

FORMULATION AND EVALUATION OF SINTERED GASTRORETENTIVE TABLETS OF VILDAGLIPTIN USING DESIGN OF EXPERIMENT

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ABSTRACT

Objective: The purpose of the study was to formulate and evaluate sintered gastro retentive tablets of Vildagliptin using the design of experiments.

Methods: Direct compression is the process by which tablets are compressed from powder mixture of API and suitable excipients and compression was done by an automatic punching machine using 6 mm punch. Prepared tablets were kept in the hot air oven at three different temperatures of 50°C, 60°C, 70°C for three different periods of 1, 2, 3 h.

Results and Discussion: The physicochemical evaluation results of the powder blend of all the trials pass the flow properties and compression properties and are of uniform density (i.e., Angle of repose, Bulk density, Compressibility index, Hausner's ratio). Among all the Formulations, Formulation F7 showed better results such as Angle of repose F7(29.9), Hausners ratio of F7(1.18), and compressibility index of F7 (15.6) which indicate the good flow properties. The prepared tablets were evaluated for the post compression properties such as thickness, hardness, Weight variation, friability, and drug content found within limits. Each formulation was analyzed spectrophotometrically, and each formulation showed drug content >80%. Formulation F7 consisting of polymers (stearic acid, carnauba wax) and gum (xanthan gum) showed percentage drug release of 95.8 at 12 h. The developed formulations were optimized by Box Behnken design to achieve desired properties.

Conclusion: Vildagliptin has good solubility in acidic pH. It has good absorption from an acidic environment. By preparing floating tablets of Vildagliptin, its bioavailability can be enhanced as more amount drug will be absorbed from stomach. Vildagliptin is having high melting point of 158–160°C which is best suitable for the thermal sintering technique. The aim of the present study to formulate and evaluate Sintered Gastro retentive tablets of Vildagliptin using Design of Expert was successfully achieved.

Keywords: Vildagliptin, Almond gum, Guar gum, Xanthan gum, Design expert.

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INTRODUCTION

Tablet

Tablets are characterized as the solid unit dose form of medication, formed by molding or compression, with or without appropriate excipients. Diluents, binders, dissolving agents, glidants and lubricants to ensure effective tablets, disintegrating agents to promote tablet disintegration in the digestive system, flavoring agents are added to improve taste, and pigmentation to make tablets visually appealing are all examples of excipients. A polymer coating is frequently used to make tablets smoother and simpler to swallow, to regulate the rate at which the active ingredient is released, to increase environmental resistance, or to improve the tablets' visual appearance [1].

To withstand mechanical shock during manufacturing, packing, shipping, dispensing, and use, a tablet must be strong and hard. The tablet's drug content must be bioavailable, which means that it must be able to release its content in a predictable and reproducible manner. The tablet must also be chemically and physically stable to maintain its chemical and physical properties during manufacture, storage, and use. The tablet should have an elegant product identity that is free of tablet defects. The weight and drug content of tablets must be consistent. Tablets have the advantage of being manufactured to safeguard unstable medicinal ingredients or unpleasant recipients. Tablets are often expensive to produce. Tablets are visually appealing and easy to use. It is simpler to disguise the bad taste of the medicine to improve the patient's condition. They are considered to be superior to conventional dosage forms in terms of chemical, physical, and microbiological stability.

As a result of the numerous unit operations necessary to produce tablets, including weighing, milling, drying, and mixing, there is a higher level of product loss at each stage of the formulation process. Some medicinal substances have poor compression qualities, which could cause issues when they are later formulated and made into tablets. Because physiological variables like gastric residence or emptying time affect drug absorption from tablets, it varies from patient to patient.

"Gastroretentive drug delivery system" refers to a dosage form that can be retained in the stomach for an extended period, promoting the delayed release of the drug. Long-term gastric retention increases drug bioavailability, lengthens the time it takes for the drug to leave the stomach, reduces drug waste, and improves the solubility of the drug that are less soluble in high pH environment [2]. Drug delivery that is gastro retentive can extend the time the drug remains in the stomach, encouraging its release into the upper gastrointestinal tract for both local and systemic effects.

There are many ways to induce gastric retention, including:

- High-density system [3] – A dose form that can be held in the stomach by sinking to the bottom
- Low-density dosage forms [4] – Dosage forms that float on the gastric fluid
- Mucoadhesive system [5] – Dosage form that causes bio adhesion to the mucosal of the stomach
- Unfoldable, extendible, or swelling systems [6] – Systems that stop the stomach's pyloric sphincter from releasing the contents of the dose form
- Superporous hydrogel system and magnetic system [7].

