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FORMULATION AND EVALUATION OF SITAGLIPTIN ORAL DISINTEGRATION TABLETS USING SYNTHETIC SUPER DISINTEGRANTS

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ABSTRACT

The goal of this research is to prepare oral disintegration tablets of Sitagliptin utilising Synthetic Superdisintegrants. By utilising a direct compression approach, oral disintegrating tablets of Sitagliptin were prepared using various ratios of synthetic super disintegrates. The goal of this study was to create and optimise oral disintegrating tablets of Sitagliptin utilising synthetic superdisintegrants to provide a speedy start of action by quickly dissolving in a few seconds without the need for water and to improve patient compliance. In such cases, drug bioavailability is substantially higher and adverse events are significantly lower than in standard tablet dose form. By using IR spectroscopy, drug-excipient compatibility experiments were done, there was no drug-excipient interaction. The 9 formulations of Sitagliptin were prepared varying the concentrations of three super disintegrants: croscarmellose sodium, sodium starch glycollate, and starch 1500. As an immediately compressible vehicle, microcrystalline cellulose was employed. Overall, the results showed that the formulation containing croscarmellose sodium, i.e. CCS3, had a significant advantage over other formulations including the superdisintegrants.

KEYWORDS: Microcrystallinecellulose, oral disintegrating tablets, superdisintegrants.

INTRODUCTION

Many people find it difficult to swallow tablets and firm gelatin capsules. As a result, they do not follow the prescription, resulting in a high rate of non-compliance and unsuccessful therapy.

Swallowing conventional tablets may be problematic in several situations, such as motion nausea, sudden episodes of allergy reactions or coughing, and a lack of water. Pediatric and geriatric patients, in particular, have difficulties. Such issues can be remedied with the use of oral disintegration tablets. When placed on the tongue, this tablet instantly disintegrates, releasing the medication, which dissolves or disperses in the saliva.

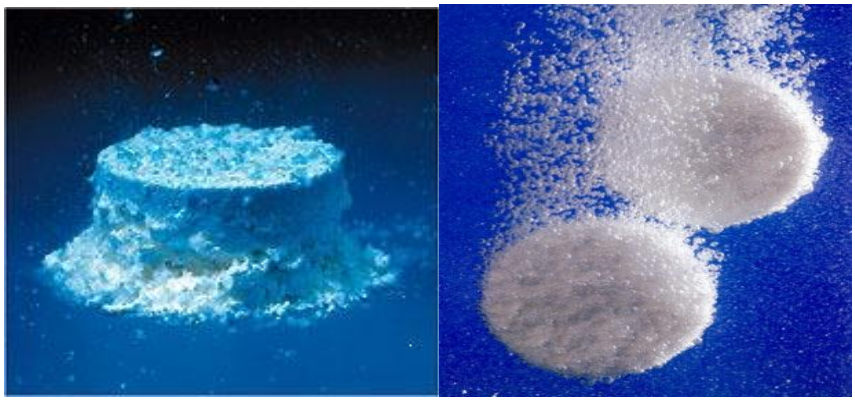

Fig. 1: Oral disintegrating tablets.

Diabetes mellitus is a metabolic disorder characterised by a relative or total absence of insulin. It is a chronic illness marked by a symptomatic rise in blood glucose concentration (hyperglycemia) as well as changes in lipid and protein metabolism. Chronic metabolic abnormalities, particularly hyperglycemia, lead to the

development of problems such as nephropathy, neuropathy, retinopathy, and cardiovascular issues. used when the oral anti-diabetic medications fail to maintain glycemic control.

The aim of the present research work is formulate the oral disintegration tablets of Sitagliptin, an antidiabetic drug, by using the Synthetic Superdisintegrants.

The objectives of the research work undertaken are as follows:

- To formulate oral disintegrating tablets of Sitagliptin using different ratios of syntheticsuper disintegrates by direct compression technique.
- To evaluate the drug content and to perform in-vitro drug release study.
- To study the physical characteristics of the individual drug by FTIR spectroscopy and the optimized formulation by FTIR spectroscopy.

METHDOLOGY

Table no 1: List of Materials.

