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Advances in Bioresearch

ORIGINAL ARTICLE

Formulation development and evaluation of Orodispersible tablet of sitagliptin by using factorial design model

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ABSTRACT
In this research work concerned with the formulation and evaluation of orodispersible tablet of sitagliptin antidiabetic drug by using direct compression method and Optimization of prepared formulation by using 3^2 Factorial design model. The aim of this study was to formulate and optimise oral disintegrating tablets of Sitagliptin utilizing synthetic superdisintegrants to provide a speedy start of action by quickly dissolving in a few seconds without the need for water and to improve the patient compliance. by using IR spectroscopy, drug-excipient compatibility experiments were done, there was no drug-excipient interaction. There are nine formulations of Sitagliptin were prepared different the concentrations of super disintegrants is cross providone. Direct compression binder, Flow property enhancer: Avicel 102. Drug – Excipient compatibility study ratio: 1:1. The melting point of Sitagliptin was found to be in the range of 214-218°C which complies with reported melting point of Sitagliptin. Phosphate buffer 6.8 pH was used as solvent system for blank as well as sample preparation. 40 µg/ml of Sitagliptin was used and λ_{max} was found as 267 nm. The drug content was found to be between 98-102% which was under specified limit. The disintegration time was found in the range of 40 – 65 sec. In this factorial design model study F7 batch was selected as optimized batch.
Keywords: Sitagliptin, Orodispersible Tablets, Factorial Design, Superdisintegrants, Formulation Development, Disintegration Time, Drug Release.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to elevated blood glucose levels. Effective management of T2DM is crucial to prevent long-term complications such as cardiovascular disease, neuropathy, retinopathy, and nephropathy. Among the various therapeutic agents available, dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as a valuable class of oral hypoglycemic agents due to their efficacy and favorable safety profile. Sitagliptin is a potent, selective DPP-4 inhibitor that enhances the body's natural ability to regulate blood glucose levels. By inhibiting the DPP-4 enzyme, sitagliptin prolongs the activity of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones increase insulin synthesis and release from pancreatic beta cells in a glucose-dependent manner, while also decreasing glucagon secretion from alpha cells, leading to reduced hepatic glucose production. The clinical efficacy of sitagliptin has been demonstrated in numerous studies, where it has been shown to significantly reduce glycated hemoglobin (HbA1c) levels, a key indicator of long-term glycemic control. Sitagliptin is typically well-tolerated, with a low risk of hypoglycemia and weight neutrality, making it an attractive option for many patients with T2DM. Despite its benefits, the development of orodispersible tablet (ODT) formulations of sitagliptin represents a significant advancement in enhancing patient compliance, particularly for those who have difficulty swallowing conventional tablets. ODTs disintegrate rapidly in the mouth without the need for water, providing a convenient and palatable alternative to traditional dosage forms. This research article focuses on the formulation development and evaluation of an orodispersible tablet of sitagliptin using a factorial design model. The objective is to optimize the tablet's properties, ensuring rapid disintegration, acceptable taste,

and effective drug release, ultimately improving patient adherence and therapeutic outcomes in the management of type 2 diabetes mellitus.

MATERIAL AND METHODS

Table 1: List of materials

Sr.no.	Ingredients	Role
1.	Sitagliptin	Anti-diabetic
2.	Cross povidone	Super disintegrant
3.	Avicel 102	Direct compression binder, Flow property enhancer
4.	Mannitol	Sweetener, Cool taste and diluent property
5.	Aspartame	Artificial sweetener
6.	Lactose	Diluent
7.	Magnesium stearate	Lubricant
8.	Talc	Glidant

Sitagliptin, Cross povidone, Avicel 102, Mannitol, Aspartame, Lactose, Magnesium stearate and Talc was passed through mesh no. 60 separately and collected. Sitagliptin, mannitol and lactose were mixed uniformly with gentle trituration using mortar and pestle to get a uniform mixture. Required quantity of Cross povidone, Avicel 102 and aspartame were taken as per formulation requirement and mixed with the above mixture. After trituration mixer was placed in a RMG (Rapid Mixer Granulator) for 30 mins at 150 rpm. Finally, magnesium stearate and talc were added and mixing was continued for further 5 min. The mixed blend of drug and excipients were compressed using 9 mm punch on 10 stations "B" Tooling Rotatory Tablet Punching Machine to produce convex faced tablets, weighing 250 mg each.

Table 2: Formulation strategy

Sr.no.	Ingredients	Quantity (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Sitagliptin	100	100	100	100	100	100	100	100	100
2.	Cross povidone	12.5	12.5	12.5	18.75	18.75	18.75	25	25	25
3.	Avicel 102	37.5	43.75	50	37.5	43.75	50	37.5	43.75	50
4.	Mannitol	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
5.	Aspartame	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
6.	Lactose	45	38.75	32.5	38.75	32.5	26.25	32.5	26.25	20

PRE FORMULATION STUDY:

Preformulation studies are a crucial phase in pharmaceutical development, where the physical and chemical properties of a drug substance are analysed before formulating it into a dosage form. This stage involves comprehensive investigation and characterization of the drug's inherent properties, including its solubility, stability, compatibility with excipients, particle size, and polymorphic forms. Understanding these characteristics helps in selecting the most suitable formulation approach and aids in predicting the drug's behaviour during the manufacturing process and after administration. Preformulation studies lay the foundation for designing an effective and stable drug formulation, ensuring its safety, efficacy, and manufacturability.

rug Characterization

Colour: A little amount of Sitagliptin was taken in butter paper and examined under well lighted area.

Odour: Small amount of Sitagliptin sample was smelled to get the odour.

Appearance: A pinch of Sitagliptin was taken between two fingers and appearance was observed.

a) **Determination of melting point:**
   Melting point is the first indication of purity of the sample. Melting point of Sitagliptin was performed by open capillary method. Sitagliptin was taken in a glass capillary whose one end was sealed by flame. The capillary was then placed inside the melting point apparatus and melting point was noted.

b) **Solubility study:**
   The solubility of Sitagliptin was determined in various solvents shown in table 1. In a test tube 10 ml of required solvent was transferred and 20 mg of Sitagliptin was added to the solvent. The mixture was then sonicated for 10min and observation was done for the particles remain if any.

Table 3: Solvents used for solubility study

Sr.no	Solvent
1.	Methanol
2.	Phosphate buffer 6.8 pH
3.	Water

c) UV-visible spectrophotometric analysis:

UV spectroscopy: The UV spectrum of Sitagliptin was obtained. Jasco Corporation, Japan V 550 Spectrophotometer and spectra manager software was used for analysis. Glassware used were rinsed thoroughly with doubled distilled water and dried.

Reagents & Materials: All reagents were of analytical grade and Phosphate buffer 6.8 pH was used as solvent to prepare dilutions.

Method: 10 mg of Sitagliptin was dissolved in 10 ml of solvent (Phosphate buffer 6.8 pH) to produce 1000 µg/ml. From this prepared solution 0.4 ml of sample was taken and further diluted with Phosphate buffer 6.8 pH up to 10ml to produce 40 µg/ml sample and spectra was observed.

Calibration Curve in Phosphate buffer 6.8 pH:

Stock solution: 10 mg of Sitagliptin was dissolved in 10 ml of solvent (Phosphate buffer 6.8 pH) to produce 1000µg/ml.

Solution A: From stock solution 1ml of sample was withdrawn and diluted up to 10ml with solvent (Phosphate buffer 6.8 pH) to produce 100 µg/ml.

Dilutions: From solution A 1ml, 2ml, 3ml, 4ml and 5ml solution were withdrawn and diluted up to 10ml with solvent (Phosphate buffer 6.8 pH) to produce 10ppm, 20ppm, 30ppm, 40ppm and 50ppm and absorbances were measured at 267 nm.

d) FT-IR of Sitagliptin:

The IR spectrum of Sitagliptin was recorded on Shimadzu IRAffinity-1. Spectrum was recorded by using potassium bromide (KBr) as blank, at a resolution of 4 cm over a range 400-4000 cm. The peaks in the spectrum of Sitagliptin were compared with the principle peaks of the IR spectrum reported in the monograph.