The bonding of adjacent particle surfaces in a mass of powder is known as sintering. For the development of prolonged-release matrix tablets and the stabilization of drug permeability of film coating formed from various pharmaceutical lattices [8], the sintering process had been applied. The pharmaceutical sciences have only recently adopted the sintering concept.

Sintering usually takes place at a high temperature and consists of three steps:

(i) The formation of interconnecting pore channels known as densification. (ii) The joining of nearby particles together known as neck growth, and (iii) the formation of sphere-shaped particles that have a tendency to flow into the pores within them because of the difference between vapor pressure and the cross-sectional area of the pore's neck. In a controlled procedure, thermal sintering involves heating a compact at a temperature below the melting points of the solid constituents. The dosage form is exposed to temperatures as part of the sintering process, which softens the polymer matrix and forms welded bonds. The drug present in tablets will become trapped in the resulting matrix, resulting in a controlled release of the active component. As compared to many drugs that deteriorate at high temperatures, this approach can be used with drugs that are temperature resistant upon exposure. Vildagliptin is an orally active anti-hyperglycemic agent that selectively inhibits the dipeptidyl peptidase-4 enzyme. It is used to manage type II diabetes mellitus. Vildagliptin works to improve glycemic control in type II diabetes mellitus by enhancing glucose sensitivity of beta cells in pancreatic islets and promoting glucose-independent insulin secretion. The goal of the study is to develop sintered gastro-retentive tablet of Vildagliptin to promote the slow release of the drug for more than 12 h.

METHODS

Materials

Vildagliptin was obtained as a gift sample from MSN Organic Pvt. Ltd., All other chemicals were obtained from S.D. Fine chemicals. All chemicals were of analytical grades as required.

Methodology

Direct compression

Direct compression is the process by which tablets are compressed from a powder mixture of API and suitable excipients and compression was done by an automatic punching machine using 6 mm punch. Prepared tablets were kept in the hot air oven at three different temperatures of 50°C, 60°C, 70°C for three different time periods of 1, 2, 3 h.

Experimental design

- The optimization of the prepared formulation was done using Box Behnken design using design expert 13 (32bit) software (Stat-Ease Inc., Minneapolis, USA). The design of the experiment is a technique developed to evaluate potential factors simultaneously, systematically, and speedily
- The amount of Gums (Guar gum, Xanthan gum, Almond gum) (X1), Polymers (Stearic acid, Carnauba wax) (X2), Temperature (50°–70°) (X3), and Time (1 h–3 h) (X4) were selected as independent variables. The time required for complete drug release was chosen as the dependent variable (Fig. 1)
- The design showed experimental runs (Fig. 2) for which the software generated the following quadratic equation: $Y = X_1 + X_2 + X_3 + X_4 + X_1X_2 + X_1X_3 + X_1X_4 + X_2X_3 + X_2X_4 + X_3X_4 + (X_1)^2 + (X_2)^2 + (X_3)^2 + (X_4)^2$

Where Y is the response, X1, X2, X3, X4 are the variables

- Analysis of variance (ANOVA) and linear regression were used to compare the actual value to the predicted value, as well as 3D response surface graphs and contour plots were generated using Design Expert Software to determine the effect of independent variables on dependent variables. The optimized formulation was selected based on the drug release profile.

RESULTS

Standard graph

A graph was plotted with concentrations on x-axis and absorbances on y-axis (Fig. 3). The absorbance was determined using ultraviolet spectrophotometer at 210 nm. The method was validated for linearity ($R = 0.9995$). The standard graph followed Beer-Lambert's law, i.e., as concentration increases absorbance also increases (Table 2).

Percentage drug release versus time profiles of sintered tablets

All the formulations (F1-F29) showed drug release up to 12 h (Fig. 4). It was observed that with increase in the concentration of the polymers stearic acid, carnauba wax and gums such as Almond gum, Guar gum, and Xanthan gum, the release rate decreased. F7 consisting of guar gum, almond gum, and xanthan gum showed the most sustained action of the drug among the formulations F1 – F29 with the percentage drug release of 95.8% at 12 h.

Box Behnken design

The obtained *in vitro* dissolution values were given as responses in the design expert software. These values were evaluated using ANOVA and linear regression by comparing the actual value with the predicted value. 3D response surface graphs and contour graphs are generated by the software. The software generates an optimized solution which is correlated with the expected values and the Percent Relative error is calculated.

The *in vitro* dissolution study values were then given as responses and ANOVA was performed (Fig. 5). ANOVA is used to determine the difference between the actual mean and the predicted mean. It describes whether the selected model is suitable for the given variables. Fit statistics (Fig. 7) gives predicted $[R^2]$ values and Adjusted $[R^2]$ values.

