactose (gm)	Cross povidone (gm)	Pvp k-30 (gm)	Water (ml)	Total (gm)
B1	15.5	3.5	0.5	0.5	20	20
B2	15.5	3	0.5	1	19	20
B3	15	3	1	1	19.5	20
B4	15	3.5	0.5	1	18	20
B5	15.5	3	1	0.5	18	20
B6	16	3	0.5	0.5	17.5	20

Table 2: Independend and Dependent Variables summary for factorial design.

Variables	Low level (−1)	Middle level (0)	High level (+1)
X_1= Crosspovidon (g)	0.5	0.7	1
X_2 = PVP K-30 (g)	0.5	1	1.5

Table 3: Composition of formulations used in 3^2 factorial design.

Batch No	Drug (gm)	Mcc (gm)	Lactose (gm)	Crosspovidone (gm)	Pvp k-30 (gm)	Water (ml)
F1	0.5	16	2.5	0.5	0.5	17
F2	0.5	16	2	0.5	1	17
F3	0.5	16	2.3	0.5	1.5	17
F4	0.5	16	2.1	0.7	0.5	17
F5	0.5	16	1.8	0.7	1	17
F6	0.5	16	2	0.7	1.5	17
F7	0.5	16	1.8	1	0.5	17
F8	0.5	16	1.5	1	1	17
F9	0.5	16	1	1	1.5	17

Table 4: Micrometric properties of blank pellets.

BlankPelltes	Percentage yield (%)	Bulk Density (gm/ml)	Tapped Density(gm/ml)	Hausner's Ratio	Carr;s Index(%)	Angle Repose (^{0})
B -1	40.32	0.556	0.64	1.16	0.163	40.21
B-2	60.23	0.489	0.788	1.611	0.611	30.22
B-3	64.66	0.581	0.747	1.285	0.285	38.66
B-4	68.48	0.584	0.723	1.238	0.238	38.55
B-5	59.88	0.555	0.805	1.388	0.387	41.20
B-6	79.66	0.761	0.800	1.051	0.512	46.5

Based on the high% yield , blank formulation B 6 was selected for incorporation drug.

Table 5: Evalution of teneligliptin pellets.

Batch No.	% Yield	Diameter (mm)	Bulk density (g/ml)	tapped density (g/ml)	Hausners ratio	Carr's index (%)	Angle of repose(°)
F-1	55.62	0.96	0.623	0.340	0.961	1.33	35.90
F-2	67.69	0.46	0.703	0.32	1.333	1.17	38.45
F-3	56.19	0.88	0.682	0.527	1.070	0.950	38.22
F-4	49.23	0.73	0.756	0.432	0.856	2.69	45.50
F-5	75.32	0.51	0.552	0.555	1.330	0.246	40.95
F-6	84.9	0.62	0.402	0.552	1.90	0.270	42.11
F-7	86.9	0.76	0.333	0.469	0.999	0.660	42.22
F-8	75.65	0.33	0.789	0.720	1.30	0.970	40.22
F-9	69.1	0.85	0.400	0.802	1.23	0.840	50.11

infrared spectrum was recorded and the spectral analysis was done.

Drug- excipients compatibility studies

The interaction study of drug and excipients was performed by FTIR spectroscopic analysis. FTIR spectra of drug, polymer and the physical mixture of drug and polymer were recorded on a Fourier-transform infrared spectrophotometer (FTIR-8400 S, Shimadzu, Japan) in the range 4000– 400 cm−1 and observed for the interaction between drug and excipients.

