Formulation and Optimization of Immediate Release Tablet of Sitagliptin Phosphate using Response Surface Methodology

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Abstract: The objective of this study was to design and evaluate Sitagliptin Phosphate immediate release (IR) 50 mg tablet using Response Surface Methodology for the managemant of Type-II diabetes mellitus. Response surface methodology (RSM) computations for this optimization study were performed employing Minitab 16. Different formulations of immediate release were prepared by applying 2 factor 2 level Central Composite Design (CCD) using Minitab 16 which gave 13 formulation for each layer. The amount of Sodium Starch Glycollate (SSG) and Croscarmellose Sodium (CCS) in IR layer were used as independent variables and the percent drug release at 15 minutes were selected as dependent (response) variables for optimization. All the formulation were prepared and evaluated using appropriate analytical technology. Based on the in-vitro dissolution data (dependent variable/response), the composition of formulation with optimum drug release for immediate release were identified and employed to formulate optimized tablets followed by its evaluation. All the physico-chemical parameters of the tablets were found satisfactory.The optimized Sitagliptin Phosphate IR tablet disintegrated in 14 sec and showed an initial release of Sitagliptin 99.072% within 15 minutes.

Keywords: Response Surface Methodology, immediate release, Sitagliptin Phosphate, Type-II diabetes mellitus, Superdisintegrants.

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1. Introduction

Sitagliptin is the first in a new class drugs that inhibit the proteplytic activity of dipeptidyl peptidase-4 (DPP-4). It was approved by the US FDA for the treatment of type 2 diabetes mellitus in October 2006. Sitagliptin phosphate is 1,2,4-triazolo[4,3-a]pyrazine,7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl),phosphate (Fig.1) with molecular formula $C_{16}H_{15}F_6N_5O.H_3O_4P.H_2O$, and a molecular weight of 523.32 g/mole. According to the Biopharmaceutics classification system (BCS) sitagliptin is a Class III (high solubility, low permeability)/borderline Class I (high solubility, high permeability) [1].

Sitagliptin prolongs the activity of proteins that increases the release of insulin after blood sugar rises, such as after meal. Sitagliptin is rapidly absorbed after oral administration with absolute bioavailability of approximately 87 %. Co-administration of a high-fat meal does not affect the pharmacokinetics of Sitagliptin. It can be given alone or in combination with other anti-hyperglycemic drugs. The elimination half life of sitagliptin is 12.4 hours.

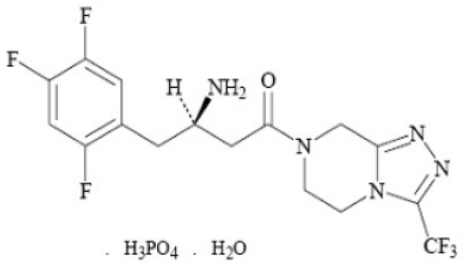

Fig.1. Structure of Sitagliptin Phosphate

In the development of tablet dosage form, an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum number of trials. The statistical experiment designs most widely used in optimization experiments are termed "Response surface designs or Response surface methodology (RSM)" utilizing a polynomial equation [2]. Different types of RSM designs include 3- level factorial design, central composite

design (CCD), Box-Behnken design and D-optimal design [2]. One of the most popular response surface methodologies is central composite design (CCD). The CCD is an effective design that is ideal for sequential experimentation and allows a reasonable amount of information for testing the lack of fit while not involving an unusually large number of design points [2].

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption [3]. The immediate action from the tablets can be attained by fast disintegration of tablets within the gastrointestinal tract. The use of super-disintegrants, surfactants and water soluble polymers in low concentration also enhances the dissolution of immediate release tablets. Crospovidone, Croscarmellose sodium (CCS) and Sodium starch glycolate (SSG) are the superdisintegrants that helps in immediate release of drug from dosage forms.