A mathematical relationship between factors and responses was generated using multiple linear regression analysis in the form of equations. The equations represent the quantitative effect of variables (X1, X2, X3, and X4) and their effect on the response Y. A positive sign represents a synergistic effect and while a negative sign indicates an antagonistic effect.

Equation Y1 (% drug release at 12 h) for formulations.

$$Y_1 = 91.46 + 0.577X_1 - 0.1667X_2 - 3.03X_3 - 2.88X_4 - 1.25X_1X_2 + 1.40X_1X_3 - 1.63X_1X_4 + 1.27X_2X_3 + 0.5250X_2X_4 - 0.7250X_3X_4 - 3.16(X_1)^2 - 0.3199(X_2)^2 - 3.64(X_3)^2 - 1.46(X_4)^2$$

Predicted values are the values predicted by the design for the formulations based on the responses and actual values are the values obtained practically. The actual values should be near to predicted values.

A graph of predicted versus actual value was generated by the software (Fig. 8).

Contours plots (Fig. 9) and Response surface graphs were generated which explains the effect of factors on responses. The plots show that as the polymer and gum concentration increases, the percent drug release decreases. It also shows the effect of interaction between factors on the responses.

3D response surface plots (Fig. 10) show similar declining trend of percent drug release with increase in gum concentration (X1) and polymer (X2).

The solution with maximum desirability is considered. This is graphically represented in overlay plot. The overlay plot (Fig. 11) highlights the point where the response criteria can be met. In an overlay plot, the region where the specifications are not met is shaded out. Flag planted is a representation of optimum. The yellow regions refer to the space where factors can be set to satisfy requirements for both responses.

Factors										
Factor	Name	Units	Type	SubType	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	Gum		Numeric	Continuous	9.00	18.00	-1 → 9.00	+1 → 18.00	13.34	2.82
B	Polymer		Numeric	Continuous	18.00	27.00	-1 → 18.00	+1 → 27.00	22.50	2.95
C	Temperature		Numeric	Continuous	50.00	70.00	-1 → 50.00	+1 → 70.00	60.00	6.55
D	time		Numeric	Continuous	1.0000	3.00	-1 → 1.00	+1 → 3.00	2.00	0.6547

Build Information			
File Version	13.0.5.0		
Study Type	Response Surface	Subtype	Randomized
Design Type	Box-Behnken	Runs	29.00
Design Model	Quadratic	Blocks	No Blocks
Build Time (ms)	200.00		

Fig. 1: Input of factors and their levels

Std	Run	Factor 1 A:Gum	Factor 2 B:Polymer	Factor 3 C:Temperature	Factor 4 D:time	Response 1 %Drug release for 12 hrs.
9	1	18	18	60	2	
13	2	13.5	22.5	60	2	
25	3	13.5	22.5	70	1	
4	4	13.5	18	50	2	
1	5	13.5	22.5	50	3	
3	6	13.5	22.5	60	2	
12	7	13.5	22.5	60	2	
21	8	13.5	18	60	3	
11	9	13.5	27	50	2	
23	10	13.5	18	60	1	
2	11	9	18	60	2	
19	12	13.5	27	60	1	
5	13	13.5	22.5	60	2	
15	14	18	22.5	70	2	
6	15	9	22.5	50	2	
24	16	13.5	27	70	2	
26	17	18	22.5	50	2	
29	18	13.5	22.5	70	3	
7	19	18	22.5	60	1	
28	20	9	22.5	60	3	
16	21	9	22.5	60	1	
14	22	13.5	22.5	60	3	
27	23	13.5	18	70	2	
20	24	9	22.5	70	2	
22	25	13.5	22.5	60	2	
8	26	9	27	60	2	
17	27	13.5	27	60	3	
18	28	18	27	60	2	
10	29	13.5	22.5	50	1	

Fig. 2: Runs generated by the software

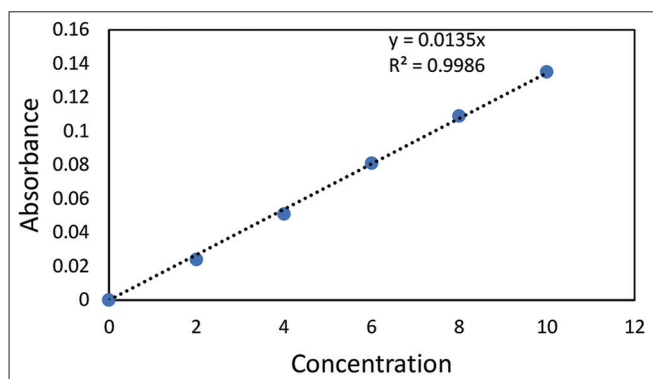


Fig. 3: Standard graph for Vildagliptin

Percent relative error was calculated between the predicted mean and the observed mean.