Procedure for preparation of blank pellets

Accurately weighed exipients were mixed to get homogeneous powder. Aqueous solution of PVPK-30 was added to powder mixture slowly to get damp mass. The

damp mass was passed through sieve number 16 to get extrudates. The extrudates were spheronized in laboratory spheronizer using 2mm plate at 900 rpm. Pellets were dried at 60ºC for about 30 min. Initially blank pellets were

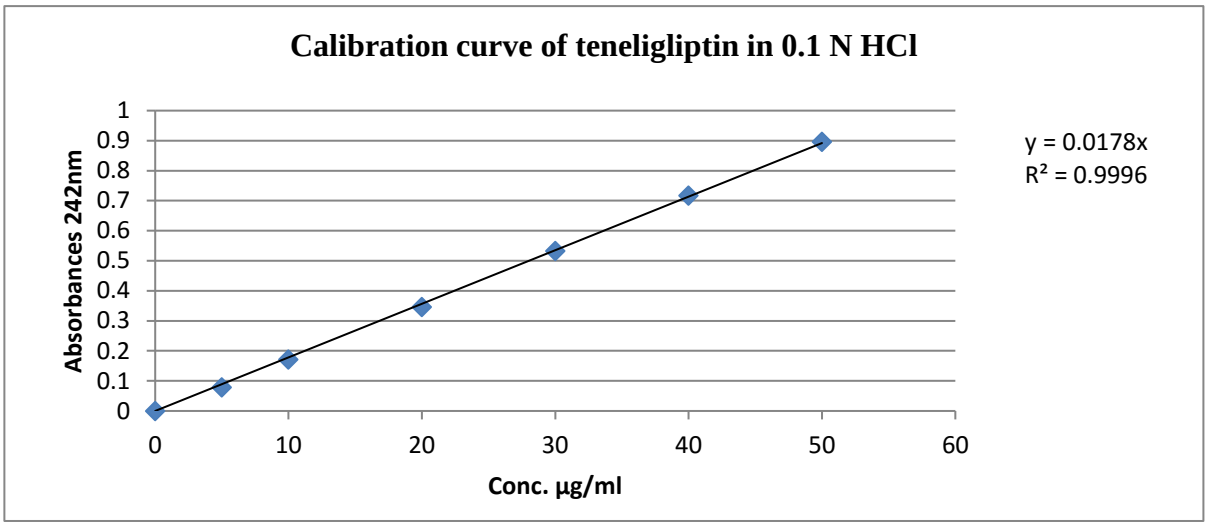

Figure 1: Calibration curve of Teneligliptin in 0.1N HCl.

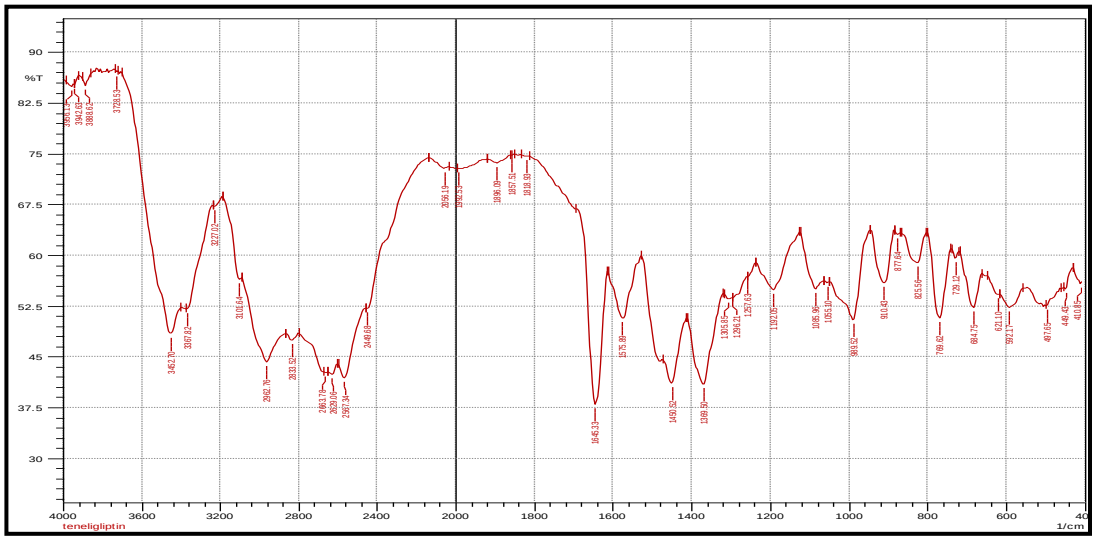

Figure 2: FT-IR spectrum of Teneligliptin hydrobromide hydrate.