Table No. 1: Materials Employed in the Project		
S.no	**Materials**	**Functional Category**
1	Sitagliptin	API
2	Cross carmellose sodium	Super-disintegrant
3	Sodium starch glycolate	Disintegrant
4	Starch 1500	Disintegrant /Lubricant
5	Mannitol	Diluenrt
6	Microcrystalline cellulose	Binder
7	Sodium saccharine	Sweetening agent
8	Magnesium stearate	Lubricant
9	Talc	Glidant / Lubricant

EXPERIMENTAL METHODOLOGY

Estimation of Sitagliptin Phosphate

An UV Spectrophotometric method based on the measurement of absorbance at 266nm in pH 6.8 Phosphate buffer was used in the estimation of Sitagliptin.

Preparation of standard solution

Sitagliptin (100 mg) was dissolved in about 10ml of pH 6.8 buffer and the volume was finally made up to 100ml using pH 6.8 Phosphate buffer in a 100 ml volumetric flask.

Procedure

A calibration curve for Sitagliptin estimation was studied using a pH 6.8 Phosphate buffer. The standard Sitagliptin solution was then diluted with pH 6.8 Phosphate buffer to produce a series of dilutions comprising 2, 4, 6, 8, and 10 g of Sitagliptin per ml of solution. The absorbance of the above dilutions was measured on a spectrophotometer at 266 nm with a blank of pH 6.8 phosphate buffer. The table shows the concentration of Sitagliptin utilised and the associated absorbance. As indicated in the figure, absorbances were plotted versus concentration. In the current investigation, this calibration curve was utilised to estimate Sitagliptin.

Method of manufacture of Oral Disintegrating tablets of Sitagliptin

Preparation of Mixed blends of drug and excipients: All the ingredients were weighed as specified in the formulation and mixed well except magnesium stearate. Then the blend was passed through sieve no 90 which was used for the evaluation of flow properties.

Table no 2: Formulation of oral disintegrating tablets of Sitagliptin.

Ingredients (mg per tablets)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sitagliptin	100	100	100	100	100	100	100	100	100
MCC	40	40	40	40	40	40	40	40	40
Mannitol	90	87	85	90	87	85	90	87	85
Sodium Starch Glycolate	13.5	16.5	18.5	_	_	_	_	_	_
Cross Carmellose sodium	_	_	_	13.5	16.5	18.5	_	_	_
Starch 1500	_	_	_	_	_	_	13.5	16.5	18.5
Sodium Saccharin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2

Evaluation of Precompression and Post Compression Parameters

1. Bulk density: Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder was determined.

Bulk density = Weight of powder / Bulk volume

2. Tapped density: The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus-11. The minimum volume occupied by the powder after tapping was measured.

Tapped density = weight of powder/tapped volume

3. Compressibility index: Compressibility index is calculated as follows

Tapped density- Bulk density/ Tapped density*100

The value below 15% indicates a powder with good flow characteristics where as above 25% indicates poor flowability.

4. Haussner's ratio: It is an indirect index of ease of powder flow, it is calculated as follows.

Tapped density/Bulk density

Haussner's ratio <1.25 indicates good flow properties, where as >1.5 indicates poor flowability.

Table no 3: Scale of Flow ability.

Compressibility index (%)	Flow character	Hausner Ratio
≤10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
>38	Very, very poor	>1.60

5. Angle of Repose: Angle of repose was determined using funnel method. The blend was poured through funnel that can rise vertically until a maximum cone height (h) was obtained. Radius of the heap(r) was measured and angle of repose was calculated as follows.

Ø= $\tan^{-1}$ h/r $\tan^{-1}$ h/r

Table no 4: Flow Properties and Corresponding Angle of Repose.

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

Evaluation of Post Compression Parameters

All the prepared tablets were evaluated for the following parameters as per the I.P guidelines.

Weight variation: Twenty tablets from each formulation were selected randomly and average weight was determined. Individual tablets were then weighed and compared with average weight.

Hardness test: The force required to break a tablet in a diametric compression was determined by using Pfizer tablet hardness tester.

Friability: The weight of twenty tablets was noted and placed in the friabilator and then subjected to100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed.

Percent friability = [initial weight – final weight / initial weight] × 100

Wetting time and Water absorption ratio: A piece of paper folded twice was kept in a petri dish (internal diameter 6cms) containing6ml of purified water. A tablet was put on the paper and time required for complete wettingwas measured. The wetted tablet was weighed. Water absorption ratio, R was determinedusing the following equation.

R = [Wa – Wb / Wb] × 100

Where Wa, Wb are the weights of tablets before and after wetting.

