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FORMULATION AND EVALUATION OF SUSTAIN RELEASE TABLETS OF NATEGLINIDE AND VILDAGLIPTIN

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Abstract

Objective: The aim of present study was to formulate sustain tablet of anti-diabetic drugs Nateglinide and Vildagliptin to improve prolongation of action and reduce dose frequency. Nateglinide and Vildagliptin have short half-life of 1.4 hours and 2-4 hours respectively so they rapidly absorbed after oral administration and upper part of intestine. The objective of the research work was to retain both the drugs for prolonged period of time.

Method: The sustained release tablets were prepared with polymers like xanthan gum and HPMC K100 M as release retarding polymers prepared by wet granulation method. The prepared sustain release tablets were optimized by Central Composite Design by using Design Expert software trial version. Precompression parameters and post compression parameters like, hardness, friability, weight variation, drug content and In Vitro dissolution drug release were performed.

Result: The results of all parameters were within acceptable limit. There was a significant difference in in vitro drug release because of xanthan gum and HPMC K100 M and its concentration. The release of Nateglinide and Vildagliptin was found to be 99.03±3.48 and 98.99±2.10 respectively in 24 hours. The release mechanism followed Higuchi release kinetic. Optimization was done by using Central Composite design. There were no any significant changes after stability study of NV9 batch.

Conclusion: The development of Sustain release tablet was attempted and present study indicate that NV9 batch shows sustain effect of Nateglinide and Vildagliptin for 24h.

Keywords: Nateglinide, Vildagliptin, Sustain release, HPMC K15 M, Xanthan gum.

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INTRODUCTION

Oral route provide excellent delivery to systemic circulation of active pharmaceutical ingredients by number of pharmaceutical dosage forms available in the market. Sustained release dosage forms are designed to provide quick achievement of a drug plasma level that remains constant value within the therapeutic range of a drug for a significant period of time. Diabetes is a disorder which affects body's ability to produce insulin. Insulin is one type of hormone and helps to transport energy to the cell when your body convert food to energy (sugar or glucose). [1]

The main reason of Type 2 diabetes is insufficient insulin production from beta cells in the setting of insulin resistance. In this type, liver inappropriately releases glucose into the blood. The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance or a lack of insulin secretion.[2] In view of the above, single drug product available in the market but none combination is available. From the literature, combination of Nateglinide and Vildagliptin exerted synergistic effect in the body. Therefore, objective of the study was to formulate sustained release tablets of Nateglinide and Vildagliptin using different polymers like Xanthan gum and HPMC K100 M by wet granulation method. [3-5]

MATERIALS AND METHOD

Nateglinide and Vildagliptin were procured as gift sample from Cadila Pharmaceuticals, Ahmedabad, India and Livmore Lifescience pvt. Ltd., Vadodara, Gujarat respectively. Excipients used in the formulation were purchased from Astron Chemicals, Gujarat, India.

Identification of drug by UV Spectroscopy Method

For the identification, different concentrations were prepared in phosphate buffer having pH 6.8 for Nateglinide (20-100 µg/ml) and Viladagliptin (25-125 µg/ml). Absorbance was measured at 270 and 205 λmax.

FORMULATION OF SUSTAINED RELEASE TABLET [3]

Sustained release tablets of Nateglinide and Vildagliptin were prepared using different concentrations of Xanthan gum and Hydroxy propyl methyl cellulose K 100 M (HPMC K100 M) by wet granulation method (Blend 1). Both the drugs were weighed and passed through sieve (#40). Other excipients like Microcrystalline cellulose (MCC), Polyvinyl pyrollidone K30 (PVP K30), Talk, and Magnesium stearate were weighed and passed through sieve (#40) (Blend 2). Both the blends were mixed and granules were prepared using water. Granules were dried at 50-60 ^{o} C for 30 minutes. Dried granules were passed through sieve # 24 to get uniform size and lubricated with magnesium stearate and talc. Lubricated granules were then compressed to get 300 mg tablet using rotary tablet press machine. (Table 1)

Table 1: Composition of Sustain release tablet of Factorial batches

Ingredients	FORMULATION BATCH								
	NV1	NV2	NV3	NV4	NV5	NV6	NV7	NV8	NV9
Nateglinide (mg)	60	60	60	60	60	60	60	60	60
Vildagliptin (mg)	50	50	50	50	50	50	50	50	50
Xanthan Gum (mg)	25	50	75	25	50	75	25	50	75
HPMC K100M (mg)	25	25	25	50	50	50	75	75	75
MCC (mg)	120	95	70	95	70	45	70	45	20
PVP K30 (mg)	15	15	15	15	15	15	15	15	15
Talc (mg)	4	4	4	4	4	4	4	4	4
Magnesium Stearate (mg)	1	1	1	1	1	1	1	1	1
Water (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total (mg)	300	300	300	300	300	300	300	300	300