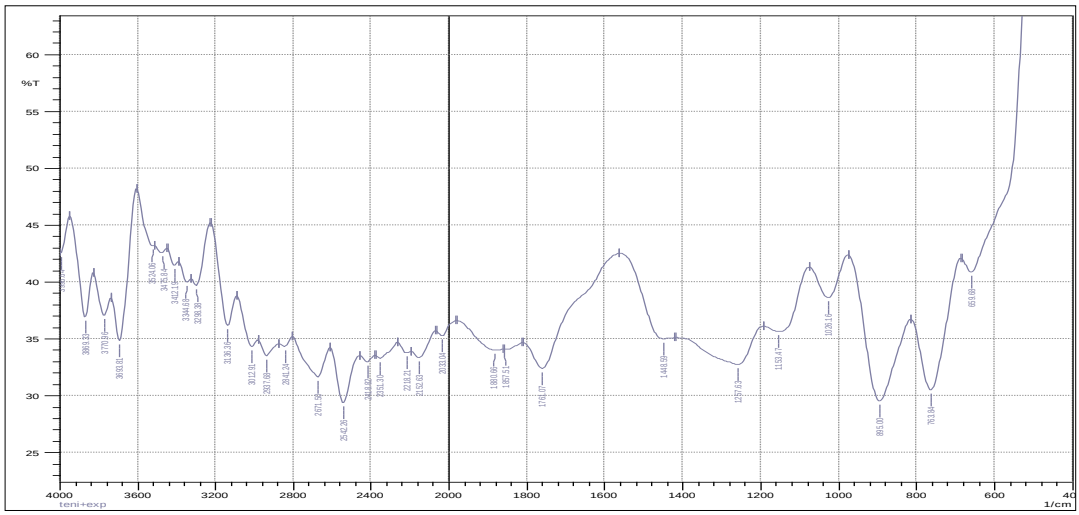

Figure 3: FT-IR spectrum of Teneligliptin hydrobromide hydrate formulation.

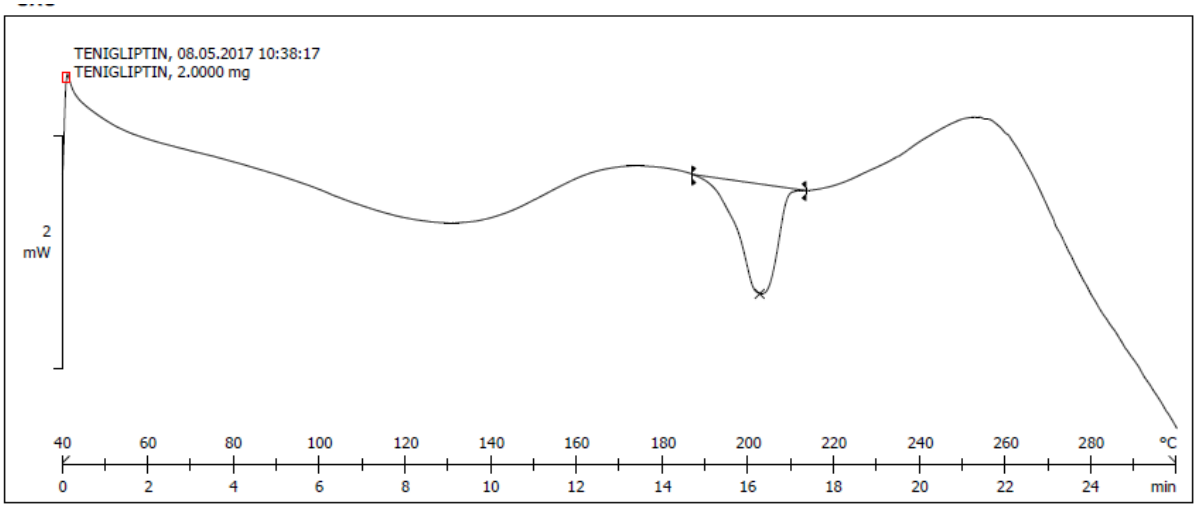

Figure 4: DSC of Teneligliptin.