***Invitro* dispersion time:** Tablet was added to 10ml of distilled water at 37± 0.5˚C, time required for complete dispersion of tablet was measured.

Drug content uniformity: The drug content uniformity was determined by taking the powder equivalent to 10mg, thenit was (n=3) dissolved in pH6.8 phosphate. Required dilution (10µg/ml) was prepared andabsorbance was taken against the blank at 266nm.

In vitro disintegration time: The disintegration was performed using an I.P 85 disintegration apparatus with distilled water at 37±0.5 ˚C.6.8.

Dissolution studies: The LABINDIA DISSO 2000, an eight-stage dissolution rate testing device with paddle, was used to determine the dissolving rate of Sitagliptin from all formulations. Each test utilised 900 ml of PH 6.8 phosphate buffer at a speed of 50 rpm and a temperature of 370.5 C as the dissolving fluid. To maintain sink conditions, 5 ml of sample was removed at varied time intervals (2.5, 5, 10, 15, 20, and 25 minutes) and fresh medium was replaced. The samples are examined using a UV- Visible spectrophotometer at a maximum wavelength of 266 nm. Dissolution tests were carried out in triplicate.

Characterization of Sitagliptin tablets

FTIR studies

The FTIR was used to investigate the drug-excipient interaction. The KBr pellet method was used to record IR spectra for medication and powdered tablets in a Fourier transform infrared spectrophotometer. This spectrum was scanned between 3600 and 500 cm-1 range.

Stability Studies

The formulations' stability was studied according to ICH guidelines for one month at 40.2 degrees centigrade /75 % RH by storing the samples in a stability chamber (Lab-care, Mumbai).

RESULTS AND DISCUSSION

A. Organoleptic evaluation

Organoleptic properties such as colour, odour, and drug solubility were examined and reported in Table No. 7. The outcomes are acceptable. The medication is soluble in both methanol and water.

Table 5: Organoleptic properties of Sitagliptin.

Organoleptic Property	Observation
Colour	White
Odour	Odourless
Solubility	Water and Methanol

B. Analytical evaluation

The maximum absorbance of Sitagliptin in pH 6.8 phosphate buffer was determined to be 266 nm. Sitagliptin standard graph in pH 6.8 phosphate was drawn with concentrations ranging from 2 to 10 g/mL and a strong correlation with R2 value of 0.999 was found. A UV spectrophotometer was used to detect absorbance at 266 nm (Lab India). Table.no.8 displays the standard calibration curve values. A graph between absorbance on the y-axis and concentration on the x-axis yields a straight line that connects the minimum of three points, as shown in fig.no.4.

Table 6: Results of Standard curve data in pH 6.8 by UV spectrophotometric method.

Concentration	Absorbance
0.2	0.041
0.4	0.119
0.6	0.206
0.8	0.295
1	0.381
1.2	0.456

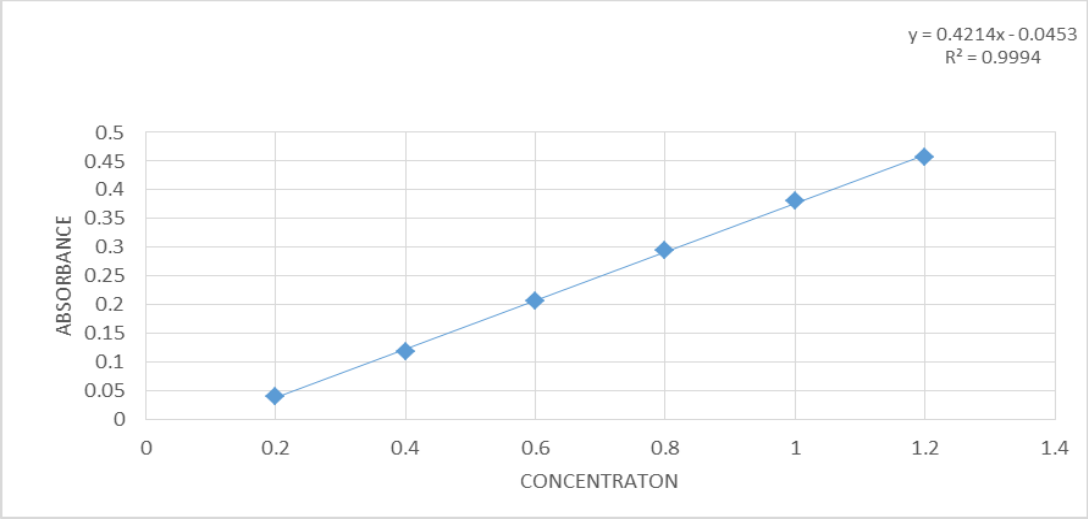

Fig. 2: Calibration Curve of Sitagliptin in pH 6.8 Phosphate Buffer.

