

## Research Article



## Formulation and Evaluation of Oro Dispersive Tablets of Saxagliptin

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### ABSTRACT

The current work focuses on the development and evaluation of oro dispersive tablets of saxagliptin in the treatment of diabetes. The formulae was developed using various individual concentrations of super disintegrating agents. The compatibility of Drug and excipients was evaluated using FTIR studies. The tablets were prepared and Pre- and Post-compression parameters, wetting time and *in-vitro* dissolution and stability studies were evaluated. The FT-IR spectra's confirms the absence of chemical interaction between drug and excipients. All the Pre- and post-compression parameters were found to be in limits. From the results of dissolution testing, it was found that the formulation F6 found to be best of all the formulations. Thus, novel oro dispersive tablet formulation of saxagliptin was successfully developed.

**Keywords:** Diabetes, Saxagliptin, Crospovidone, Mannitol, Chemical interaction.

### INTRODUCTION

Recent advances in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for the administration. To improve quality of life and fastening of treatment, orally disintegrating tablets (ODT) dosage form is a better alternative for oral medication. These dosage forms dissolve or disintegrate within matter of seconds. Oro dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people<sup>1</sup>. Fast dissolving tablets are those when put on tongue disintegrate instantaneously to release the drug which dissolve or disperses in the saliva<sup>2</sup>. The faster the drug release into solution, quicker the absorption and onset of clinical effect. Usually Super disintegrating agents are added to a drug formulation to facilitate the breakup of or disintegration of tablet content into smaller particles that can dissolve more rapidly than in the absence of disintegrants. Many substances like microcrystalline cellulose, Crospovidone, crosscarmellose sodium, sodium starch glycolate have been used in the formulation of fast disintegrating tablets.

Saxagliptin is used as alone or in combination with other drugs for the treatment of Type 2 diabetes. It does not appear to decrease the risk of heart attacks or strokes<sup>3</sup>. Saxagliptin slows down the breakdown of incretin hormones, increasing the level of these hormones in the body. It is this increase in incretin hormones that is responsible for the beneficial actions of Saxagliptin, including increasing insulin production in response to meals and decreasing the rate of gluconeogenesis in the liver<sup>4</sup>.

The drug is currently available as conventional tablets taken in 2.5 - 5 mg/day<sup>5</sup>, so it is good candidate to

formulate oral disintegrating tablet which disintegrates within a matter of second and provide quick onset of action. Hence, it is very useful to pediatric and geriatric patients who generally shows problem in swallowing ODT not require water to swallow dosage form.

### MATERIALS AND METHODS

#### Materials

Saxagliptin was received as a gift sample from Rainbow Pharma Pvt. Ltd., Crosscarmellose Sodium (Ac-Di -Sol SD-711) from FMC Biopolymers, Avicel pH102 and Crospovidone XL 10 was obtained as gift from Vapi care Ltd. SSG, Pearlitol and CP purchased from S.D Fine Chemicals Ltd. All other reagents were of analytical grade.

#### Methods

##### Pre – compression parameters

##### Drug Excipients Compatibility Studies

The compatibility studies were performed by using FTIR analysis. The FTIR was performed on a Shimadzu electronic system. The samples of pure drug and its combination with excipients were mixed with required quantity of potassium bromide (KBr) sealed in an aluminum pan and heated at a constant rate 100c/minute, over a temperature range 250 °C to 4000 °C. The FTIR studies performed to standard Saxagliptin and excipients.

##### Bulk Density (Pb)

Apparent bulk density (Pb) was determined by pouring the blend into a graduated cylinder. The bulk volume (V) and weight of the powder (M) was determined. The bulk density was calculated using the following formula

$$Pb = M/V$$



**Tapped Density (Pt)**

The measuring cylinder containing a know mass of blend was tapped for a fixed number of tapings. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (Pt) calculated using following formula:

$$Pt = M/Vt$$

**Compressibility Index (I)**

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows:

$$I = V_0 - Vt / Vbx$$

Where, V<sub>0</sub> is bulk volume and Vt is tapped volume. The value below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flowability.

**Hausner's Ratio**

Hausner's ratio is an indirect index of ease of powder flow calculated by following formula:

$$\text{Hausner's Ratio} = \frac{Pt}{Pd}$$

Where Pt is tapped density and Pd is bulk density.

**Angle of Repose (θ)**

Angle of repose was determined using funnel method. The blend was poured through a funnel fixed at a height of 2cm that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated using following the formula:

$$\theta = \tan^{-1} \left( \frac{h}{r} \right)$$

**Preparation of Oro Dispersive Tablets**

Oro dispersible tablets of saxagliptin were prepared by direct compression method. All the ingredients (as shown in Table 1) were passed through mesh no 60. Required quantity of each ingredient was taken and all the ingredients were subjected to grinding to a required degree of fineness and are blended properly. The resulting blend of powder is compressed by using 8 mm sized punch using 8 station rotary press.