EVALUATION OF SUSTAINED RELEASE TABLET

Pre-compression study[4]

Flow properties have direct impact on particle size, shape, particle size distribution, surface texture, moisture content. Hence, Bulk density, Tapped density, Carr's index, Hausner ratio, and Angle of repose were assessed.

Bulk density (BD)

The BD was assessed by transferring the weighed quantity of sample into the 50 mL of graduated cylinder. The mass to bulk volume ratio was recorded as Bulk density.

Tapped density (TD)

TD was examined by transferring the weighed quantity of sample into a 50 mL of measuring cylinder. The cylinder was placed in Tapped density apparatus (Electro lab). The cylinder having Initial volume (V_0) was recorded and subjected to tapping for 100 times then the final volume was recorded (V_t). The mass (M) to tapped volume ratio was recorded as TD.

$TD = M/ Vt$

Carr's index (CI)

The CI is an indication of the compressibility of a powder. It was calculated by using formula:

$CI = (TD – BD/TD) \times 100$

Hausner ratio (HR)

HR was determined using formula:

$HR = TD/BD$

Angle of repose (AR)

This is used to measure the resistance to particle movement. AR was determined using equation:

$AR (\theta) = \tan^{-1} (h/r)$

Post-compression study

Hardness[5]

Hardness provides an idea about mechanical strength of tablet. The hardness test of the tablets was measured using Monsanto hardness tester. Six tablets were randomly picked and hardness of the tablets was determined.

Friability test [5]

The friability of tablets was determined by using Roche friabilator. Ten tablets were initially weighed (W_1) and tumbled in the friabilator at a 25 rpm for 4 minutes The tablets were then removed, dusted and then

weighed once again (W_2). The % friability was calculated by using:

Percentage friability= $(W_1-W_2)/W_1\times100$

Weight Variation[6]

Twenty tablets were collected randomly from each batch and weighed. The average weight and standard deviation of tablets were computed.

Drug content [7]

10 tablets were weighed and crushed using mortar and pestle. Powder equivalent to 60 mg for Nateglinide and 50 mg for Vildagliptin was dissolved in 10 ml of phosphate buffer (pH 6.8) using few amount of methanol. Sample was filtered and drug content was determined using UV Spectrophotometry at 270 nm for Nateglinide and 205 nm for Vildagliptin.

***In Vitro* Dissolution study[8-9]**

The release of Nateglinide and Vildagliptin from Sustained Release Tablets was determined using USP dissolution testing apparatus II (paddle type) by using 900 ml 0.1 N HCl media at 37±0.5 ^{0}C and 50 rpm up to 2 h. Aliquot 5 ml was withdrawn from the dissolution test apparatus at the time intervals of 2 h and the samples were replaced with 6.8 pH buffer dissolution medium up to 24 h. After filtration, the amount of drug released was determined using UV Spectrophotometer at 270 nm for Nateglinide and 205 nm for Vildagliptin.

Optimization of sustain release tablet[10-11]

Central Composite design was employed to study the effect of independent variables like Xanthan Gum (X1) and HPMC K100M (X2) on dependent variables like % cumulative drug release (CDR) at 2 and 8 h of Nateglinide (Y1 and Y3); and Vildagliptin (Y2 and Y4). (Table 2)

Table 2: Levels of independent variables

Variable	Low (-1)	Medium (0)	High (+1)
Concentration of Xanthan Gum (X1)	25 mg	50 mg	75 mg
Concentration of HPMC K100M (X2)	25 mg	50 mg	75 mg

Drug release kinetic study[12]

Different kinetic models (Zero order, First order, Higuchi and Korsmeyer-peppas model) were used for *in-vitro* release study. The interpretation was performed and reported which is based on the values of the regression co-efficient.

Stability study[13]

For three months, a stability study of prepared tabltes were conducted at 40°C /75% RH. The tablets were wrapped with aluminum foil and kept in a stability chamber. Hardness, friability, weight variation, Drug content, and *in vitro* drug release study were analyzed at 1, 2 and 3 months.