2. Materials and Methods

2.1 Materials

Sitagliptin Phosphate Monohydrate (Glenmark Generics Ltd., India), Croscarmellose Sodium (DMV-fonterra Excipients, The Netherlands), Sodium Starch Glycollate (Maruti Chemicals, Ratanpur, India), Dibasic Calcium Phosphate Anhydrous (Hindustan Phosphate Pvt. Ltd., India), Magnesium Stearate (Amishi Drugs and Chemical Pvt. Ltd, India) and Avicel PH 101(FMC Biopolymer, Ireland). All the materials used were provided by Deurali Janta Pharmaceuticals Pvt.Ltd as gift samples.

2.2 Methods

2.2.1 Preparation of Sitagliptin 50mg Tablets

Sitagliptin 50mg tablets were prepared by direct compression method by using two different types of superdisintegrants. Composition of the thirteen formulations of sitagliptin tablet using Two level full factorial central composite Design (CCD) has been illustrated in Table 1. Based on this %concentration of CCS and SSG, composition of thirteen formulations has been designed with an average tablet weight of 250mg as illustrated in Table 2. SSG and CCS were used as disintegrating agent for burst release of tablet, Dibasic Calcium Phosphate Anhydrous (DCPA) as diluents, Avicel pH 101 as binder, Magnesium Stearate as lubricants and Brilliant Blue Lake as colouring agent. All ingredients sifted through sieve no. #60 was thoroughly mixed and lubricated.

The lubricated powder was then compressed using 10 station compression machines with round, circular punches of diameter 9.1mm. Hence, the tablets produced were subjected to In-Vitro evaluation and the formulation was optimized.

Table 1: Two level full factorial central composite

StdOrder	RunOrder	CCS(%)	SSG(%)
10	1	3.500	6.500
6	2	5.621	6.500
5	3	1.379	6.500
12	4	3.500	6.500
3	5	2.000	8.000
1	6	2.000	5.000
9	7	3.500	6.500
8	8	3.500	8.621
7	9	3.500	4.379
11	10	3.500	6.500
4	11	5.000	8.000
2	12	5.000	5.000
13	13	3.500	6.500

2.2.2 Tablet Assay and Physical Evaluation

Twenty tablets were taken and crushed to powder with mortar and pestle. Powder equivalent to 50 mg of Sitagliptin Phosphate (average weight) was taken and diluted with mobile phase up to 100 ml of volumetric flask. After sonication for 10 minutes, solution was filtered through filter paper (No. 42). The total amount of drugs within the tablets was analysed after appropriate dilution of test solution by using HPLC method as described below against the reference solution of Sitagliptin pure powder prepared in the same method.

Column: Inertsil C18, 150mm × 4.6mm, 5µ particle size

Mobile phase: 0.05M phosphate buffer of pH 5.8: Acetonitrile in ratio = (65:35 v/v)

Detection wavelength: UV detection with 254nm

Injection volume: 20µl

Tablets were also evaluated for hardness (n-10), friability (n=20), weight variation (n=20) and thickness (n=10).

Table 2. Formulation of Sitagliptin Tablet as per CCD

	Sitagliptin Phosphate (mg)	CCS (mg)	SSG (mg)	DCPA (mg)	Magnesium Stearate (mg)	BBL Colour (mg)	Avicel pH 101 (mg)	Total (mg)
FS-1	65.700	8.75	16.25	37.500	3.500	0.500	117.80	250.00
FS-2	65.700	14.05	16.25	37.500	3.500	0.500	112.50	250.00
FS-3	65.700	3.45	16.25	37.500	3.500	0.500	123.10	250.00
FS-4	65.700	8.75	16.25	37.500	3.500	0.500	117.80	250.00
FS-5	65.700	5.00	20.00	37.500	3.500	0.500	117.80	250.00
FS-6	65.700	5.00	12.50	37.500	3.500	0.500	125.30	250.00
FS-7	65.700	8.75	16.25	37.500	3.500	0.500	117.80	250.00
FS-8	65.700	8.75	21.55	37.500	3.500	0.500	112.50	250.00
FS-9	65.700	8.75	10.95	37.500	3.500	0.500	123.10	250.00
FS-10	65.700	8.75	16.25	37.500	3.500	0.500	117.80	250.00
FS-11	65.700	12.50	20.00	37.500	3.500	0.500	110.30	250.00
FS-12	65.700	12.50	12.50	37.500	3.500	0.500	117.80	250.00
FS-13	65.700	8.75	16.25	37.500	3.500	0.500	117.80	250.00

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Detection wavelength: UV detection with 254nm

Injection volume: 20µl

Tablets were also evaluated for hardness (n-10), friability (n=20), weight variation (n=20) and thickness (n=10).