Kinetic studies

To know release mechanism kinetics of Vildagliptin were attempted to fit into mathematical model and n , $[R]$ values for zero order is calculated. First order, Higuchi and Peppas models were represented in the Fig. 13.

DISCUSSION

Vildagliptin is an Anti-Diabetic drug that is used to treat type II diabetes mellitus. It belongs to BCS class 1 with half-life of 2–3 h. Oral dose of Vildagliptin is 50 mg twice daily. To improve patient

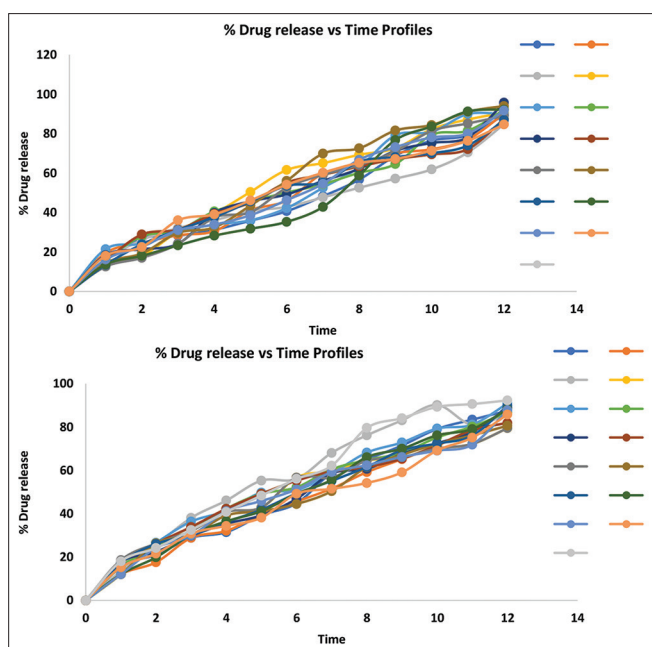


Fig. 4: Percent drug release versus time profile

Std	Run	Factor 1 A:Gum	Factor 2 B:Polymer	Factor 3 C:Temperature	Factor 4 D:time	Response 1 % Drug release at 12hrs
9	1	18	18	60	2	89.5
13	2	13.5	22.5	60	2	90.2
25	3	13.5	22.5	70	1	84.9
4	4	13.5	18	50	2	90.6
1	5	13.5	22.5	50	3	89.8
3	6	13.5	22.5	60	2	92.2
12	7	13.5	22.5	60	2	95.8
21	8	13.5	18	60	3	87.5
11	9	13.5	27	50	2	89
23	10	13.5	18	60	1	94
2	11	9	18	60	2	86.9
19	12	13.5	27	60	1	92.2
5	13	13.5	22.5	60	2	91.8
15	14	18	22.5	70	2	84.7
6	15	9	22.5	50	2	87.5
24	16	13.5	27	70	2	86.3
26	17	18	22.5	50	2	86
29	18	13.5	22.5	70	3	79.5
7	19	18	22.5	60	1	90.9
28	20	9	22.5	60	3	86.7
16	21	9	22.5	60	1	88.7
14	22	13.5	22.5	60	3	81.9
27	23	13.5	18	70	2	82.8
20	24	9	22.5	70	2	80.6
22	25	13.5	22.5	60	2	89.9
8	26	9	27	60	2	88.2
17	27	13.5	27	60	3	87.8
18	28	18	27	60	2	85.8
10	29	13.5	22.5	50	1	92.3

Fig. 5: Responses input in the statistical design

compliance, it is required to decrease the dose and dosing frequency of the drug.

The thermal sintering technique is a process of heating the polymer matrix in the heating furnace at a temperature below the melting point in a controlled environment, by which the drug gets enclosed within the polymer forming the matrix. This technique could be suitable only for the drugs having high melting point. Tablets were prepared by direct compression and subjected to sintering.

Design of experiments, a mathematical tool is used for generating optimized formulations which increase the number of trials. A standard graph of Vildagliptin was constructed by plotting a graph with concentration on x-axis and absorbance on y-axis. The standard graph followed Beer-Lambert' law, i.e., as concentration increases absorbance also increases.