**Post Compression Parameters****Weight Variation**

20 tablets were selected randomly and average weight was determined. The individual tablets were weighted and compared with average weight to determine weight variation. The deviation if any in the weight of individual tablets from the average weight was checked. This test highly describes that all the tablets of a particular batch should be uniform in weight. If any weight variation is

there, that should be within IP limits. The test was considered correct if not more than two tablets fall outside the IP limits out of twenty tablets taken for the test.

**Friability**

Friability of tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. 10 tablets were randomly selected, weighed (W<sub>1</sub>) and were placed in the friabilator and were subjected to 100 revolutions. The tablets were de dusted using a soft muslin cloth and reweighed (W<sub>2</sub>). The friability (f) is calculated by following formula:

$$f = (1 - W_1 / W_2) \times 100$$

Where, W<sub>1</sub> is weight of the tablets before revolutions and W<sub>2</sub> is the weight of the tablets after revolutions.

**Hardness**

Hardness of tablet crushing strength is the force required to break a tablet in a diametric dimension was measured using Monsanto hardness tester.

**Drug Content**

Five tablets were powdered and the blend equivalent to 12.5 mg of saxagliptin was weighed and dissolved in suitable quantity of 0.01N HCl. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically at 274nm. Each sample was analyzed in triplicate.

**In-Vitro Disintegration Time**

The disintegration time of the tablets was determined as per Indian Pharmacopoeia monograph. The time required for disintegration of six tablets placed in each tube of disintegration test apparatus were measured at 37 ± 0.50 °C using 900 ml of distilled water. The time required to obtain complete disintegration of all the six tablets was measured.

**Wetting Time**

Circular tissue paper placed in a petridish with a 10cm diameter. Ten milliliters of water containing eosin, a water soluble dye was added to the petridish. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface and wet the tablets completely wet was noted as the wetting time. The measurements were carried out in triplicates (n=3).

**In-vitro drug Release Studies**

The *In-vitro* drug release studies were carried out in USP Type II (Paddle) dissolution apparatus to suit the physiological conditions of the GIT. The medium used for



dissolution is 0.01N HCl. The volume of the medium in the dissolution apparatus was maintained at 900 ml. The paddle allowed to rotate at a rate of 50 rpm and the temperature was maintained at  $37 \pm 0.5$  °C. Aliquots of dissolution medium (5ml) were withdrawn at predetermined time intervals 5, 10, 15, 20 and 30 min and the same volume of medium was replaced to maintain the sink condition.

### Stability Studies

Stability studies were carried out according to ICH guidelines by exposing the. Formulations SF6 and CF6 in their final packing mode to the temperature  $40 \pm 2$  °C and relative humidity  $75 \pm 5$  % in programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Aliquot were withdrawn at 30 and 60 days and analyzed for change in drug content, hardness, friability, disintegration time and *In-vitro* dissolution profile.

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing:

1. 21°C / 45% RH analyzed every month for period of three months.
2. 25°C / 60% RH analyzed every month for period of three months.
3. 30°C / 70% RH analyzed every month for period of three months.

The optimized formulation F7 and Innovator sample are also kept for stability at room temperature for 3 months and evaluated dissolution study & drug content.

## RESULTS AND DISCUSSION

Ten formulations Saxagliptin were prepared with varying concentration of super disintegrants: croscarmellose sodium, sodium starch glycolate and Crospovidone XL 10. Pearlitol SD 200 was used as diluent and sweetener. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique.

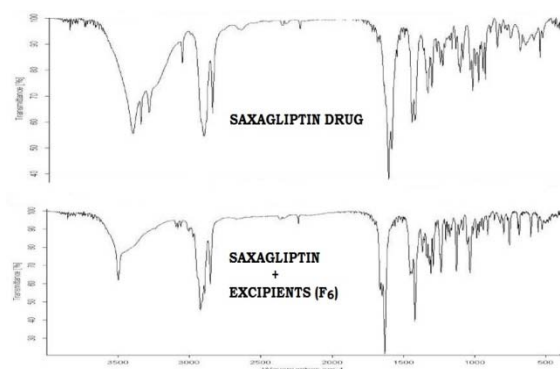


Figure 1: FTIR Spectra of pure drug and Formulation F6

### Drug Excipients Interaction Studies

When the spectra's of pure drug and its combination with excipients were taken as shown in Figure 1 it was found that all the peaks corresponding to the constituents were found to be present in its higher spectra indicating that none of the functional groups of either drug or polymer have undergone any chemical reaction. All functional groups are intact. Hence, it is a confirmation that no chemical reaction has taken place amongst any of the constituents in the oro dispersive tablet formulation and thus it can be used for its desired purpose.