EVALUATION OF PRE-COMPRESSION PARAMETERS

Table 7: Results of pre-compression studies of Sitagliptin.

Formulations	Bulk Density gm/cm^2	Tapped Density gm/cm^2	Angle of Repose (θ)	Carr's Index (%)	Hausner Ratio
F1	0.593±0.20	0.735±0.48	33.16±0.22	19.13	1.23
F2	0.491±0.43	0.612±0.03	32.14±0.62	19.60	1.24
F3	0.475±0.28	0.538±0.42	29.02±0.37	11.71	1.13
F4	0.490±0.16	0.592±0.69	36.15±0.33	17.22	1.20
F5	0.492±0.05	0.549±0.03	31.89±0.15	10.38	1.11
F6	0.511±0.16	0.638±0.06	35.98±0.13	19.90	1.24
F7	0.512±0.22	0.621±0.53	36.24±0.12	17.55	1.21
F8	0.523±0.82	0.642±0.12	30.19±0.43	18.53	1.22
F9	0.497±0.32	0.561±0.03	34.12±0.11	11.40	1.12

*All the values are expressed as mean ± S.D, where n=3.

Discussion: Indicates good flow and compressibility of all the blends. The angle of repose values was in the range of 29.02° to 36.24°, CI in the range of 11.40 to 19.90 % and HR in the range of 1.11 to 1.24 (Table 9).

Table 8: Results of post-compression studies of Sitagliptin.

Formulations	Avg.Tab.Wt. mg	Thickness (mm±SD)	Hardness (kP±SD)	Friability %
F1	249±0.72	2.46±0.05	5.21±0.75	0.85
F2	250±0.36	2.59±0.15	5.27±0.19	0.47
F3	251±0.73	2.81±0.08	5.21±0.25	0.82
F4	252±0.15	2.54±0.48	5.21±0.83	0.45
F5	249±0.24	2.87±0.25	4.97±0.25	0.84
F6	259±0.13	2.62±0.75	5.35±0.05	0.13
F7	249±0.42	2.62±0.75	5.72±0.24	0.35
F8	252±0.84	2.62±0.75	4.99±0.59	0.21
F9	499±0.28	2.62±0.75	5.01±0.13	0.77

*All the values are expressed as mean ± SD, where n=3 except for Avg. Wt. determination where n=20.
#Test for friability was performed for once on 10 tablets from each batch.

Discussion

Post-compression studies: They passed the % wt. variation test as per IP. The thickness of tablets was found to be between 2.46 to 2.87 mm. The hardness (4.97 to 5.72 kg/cm^2) and % friability (NMT 1.0%) are satisfactory for all the batches., they passed the content uniformity test as per IP (Table 9.1).

Table 9: Post-compression parameters of Sitagliptin tablets.

Formulation	Disintegration time (s±SD)	Wetting time (s±SD)	Dispersion time (s±SD)
F1	32±0.57	13±0.05	57±0.82
F2	28±0.19	10±0.11	32±0.15
F3	34±0.59	13±0.31	54±0.21
F4	39±0.37	12±0.06	72±0.06
F5	44±0.15	12±0.03	67±0.23
F6	46±0.05	15±0.76	58±0.32
F7	52±0.24	13±0.82	62±0.38
F8	45±0.12	12±0.13	54±0.82
F9	33±0.77	12±0.72	59±0.32

*All the values are expressed as mean ± SD, where n=3.

The samples were analyzed at intervals of 0, 2.5, 5, 10, 15, 20 and 25 mins. There were no significant change in the physical appearance of the tablets, disintegration time and wetting time.

Table 10: Dissolution data of the oral disintegrating tablets of Sitagliptin F1 to F5.