2.2.4 Drug Release Study

Drug release from 6 tablets of each formulation, in triplicate, was determined using USP Type I apparatus (basket) where 900 ml of distilled water was used as medium maintained at 37±0.5°C at 100 RPM [4]. The release rates from the tablets were conducted in a dissolution medium for 30 minutes.

10 ml of aliquot were withdrawn at 5, 10, 15, 20 and 30 minutes with replacement of fresh media and filtered through whatman Filter paper No. 1. Solution samples were analysed by UV spectrophotometer at 266 nm for Sitagliptin Phosphate. Limits: Not less than 80% (Q) of the labeled amount of Sitagliptin is dissolved in 30minutes.

2.2.5 Optimization Data analysis

Response surface methodology (RSM) computations for this optimization study were performed employing Minitab 16. Polynomial equations including interaction and quadratic terms for dissolution of release tablet were generated for all the response variables using multiple linear regression analysis (MLRA) approach. Polynomial equation for factorial design in general form is given by:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{11}X_1^2 + B_{22}X_2^2 + B_{12}X_1X_2 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where,

Y is dependent variable,

B_0 is intercept representing the arithmetic average of thirteen batches/runs and

B_1 is estimated coefficient for factor X_1.

The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. They are the coded levels of the independent variable(s). The interaction term (X_1X_2) shows how the response changes when two

factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

In the linear model equation, the positive sign of the coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response. The largest coefficient means the casual factor has more potent influence on the response. The statistical validity of the polynomials was established on the basis of ANOVA provision in Minitab 16.

2.2.6 Release Profiles Comparison

Similarity and Dissimilarity Factor are more adequate to dissolution profile comparisons when more than three or four dissolution time points are available.

Similarity Factor

Similarity between the two products is assessed by using similarity factor. The similarity factor (F_s) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference products R_j over all points [5].

$$F_s = 50\, X\, log\, \left\{\left[1 + \left(\frac{1}{n}\right)\Sigma_{j=1}^{n}(Rj - Tj)^2\right]^{-0.5} X\, 100\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where n is the sampling number, R_j and T_j are the % dissolved of reference and the test products at each time points j respectively. f_s value higher than 50 and close to 100 show the similarity of the dissolution profiles [5].

Dissimilarity Factor

The difference factor (F_d) measures the percent error between two curves over all time points:

$$F_d = \left[\frac{\Sigma_{i=1}^{n}(Rj - Tj)}{\Sigma_{i=1}^{n} Rj}\right] X100 \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

The percentage error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. f_d values should be close to 0 to be similar. In general, the values lower than 15 or between 0 and 15 show the similarity of the dissolution profiles [5].

2.2.7 Comparison of Formulated Tablets with Marketed Tablets

Optimized batch compared with marketed tablet for dissolution study to know about the dissolution profile of the optimized batch.

3. Result and Discussions

3.1 Drug Content and Physical Evaluation

Drug content in various formulations varied between 98.00 and 102.75% (mean 100.25%). Tablet weights varied between 248.50 mg and 260.20 mg (mean 253.00 mg), thickness between 3.47 mm and 3.67 mm (mean 3.55 mm), hardness between 5.00 kg/cm^2 and 6.50 kg/cm^2 (mean 5.67 kg/cm^2) and friability ranged between 0.65% and 0.30% (mean 0.45%). The friability values of none of the formulations exceeded 1%. The results indicated that the tablets were mechanically stable. Disintegration time was found in the range of 11-17 seconds. Thus all the physical parameters of the tablets were practically within control.

3.2 In-vitro Drug Realease Studies

Dissolution study of all formulations was conducted as per dissolution method described in method 2. Dissolution profiles of different formulation are illustrated in Fig.2 and Fig.3.