Drug excipient compatibility study:

Drug excipient compatibility studies represent an important phase in drug development. Before a drug substance is formulated into a desired dosage form, there is need for the formulator to fully consider the chemical structure of the drug substance, type of delivery system required and the proposed manufacturing process. Drug substances are usually combined with the excipients which serve different and specialized purpose. Excipients are pharmacologically inert, but given the right conditions they can undergo chemical reactions and physical interactions with drug molecules under favorable environmental conditions. Compatibility test on drug excipient have been used to approve or reject excipients for use in pharmaceutical formulation. The API alone and with individual excipients were taken in different ratios and mixed well. Passed through sieve, the blend was filled into the glass vials and kept in stability chamber at 40± 2°C/75 ± 5%RH.

Table 5: Drug – Excipient compatibility study ratio

Sr. No.	Sample	Ratio
1	Sitagliptin: Cross povidone	1:1
2	Sitagliptin: Avicel 102	1:1
3	Sitagliptin: Mannitol	1:1
4	Sitagliptin: Aspartame	1:1
5	Sitagliptin: Lactose	1:1
6	Sitagliptin: Magnesium stearate	1:1
7	Sitagliptin: Talc	1:1

Factorial Design model:

In order to formulate stable orodispersible tablet, 3^2 full factorial design was applied to the formulation that showed the satisfactory results to see the effect of varying the concentrations of variables such as Cross povidone (X1) and Avicel 102 (X2) on responses like disintegration time and hardness. The levels of two factors were selected on the basis of studies carried out before implementing the experimental design.

Table summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study.

Table 6: Factorial design model parameters

Independent variables	Name	Unit	Levels	
			Low (-1)	High (+1)
X1	Cross povidone	%	5	10
X2	Avicel 102	%	15	20

Formulation strategy:

Table 7: Formulation strategy

Sr.no.	Ingredients	Quantity (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Sitagliptin	100	100	100	100	100	100	100	100	100
2.	Cross povidone	12.5	12.5	12.5	18.75	18.75	18.75	25	25	25
3.	Avicel 102	37.5	43.75	50	37.5	43.75	50	37.5	43.75	50
4.	Mannitol	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
5.	Aspartame	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
6.	Lactose	45	38.75	32.5	38.75	32.5	26.25	32.5	26.25	20
7.	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8.	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight of tablet		250 mg.								

Evaluation procedures:

Pre-compression Parameter

Bulk Density:

Bulk density or apparent density may be defined as the mass per unit volume of loose powder including the space between the particles, the volume & the envelop volume of the particles. Bulk density of a powder depends primarily on particle size distribution, shape and their tendency of adherence to one another.

Method:

Powder blend was accurately weighed & passed through sieve # 80 and was carefully poured into 100 ml graduated cylinder. The capacity was calculated as ml using the graduation marking on cylinder. The bulk volume is a volume measurement and the bulk density is determined using the formula below:

$$\rho b = m / Vb$$

Where,

ρ_b = Bulk density

m = Mass of powder

V_b = Bulk volume of powder

Maximally 60% powder should be filled into the cylinder. Bulk density is an essential parameter used to determine occupancy in blender or hopper or capsule filler etc.

Tapped Density:

The tapped density is a limited density attained after "tapping" usually in a device that lifts and drops a volumetric measuring cylinder (Tapping density apparatus) containing the powder blend from a fixed distance. Tapped density was determined by using Electro lab USP Apparatus.

Method:

After measuring the bulk volume, the same measuring cylinder containing the powder blend was set into tap density apparatus and was mechanically tapped, allowing it to drop under its own weight that provides a fixed drop from 14±2mm. The tap density apparatus was run for 500 taps volume was recorded as (V_b). The following formula is used to determine tap density.

$$\rho t = m/Vt$$

Where,

ρ_t = Tapped density

m = Mass of powder

V_t= Tapped volume of powder

Tapped Density represents dense packing. Regularly shaped particles (spheres) have a greater tapped density value than irregularly shaped particles (needles).

Flow Properties:

Flow assessment of API and excipients made to ensure that the powder will flow adequately through processing equipment's such as compactor, hopper or tablet press. Poor flow ability can lead to tablet weight variation due to in ability to feed powder into die.

Compressibility index (C.I.):

It is the measure of propensity of a powder to consolidate. It is the measure of inter particulate interaction in free-flowing powder, such interaction is generally less significant and BD and TD value will be close. For poor flowing material it causes frequently greater inter particle interaction, bridging between particles often results in lower bulk density and greater difference between BD and TD and this difference is reflected in compressibility index. The packing ability of powder was evaluated from change in volume, which is due to rearrangement of packing occurred during tapping Carr's or compressibility index (CI) can be calculated as follows.

$$C.I\ (\%) = (\rho t - \rho b)/\ \rho t * 100$$

Where,

ρt = Tapped density

ρb = Bulk density

Table 8: Standard values for Compressibility index

Compressibility Index (%)	Flow Character
≤ 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
> 30	Very very poor

ii) Hausner's ratio:

Hausner's ratio is a measurement used to describe the compressibility of powder. It was the ratio of tapped density to bulk density. It is calculated by the formula

$$\text{Hausner's Ratio} = \rho t/\rho b$$

Where,

ρt = Tapped density

ρb = Bulk density

Table 9: Standard values for Hausner's ratio

Hausner's Ratio	Flow Character
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor

Angle of Repose:

Angle of repose is a property linked to interarticular friction or resistance to particle movement. The angle of repose may be used to calculate the frictional forces in a loose powder. This is the most extreme angle that a pile of powder can may with the horizontal plane. The tangent of the angle of repose is equal to the coefficient of friction (μ) between the particles.

Method:

Angle of repose was determined using funnel method. To keep a coating of powder on the base an Angle of repose was created on a fixed base with a retaining lip. The base should be free of vibration. The height of the funnel was adjusted to create a symmetrical cone of powder. Care was taken to prevent vibration as the funnel was moved. In order to minimize the impact of falling powder on the tip of the cone the funnel height was maintained approximately 2 cm from the top of the powder, by measuring the height of the powder cone and using the following equation to get the angle of repose

Tan θ = height/radius

Table 10: Standard values for Angle of repose

Angle of repose	Flow Character
25-30	Excellent
31-35	Good
36-40	Fair – aid not needed
41-45	Passable – may hang up
46-55	Poor – must agitate, vibrate
56-65	Very poor
>66	Very very poor

Post Compression Parameters

Physical appearance:

The appearance of the core tablet i.e., surface texture, chipping and cracks if any were observed.

Thickness and diameter:

Using vernier calipers the thickness and diameter of tablets were measured during compression.

Hardness:

Hardness crushing strength is used to assess whether a tablet machine require a pressure modification or not. If the tablet is too hard, it may not disintegrate in time necessary to fulfil the disintegrating criteria, if it is too soft it may not be able to resist packing and shipping procedures.

Friability:

The factors that cause tablets to chip, cap or shatter are friction and shock. The friability test is linked to tablet hardness is used to asses a tablets ability to tolerate abrasion during packing, handling and shipping. The Roche Friabilator was used to measure it.

Method:

A total of 20 pre-weighted tablets were put in the device and subjected to rolling and repeated shock as they fall 6 inches in each rotation. After four minutes of this treatment or 100 revolutions, the tablets were weighed and the weight was compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test was considered generally acceptable and any broken or smashed tablets were not picked. The percentage friability was determined by the formula

% Friability = (w1-w2) / w1 * 100

Where,

W1 = Weight of tablets before test

W2 = Weight of tablets after test

Drug content:

20 tablets were weighed to determine the mean weight and finely powdered in mortar. An amount of powered mass equivalent to 10 mg of Sitagliptin was accurately weighed and transferred to a 10 ml of volumetric flask. The volume was made up with solvent (methanol) and the mixture was sonicated for 15 min. An aliquot was filtered through 0.45µm nylon filter. The final tablet solution was further diluted with solvent (Phosphate buffer 6.8 pH) up to a concentration of 10 µg/ml and was analyzed by UV at 267 nm for determination of drug content.

Weight Variation:

To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method. As per IP & USP not more than two tablets should differ in their average weight by more than percentages stated and no tablet must differ by more than double the relevant percentage.