Time (min)	% Cumulative Drug Dissolved (% CDD)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2.5	24.64±0.16	38.40±0.25	29.80±0.14	35.13±1.23	32.41±0.26
5	43.23±2.35	41.82±0.12	43.20±2.51	52.21±0.19	50.42±0.84
10	56.88±0.42	55.86±0.29	52.21±0.28	64.25±0.25	66.61±0.23
15	64.09±0.29	72.17±0.33	65.53±0.32	77.32±0.13	72.12±0.74
20	72.61±0.23	88.34±0.89	72.73±0.25	84.17±0.29	81.26±0.73
25	83.21±0.19	102.43±0.42	80.65± 0.82	106.22±0.32	92.06±0.25

Table 10.1: Dissolution data of the oral disintegrating tablets of Sitagliptin F6 to F9.

T (min)	% Cumulative Drug Dissolved (% CDD)			
	F6	F7	F8	F9
0	0	0	0	0
2.5	39.04±0.32	29.14±0.18	42.17±2.49	32.46±0.27
5	52.25±0.29	42.48±2.27	56.35±0.28	56.32±0.28
10	64.56±0.28	54.26±0.23	62.53±0.23	63.52±0.33
15	79.41±0.17	64.82±0.32	72.14±0.25	77.23±0.24
20	92.13±0.26	74.13±0.52	82.19±0.32	81.20±0.69
25	101.06±0.28	81.26±0.62	90.23±0.24	84.04±0.31

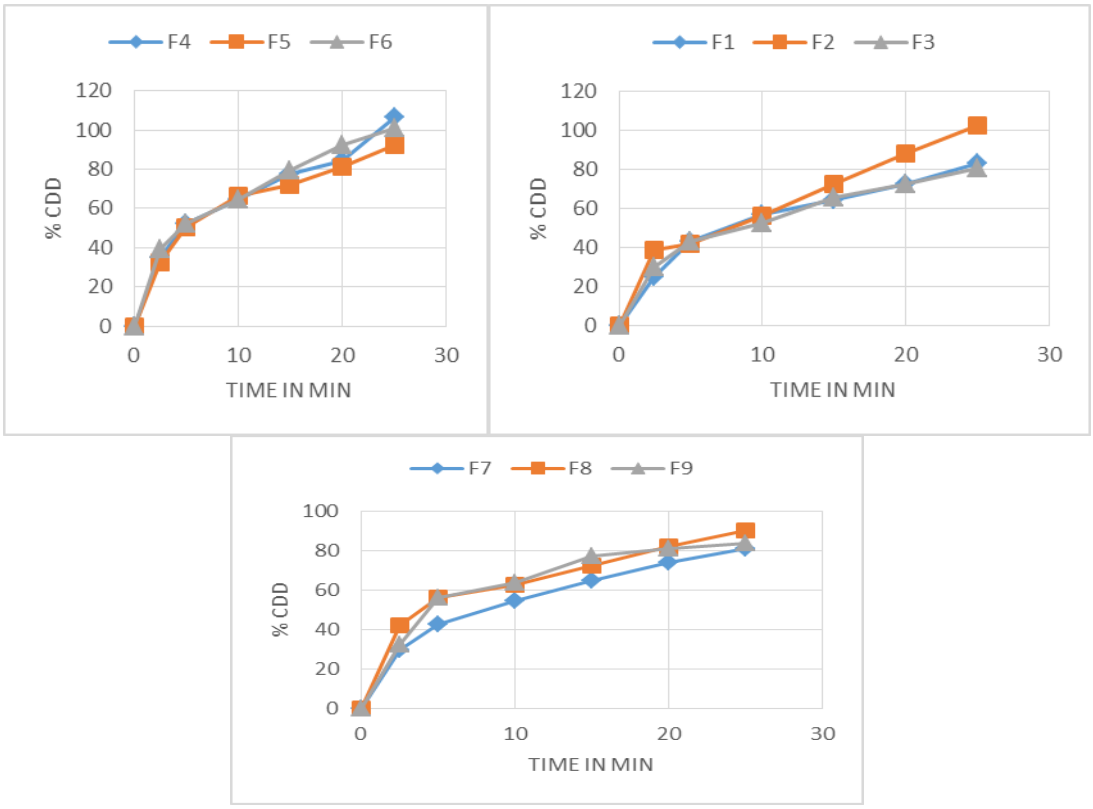

Figure 3: In vitro dissolution Profile of tablet formulations

Dissolution: These rapid dissolving tablets are intended to dissolve in the oral cavity and increase bioavailability. For 10 minutes, dissolution is performed in 900ml dissolving fluid (phosphate buffer pH 6.8) in a USP apparatus type-2 equipment at 50rpm. After 25 minutes, nearly the whole amount of the medication is released from the formulation prepared using the direct compression approach. The order of dissolution rate increase with several super disintegrants was shown to be croscarmellose sodium > sodium starch glycollate > Starch 1500.