ANOVA for Quadratic model						
Response 1: R1						
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	346.80	14	24.77	4.58	0.0037	significant
A-Gum	0.0335	1	0.0335	0.0062	0.9383	
B-Polymer	0.3333	1	0.3333	0.0617	0.8075	
C-Temperature	110.41	1	110.41	20.42	0.0005	
D-time	92.44	1	92.44	17.10	0.0010	
AB	6.25	1	6.25	1.16	0.3005	
AC	7.84	1	7.84	1.45	0.2485	
AD	6.75	1	6.75	1.25	0.2827	
BC	6.50	1	6.50	1.20	0.2913	
BD	1.10	1	1.10	0.2039	0.6585	
CD	2.10	1	2.10	0.3889	0.5429	
A ²	58.76	1	58.76	10.87	0.0053	
B ²	0.6714	1	0.6714	0.1242	0.7298	
C ²	87.14	1	87.14	16.12	0.0013	
D ²	12.94	1	12.94	2.39	0.1442	
Residual	75.68	14	5.41			
Lack of Fit	53.52	10	5.35	0.9656	0.5644	not significant
Pure Error	22.17	4	5.54			
Cor Total	422.48	28				

Fig. 6: Analysis of variance performed by software

Factor coding is Coded.
Sum of squares is Type III - Partial

The Model F-value of 4.58 implies the model is significant. There is only a 0.37% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case C, D, A², C² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The Lack of Fit F-value of 0.97 implies the Lack of Fit is not significant relative to the pure error. There is a 56.44% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Fit Statistics

Std. Dev.	2.33	R ²	0.8209
Mean	88.07	Adjusted R ²	0.6417
C.V. %	2.64	Predicted R ²	0.4423
		Adeq Precision	8.0910

The Predicted R² of 0.4423 is in reasonable agreement with the Adjusted R² of 0.6417; i.e. the difference is less than 0.2.

Fig. 7: Fit statistics for response 1

The tablets were prepared using stearic acid, carnauba wax, xanthan gum, guar gum, and almond gum by direct compression method. The tablets were subjected to sintering at 50°C, 60°C, and 70°C for three different periods (Table 1). The tablets were then evaluated for hardness, friability, and weight variation, and *in vitro* drug release studies were performed before and after the sintering.

Angle of repose for the Formulations F1, F2, F3, F4, F5, F10, F11, F13, F20, F21, F26 found to have good flow property (31°-35°). Formulations F7, F12, F15, F16, F18, F19, F23, F29 found to have excellent flow property (range 25°-30°). Formulations F6, F8, F9, F17, F22, F24, F25, F27, F28 found to have fair flow property (36°-40°).

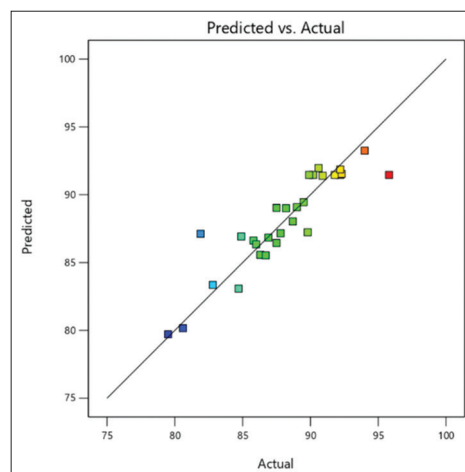


Fig. 8: Predicted versus actual values for responses

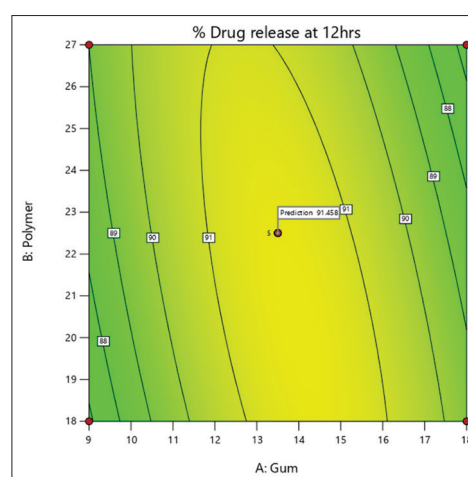


Fig. 9: Contour plot for the effect of gums and polymers on responses

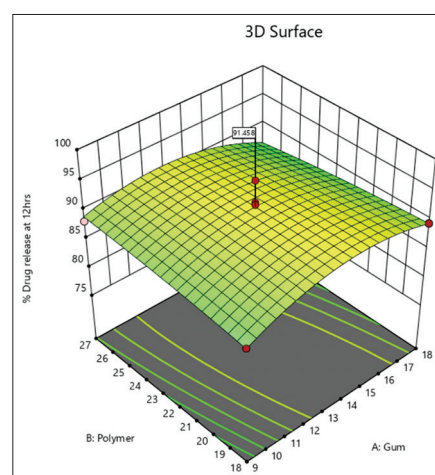


Fig. 10: 3D response surface graph

Carr's index for the Formulations F4, F5, F9, F13, F16, F18, F24, F28, F29 found to have free flow characteristics (5-15), Formulations F1, F6, F7, F8, F14, F15 found to have good flow property (12-16) and formulations F2, F12, F17, F19, F20, F22, F23, F25, F26, F27 found to have fair flow characteristics (18-21), formulations F3, F10, F11, F12, F21 found to have poor flow property(23-25).