Table 11: Standard values for Weight variation

Sr. No.	Average weight of tablet (IP)	Average weight of tablet (USP)	% Deviation
1	≤ 80 mg	≤ 130 mg	10
2	>80 mg – 250 mg	>130 mg – 324 mg	7.5
3	≥ 250 mg	≥ 324 mg	5

Disintegration test:

In order for a medication to be absorbed from solid dosage form after oral administration, it must first be in solution and the first critical step towards this step was generally tablet disintegration. Disintegration

time was an important test in ODT technology since the tablet has to complete disintegration within 1 min as per USP requirement. Tablet disintegration was measured using USP disintegration apparatus. 6 tablets were introduced in each tube and the basket rack was placed in a beaker of water at 37 ± 2˚C. The basket assembly was moved up and down the beaker and the apparatus were operated until no residue was left. The time taken to achieve zero residue was recorded.

Dissolution time:

In-vitro dissolution studies for orodispersible tablets of Sitagliptin were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was Phosphate buffer 6.8 pH (900ml) maintained at 37 ± 0.5^0C.

Aliquots of dissolution media were withdrawn (10 ml) at different intervals and content of Sitagliptin was measured by determining absorbance at 267 nm. 10 ml aliquot was withdrawn at the 5min, 10min, 15min, 20min, 25min and 30min at 5min intervals and filter by Whatman filter paper. And analyzed at 267 nm using- visible spectrophotometer.

- Apparatus: Type II (Paddle)
- Medium: Phosphate buffer 6.8 pH
- Speed: 50 RPM
- Volume: 900ml
- Temperature: 37 ± 0.5^0C
- Sampling time (min): 0, 5, 10, 15, 20, 25, 30.

Preparation of Phosphate buffer 6.8 pH:

0.2 M potassium dihydrogen phosphate:

Weighed 27.22 gm of potassium dihydrogen ortho-phosphate and dissolved 1000 ml of water.

0.2 M NaOH solution:

Weighed 1.6 gm of sodium hydroxide and dissolved 200 ml of water.

Preparation of Phosphate buffer pH 6.8:

Measured and transferred 50 ml of 0.2 M potassium dihydrogen phosphate and 22.4 ml of 0.2 M sodium hydroxide in 200 ml of volumetric flask and volume made up to the mark with water.

RESULT AND DISCUSSION:

Reformulation study:

A. Drug Characterization:

Drug characterization parameters such as colour, odour and appearance were analysed for the procured drug samples and the results were shown in table 12

Table 12: Drug characterization parameters

Colour	**White**
Odour	**Odourless**
Appearance	**Fine powder**

B. Determination of melting point:

The melting point of Sitagliptin was found to be in the range of **214-218°C** which comply with reported melting point of Sitagliptin.

C. Solubility study:

The solubility study of Sitagliptin was carried out by using different solvent systems as per the literature. The solubility results were shown in table 13.

Table 13: Results for solubility study

Sr.no	Solvent	Observation
1.	Methanol	Soluble
2.	Phosphate buffer 6.8 pH	Soluble
3.	Water	Soluble

D. UV-visible spectrophotometric analysis:

The UV-visible spectrophotometric analysis was carried out by using Jasco Corporation, Japan V 550 Spectrophotometer and spectra manager software was used for analysis. Phosphate buffer 6.8 pH was used as solvent system for blank as well as sample preparation. 40 µg/ml of Sitagliptin was used and λ_{max} was found as 267 nm. The spectra for results were expressed in figure 1 and 2.

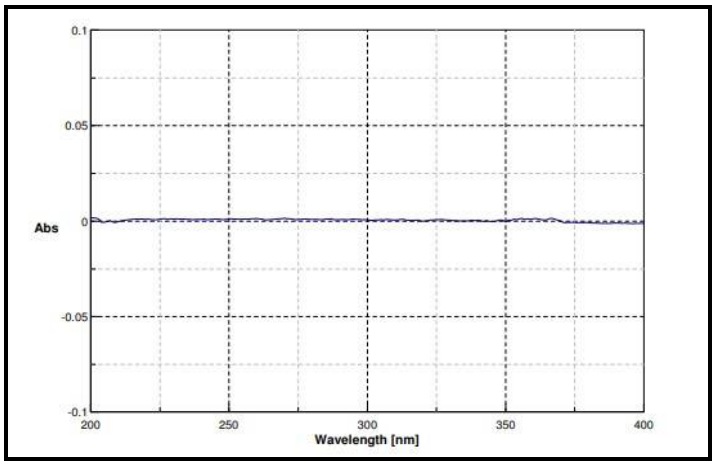

Figure 1: Blank in Phosphate buffer 6.8 pH

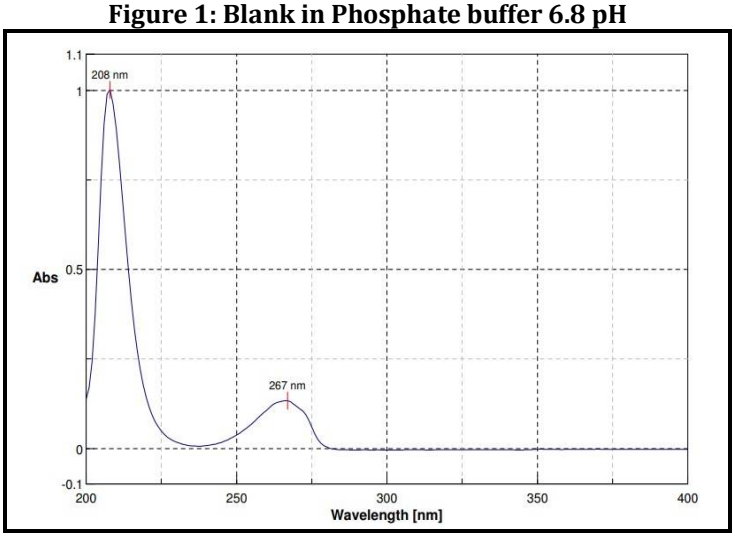

Figure 2: 40 PPM solution of Sitagliptin in Phosphate buffer 6.8 pH

Preparation of Calibration curve for Sitagliptin:

The calibration curve of Sitagliptin was drawn by measuring the absorbance of different concentrations in Phosphate buffer 6.8 pH at 267 nm. The calibration curve obtained was shown in table 14 and figure 3.

Table 14: Calibration curve for Sitagliptin

Sr.no.	Concentration (ppm)	Absorbance
1.	10	0.0431
2.	20	0.0772
3.	30	0.1059
4.	40	0.1317
5.	50	0.1775

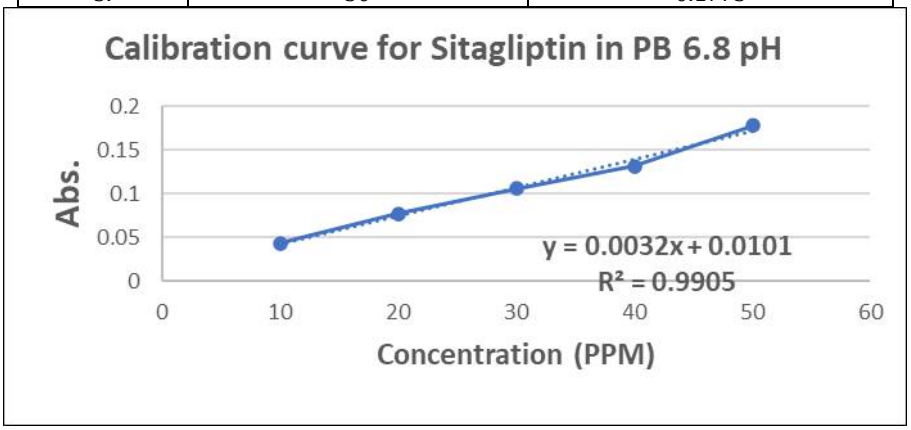

Figure 3: Calibration curve for Sitagliptin in phosphate buffer 6.8 pH

The calibration curves were linear and obeyed Beer-Lambert's law in the concentration range 10-50µg/ml. The correlation coefficient values were 0.9905 indicating excellent linearity of the data.

FT-IR of Sitagliptin:

The IR spectrum of Sitagliptin was recorded by using FTIR spectrometer. IR spectra was shown in figure 4. Characteristic functional groups were observed in FTIR spectrum as shown in table 4.