RESULT AND DISCUSSION

Identification of drug by UV Spectroscopy Method

For the identification, Absorbance was measured for Nateglinide (20-100 µg/ml) and Vildagliptin (25-120 µg/ml) at 270 and 205 nm respectively.

Pre-compression study

Bulk density, tapeed density, Carr's index, Hausner's ratio and Angle of repose were determined. All the parameters were found to have satisfactory flow properties (Table 3) The results of bulk density and tapped density ranges from 0.38 ± 0.03 to 0.46 ± 0.06 and 0.42 ± 0.08 to 0.57 ± 0.03 g/cm^3 which indicated good flow property. The values of Carr's index and Hausner's ratio ranged from 12.92 ± 1.04 to 26.67 ± 1.04 and 1.147 ± 0.011 to 1.363 ± 0.012 respectively. The value of Angle of repose of all formulations ranges from 23.48 ± 1.21 to 29.34 ± 1.24 θ.

Table 3: Pre compression parameters of factorial design batches

Batch	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index	Hausner's ratio	Angle of repose (θ)
NV1	0.39 ± 0.04	0.47 ± 0.02	17.68 ± 1.13	1.214 ± 0.020	27.74 ± 1.14
NV2	0.40 ± 0.03	0.54 ± 0.06	26.46 ± 1.08	1.362 ± 0.001	29.34 ± 1.24
NV3	0.38 ± 0.03	0.42 ± 0.08	12.92 ± 1.04	1.147 ± 0.011	26.79 ± 0.89
NV4	0.40 ± 0.05	0.54 ± 0.06	18.92 ± 0.78	1.363 ± 0.012	28.10 ± 1.23
NV5	0.41 ± 0.02	0.47 ± 0.05	13.73 ± 0.75	1.159 ± 0.002	27.50 ± 0.88
NV6	0.45 ± 0.02	0.55 ± 0.06	26.67 ± 1.04	1.236 ± 0.031	26.93 ± 1.10
NV7	0.46 ± 0.04	0.57 ± 0.03	18.71 ± 1.14	1.230 ± 0.021	23.48 ± 1.21
NV8	0.43 ± 0.05	0.52 ± 0.05	17.39 ± 0.86	1.273 ± 0.011	27.06 ± 1.06
NV9	0.46 ± 0.06	0.54 ± 0.06	16.41 ± 0.84	1.254 ± 0.012	25.82 ± 1.39

Post-compression study

Hardness, friability, weight variation and % Drug content were determined. The hardness of tablets was found to be in the ranges of 4.0 ± 0.21 to 5.8 ± 0.03 kg/cm^2. The friability of tablets was found to be in the ranges of 0.23 ± 0.12 to 0.48 ± 0.09 %. The weight of sustained release tablets was found to be in the ranges of 299.1 ± 1.31 to 304.0 ± 1.42 mg. % drug content for Nateglinide was found in the ranges 96.24 ± 0.57 to 99.92 ± 0.61 and for Vildagliptin was in the ranges of 96.22 ± 0.24 to 99.26 ± 0.34. (Table 3)

Table 4: Post Compression Parameters of factorial batches

Batch code	Hardness (kg/cm^2± S.D.)	Friability (%)	Weight variation (mg ± S.D.)	% Drug content-Nateglinide	% Drug content-Vildagliptin
NV1	4.0 ± 0.21	0.48 ± 0.09	301.3 ± 1.61	97.36 ± 0.23	97.33 ± 0.54
NV2	4.8 ± 0.25	0.41 ± 0.15	300.2 ± 1.50	98.21 ± 0.42	98.17 ± 0.32
NV3	4.9 ± 0.15	0.38 ± 0.10	302.1 ± 1.00	97.67 ± 0.39	98.24 ± 0.36
NV4	4.8 ± 0.06	0.42 ± 0.16	303.1 ± 1.42	98.83 ± 0.27	98.83 ± 0.37
NV5	4.9 ± 0.12	0.39 ± 0.08	304.0 ± 1.42	99.92 ± 0.61	98.21 ± 0.69
NV6	5.3 ± 0.21	0.29 ± 0.11	299.1 ± 1.31	96.24 ± 0.57	99.26 ± 0.34
NV7	5.0 ± 0.15	0.33 ± 0.13	301.2 ± 1.30	99.42 ± 0.38	96.25 ± 0.65
NV8	5.3 ± 0.06	0.28 ± 0.08	302.0 ± 1.42	96.48 ± 0.69	96.22 ± 0.24
NV9	5.8 ± 0.03	0.23 ± 0.12	300.1 ± 1.21	99.75 ± 0.34	99.03 ± 0.68