Table 6: Hardness, friability and % of drug release of Teneligliptin loaded pellets at different formulation parameters.

Batch no.	Crosspovidone (X_1)	PVP K-30 (X_2)	Hardness (kg/cm^2)	Friabilty	% of drug release at 60 mim
F-1	-1	-1	0.157	0.71	80.23
F-2	-1	0	0.124	0.69	75.36
F-3	-1	+1	0.658	0.65	70.89
F-4	0	-1	0.241	0.70	85.65
F-5	0	0	0.452	0.65	82.96
F-6	0	+1	0.562	0.56	79.39
F-7	+1	-1	0.236	0.999	95.14
F-8	+1	0	0.354	0.863	90.32
F-9	+1	+1	0.258	0.385	88.96

prepared and evaluated. Table 1 gives formulation of blank pellets.

3^2 Full Factorial design

In this study, a 3^2 full factorial design was used to determine effect of two independent variable (factors) on dependent (reponse) variable. Independent variables were crosspovidone (disintegrant) and PVPK-30 (binder) concentration. These were studied at 3 levels those are low, medium, and high. Table 2 gives coding of levels and table 3 shows formulation of nine batches.

RESULT AND DISCUSSION

Calibration curve of Teneligliptin in 0.1N HCl:

eneligliptin Hydrobromide Hydrate showed wavelength of maximum absorption (ʎmax) at 242nm**.** Fig.1 shows calibration curve of teneligliptin in 0.1 HCl at 242 nm. It is linear in range of 5 to 50 µg/ml.

Drug excipients compatibility study by FT-IR

The FTIR spectra of pure drug showed (fig.2) functional peak at 3367.82, 3259.81, 3049.56, 2885, 1635.69, 1518.03, 725.26, cm^{-1} while physical mixture shows peaks at 3344.68 2937, 1761.07, 1448.59, 763.84, cm^{-1}with negligible shift in wave number. It might be due to presence of amorphous nature of excipients used. The FTIR spectra of drug and physical mixture indicate compatibility of teneligliptin formulation as shown in fig.2 and 3.

DSC study of Teneligliptin

The DSC thermogram of pure Teneligliptin is shown in Fig.4 DSC curve indicated the endothermic peak at 203 ^{0}C. It indicated the melting point of pure Tenegliptin. Thus, the sample was confirmed as Teneligliptin.

Micromeritric properties of blank pellets:

Micromeritic properties of blank pellets are given in Table 4

Optimization of Disintigratigrant and binder for Teneligliptin loaded pellets using factorial design

Evalution of teneligliptin pellets is shown in Table 5 and 6. Effect of independent variables that is crosspovidone concentration (X_1) and PVPK-30 concentration (X_2) was evaluated on Hardness (Y_1), friability (Y_2) and drug release (Y_3) in 0.1 N HCl at 60 min.

Hardness(Y_1), friability(Y_2), and drug release (Y_3) by using design expert 10.0 the equations obtained are as below

Hardness (Y_1)= $+0.55-0.036X_1+0.36X_2$…….(1)

Friability (Y_2)= $+6.69+0.033X_1-0.14X_2-0.14X_1X_2$…..(2)

Drug release (Y_3) = $+83.74+7.94X_1-3.63X_2$……(3)

Effect on Hardness

Mathematical relationship generated for hardness is expressed in following equation

Hardness (Y_1) = $+0.55-0.036X_1+0.36X_2$….(1)

From Equation 1, it can be seen that negative coefficient of X_1 indicates decrease in hardness with increase in concentration of crosspovidone. The positive coefficient of (X_2) indicates increase in hardness with increase in