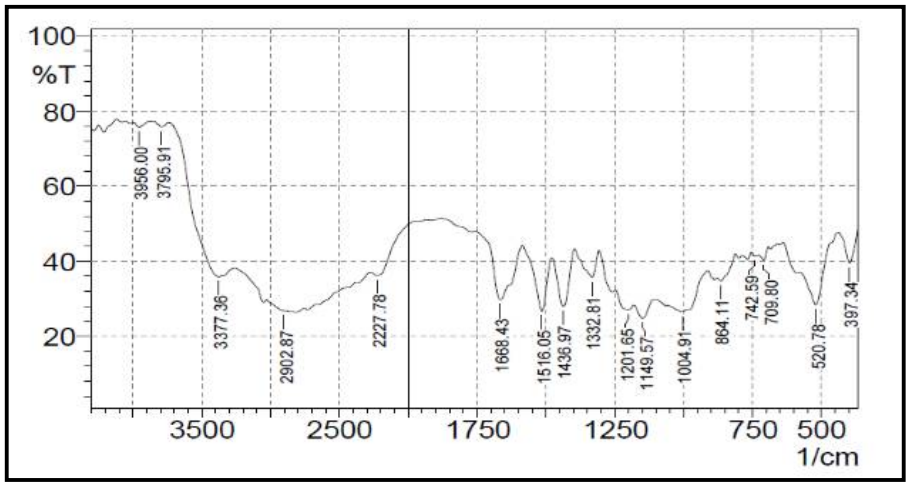

Figure 4: IR of Sitagliptin

Table 15: IR frequencies of Sitagliptin functional group

Functional group	Observed Frequency	Reported Frequency
N-H stretching (aliphatic primary amine)	3377.36	3400-3300
N-H stretching (amine salt)	2902.87	3000-2800
C = O stretching (conjugated ketone)	1668.43	1695-1666
C-N stretching (aromatic amine)	1332.81	1342-1266
C-H bending (Methyl group)	1436.97	1450
C-F stretching (fluoro compound)	1201.65, 1149.57, 1004.91	1400-1000

Drug excipient compatibility study:

The FTIR Spectra of Sitagliptin in pure form and their physical mixture was observed, the result showed that there was no interaction between drug, polymer and excipients. IR spectra for compatibility study were shown in figure 5, 6, 7, 8, 9, 10, 11 and their respective functional group detection data were shown in 5.