Hausners ratio for the formulations F3, F4, F5, F6, F7, F8, F9, F13, F24, F28, F29 found to have excellent flow characteristics (1.14 -1.20), formulations F14, F15, F18 found to have good flow characteristics (1.14-1.20), formulations F1, F2, F10, F12, F16, F17, F19, F20, F22, F23, F25, F26, F27 found to have fair-passable flow characteristics (1.22-1.26), formulations F10, F11, F21 found to have poor flow property(1.30-1.54). Among all the formulations, optimized Formulation F7 showed better results like Angle of repose F7(29.9), Hausners ratio of F7(1.18), and Compressibility index of F7(15.6) that indicate the good flow properties.

All the formulations (F1-F29) showed optimum hardness values, i.e., between 3 and 5kg/cm. The lower standard deviation values indicated that hardness of all formulations was about uniform and possess good mechanical strength with sufficient hardness.

All the formulations (F1-F29) showed the accepted limits of friability, i.e., <1%. The results showed that the tablets possess good mechanical strength. Weight variation for 20 tablets was under the accepted limits of official compendia, i.e., not more than 2 tablets showed variation greater than 5%. Each formulation was analyzed spectrophotometric ally, and each formulation showed drug content >80%.

All the formulations showed drug release up to 12 h. It was observed that within the crease in concentration of the polymers and gums, the release rate decreased. The combination of polymers and gums showed combined effect on the drug release rate. Formulation F7 consisting of polymers (stearic acid, carnauba wax) and gum (xanthan gum) showed percentage drug release of 95.8 at 12 h.

With the purpose of gaining a better perception of how sustained release tablet critical properties are influenced by variations in tablet composition and concentrations, the Box Behnken design was applied in the present study. Besides sunder standing the individual effect of the investigated factors, this design experiments technique allows to elucidate, with the reduced number of experiments, various interactions between independent variables which could not be detected with traditional methods.

The responses were calculated, then statistical analysis (ANOVA) was performed. The results of the statistical analysis (ANOVA) showed that generated models for percent drug release at 12 h were significant (p<0.05) (Fig. 6), indicating that the listed responses were well described by the proposed models.

Experimental design results revealed that the release rate of the drug was significantly affected by the concentration of polymers used. A negative sign for the coefficients of these model terms in Eq.

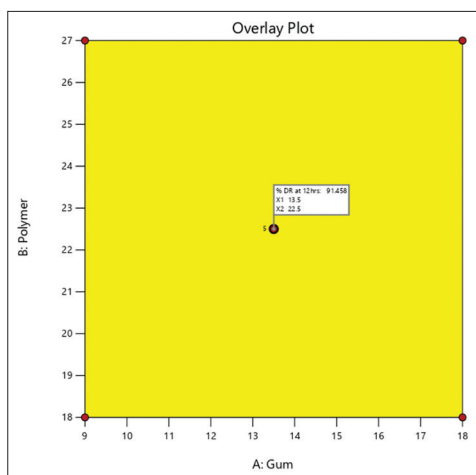


Fig. 11: Overlay plot for optimized formulations

Point Prediction										
Two-sided Confidence = 95% Population = 99%										
Run	Response	Predicted Mean	Predicted Median	Observed	Std Dev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
7	% Drug release at 12hrs	91.458	91.458	95.8	2.32507	1.01968	89.271	93.645	80.92	101.996

