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DESIGN CHARACTERIZATION AND OPTIMIZATION OF ORALLY DISINTEGRATING TABLETS OF SITAGLIPTIN USING 3^2 FACTORIAL DESIGN

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ABSTRACT

The aim of the investigation was to employ experimental design to formulate and optimize sitagliptine. oral disintegrating tablet (ODTs) by direct compression technique, using the mutual effect of synthetic sodium starch glycolate (SSG) and Natural Fenugreek mucilage as disintegrants in the formulation. 3^2 factorial design was applied to optimize the influence of three levels each of SSG (X1) and ND (X2) concentrations (independent variables) for investigated responses: Disintegration time (Y1) , % of drug release in 5 min (Y2), and % drug release (Y3) (dependent variables). This face-centered second-order model's reliability was verified by the probability and adequate precision values from the analysis of variance, while the significant factor effects influencing the studied responses were identified using multiple linear regression analysis. Counter plot and response surface plots were interpreted to evaluate the responses' sensitivity towards the variables. During optimization, the concentrations of the processed factors were evaluated, and the resulting values were in good agreement with predicted estimates endorsing the validity. Spectral study by Fourier Transform Infrared Spectroscopy (FTIR) and thermograms from demonstrated the drug-excipients compatibility of the optimized formulation. The model predicted DT of 25 sec and DR% of 99.9% 25minute.

INTRODUCTION:

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Blood glucose is your main source of energy and comes from that food you eat. Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy. Sometimes your body doesn't make enough or any insulin or doesn't use insulin well [1,2]. Glucose then stays in your blood and doesn't reach your cells. Over time, having too much glucose in your blood can cause health problems. Although diabetes has no cure, you can take steps to manage your diabetes and stay healthy.Sometimes people call diabetes "a touch of sugar" or "borderline diabetes". These terms suggest that someone doesn't really have diabetes or has less serious case, but every case of diabetes is serious. Oral disintegrating tablets are becoming popular as novel drug delivery systems for

drug administration. They are more convenient for children, elderly patients ,patients with swallowing difficulties and in the absence of potable liquids. The most desirable formulation for use by the elderly is one that is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place Sitagliptin is an oral drug that reduces blood sugar (glucose) levels in patientswith type 2 diabetes. Sitagliptin is a member of a class of drugs that inhibit the enzyme,dipeptidyl peptidase-4 (DPP-4) and are therefore called DPP-4 inhibitors. It is used in either alone or in combination with metformin or thiazolidinedione for control of type -2 diabetes mellitus.[3,4]

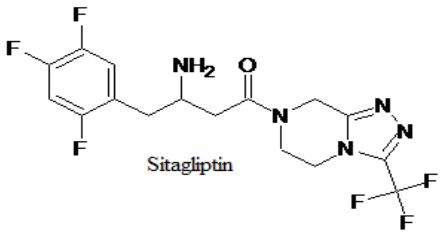


Figure: 1- Structure of Sitagliptin

MATERIALS AND METHODS:

Sitagliptin drug was obtained as a gift sample from Syncorp laboratories, Hyderabad. Other excepients like lactose, talc, mannitol, tragacanth, magnesium stearate was obtained from the lab of Anurag Group of Institutions; Hyderabad. The super disintegrant like Sodium Starch Glycolate was obtained from lab of Anurag Group of Institutions, Hyderabad. The other disintegrant used is the powder of mucilage of fenugreek seeds. It is naturally extracted[5,6].

EXTRACTION AND ISOLATION OF FENUGREEK MUCILAGE:

EXTRACTION: 150g of fenugreek seeds are washed and dried at room temperature. The dried seeds are then boiled in water until mucilage is released into water. The mucilage is then squeezed using muslin cloth. Then separate the marc from filtrate and keep it in refrigerator overnight for cooling.

ISOLATION: The above cooled filtrate is mixed with Ethyl alcohol in 1:1 ratio. Keep it aside for 5 to 10 mins. Precipitation of mucilage takes place on the above of the solution. Separate the mucilage using muslin cloth. Dry the mucilage in oven at 50°C. The dried mucilage is scrapped and finely dried into powder. This powder is then used as natural disintegrant in the formulation of orally disintegrating tablets.