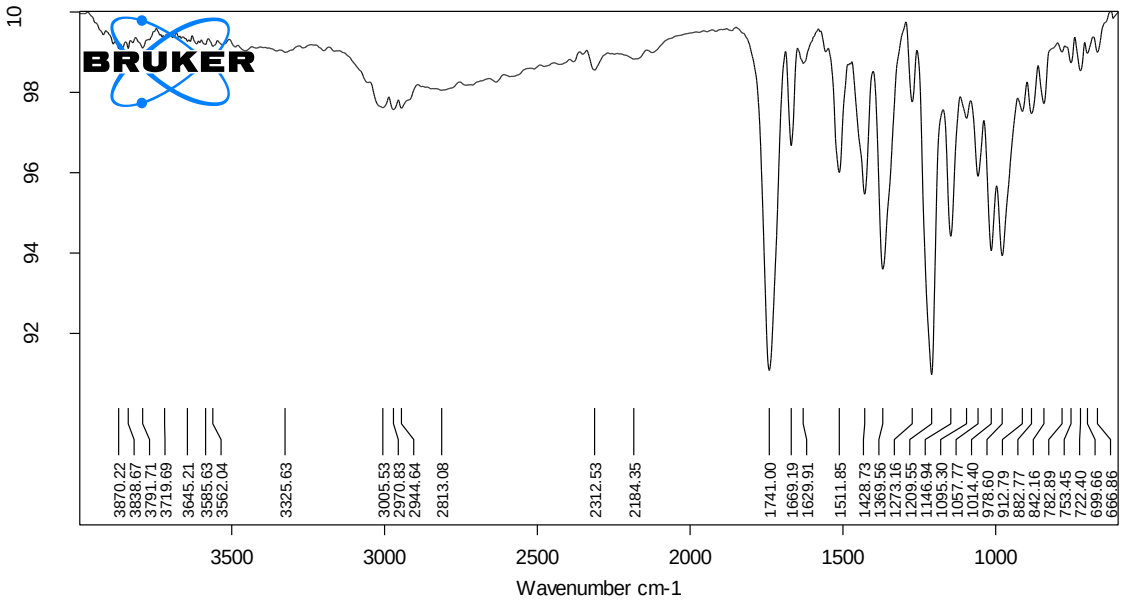

Figure 4: FTIR of Sitagliptin pure drug.

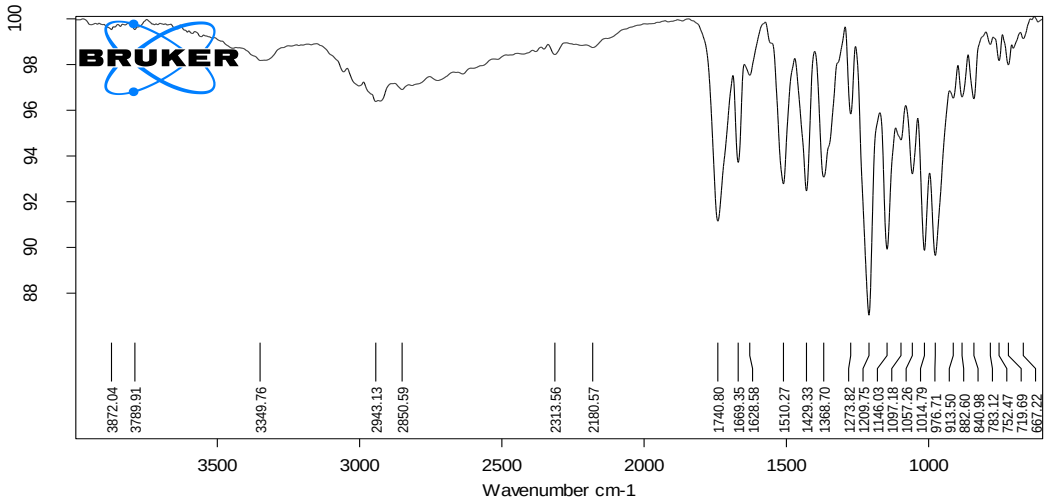

Figure 5: FTIR spectrum of Sitagliptin+ SSG.