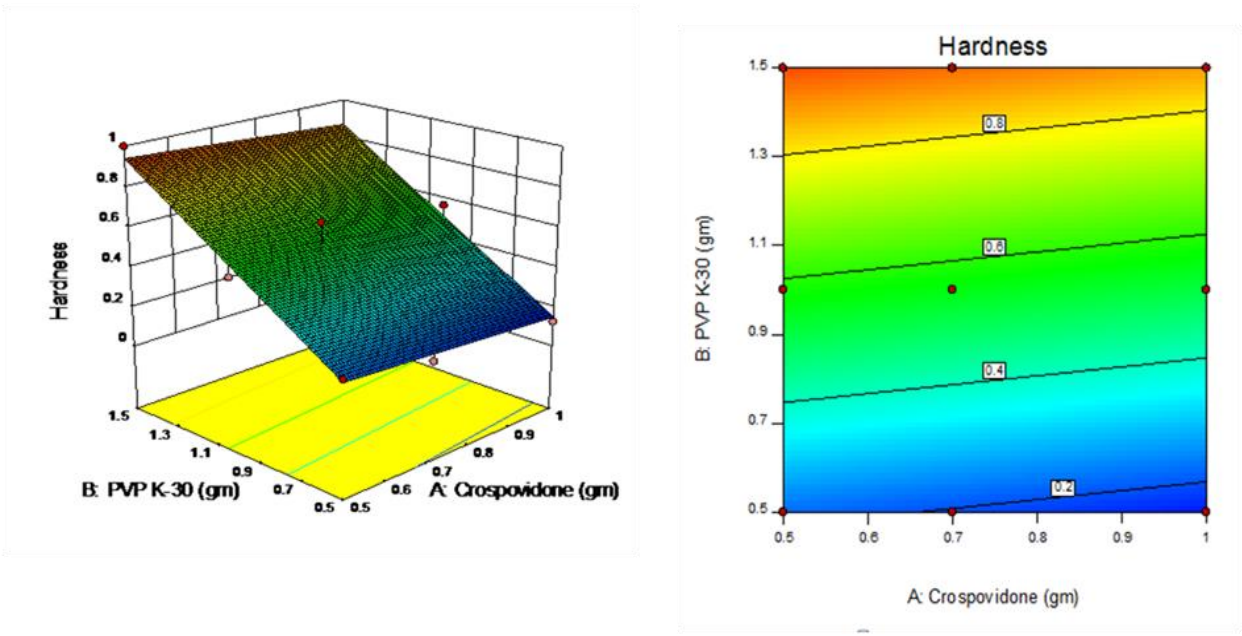

Figure 5: Different plots showing effect of independent variables on hardness of pellets. (A) Response surface plot showing the influence of concentration of crosspovidone and PVP K-30 on the hardness of pellets. (B) Counterplot showing the relationship between various levels of crosspovidone and PVPK-30.