Experimental Design: Two factors, three levels (3^2) full factorial design was used to optimize Sitagliptine orally disintegrating tablets, namely SSG (X1) and Natural disintegrant (X2) concentrations using a statistical package (Design Exper, version 11). Statistical models with interaction terms were derived to evaluate the effect of the two factors on the disintegration time in seconds (Y1), percentage of Sitagliptine dissolved within 5 min (Y2), and percentage of Sitagliptine dissolved within 25 min (Y3) of the manufactured orally disintegrating tablets. The selected two factors as well as their levels and analyzed response are shown in Table 1 and the matrix of the factorial design is represented in Table 2. Each row in the matrix identifies an experiment and each experiment provides a result (response). This design provided an empirical second order polynomial model

FORMULATION OF ODTs OF SITAGLIPTIN:

Formulation of orally disintegrating tablets of Sitagliptin was done by the direct compression method.

Direct Compression method: Direct compression is a simple method of tableting that can only be utilized when the powder mixture possesses adequate flowing properties and compressibility. The most important aspect in direct compression is the diluent selection. The diluent contributes the main flowing and compressibility aspects to the powder mixture. Binders, diluents, disintegrants, glidants, lubricants, and the API are all mixed together to form a powder mixture that can easily be compressed into tablets without any additional steps.

Evaluation of Orally disintegrating Tablets of Sitagliptin :

Weight variation: Ten randomly selected tablets are to be carefully weighed on an electronic analytical balance using forceps and tarred weighing paper . Tablets with a total tablet mass less than 120 mg have a 10% weight variation limit; therefore 90-110 mg tablets containing Sitagliptin are within acceptable limits for the goal tablet weight of 120 mg[7,8].

Hardness testing: Place the sample tablet in the vertically holding edges of the anvil of Monsanto Hardness Tester. Adjust the pointer at zero position on the scale by rotating the screw in forward direction. Now rotate the screw till break point of the tester. The breakage of tablet shows hardness on the scale. Repeat the procedure 8-10 times for average reading. Record the observation in Inspection Sheet and attach in BMR.

Friability of Tablet: Friability of compressed uncoated tablets can be determined using the FT 1020 method to simulate shipping and packaging stress. Tablets are to be brushed to remove excess powder prior to their initial weight determination and after 100 revolutions (25 revolutions per minute for four minutes). According to the USP, less than 1% loss and no tablet breakage is acceptable for tablet friability. The test can be performed additional times if tablets are cracked, breakage occurs, or results are inconclusive.

Wetting time: Wetting time is relative to the inner structure of tablets and the hydrophilicity of excipients and therefore is important for orally disintegrating tablets. Slight variations have been employed to determine the wetting time of uncoated tablets. The typical wetting test utilizes tissue paper folded in a six-inch diameter petridish. The tablet is placed on the tissue paper near the center of the petridish and 15 mL of 6.8 pH buffer solution is added [8]. The tissue paper wicks the solution and the tablet begins to uptake water. The wetting time is recorded as the time when complete wetting of the tablet occurs.

Disintegrating time: Disintegration time of uncoated tablets was determined by combining the USP 30 standard method. The disintegration apparatus consists of a basket-rack assembly, a 1000 mL beaker, and a device that consistently raises and lowers the basket-rack assembly at a rate of 29 and 32 times per minute. The USP 30 recommends placing one tablet in each of the six-tubes of the basket with disks [9]. The disintegration medium should be maintained at 37 ± 2°C [9]. Allow the device to raise and lower the basket-rack assembly in the disintegration medium for the prescribed amount of time (described in the monograph or research protocol), then remove the baskets from the medium and observe if the tablets completely disintegrated and passed through the mesh.

***In vitro* Dissolution Studies:** The dissolution of Sitagliptin from ODT was determined by USP dissolution testing apparatus II (paddle method). The dissolution test was carried out using 900 mL of 0.1 N HCl, at 37±0.5 °C and 50 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at different time interval. An aliquot of 5 ml was collected at predetermined time

intervals and replaced with fresh dissolution medium. Then all the solutions are diluted by taking 1ml of aliquote with 49ml of 0.1 N HCl. These are then observed for absorbances under U.V. Spectrophotometer.Then the % drug release is calculated using these absorbances.