In Vitro Dissolution study of sustain release tablet

In Vitro Drug Release study was performed using dissolution test apparatus type II (paddle). The % *in Vitro* drug release of **NV1 formulation** was determined and reported at 2 h (35.23 ± 1.25 for Nateglinide and 41.23 ± 3.91 for Vildagliptin) and at 16 h (99.24 ± 2.47 for Nateglinide and 99.21 ± 2.36 for Vildagliptin); **for NV2 formulation**, at 2 h (40.25 ± 1.78 for Nateglinide and 39.5 ± 2.74 for Vildagliptin) and at 20 h as 98.24 ± 3.24 for Nateglinide and at 16 h as 96.00 ± 2.04 for Vildagliptin); **for NV3 formulation**, at 2 h (38.24 ± 2.48 for Nateglinide and 38.2 ± 2.43 for Vildagliptin) and at 16 h (98.24 ± 2.80 for Nateglinide and 98.02 ± 2.09 for Vildagliptin); **for NV4 formulation**, at 2 h (33.25 ± 2.72 for Nateglinide and 31.7 ± 2.78 for Vildagliptin) and at 20 h (98.65 ± 2.70 for Nateglinide and 98.34 ± 3.19 for Vildagliptin); **for NV5 formulation**, at 2 h (30.45 ± 2.70 for Nateglinide and 30.14 ± 2.48 for Vildagliptin) and at 20 h (96.24 ± 2.67 for Nateglinide and 97.31 ± 3.18 for Vildagliptin); **for NV6 formulation**, at 2 h (28.29 ± 2.48 for Nateglinide and 23.21 ± 2.75 for Vildagliptin) and at 20 h (96.12 ± 2.69 for Nateglinide and 98.06 ± 2.82 for Vildagliptin); **for NV7 formulation**, at 2 h (18.52 ± 2.73 for Nateglinide and 18.25 ± 2.10 for Vildagliptin) and at 20 h (98.43 ± 2.83 for Nateglinide and 97.2 ± 2.0 for Vildagliptin); **for NV8 formulation**, at 2 h (14.45 ± 2.70 for Nateglinide and 14.2 ± 2.79 for Vildagliptin) and at 24 h (96.59 ± 2.71 for Nateglinide and 96.5 ± 2.97 for Vildagliptin) and **for NV9 formulation**, at 2 h (9.89 ± 2.52 for Nateglinide and 10.11 ± 2.42 for Vildagliptin) and at 24 h (99.03 ± 3.48 for Nateglinide and 98.99 ± 2.10 for Vildagliptin). Above results suggest that increase in concentration of polymers responsible for decrease in drug release (in sustained pattern) in the formulation. (Figure 1and Figure 2)