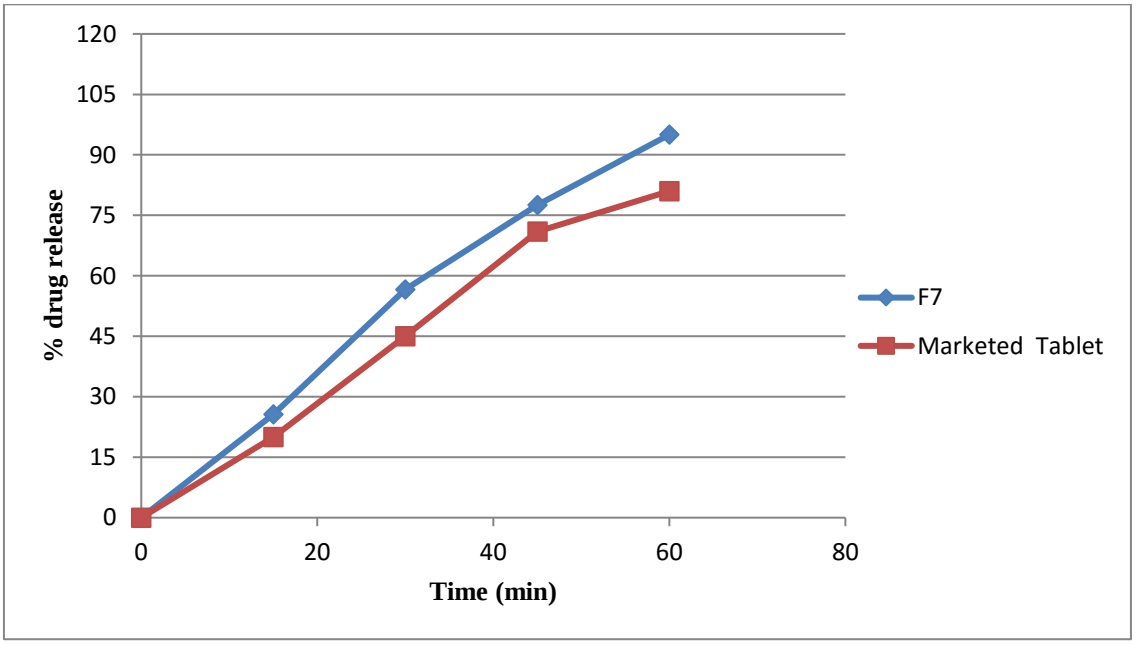

Figure 9: Comparison between optimizes batch and Marketed preparation.

concentration of PVPK-30. At three different levels of crosspovidone (-1,0,+1) as concentration increased from 0.5gm to 1.5gm, hardness decreased. At different concentration (-1, 0, +1) of PVP K-30 the hardness increased when concentration increased from 0.5 to 1gm . The selected surface linear model showed >F value of 3.33 which indicated there was no significant effect of concentration of crosspovidone and PVPK-30 on hardness.

Effect on Friability

Friability (Y_2)= $+6.69+0.033X_1-0.14X_2-0.14X_1X_2$…(2)

From Equation 2, it can be seen that positive coefficient of X_1 indicates increase in friability with increase in concentration of crosspovidone . The negative coefficient of (X_2) decrease in friabilty with increase in concentration of PVPK-30. At three different levels of crosspovidone (-1, 0, +1) as concentration increased from 0.5gm to 1.5gm, friability increased. At different concentration (-1, 0, +1) of PVP K-30 the friability decreased when concentration increased from 0.5 to 1gm. The selected surface linear model showed > F value of 8.77which indicated there was significant effect of concentration of crosspovidone and PVP K-30 on friability.

Effect on % Drug release

% drug release (Y_3) = $+83.74+7.94X_1-3.63X_2$…(3)

From Equation 3, it can be seen that positive coefficient of X_1 indicates increase in drug release with increase in