RESULTS & DISCUSSION

Preparation of standard calibration curve of Sitagliptine in 0.1N HCI at 267nm: Calibration curve of Sitagliptine was developed in 0.1 N HCI at 267 nm wave length. Sitagliptine in 0.1 N HCI showed good linearity (r^2=0.992) and intercept 0.002over the concentration range of 2-12 µg/ml at λmax 267 nm.

Drug -excipent compatibility study: It was observed that there were no or very minor changes in drug main peaks in the IR spectra of a mixture of drug and pure drug The FTIR study revealed no physical or chemical interactions of Sitagliptine with excipient each as evident from Figure :14 &15

Pre formulation study results: In this research. All Nine formulation were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. The findings of pre-compression evaluation was given in **Table-7,** Angle of repose was found to be ranging from 29.02^0 to 36.34^0 all formulation shows good flow property . Carr's index was found to be ranging from 10.07% to19.62 % for the powders of all the formulations.

Post compression results: The results of physical evaluation of tablets is given below in **Table-8** The tablets of different batches were found uniform with respect to hardness within the range of 4.93 to 5.83 kg/cm2. Another measure of a tablet's strength is friability. Results of friability test were also has been found within limit. In weight variation test, the pharmacopoeial limit for percentage deviation for tablets of more than 200 mg is ±5% and all the formulations were found to comply with the specifications given in I.P. for weight variation test. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 95%. All the tablet formulations showed acceptable pharmaco -technical properties[9,10].

Disintegration and Wetting study: The tablets of different batches were subjected to disintegration and wetting test. the results are presented in Table-8 & figure 17, **F2** formulation containing 32mg of SSG and 24mg of natural disintegrant ,extracted from fenu greek seeds showed the least wetting time10 second and disintegration time 27 second. **F7** formulation showed maximum wetting time 13 second and disintegration time 51 second

***In - vitro* drug release study:** The release profile of Sitagliptine from different batches of formulated ODT tablets were illustrated in Table-9 and % drug release profile graph is given in Figure-18 &19 . among all the formulation F2 showed the maximum drug release of 99.12% in 25 minutes. an uniform release pattern was observed in F8 formulation ,showed low drug release of 79.31% in 30minutes .

Statistical analysis:

Fitting data to model and validation: The developed Sitagliptine formulations were optimized using 3^2 Factorial design. using design expert V.11 software The formulation was prepared by direct compression method. The response surface analysis was carried out to understand the effect of selected independent variables on the observed responses. The effect of SSG concentration (X_1), Natural disintegrant concentration (X_2) were selected as independent variables and their pronounced effect was observed on dependent variables [Y_1= Disintegration time(s) Y_2= Drug Release % at 5 min, Y_3= Drug Release % at 25 min] has been investigated.

Figure: 2 Isolation process of natural disintegrant

Table no: 1 **Variables in 3^2 full factorial design**

Independent Variable	Low (-1)	Middle(0)	High(+1)
X1 : SSG (mg)	16	24	32
X2 : Natural disintegrant (mg)	16	24	32
Dependent Variable Response			
Y1 : Disintegration time (s) Y2 : DR% After 5 min Y3 : DR% After 30 min			

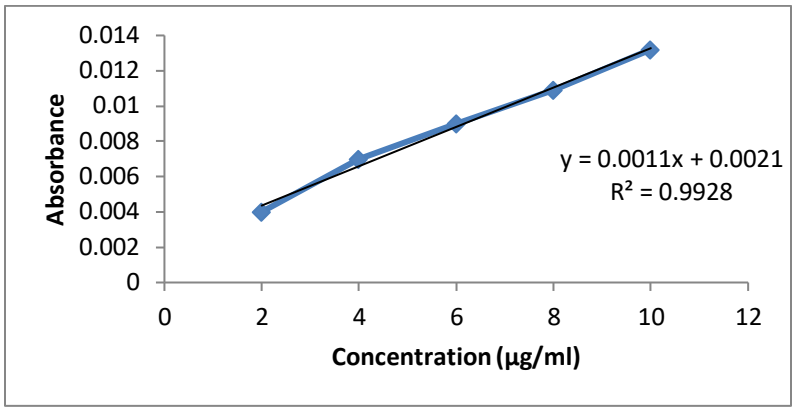
Table no:2 **Composition of different Sitagliptine ODT Tablet**

INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Sitagliptine	65	65	65	65	65	65	65	65	65
Sodium Starch Glycolate	32	32	32	24	24	24	16	16	16
Natural Disintegrant	16	24	32	16	24	32	16	24	32
Tragacanth	20	20	20	20	20	20	20	20	20
Mannitol	40	40	40	40	40	40	40	40	40
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	17	9	11	25	17	9	33	25	17
TOTAL	200	200	200	200	200	200	200	200	200

Table no:3 **Calibration Curve data of Sitagliptine in 0.1N HCI at 267nm**

S.no	Concentration(µg/ml)	Absorbance			Average Absorbance	Standard Deviation
		1	2	3		
1	2	0.0043	0.0048	0.0041	0.004	0
2	4	0.0063	0.0068	0.0065	0.006	0.003
3	6	0.0086	0.0093	0.0089	0.008	0.012
4	8	0.0104	0.0113	0.0111	0.010	0.012
5	10	0.013	0.0135	0.0131	0.0132	0.004

Figure: 3 Standard curve of Sitagliptine in 0.1N HCI at 267nm



. Figure: 4 FTIR of Sitagliptin pure drug

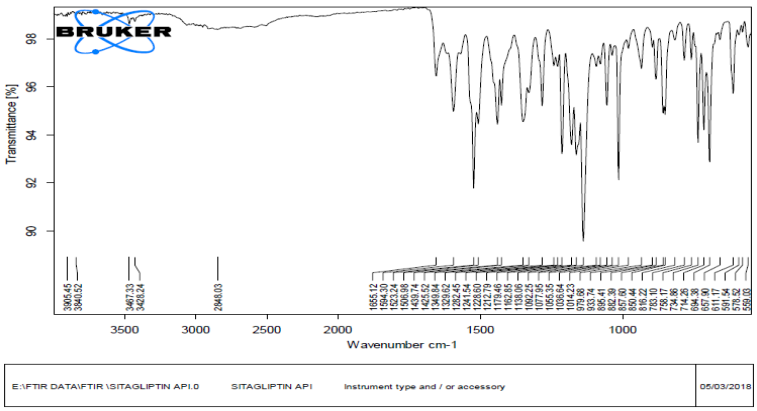


Figure :5 FTIR of Optimized SitagliptinFormulation

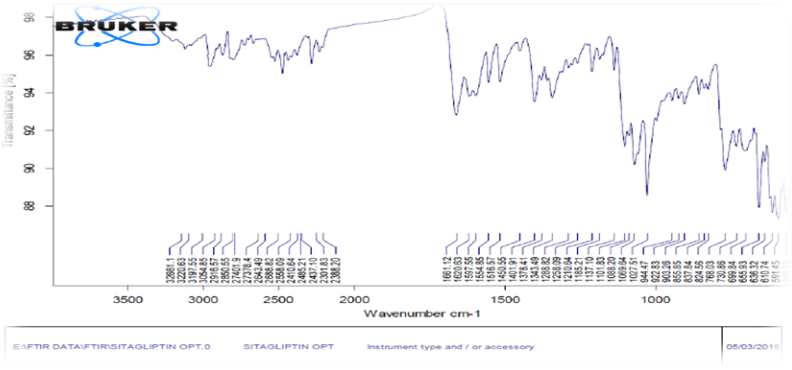


Figure: 6 DSC of pure sitagliptin :

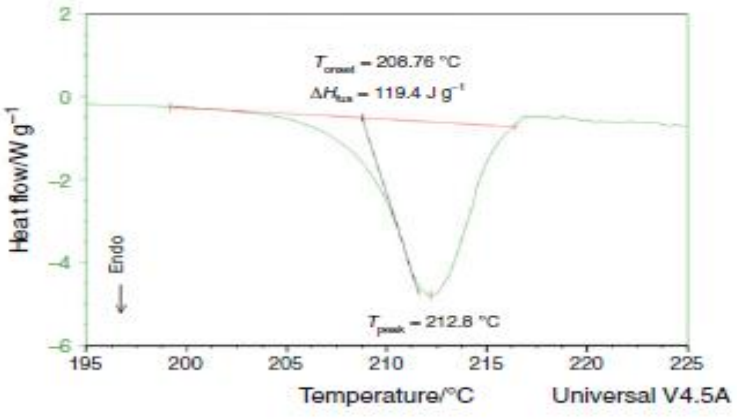


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Table: 4- Pre compression parameters of powder blend:

Formulation	Angle of Repose (ɵ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner Ratio
F1	33.14±0.23	0.601±0.22	0.746±0.03	19.43	1.24
F2	29.02±0.43	0.508±0.09	0.632±0.03	19.62	1.24
F3	34.14±0.03	0.492±0.46	0.523±0.03	17.26	1.06
F4	32.19±0.63	0.490±0.11	0.599±0.73	18.19	1.22
F5	31.98±0.11	0.491±0.07	0.546±0.03	10.07	1.11
F6	36.34±0.03	0.513±0.20	0.641±0.03	19.96	1.24
F7	30.14±0.53	0.512±0.32	0.625±0.53	18.08	1.22
F8	36.14±0.33	0.539±0.83	0.646±0.08	16.56	1.19
F9	31.04±0.13	0.499±0.12	0.546±0.13	11.22	1.09

Table: 5 Post compression results of ODTs

Formulation	Weight variation (mg±SD)	Thickness (mm±SD)	Friability %	Hardness (kP±SD)	Disintegration time (s±SD)	Wetting time (s±SD)	Dispersion time (s±SD)
F1	199±0.77	2.43±0.07	0.85	5.23±0.77	33±0.77	13±0.04	53±0.11
F2	200±0.37	2.62±0.12	0.46	5.25±0.17	27±0.17	10±0.11	33±0.17
F3	201±0.78	2.88±0.09	0.95	5.23±0.11	31±0.43	14±0.14	58±0.23
F4	197±0.17	2.53±0.47	0.45	5.23±0.88	38±0.33	13±0.34	73±0.07
F5	198±0.23	2.85±0.21	0.83	4.93±0.27	45±0.11	12±0.05	67±0.22
F6	209±0.11	2.63±0.77	0.11	5.33±0.07	47±0.07	15±0.77	59±0.32
F7	199±0.44	2.63±0.77	0.34	5.83±0.23	51±0.24	13±0.86	61±0.31
F8	202±0.87	2.63±0.77	0.23	4.99±0.67	43±0.17	12±0.11	55±0.87
F9	199±0.31	2.63±0.77	0.77	5.03±0.17	32±0.57	12±0.74	53±0.47

Table: 6- *In vitro* dissolution studies:

Formulation	% Drug Release								
Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	55.12	80.67	60.21	61.22	56.23	93.44	90.22	20.41	31.41
10	75.03	85.11	65.11	85.31	64.01	98.77	95.11	43.12	53.12
15	82.11	89.72	72.33	97.33	72.33	99.15	98.23	53.83	69.82
20	85.32	94.11	75.66	-	80.21	-	99.86	68.32	78.02
25	87.01	99.12	89.09	-	87.11	-		75.32	89.31
30	90.11	-	92.11	-	-	-		79.31	92.11