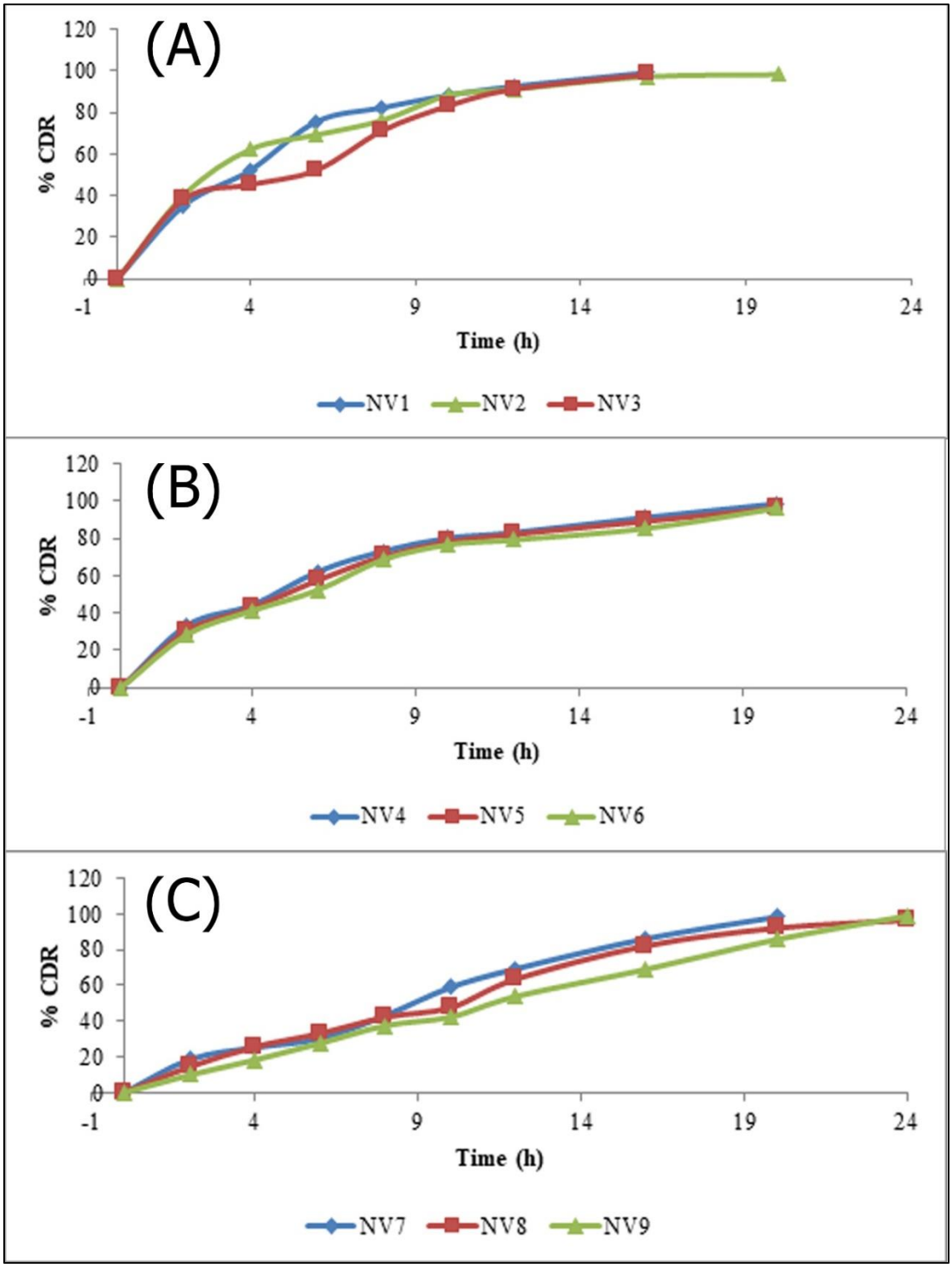


Figure 1: % CDR of Nateglinide (A) Batch NV1 to NV3 (B) Batch NV4 to NV6 (C) Batch NV7 to NV9