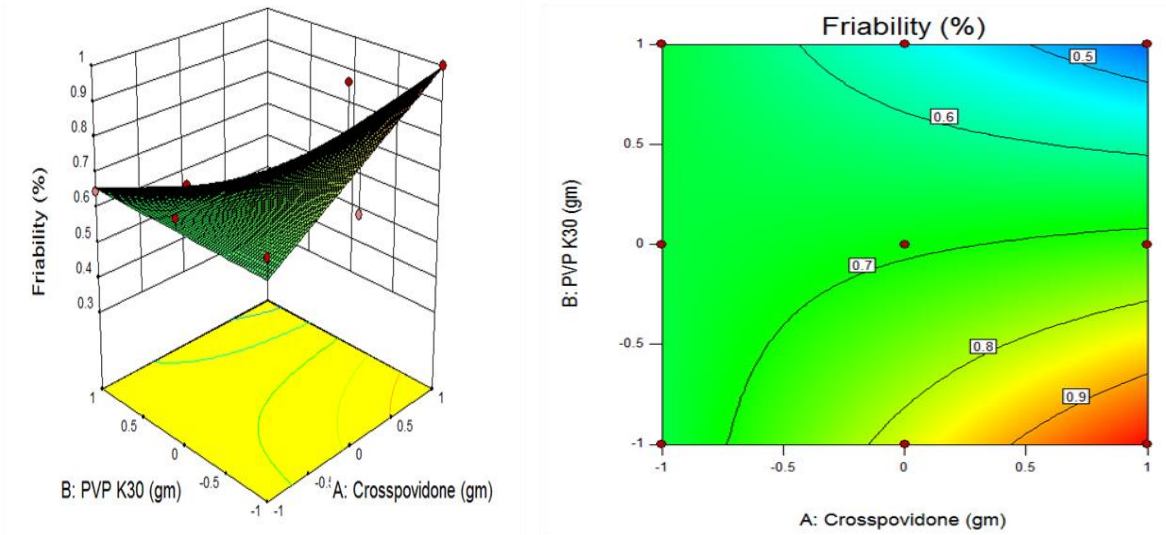

Figure 7: Different plots showing effect of independent variables on hardness of pellets. (A) Response surface plot showing the influence of concentration of crosspovidone and PVP K-30 on the friability of pellets. (B) Counterplot showing the relationship between various levels of crosspovidone and PVP K-30.

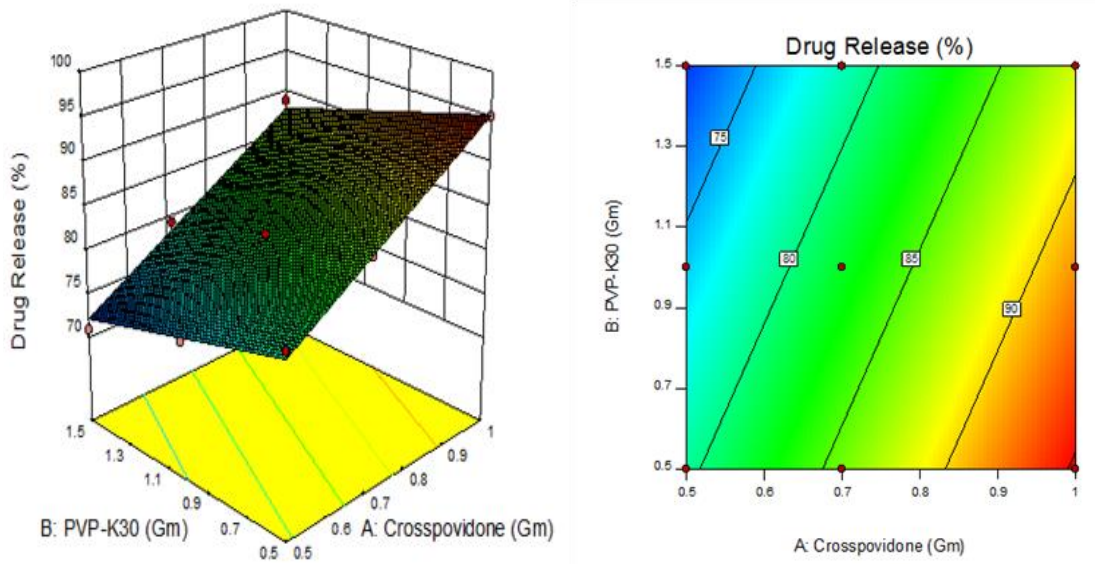

Figure 8: Different plots showing effect of independent variables on % of drug release of pellets. (A) Response surface plot showing the influence of concentration of crosspovidone and PVP K-30 on the Drug release of pellets. (B) Counterplot showing the relationship between various levels of crosspovidone and PVP K-30.

concentration of crosspovidone. The positive coefficient of (X_2) indicates decrease in drug release with increase in concentration of PVP K-30. At three different levels of crosspovidone (-1, 0, +1) as concentration increased from 0.5gm to 1.5gm, drug release decreased. The selected surface linear model showed > F value of 210.03 which indicated there was significant effect of concentration of crosspovidone and PVPK-30 on drug release.

Comparison between optimizes batch and Marketed preparation

From drug release data and other evaluation parameter batch F-7 was considered to be best batch so drug release from batch F-7 was compared with drug release from market formulation. F-7 batch showed better drug release profile.

CONCLUSION

The Multi unit drug delivery system of teneligliptin was formulated by Extrusion Spheronization technique. The pellets of batch (F-7) prepared with Crosspovidone and PVP k-30spheronized at 900rpm were found to be optimized. The optimized batch showed good physicochemicals properties, such as hardness and friability. The study suggested that F-7 gave better release in 0.1 N HCl in 60min when compared to release from marketed formulation (Dynaglipt Tablet).

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