Figure: 7 - Disintegration time

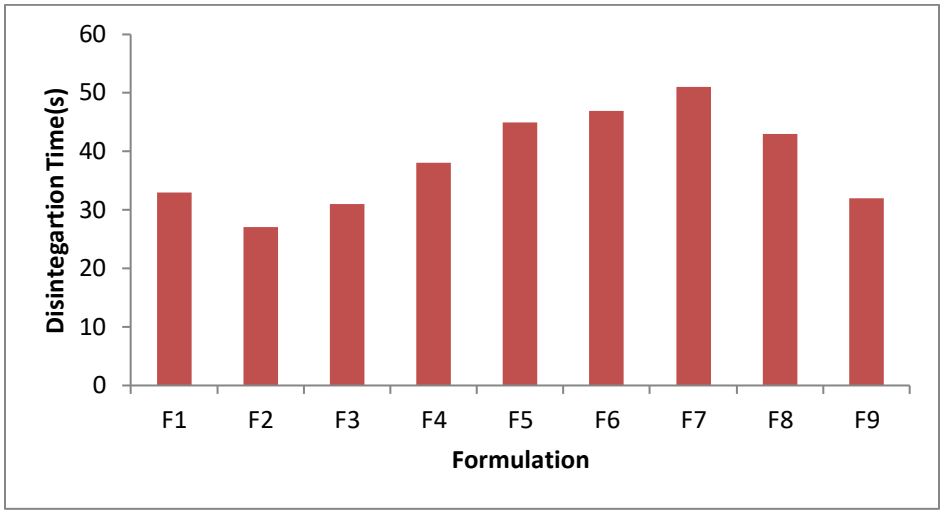


Figure: 8- % Drug release profile of formulations (F1 – F5)

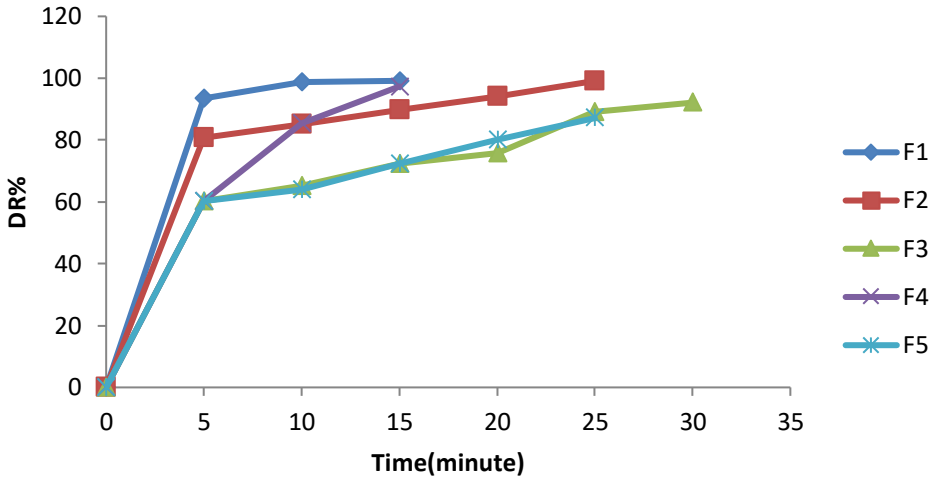
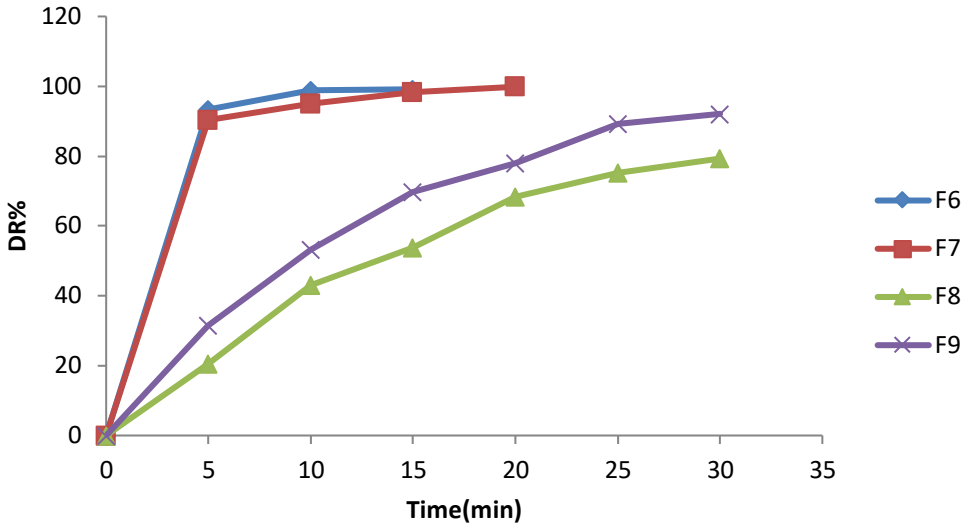
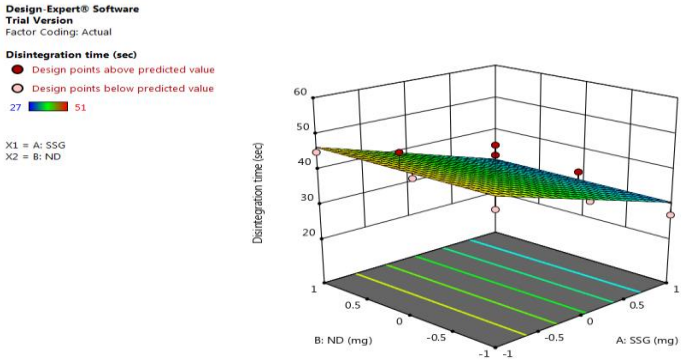
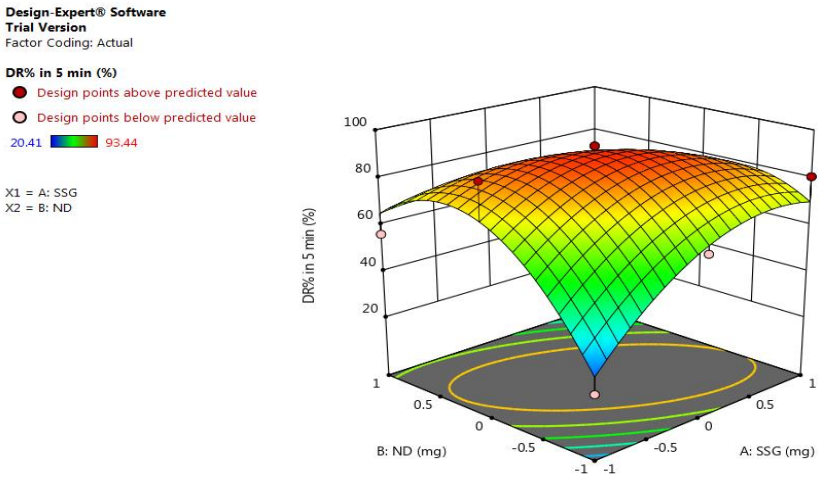