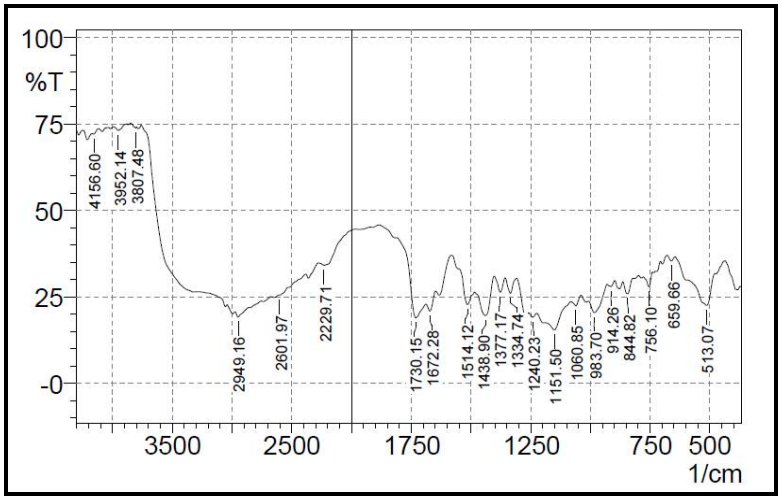

Figure 5: Compatibility IR for Sitagliptin: Cross povidone

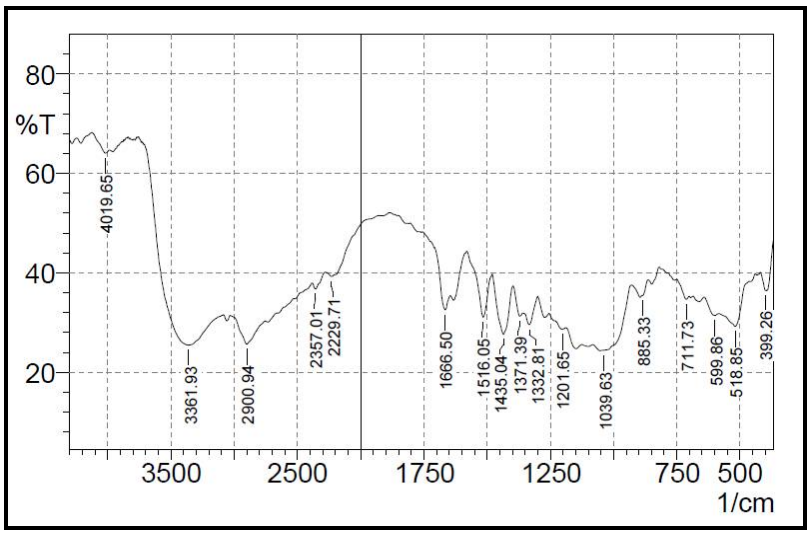

Figure 6: Compatibility IR for Sitagliptin: Avicel 102

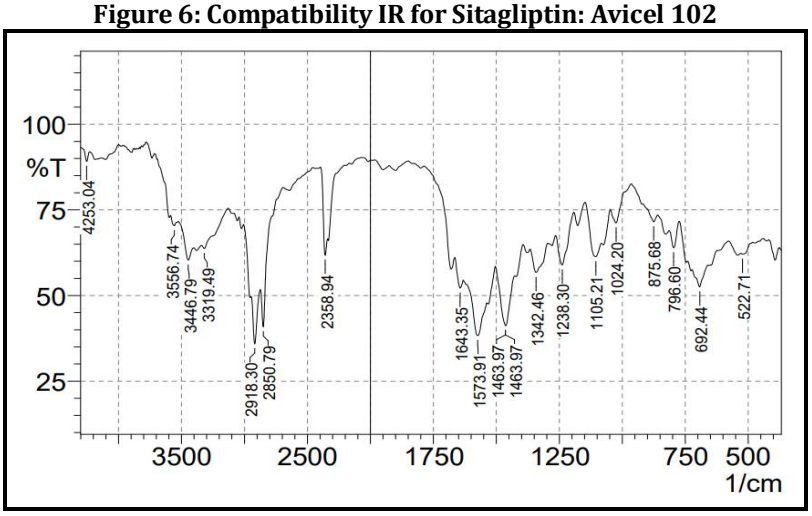

Figure 7: Compatibility IR for Sitagliptin: Mannitol

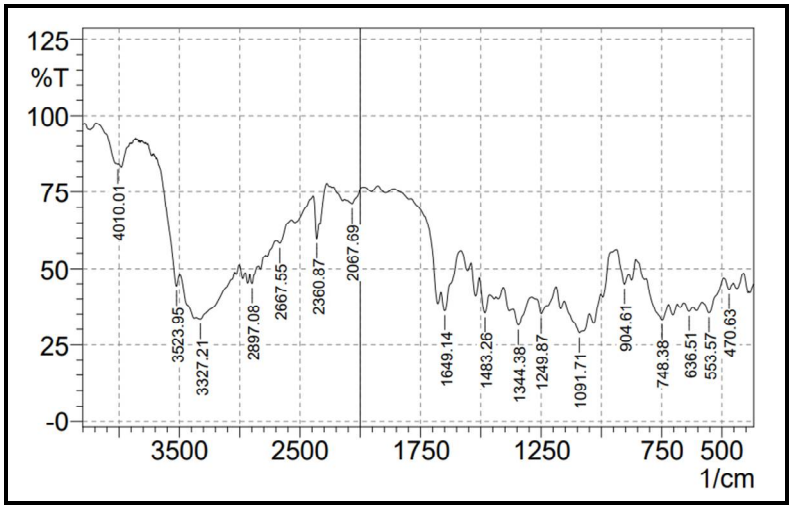

Figure 8: Compatibility IR for Sitagliptin: Aspartame

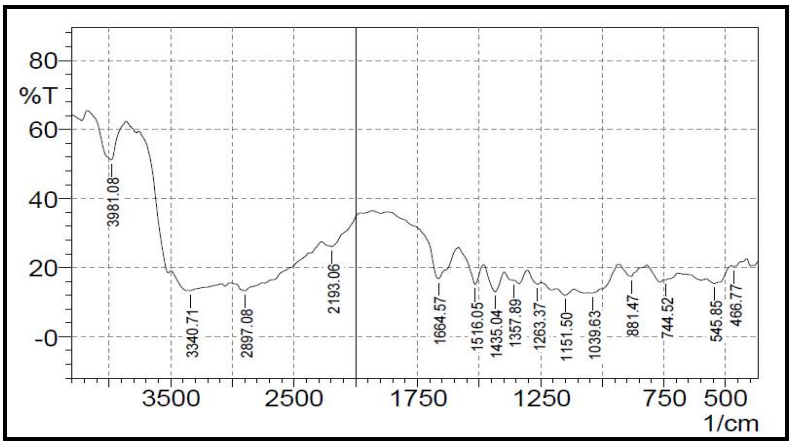

Figure 9: Compatibility IR for Sitagliptin: Lactose

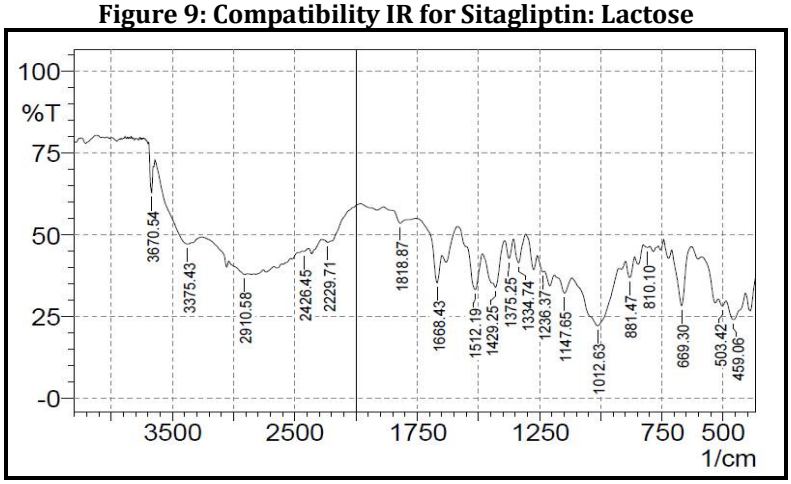

Figure 10: Compatibility IR for Sitagliptin: Talc

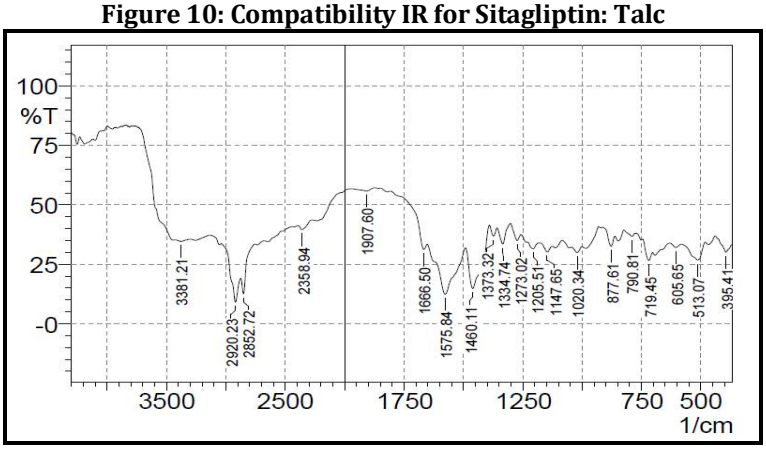

Figure 11: Compatibility IR for Sitagliptin: Magnesium stearate

Ingredient	Ratio	Initial	Condition
			40°C/75% RH (Accelerated)
			1 month
Sitagliptin	NA	White	NCC
Sitagliptin: Cross povidone	1:1	White	NCC
Sitagliptin: Avicel 102	1:1	White	NCC
Sitagliptin: Mannitol	1:1	White	NCC
Sitagliptin: Aspartame	1:1	White	NCC
Sitagliptin: Lactose	1:1	Off White	NCC
Sitagliptin: Talc	1:1	White	NCC
Sitagliptin: Magnesium stearate	1:1	White	NCC

Table 16: Drug excipient compatibility

Note- NCC (No conformational change) in physical appearance from initial description, RH (Relative Humidity).

It can be seen from the above data that Sitagliptin combination was stable with all the excipients used for formulation and development.

Formulation of Orodispersible tablet:

Table 17: Formulation ingredients and its roles

Sr.no.	Ingredients	Role
1.	Sitagliptin	Anti-diabetic
2.	Cross povidone	Super disintegrant
3.	Avicel 102	Direct compression binder, Flow property enhancer
4.	Mannitol	Sweetener, Cool taste and diluent property
5.	Aspartame	Artificial sweetener
6.	Lactose	Diluents
7.	Magnesium stearate	Lubricant
8.	Talc	Glidant

Formulation strategy:

Table 18: Formulation strategy

Sr.no.	Ingredients	Quantity (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Sitagliptin	100	100	100	100	100	100	100	100	100
2.	Cross povidone	12.5	12.5	12.5	18.75	18.75	18.75	25	25	25
3.	Avicel 102	37.5	43.75	50	37.5	43.75	50	37.5	43.75	50
4.	Mannitol	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
5.	Aspartame	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
6.	Lactose	45	38.75	32.5	38.75	32.5	26.25	32.5	26.25	20
7.	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8.	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight of tablet		250 mg.								

Evaluation of formulated batches:

A. Pre compression parameters:

The powder blend from all the batches were evaluated for density and flow property parameters which includes Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. The results were expressed as follows in table 8.

Table 19: Precompression parameters

Batches	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose
F1	0.62	0.711	12.80	1.15	28.34
F2	0.61	0.711	14.21	1.17	29.45
F3	0.608	0.721	15.67	1.19	29.98
F4	0.609	0.717	15.06	1.18	28.34
F5	0.597	0.708	15.68	1.19	28.15
F6	0.588	0.681	13.66	1.16	29.2
F7	0.599	0.687	12.81	1.15	31.24
F8	0.596	0.691	13.75	1.16	30.36
F9	0.606	0.701	13.55	1.16	29.74

Post compression parameters:

Physical appearance:

The tablets from all trial batches were White round convex shaped beveled edge with having plane upper and lower side.

Thickness and diameter:

The thickness and diameter for all the tablets were measured by using Vernier caliper by picking the tablets randomly. The mean values were shown in table 9. The values are almost uniform in all formulations. Thickness was found in the range from 4.50 ± 0.02 mm to 4.55 ± 0.05 mm respectively and diameter was found in the range of 8.80 – 8.85mm. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches.

Hardness:

Monsanto hardness tester was used for the determination of hardness for all the batches and results were expressed in table 9. Hardness was found to be in range of 4 kg/cm^2 to 5.5 kg/cm^2. The hardness for all formulated batches were uniform and possess good mechanical strength with sufficient hardness.

Friability:
Tablets from all batches were evaluated by using Roche Friabilator and Friability of tablets was observed in acceptable range 0.23 to 0.62 (Less than 1%). The result was given in table 9.

Batches	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Friability (%)
F1	4.50±0.01	8.80±0.01	4	0.37
F2	4.53±0.05	8.84±0.03	4.5	0.32
F3	4.53±0.05	8.85±0.02	5	0.57
F4	4.54±0.02	8.80±0.02	4.5	0.39
F5	4.55±0.01	8.82±0.02	4.5	0.23
F6	4.55±0.05	8.85±0.02	5	0.37
F7	4.50±0.05	8.83±0.02	4.5	0.52
F8	4.52±0.02	8.84±0.02	5	0.49
F9	4.52±0.01	8.83±0.02	5.5	0.62

Table 20: Post compression parameters

Drug content:
Drug content uniformity test was performed for all formulated batches and results were expressed in table 10. The drug content was found to be between 98- 102 % which was under specified limit.

Table 21: Drug content

Batches	Drug content
F1	100.41
F2	98.07
F3	99.70
F4	99.85
F5	101.51
F6	101.14
F7	100.36
F8	100.27
F9	100.31

Weight Variation:
Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniforms weight due to uniform die fill. The tablets for all prepared batches were obtained in the range with acceptable weight variations as per pharmacopoeia specifications less than 5%. The results were given in table 11.