Fig. 12: Point prediction for the responses

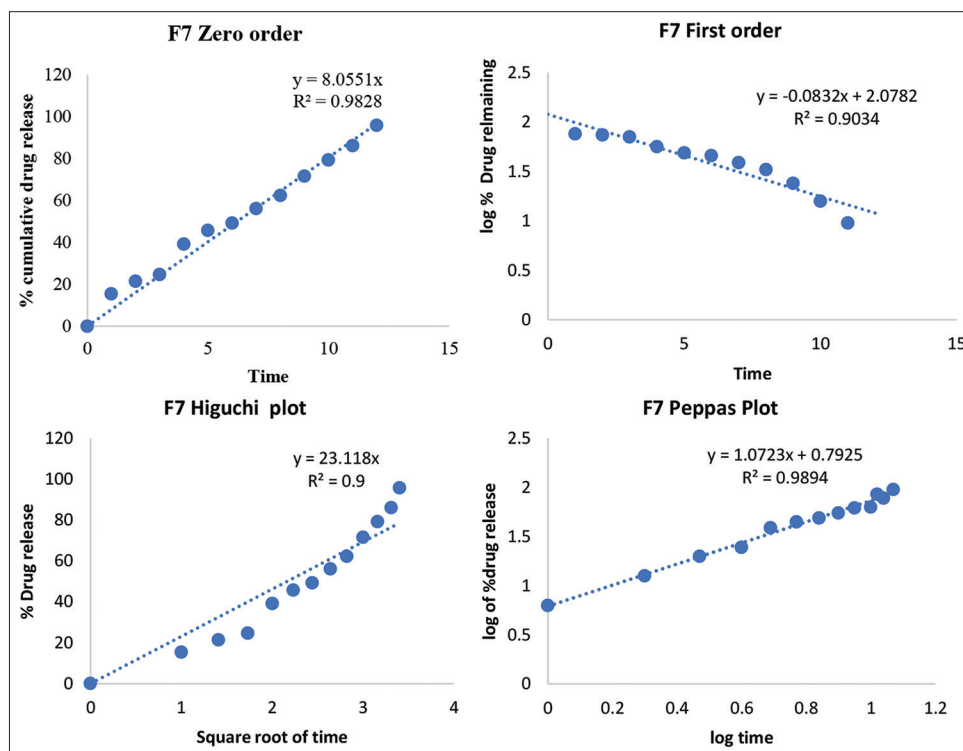


Fig. 13: Kinetic profiles for formulation 7

Table 1: Formulation table of Vildagliptin tablets

Formulation table										
Ingredients	Temperature									
	50°					60°				
	1 h		2 h			3 h			1 h	
	F29 (mg)	F4 (mg)	F9 (mg)	F15 (mg)	F17 (mg)	F5 (mg)	F10 (mg)	F12 (mg)	F19 (mg)	F21 (mg)
Vildagliptin	100	100	100	100	100	100	100	100	100	100
Stearic acid	13.5	18	27	22.5	22.5	22.5	18	27	22.5	22.5
Carnauba wax	13.5	18	27	22.5	22.5	22.5	18	27	22.5	22.5
Xanthun gum	-	13.5	-	-	-	-	13.5	-	18	-
Guar gum	13.5	-	-	-	18	13.5	-	-	-	-
Almond gum	-	-	13.5	9	-	-	-	13.5	-	9
PVP	6	6	6	6	6	6	6	6	6	6
MCC	12	12	12	12	12	12	12	12	12	12
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Lactose	32.5	23.5	5.5	19	10	23.5	23.3	5.5	10	10
Sodium carbonate	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Total	200	200	200	200	200	200	200	200	200	200

Ingredients	Temperature								
	60°								
	2 h								
	F1 (mg)	F2 (mg)	F6 (mg)	F7 (mg)	F11 (mg)	F13 (mg)	F25 (mg)	F26 (mg)	F28 (mg)
Vildagliptin	100	100	100	100	100	100	100	100	100
Stearic acid	18	22.5	22.5	13.5	18	22.5	22.5	27	27
Carnauba wax	18	22.5	22.5	13.5	18	22.5	22.5	27	27
Xanthun gum	18	-	-	13.5	-	13.5	13.5	-	18
Guar gum	-	13.5	-	-	9	-	-	9	-
Almond gum	-	-	13.5	-	-	-	-	-	-
PVP	6	6	6	6	6	6	6	6	6
MCC	12	12	12	12	12	12	12	12	12
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Lactose	19	14.5	14.5	32.5	28	14.5	14.5	10	1
Sodium carbonate	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Total	200	200	200	200	200	200	200	200	200

Ingredients	Temperature									
	60°					70°				
	3 h				1 h	2 h			3 h	
	F8 (mg)	F20 (mg)	F22 (mg)	F27 (mg)	F3 (mg)	F14 (mg)	F16 (mg)	F23 (mg)	F24 (mg)	F18 (mg)
	Vildagliptin	100	100	100	100	100	100	100	100	100
Stearic acid	18	22.5	22.5	27	22.5	22.5	27	18	22.5	22.5
Carnauba wax	18	22.5	22.5	27	22.5	22.5	27	18	22.5	22.5
Xanthun gum	-	-	18	-	-	-	13.5	-	-	-
Guar gum	13.5	9	-	-	-	18	-	13.5	-	-
Almond gum	-	-	-	13.5	13.5	-	-	-	9	13.5
PVP	6	6	6	6	6	6	6	6	6	6
MCC	12	12	12	12	12	12	12	12	12	12
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Lactose	23.5	19	10	5.5	14.5	10	5.5	22.5	19	14.5
Sodium carbonate	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Total	200	200	200	200	200	200	200	200	200	200

PVP- Polyvinyl Pyrrolidone, MCC-Microcrystalline cellulose

Table 2: Standard graph for Vildagliptin

Concentration (µg/mL)	Absorbance at 210 nm
2	0.024±0.01
4	0.051±0.001
6	0.081±0.008
8	0.109±0.004
10	0.135±0.008

(Y1) represented an antagonistic effect on the drug release, meaning that the drug release decreased with the increase in polymer concentration.