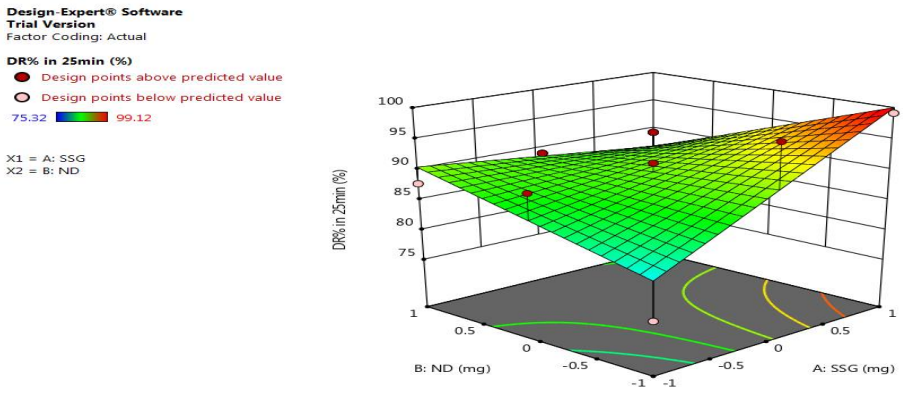
Figure: 9- % Drug release profile of formulations (F6 – F9)