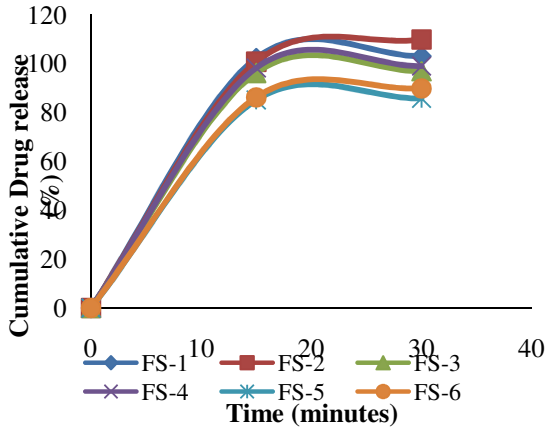

Fig.2. Drug release profile for IR formulation (FS-1 to FS-6)

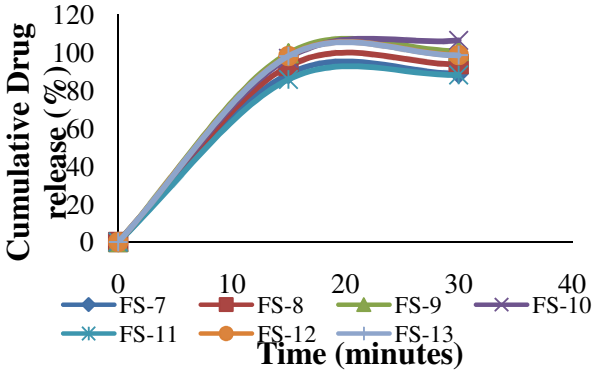

Fig.3. Drug release profile for IR formulation (FS-7 to FS-13)

The results of drug release show that all of the above formulations released not less than 85% of the drug (Q=80%) within 15 minutes, which lies within the specification for immediate release dosage form [6].

3.3 Optimized Immediate Release Formulation

Dissolution of all the formulations were within limits i.e. NLT 85% (Q=80%). With response target of dissolution at 15 minutes set 100% ± 10%, the optimization plot (Fig.4) suggested the optimal value of factors by the vertical red line or value at top row in red i.e. CCS 4.59% (11.48 mg) and SSG 5.57% (13.92 mg) of the total weight of tablet. Horizontal dotted blue line in Fig.4 represents the predicted response from the optimal values of factors. Composite desirability of obtaining the targeted response is 0.997 out of 1 and the grey region in the graph represents zero composite desirability.

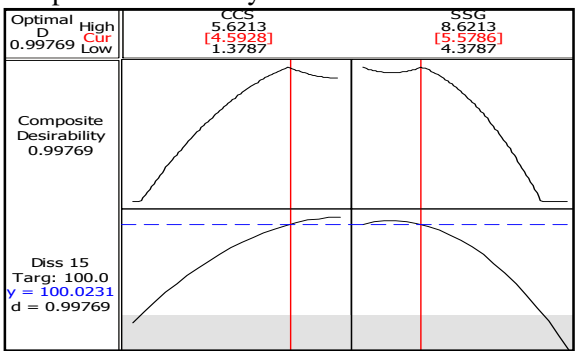

Fig.4. Optimization plot for immediate release tablet

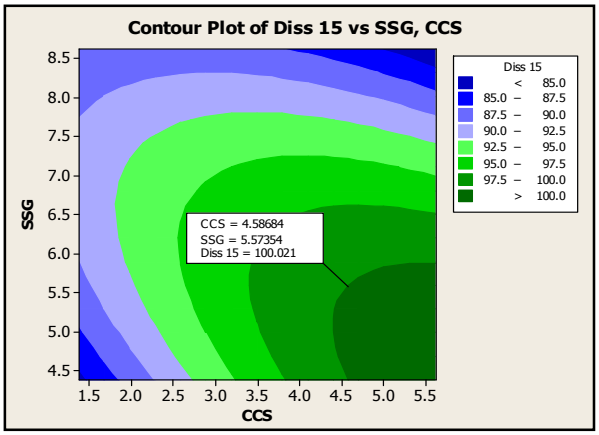

Fig.5. Contour plot of drug release at 15 minutes of Immediate release tablet

Similarly, CCS 4.59% (11.48 mg) and SSG 5.57% (13.92 mg) concentration was flag in contour plots as shown in Fig.5. It showed the desired target dissolution as 100.021%. Hence, the optimized IR formulation was selected with concentration of 4.59% of CCS (i.e. 11.48 mg /tablet) and 5.57% of SSG (i.e. 13.92 mg/tablet).