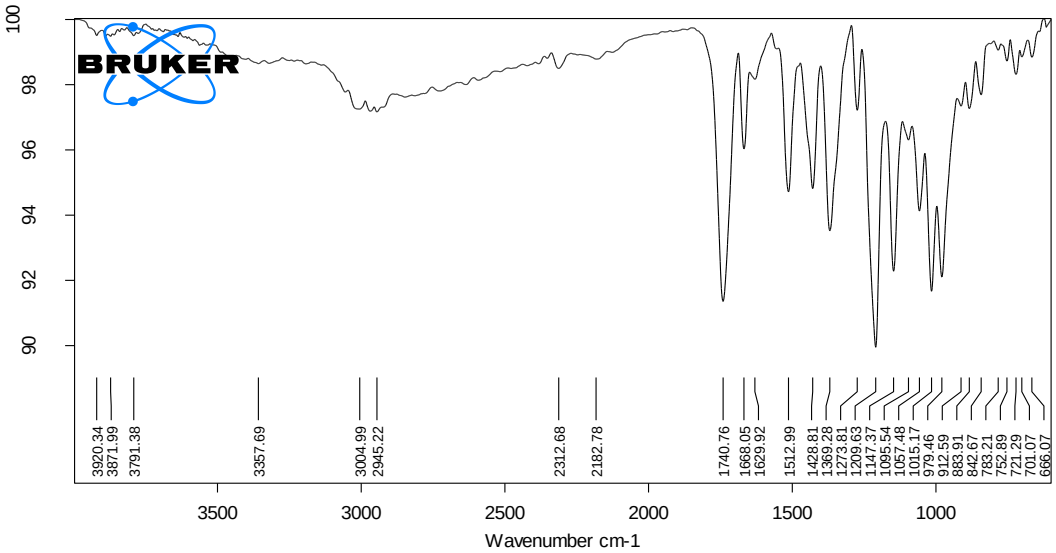

Figure 6: FTIR spectrum of Sitagliptin+ CCS.

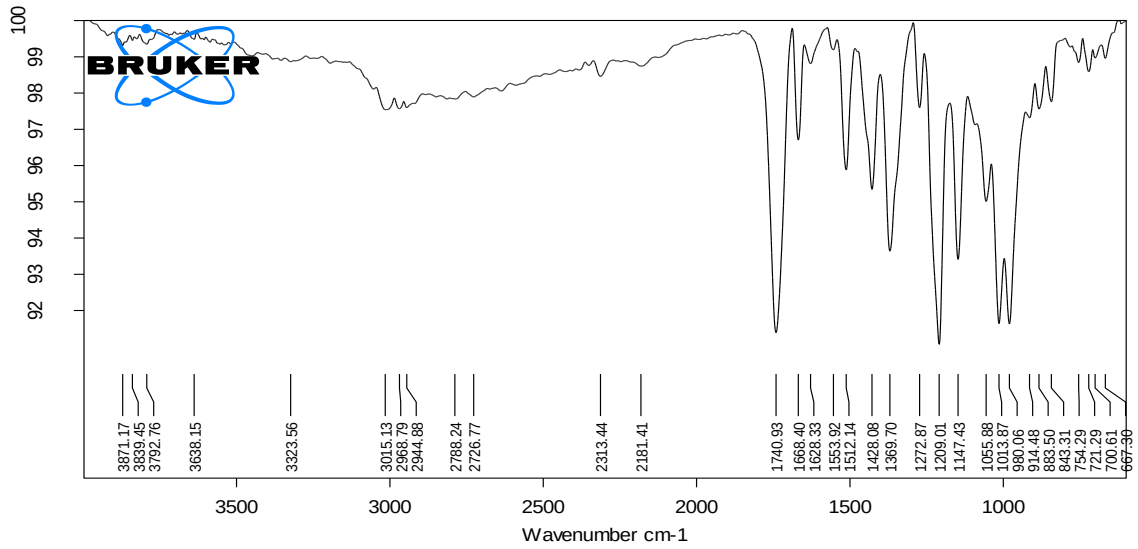

Figure 7: FTIR spectrum of Sitagliptin+ Starch 1500.