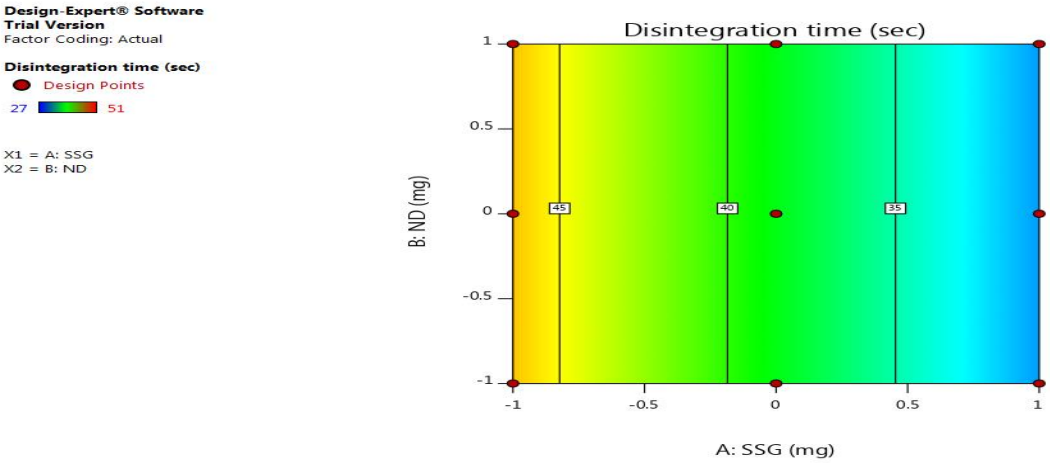
RESPONSE SURFACE RESULTS

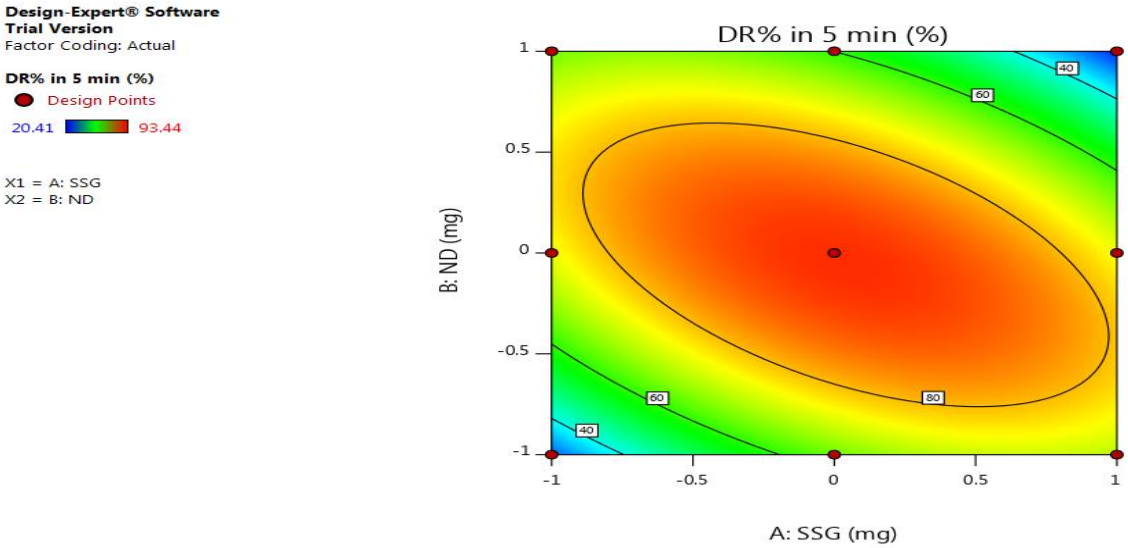






COUNTER PLOTS





Their kinetics was found to be quadratic in nature ($p < 0.0001$) with interaction terms. The mathematical relationships were established and coefficients of the second order polynomial equation generated using MLRA for all the above factors.A positive valuein regression equation for a response represents an effect that favors the optimization (synergistic effect), whereas a negative value indicates an inverse relationship (antagonistic effect)between the factor and the response**(Imam et al., 2015).** A total of 9 experiments were performed and the selected independent variables were significantly influenced the observed responses, i.e., Disintegration time (Y_1=38.56-7.83X_1+.0000X_2), drug release% after 5 min (Y_2=90.22+0.567X_1-2.41X_2-21.27 X_1 X_2-15.95 X_1^2) and drug release % after 25min (Y_3=89.67+3.69 X_1 – 1.06 X_2 – 5.56 X_1 X_2) as shown in **Table 2**. Fitting of the data for observed responses to various models

CONCLUSION: The study was undertaken with the aim to design and evaluate the Sitagliptine oral disintegrating tablets using Fenugreek mucilage as disintegrant extracted from natural source. The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug Sitagliptine and in the physical mixture which confirms the absence of chemical interaction between drug and polymers. **F2** formulation containing 24mg natural disintegrant and 32 mg of SSG showed the least wetting time 10 second and disintegration time 27second. **F7** formulation showed maximum wetting time 13 second and disintegration time 51 second

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