Based on responses, a solution with maximum desirability is generated by the software. This is graphically represented in the overlay plot. The overlay plot highlights the point where their sponse criteria can be met.

Table 3: Kinetic modelling for optimized formulation F7

Formulation	Zero order (R)	First order (R)	Higuchi plot (R)	Peppas plot (R)	n
F7	0.995	0.903	0.975	0.989	0.858

Percent relative error calculated between the predicted mean and observed mean (Fig. 12). The percent relative error of formulation F7 was found to be 0.8%. Since the percent relative error is within the limits i.e., <1%, the software-generated data is found to be close agreement with the practical data.

Then an optimized formulation was determined by correlating the actual values with the solution generated by the software. F7 was found to be the optimized formulation with polymers (stearic acid, carnauba wax) and gums (Xanthan gum).

In order to determine the mechanism of drug release from the formulation, the *in vitro* dissolution data were fitted to Zero order, First order, Higuchi plot, and Korsmeyer–Peppasplot. Interpretation of release exponent value (n) was calculated (Table 3). It was observed that the formulation F7 followed zero order release rate as the regression coefficient ($R = 0.995$) was found to be greater than first-order graph ($R = 0.903$) and the diffusion from the system was observed to be non-Fickian diffusionism value from Peppas plot was found to be between 0.5 and 1.

Stability studies were conducted for optimized formulation as per ICH guidelines at 35°C and 75% RH for 30, 60, and 90 days. The tablets remained intact and there was no major change in drug content and percentage drug release at 12 h after 3 months.

CONCLUSION

Vildagliptin has good solubility in acidic pH. It has good absorption from an acidic environment. By preparing floating tablets of Vildagliptin, its bioavailability can be enhanced as more amount drug will be absorbed from stomach. Vildagliptin is having high melting point of 158–160°C which is best suitable for thermal sintering technique. When the tablets were exposed to higher temperature such as 50°, 60°, 70°C and for 1, 2, 3 h the polymer will melt and entrap the drug by forming matrix. The formation of matrix in sintering depends on both on temperature and time of exposure of tablets. If both are increased, stronger matrices will be for med promoting prolong drug release. Among all the formulations, optimized formulation F7 showed better results like angle of repose F7(29.9), Hausners ratio of F7(1.18), compressibility index of F7(15.6) that indicate the good flow properties. All the formulations (F1-F29) showed optimum hardness values, i.e., between 3 and 5 kg/cm. The lower standard deviation values indicated that hardness of all formulations was about uniform and possess good mechanical strength with sufficient hardness. The hardness of the formulation F7 increased with increase in sintering temperature and duration of exposure, whereas the friability decreases with increasing in sintering temperature and time of exposure. All the formulations (F1-F29) showed the accepted limits of friability i.e., <1%. The results showed that the tablets possess good mechanical strength. Weight variation

for 20 tablets was under the accepted limits of official compendia, i.e., not more than 2 tablets showed variation >5%. Each formulation was analyzed spectrophotometric ally, and each formulation showed drug content >80%. Formulation F7 consisting of polymers (stearic acid, carnauba wax) and gum (xanthan gum) showed percentage drug release of 95.8 at 12h.

The concentration of polymers showed a great impact on the release of the drug as the concentration of polymer increased, the release of the drug decreased. The developed formulations were optimized by Box Behnken design to achieve desired properties. The responses were calculated, then statistical analysis (ANOVA) was performed. The results of the statistical analysis (ANOVA) showed that generated models for percent drug release at 12h were significant ($p < 0.05$), indicating that the listed responses were well described by the proposed models. Experimental design results revealed that the release rate of drug was significantly affected by the concentration of polymers used. Then an optimized formulation was determined by correlating the actual values with the solution generated by the software. F7 was found to be the optimized formulation with polymers (stearic acid, carnauba wax) and gums (Xanthan gum). The swelling was not much seen in the formulation as it forms a mesh-like structure on sintering which indicates a matrix formation.

The floating behavior of tablets showed an acceptable floating lag time of <15 min and total floating time of more than 12 h. Further increase in sintering temperature and time of exposure made the tablet lightweight that permits the faster-floating behavior. From the above results, the aim of the present study to formulate and evaluate Sintered Gastro retentive tablets of Vildagliptin by using Design of Expert was successfully achieved.

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