3.4 Optimization for the Sitagliptin Immediate Release

Equation derived from the regression coefficients of Immediate drug release at 15 minutes is expressed as equation 4,

$$Y = 22.150 + 13.956X1 + 16.560X2 - 0.219X1X1 - 1.086X2X2 - 1.168X1X2 \ldots\ldots\ldots\ldots (4)$$

Where, X_1 is CCS, X_2 is SSG, X1X1, X2X2 and X1X2 are their interaction terms.

Equation 4 reflects that regression coefficient of SSG is more as compared to CCS which indicates that SSG have more contribution towards the response. The CCS and SSG have positive effect on drug release whereas the interaction between CCS-CCS, SSG-SSG and interaction between CCS and SSG have an antagonistic effect on drug release. From ANOVA analysis, it was found that SSG (P = 0.019) is significant factor than CCS (P = 0.345) whereas Interaction between CCS and CCS (P = 0.567), the interaction between SSG and SSG (P = 0.316) and interaction between CCS and SSG (P = 0.377) are not significant.

3.5 Comparison of Drug Release with Market Formulations

Comparison of dissolution profiles of optimized Sitagliptin tablet with marketed product MP1 was performed. The results showed that the dissolution profile of optimized tablet and MP1 market have similar pattern of drug release. The cumulative drug release is reported in Table 3. The release profiles obtained are shown in Fig.6.

Table 3: *In-vitro* drug release profile of the Optimized Tablet and Marketed Product

Time interval	Cumulative % drug release	
	Sitagliptin Phosphate (OPS)	MP1 (Siptin 50)
15 minutes	99.072	94.107
30 minutes	100.443	95.257

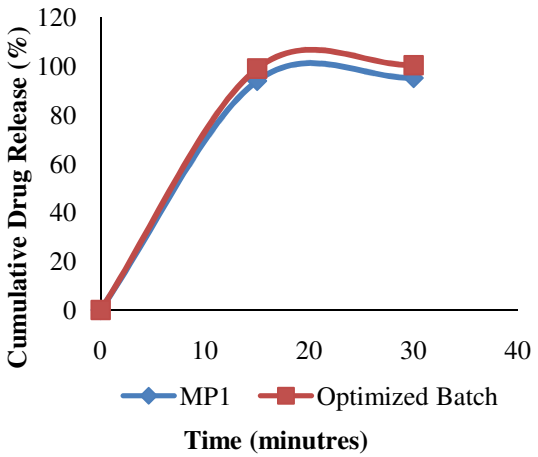

Fig. 6. Showing Dissolution Profile of MP1 Market Product and Optimized Batch for Immediate Release

3.6 Similarity and Dissimilarity Factor

The predicted values from the response optimizer were compared with the value observed from optimized batch with the application of similarity and dissimilarity factor. The data are depicted in Table 4 which shows that the cumulative drug release obtained from the optimized formulation was similar to the predicted cumulative drug release.

Table 4. Similarity and Dissimilarity factors between Predicted and Observed Drug Release Percentage of Optimized batch

Time (minutes)	Drug Release Percentage of Immediate Release		Similarity Factor F_s	Dissimilarity Factor F_d
	Predicted	Observed		
15	100.021	99.072	95.961	0.949

4. Conclusion

It can be concluded that the immediate release tablet of Sitagliptin Phosphate can be developed and optimized using response surface methodology. The optimized immediate release tablet provided the satisfactory drug release profile with an increased therapeutic efficacy for the managemant of Type-II diabetes mellitus.

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