From IR studies, it was observed that the same characteristic peaks of Sitagliptin were appeared in the formulations containing Sitagliptin apart from excipients peaks. So it was concluded that, these peaks were not affected, they were prominently observed in IR-spectra of Sitagliptin along with super-disintegrants. The spectral details of the drug and the excipients are shown in (Fig.No.3 to 6). There was no difference in the position of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between pure drug & the excipients.

Stability Studies

Results of accelerated stability studies of optimized Sitagliptin (F4) as per ICH guidelines

Table 11: Results of accelerated stability studies (post compression studies) of optimized Sitagliptin (F4).

Time Interval	Post compression studies			
	Avg. Wt. (mg)*	Thickness (mg)*	Hardness (kg/cm^2)*	Friability (%)#
Initial	252 ± 0.15	2.63 ± 0.02	5.2 ± 0.03	0.83
1 Month	249 ± 0.72	2.85 ± 0.08	5.4 ± 0.02	0.43
2 Month	250 ± 0.35	2.59 ± 0.05	5.3± 0.03	0.39
3 Month	250 ± 0.23	2.73 ± 0.01	5.2 ± 0.01	0.82
6 Month	251 ± 0.45	2.54 ± 0.02	5.2 ± 0.02	0.82

*All the values are expressed as mean ± SD, where n=3 except for Avg. Wt. determination where n=20.
#Test for friability was performed for once on 10 tablets from each batch.

Table 12: Dissolution data of F4 batch during stability studies.

Time (min)	% Cumulative Drug Release (% CDD)			
	Initial	1st month	2nd month	3rd month
0	0	0	0	0
2.5	33.12± 0.23	33.24 ± 0.19	33.52 ± 0.24	33.54 ± 0.22
5	51.19± 0.19	52.21 ± 0.18	51.23± 0.18	52.16 ± 0.13
10	62.23± 0.24	63.25 ± 0.27	63.29 ± 0.32	64.12 ± 0.16
15	76.28± 0.12	77.13 ± 0.13	77.23 ± 0.21	77.32 ± 0.19
20	83.15± 0.29	84.17 ± 0.07	84.21 ± 0.05	83.19 ± 0.04
25	105.19± 0.32	103.12 ± 0.27	103.15 ± 0.29	105.17 ± 0.25

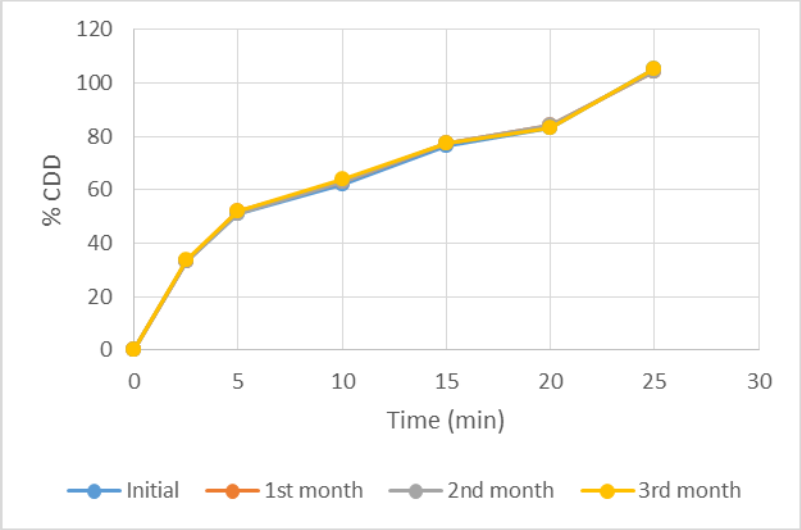

Figure 8: *In vitro* dissolution plots of accelerated stability samples of optimized CCS (F4).

The stability studies for the optimized formulations CCS(Cross carmellose Sodium) were performed for about 3 months at 40˚C / 75% RH AND 25˚C /60%RH. The samples were analyzed at intervals of 0,2.5, 5,10, 15,20 and 25. There were no significant change in the physical appearance of the tablets.

CONCLUSION

The above results suggest that the formulated oral disintegrating tablets of Sitagliptin have good physical characteristics, disintegrate quickly without affecting the release profile, and are extremely effective in elderly and paediatric patients. Overall, the results showed that formulations containing croscarmallose sodium had a major benefit over other formulations including superdisintegrants. They meet all of the requirements for oral disintegrating tablets. To manufacture sitagliptin orally disintegrating tablets, this direct compression technique is simple, reproducible, and robust.

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