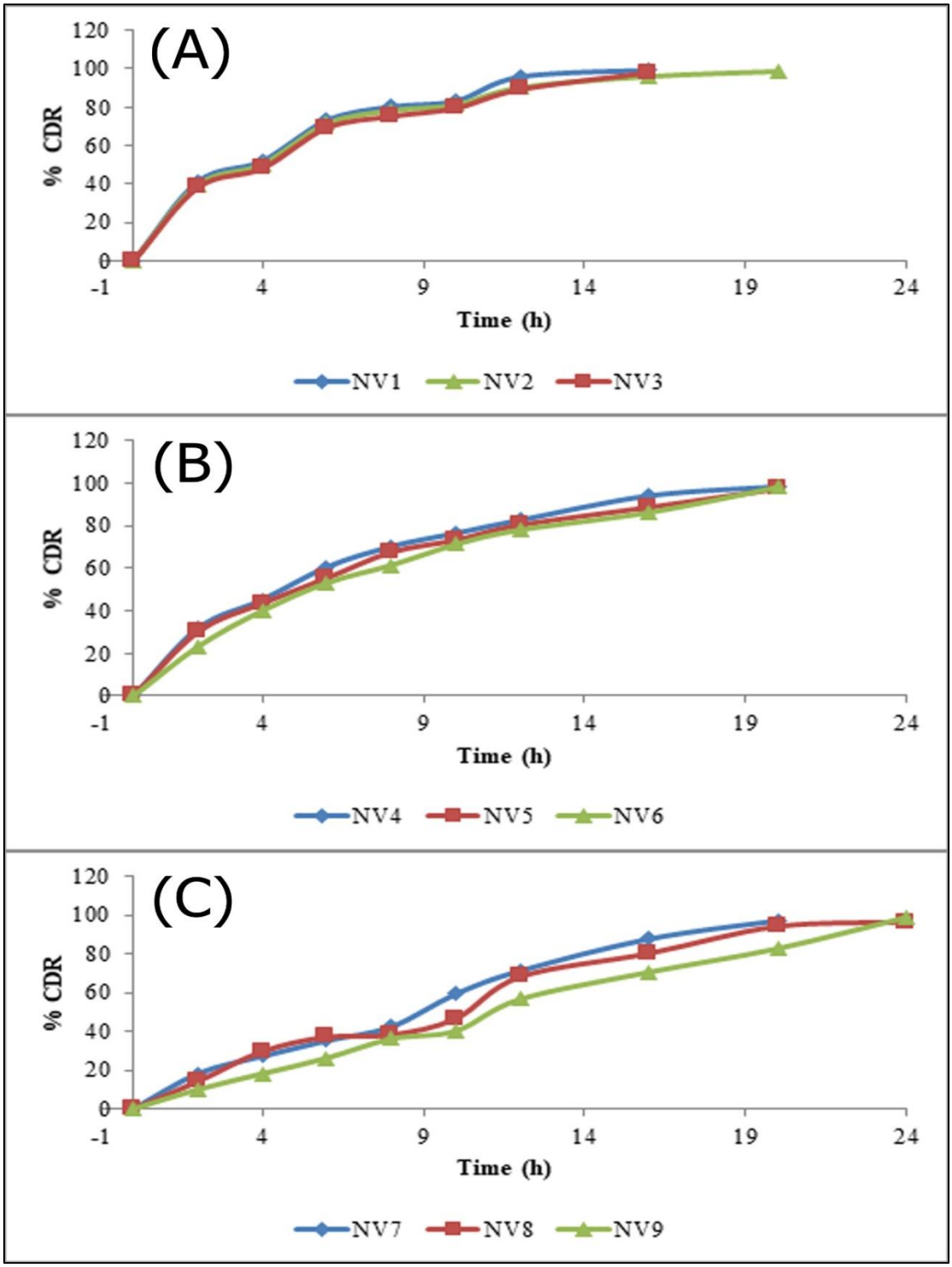


Figure 2: % CDR of Vildagliptin (A) Batch NV1 to NV3 (B) Batch NV4 to NV6 (C) Batch NV7 to NV9

Optimization of sustain release tablet

Optimization of sustain release tablet was performed on the basis of Central Composite Design by design expert software by stat ease. A statistical model incorporating polynomial and interactive terms is utilized to assess the response as:

$Y= B_0+ B_1X_1+ B_2X_2+ B_{12}X_1X_2+ B_{11}X_{12}+ B_{22}X_{22}+ E$

A polynomial equation is used to draw the conclusion after considering the magnitude of coefficient and mathematical signs (positive or negative). Independent variables and list of level of variables are shown in Table 10 and 11 respectively.

Summary of ANOVA Analysis

Equations for factorial design, ANOVA analysis and summary of polynomial equation as shown in Table 5 and Table 6 for all dependent variables. From the result, it was found that F_{cal} values were much greater than F_{tab} for all formulations indicating that all factors had statistically significant effect on all dependent variables.

Table 5: ANOVA Analysis

Source	Sum of Square	Degree of Freedom	Mean Square	F Value	P Value
% Cumulative Drug Release at 2 hours – Nateglinide (Y_1)					
Regression	1360.57	5	272.11	4.96	0.0249
Residual	384.30	7	54.90	-	-
Total	1744.85	12	-	-	-
% Cumulative Drug Release at 2 hours – Vildagliptin (Y_2)					
Regression	1244.45	5	248.89	4	0.0491
Residual	435.33	7	62.19	-	-
Total	1679.78	12	-	-	-
% Cumulative Drug Release at 8 hours – Nateglinide (Y_3)					
Regression	3265.69	5	653.14	5.46	0.0201
Residual	794.02	7	111.43	-	-
Total	4059.71	12	-	-	-
% Cumulative Drug Release at 8 hours – Vildagliptin (Y_4)					
Regression	2910.90	5	582.18	4.33	0.0409
Residual	941.45	7	134.49	-	-
Total	3852.35	12	-	-	-

Table 6: Summary of polynomial equation

Response Y1	B_0	B_1	B_2	B_{12}	B_{11}	B_{22}
% Cumulative Drug Release at 2 hours – Nateglinide (Y_1)						
Coefficient	+10.45	-0.3781	-1.22	-2.50	+12.91	+6.47
P Value	0.0294					
% Cumulative Drug Release at 2 hours – Vildagliptin (Y_2)						
Coefficient	+10.28	-3.06	-1.04	0.8625	+11.83	+6.63
P Value	0.0491					
% Cumulative Drug Release at 8 hours – Nateglinide (Y_3)						
Coefficient	+37.45	-0.8138	-1.93	+2.03	+20.93	+7.57
P Value	0.0201					
% Cumulative Drug Release at 8 hours – Vildagliptin (Y_4)						
Coefficient	+36.27	-2.95	-1.36	+1.26	+19.53	+7.41
P Value	0.0409					