Table 22: Weight variation results

Batches	Weight variation	
	Weight (mg) ± S. D	Weight variation (5%)
F1	240 ± 8	Passes
F2	245 ± 4	Passes
F3	244 ± 6	Passes
F4	245 ± 2	Passes
F5	255 ± 5	Passes
F6	250 ± 7	Passes
F7	258 ± 3	Passes
F8	252 ± 6	Passes
F9	249 ± 5	Passes

Disintegration test:
Disintegration time was performed for all formulated batches and results were expressed in table 12. The disintegration time was found in the range of 40 – 65 sec. Disintegration time was inversely proportional to concentration of super disintegrating agent and directly proportional with binder concentration.

Table 23: Disintegration time results

Batches	Disintegration time (Sec)
F1	55 ± 2
F2	58 ± 4
F3	65 ± 3
F4	45 ± 4
F5	53 ± 3
F6	57 ± 2
F7	40 ± 2
F8	43 ± 4
F9	45 ± 3

In vitro dissolution test:

The in vitro evaluation of all the formulated batches were carried out for 30 mins by using Phosphate buffer 6.8 pH as dissolution medium and % CDR was determined by using its respective equation of line. The results were expressed in table 13 and figure 12.

Table 24: In vitro dissolution

Time (min)	Batches	% Cumulative Drug Release (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
5		20.77	17.00	17.88	23.91	23.87	19.58	25.87	23.89	21.67
10		40.21	35.31	35.12	39.01	40.88	38.5	44.01	43.43	41.43
15		59.63	55.47	53.64	62.43	55.4	51.02	64.64	61.5	61.21
20		80.18	76.72	70.75	80.65	75.99	74.98	80.09	79.46	76.66
25		91.45	89.16	85.95	90.96	88.08	86.59	89.05	87.95	84.76
30		96.67	96.22	95.71	97.49	97.58	97.00	99.44	99.17	98.48

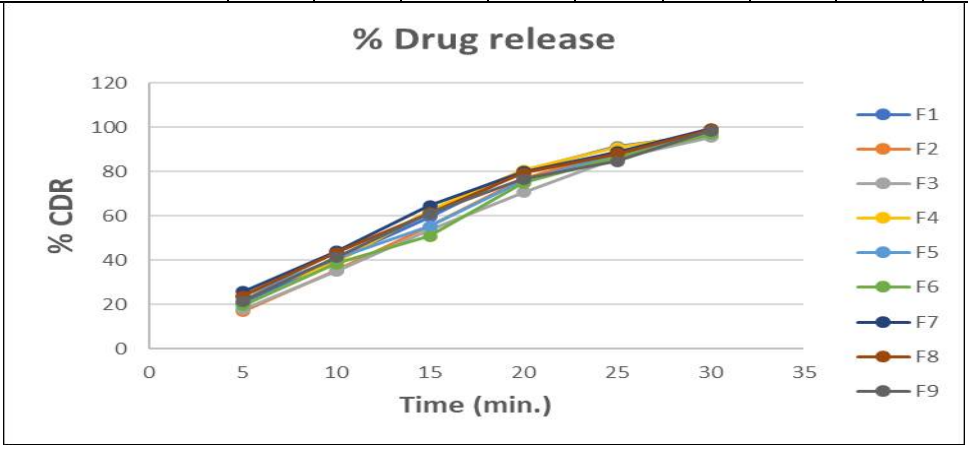

Figure 12: In vitro dissolution

Optimization of Orodispersible tablet:

To study the effect of independent variables on responses Design Expert 7.0 software was used. Experimental design layout developed for 9 possible batches of Sitagliptin orodispersible tablet as shown in table 14. Out of the various models such as Linear, 2FI, Quadratic and Cubic which fit well was suggested by software and was tested for analysis of variance (ANOVA). Regression polynomials were calculated for the individual dependent variables and then one factor and perturbation graphs were obtained for each individual dependent variable. Mathematical models were generated for each individual dependent variable or response (R) and expressed as equation 1-2. X_1 and X_2 are the main effects which represent the average result of changing one factor at a time from its low to high value and X_1 X_2 are interaction terms show how the response changes when two factors are simultaneously changed.

Table 25: The layout of the Actual Design

Runs	Factor1	Factor 2	Response 1	Response 2
	A: % Cross povidone	B: % Avicel 102	Disintegration time (sec)	Hardness (kg/cm²)
1	7.5	15	45	4.5
2	10	15	40	4.5
3	10	20	45	5.5
4	10	17.5	43	5
5	5	17.5	58	4.5
6	5	20	65	5
7	7.5	17.5	53	4.5
8	7.5	20	57	5
9	5	15	55	4

Results for the Disintegration time of DOE:

Fit Summary: After entering the data in Design-Expert software, fit summary applied to the data after which the " Linear vs Mean " was suggested by the software.

Table 26: Fit summary table for Disintegration time of DOE

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Mean vs Total	23613.44	1	23613.44			
Linear vs Mean	538.1667	2	269.0833	83.26934	< 0.0001	Suggested
2FI vs Linear	6.25	1	6.25	2.378436	0.1837	
Quadratic vs 2FI	0.944444	2	0.472222	0.116173	0.8941	
Cubic vs Quadratic	8.833333	2	4.416667	1.31405	0.5250	Aliased
Residual	3.361111	1	3.361111			
Total	24171	9	2685.667			

ANOVA for Disintegration time:

The analysis of variance (ANOVA) was performed to identify significant and insignificant factors. The results of ANOVA for the disintegration time are as following table 16.

Table 27: ANOVA table for a disintegration time

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	538.17	2	269.08	83.26934	< 0.0001	significant
A-Cross povidone	416.67	1	416.67	128.94	< 0.0001	
B-Avicel 102	121.50	1	121.50	37.60	0.0009	
Residual	19.39	6	3.23			
Cor Total	557.56	8				

The Model F-value of 83.27 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case A and B are significant model terms.

Fit Statistics for disintegration time

Table 28: Fit statistics for disintegration time

Std. Dev.	1.80	R-Squared	0.9652
Mean	48.22	Adj R-Squared	0.9536
C.V. %	3.73	Pred R-Squared	0.9152
PRESS	47.28	Adeq Precision	24.730

The “Pred R-Squared” of 0.9152 is in reasonable agreement with the “Adj R-Squared” of 0.9536. “Adeq Precision” measures the signal to noise ratio. A ratio greater than 4 is desirable. ratio of 24.730 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of coded Factors for disintegration time:

Table 29: Final equation in terms of coded factors

Disintegration time	=
+51.22	
-8.33	* A
+4.50	* B

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor.

Graphical Presentation: Diagnostics of disintegration time

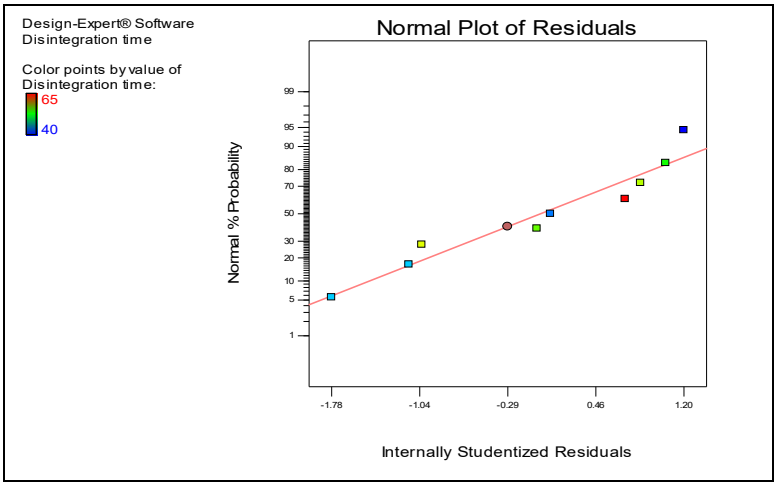

Figure 13: Normal % Probability for DOE of disintegration time

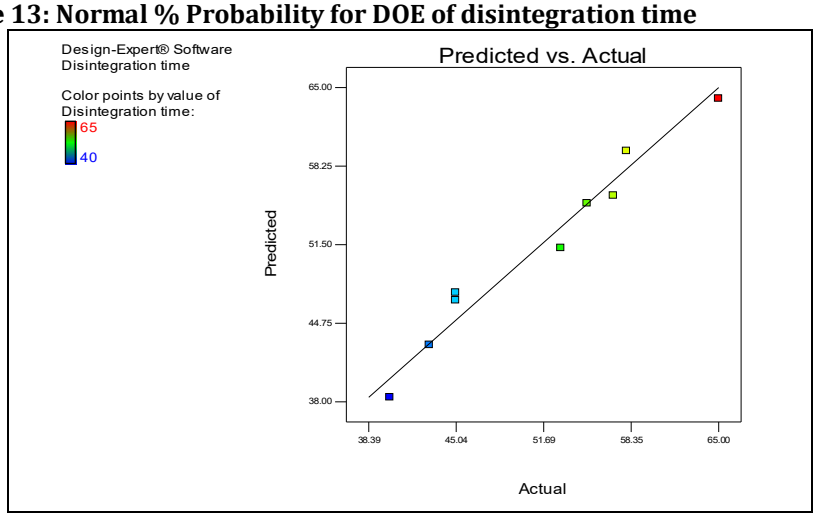

Figure 14: Predicted Vs Actual for DOE of disintegration time

Model Graphs of disintegration time: One-factor Graphs of disintegration time:

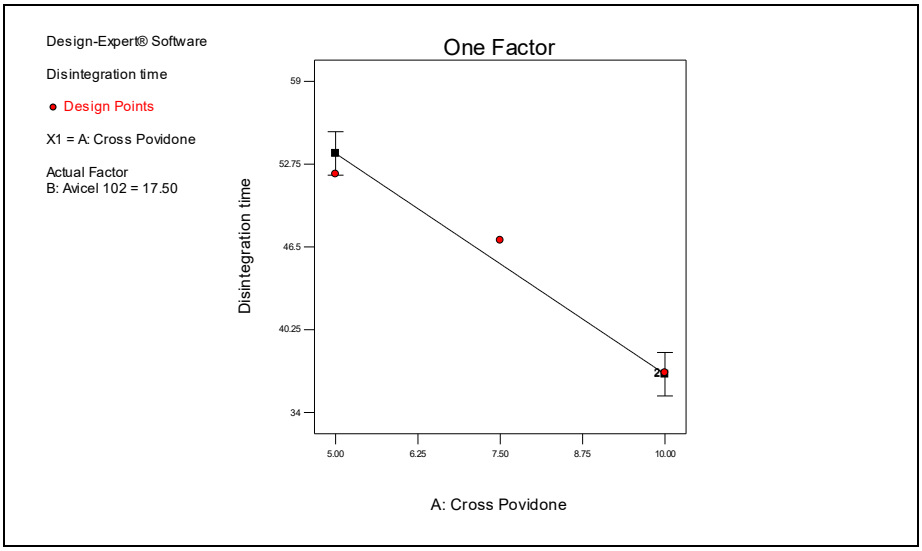

Figure 15: Effect of % Cross povidone on disintegration time

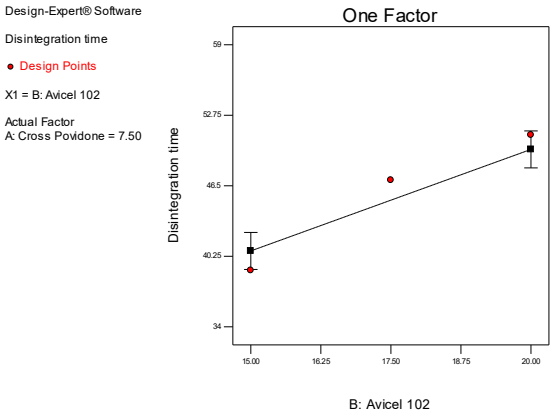

Figure 16: Effect of % Avicel 102 on disintegration time

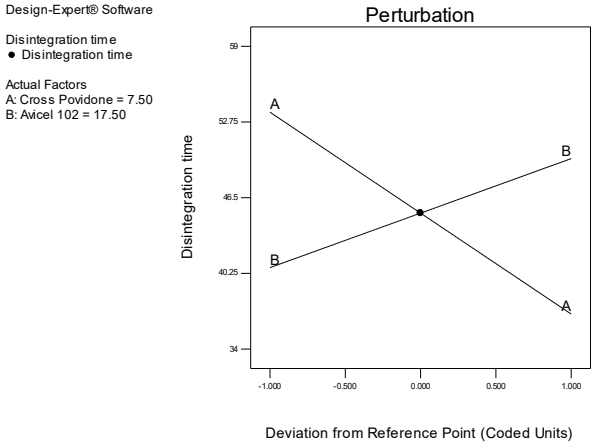

Figure 17: Effect of All 2 factors on disintegration time

Conclusion: Percentage of Cross povidone and Avicel 102 in formulation having impact on disintegration time of drug. As % Cross povidone increases disintegration time decreases. As % Avicel 102 increases in formulation disintegration time also increases.

Cross povidone is having high impact on disintegration time as compare to Avicel 102 as its P value is very low as compare to Avicel 102.

Results for the Hardness:

Fit Summary: After entering the data in Design-Expert software, fit summary applied to the data after which the "Linear vs Mean" was suggested by the software.

Table 30: Fit summary table for Hardness

Source	Sum of Squares	df	Square Mean	F Value	p-value Prob > F	
Mean vs Total	200.69	1	200.69			
Linear vs Mean	1.42	2	0.71	30.60	0.0007	Suggested
2FI vs Linear	0.00	1	0.00	0.00	1.0000	
Quadratic vs 2FI	0.03	2	0.01	0.38	0.7155	
Cubic vs Quadratic	0.08	2	0.04	1.50	0.5000	Aliased
Residual	0.03	1	0.03			
Total	202.25	9	22.47			

ANOVA for Hardness:

The analysis of variance (ANOVA) was performed to identify significant and insignificant factors. The results of ANOVA for the hardness factor are as following table 20.

Table 31: ANOVA table for hardness

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	1.42	2	0.71	30.6	0.0007	significant
A-Cross povidone	0.38	1	0.38	16.20	0.0069	
B-Avicel 102	1.04	1	1.04	45.00	0.0005	
Residual	0.14	6	0.02			
Cor Total	1.56	8				

The Model F-value of 30.60 implies the model is significant. There is only a 0.07% chance that a "Model F-Value" this large could occur due to noise.
Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A and B are significant model terms.

Fit Statistics for hardness

Table 32: Fit statistics for hardness

Std. Dev.	0.15	R-Squared	0.9107
Mean	4.72	Adj R-Squared	0.8810
C.V. %	3.22	Pred R-Squared	0.8233
PRESS	0.27	Adeq Precision	15.179

The “Pred R-Squared” of 0.8233 is in reasonable agreement with the “Adj R-Squared” of 0.0.8810 “Adeq Precision” measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 15.179 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors of hardness:

Table 33: Final equation in terms of coded factor of hardness

Hardness	=
+4.72	
+0.25	* A
+0.42	* B

Graphical Presentation: Diagnostics of hardness:

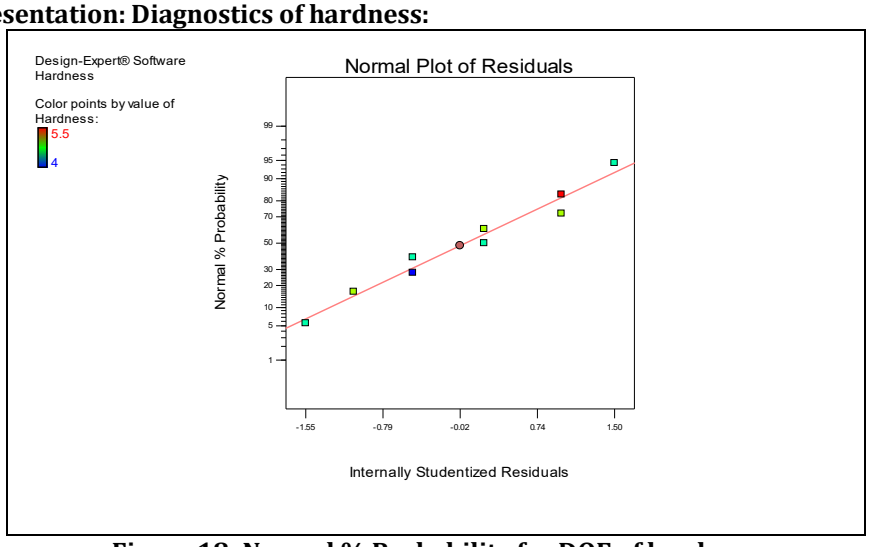

Figure 18: Normal % Probability for DOE of hardness

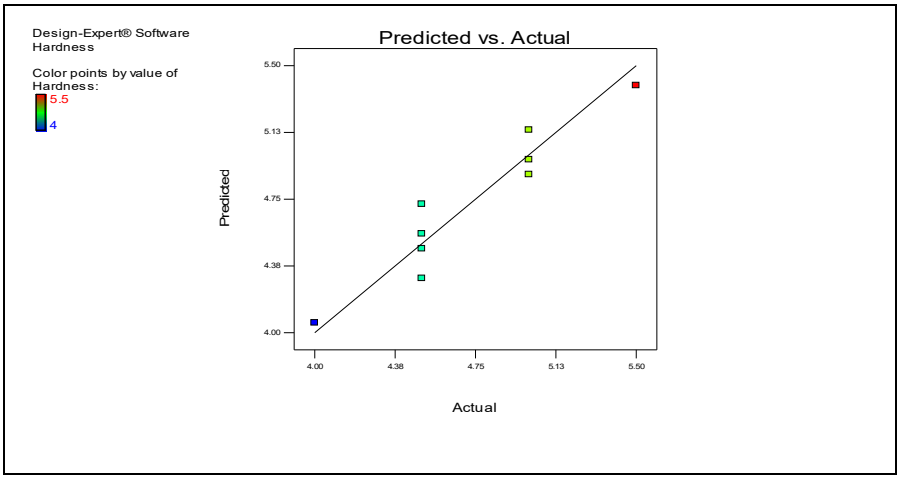

Figure 19: Predicted Vs Actual of hardness

Model Graphs of hardness: One-factor Graphs of hardness

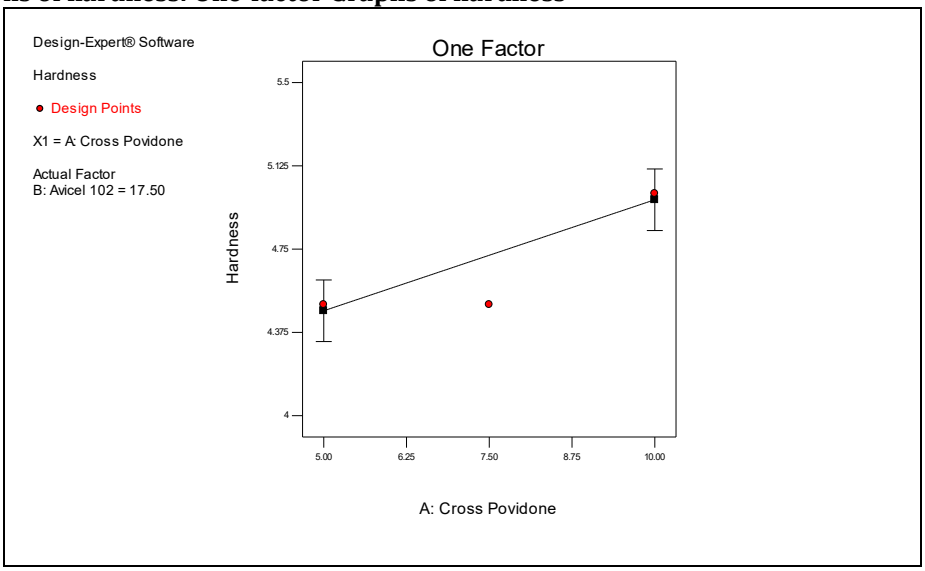

Figure 20: Effect of % Cross Povidone on hardness

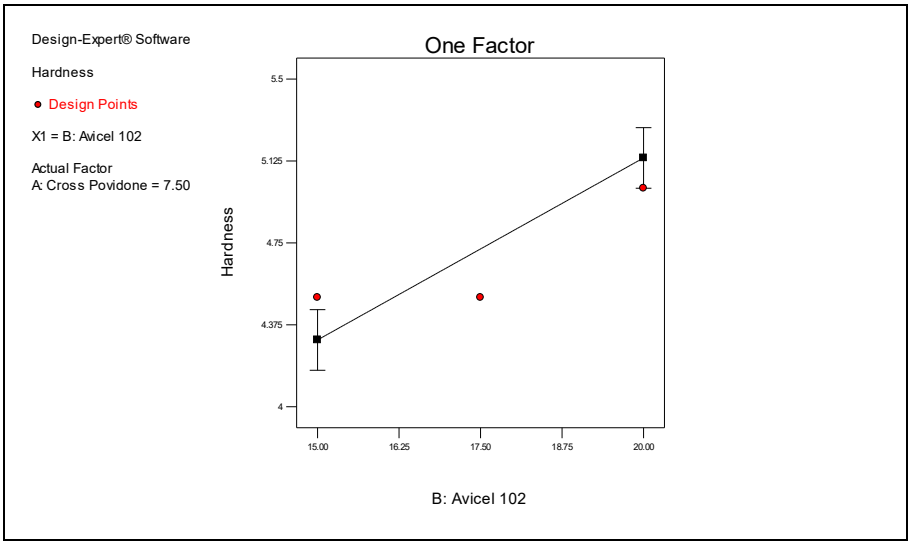

Figure 21: Effect of % Avicel 102 on hardness

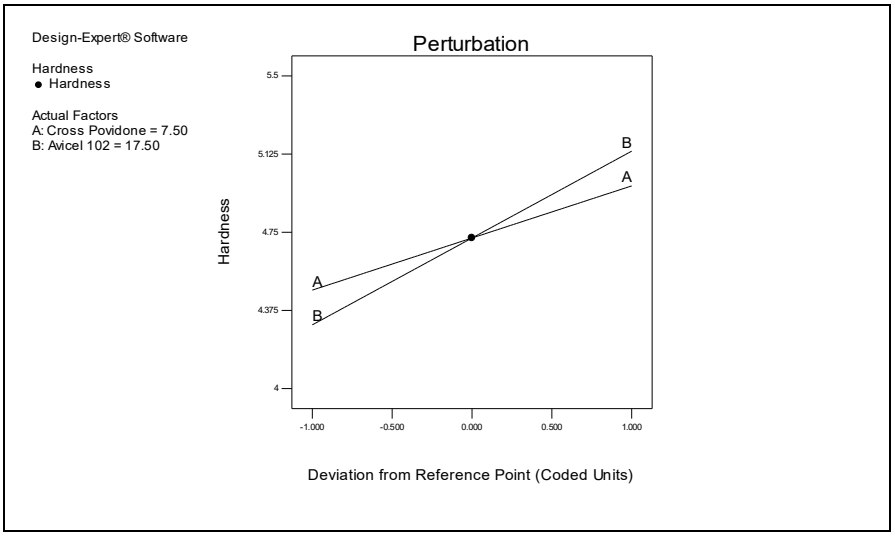

Figure 22: Effect of All 2 independent parameters on hardness

Conclusion: Percentage of Cross povidone and Avicel 102 in formulation having impact on hardness. As % Cross povidone increases hardness increases. As % Avicel 102 increases in formulation hardness also increases.

Avicel 102 is having high impact on hardness as compare to Cross povidone as its P value is very low as compare to Cross povidone.

Table 34: Summary of effect of independent variable on dependent variables

Sr. No.	Independent variables	Disintegration time	Hardness
1	% Cross povidone in formulation	Inversely proportional (As Cross povidone increases, disintegration time decreases)	Directly proportional (As Cross povidone increases, hardness also increases)
2	% Avicel 102 in formulation	Directly proportional (As Avicel 102 increases, disintegration time increases)	Directly proportional (As Avicel 102 increases, hardness also increases)

Evaluation of optimized batch (F7):

Table 35: Evaluation of optimized batch (F7)

Sr.no.	Evaluation parameter	Results
1.	Thickness	4.5 mm
2.	Diameter	8.8 mm
3.	Hardness	4.5 kg/cm^2
4.	Friability	0.52 %
5.	Drug content	99.73 %
6.	Disintegration time	40 sec
7.	Weight variation test	Passed
8.	In vitro dissolution (%CDR)	99.18 %

CONCLUSION

On the basis of data obtained from pre compression and post compression evaluation of batches as well as factorial design model study F7 batch was selected as optimized batch.

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