Response Surface Analysis

The 3-D response surface plot analyses indicated that coefficient B1 and B2 bear a negative sign respectively, whereas their combination coefficient bears a positive sign. The negative coefficient indicated that decrease in the amount of Xanthan gum and HPMC K100M responsible for decrease in the % drug release, but when increase in the amount of Xanthan gum in combination with HPMC K100M resulted in increase in the % drug release. (Figure 3)

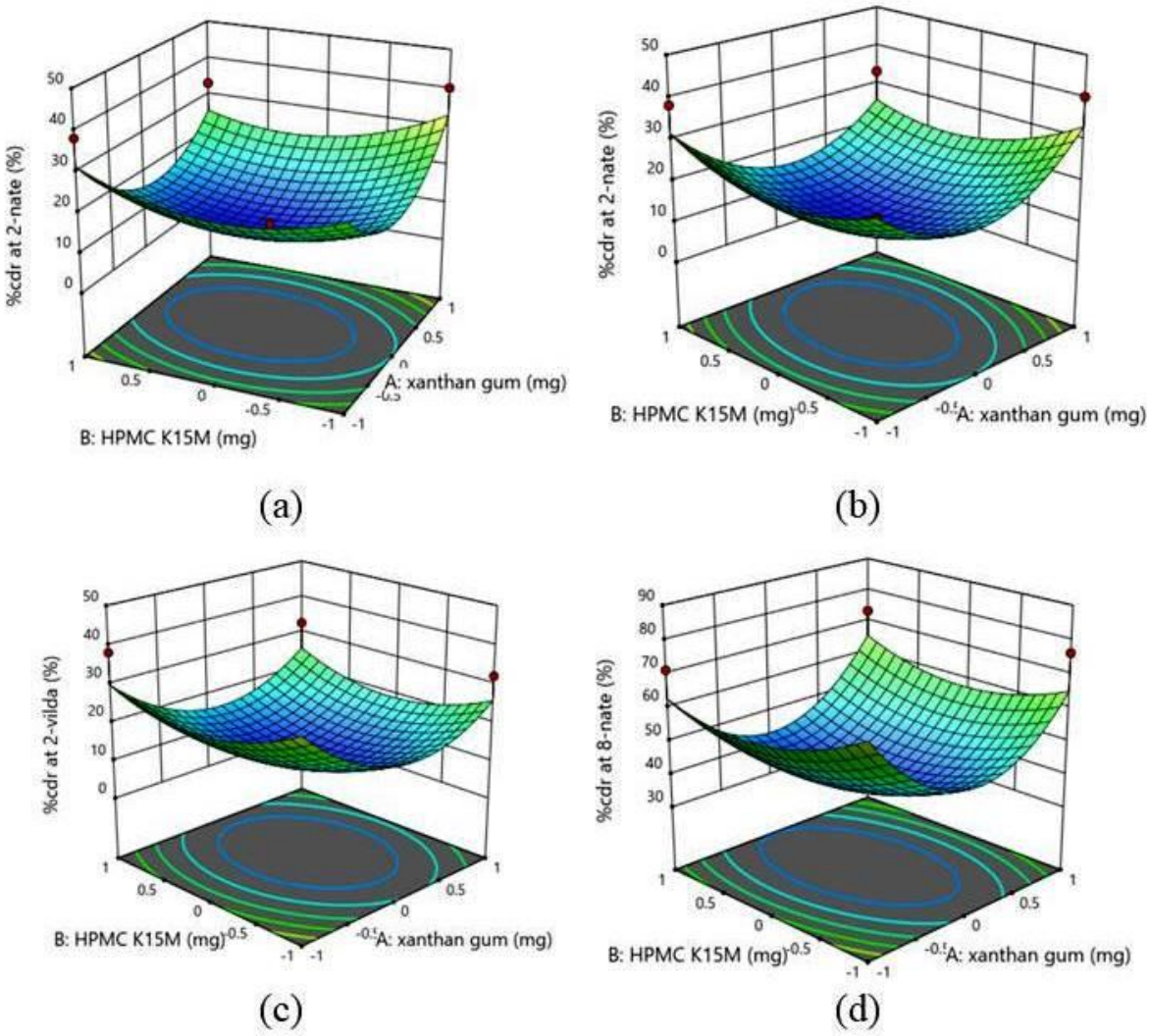


Figure 3: 3D surface plot showing the effect of Xanthan Gum (X_1) and HPMC K100M (X_2) on % CDR (a) after 2 hours- Nateglinide (b) after 2 hours- Vildagliptin (c) after 8 hours- Nateglinide (d) after 8 hours- Vildagliptin

Drug release kinetic study

Different kinetic models (Zero order, first order, Higuchi and Korsmeyer-peppas model) were used for *in-vitro* release study. The interpretation was performed and based on interpretation Higuchi model was found to be suited. Correlation co-efficient of Nateglinide and Vildagliptin was found to be 0.9808 and 0.9796, respectively. (Table 7)

Table 7: Drug release kinetic study for Nateglinide and Vildagliptin

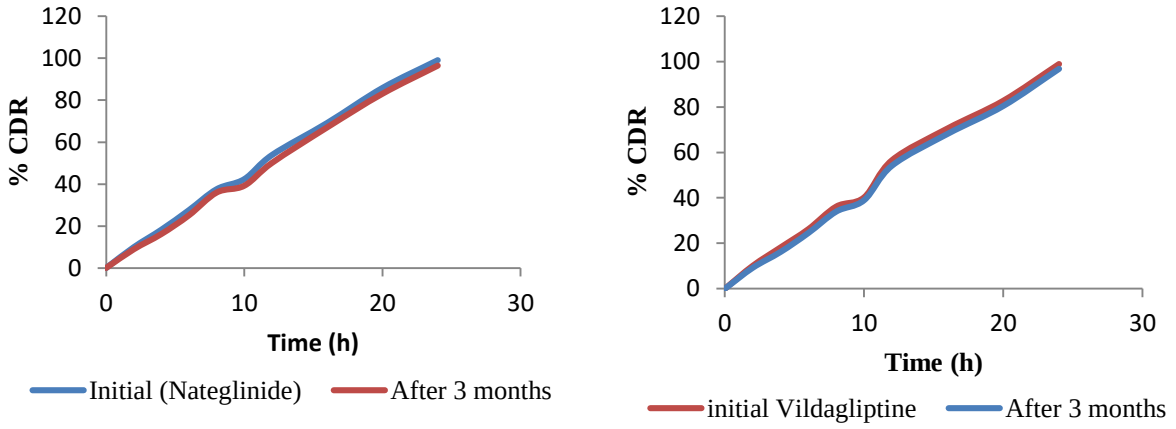
Model	Firstorder	Zeroorder	Higuchi Release model	Korsmeyer-Peppas Release model
Drug release kinetics of optimized batch (Nateglinide)				
R2	0.8799	0.9969	0.9989	0.9987
Slope	0.0412	4.0949	0.2648	0.9374
Intercept	1.1325	2.8544	-0.3468	-1.2864
Drug release kinetics of optimized batch (Vildagliptin)				
R2	0.7656	0.9901	0.9906	0.984
Slope	0.0471	4.2091	0.2494	0.8751
Intercept	1.134	6.6798	-0.2571	-1.1792

Stability studies

The optimized tablet was subjected to stability studies for three months and found to be stable in terms of Hardness, Friability, weight variation and % drug content (Table 8; Figure 4)

Table 8: Post compression evaluation of Stability batch

Stability Study	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg ± S.D.)	Drug Content (%)
Before	5.8 ± 0.03	0.23 ± 0.12	300.1 ± 1.2	99.75 Nateglinide) 99.03 (Vildagliptin)
After 3 month	5.2 ± 0.21	0.29 ± 0.17	303.2 ± 1.0	97.24 (Nateglinide) 98.17 (Vildagliptin)



(a) (b)

Figure 4: Comparison of % CDR of Optimized batch and Stability batch (a) Nateglinide (b) Vildagliptin

CONCLUSION

For the formulation, Nateglinide and Vildagliptin sustained release tablet was prepared by using wet granulation method. Different concentrations of polymers HPMC K100 M and Xanthan gum were used. Based on results, NV9 batch was more better in terms of precompression and post compression study and selected as optimized batch. The optimized formulation was subjected to accelerated stability studies and was found to be stable without any remarkable physicochemical changes. The above results indicated that the formulation of sustain release tablet of Nateglinide and Vildagliptin is a suitable alternative to administering the drugs in conventional form.

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