### Evaluation of Powder Blend

The bulk density was found to be in the range of 0.44 – 0.59 g/cm<sup>3</sup> and tapped density between 0.56 – 0.68 g/cm<sup>3</sup> as mentioned in Table 2. Using these two density data Hausner's and compressibility index was calculated. The powder blends of all the formulations had Hausner's ratio ranging from 1.15 to 1.25 indicating good flowability. The compressibility index was found to be 13.2 – 24.6. The compressibility flowability correlation data indicated a fairly good flowability of the powder blend. The good flowability of the powder blend was also evidenced with angle of repose (range of 23 – 32 °), which is below 40° indicating good flowability.

The tablets were prepared by direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight variations as per Pharmacopoeia specifications. The drug content was found in the acceptable limit and the hardness of the tablet between 2.9 – 3.2 kg/cm<sup>2</sup> as mentioned in Table 3. Friability of the tablets was found below 1% indicating a good mechanical resistance of tablets. The wetting time and disintegration time was found practically well for all formulations.

The *in vitro* disintegration time (DT) of the tablets was found to be less than 60 sec. The *in vitro* dissolution indicated a faster and maximum of 99% drug release (Figure 2) from formulation F6 proving the best disintegrants property of Crospovidone XL 10. The stability studies of formulation F6 indicated a stable formulation.

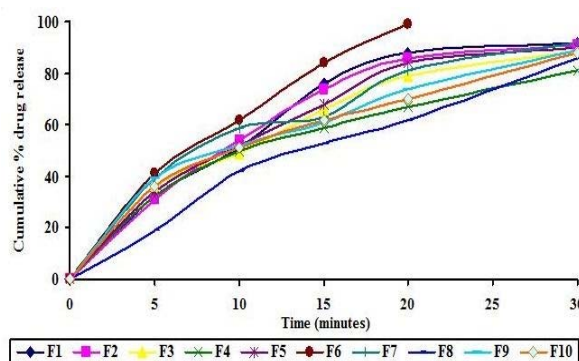


Figure 2: *In-vitro* drug dissolution profile of Formulations F<sub>1</sub> – F<sub>10</sub>

**Table 1:** Formulation of oro dispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Saxagliptin	5	5	5	5	5	5	5	5	5
Sodium Starch Glycolate	2	3	4	--	--	--	--	--	--
Croscopovidone	--	--	--	2	3	4	--	--	--
Crosscarmellose Sodium	--	--	--	--	--	--	2	3	4
Pearlitol	5	5	5	5	5	5	5	5	5
MCC	74	73	72	74	73	72	74	73	72
Mannitol	10	10	10	10	10	10	10	10	10
Aerosil	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
<b>Total wt in mg</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>

**Table 2:** Results of pre-formulation studies

Formulation code	Angle of repose	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)	Hausner's Ratio
F1	26.06 ± 0.29	0.46 ± 0.09	0.59 ± 0.15	21.8 ± 0.18	1.25 ± 0.02
F2	25.42 ± 0.15	0.46 ± 0.18	0.56 ± 0.17	16.3 ± 0.26	1.19 ± 0.02
F3	32.62 ± 0.37	0.59 ± 0.14	0.68 ± 0.09	13.2 ± 0.09	1.15 ± 0.03
F4	29.19 ± 0.41	0.48 ± 0.09	0.63 ± 0.12	24.6 ± 0.16	1.25 ± 0.01
F5	25.72 ± 0.21	0.47 ± 0.14	0.56 ± 0.19	15.9 ± 0.11	1.19 ± 0.04
F6	26.45 ± 0.26	0.48 ± 0.13	0.56 ± 0.15	14.2 ± 0.18	1.16 ± 0.02
F7	24.61 ± 0.18	0.45 ± 0.20	0.56 ± 0.13	20.1 ± 0.21	1.25 ± 0.03
F8	23.34 ± 0.25	0.46 ± 0.16	0.59 ± 0.11	21.8 ± 0.13	1.25 ± 0.01
F9	26.06 ± 0.48	0.52 ± 0.11	0.62 ± 0.19	16.1 ± 0.23	1.19 ± 0.01
F10	29.24 ± 0.42	0.44 ± 0.16	0.56 ± 0.16	20.3 ± 0.19	1.25 ± 0.02

**Table 3:** Results of post-compression parameters

Formulation code	Average Weight variation (mg)	Thickness (Mm)	Average Hardness (Kg/Cm <sup>2</sup> )	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Drug content (%)
F1	101 ± 0.09	2.0 ± 0.14	3.0 ± 0.21	0.16 ± 0.05	21 ± 0.17	42 ± 0.14	99.17 ± 0.24
F2	98 ± 0.10	2.2 ± 0.16	3.1 ± 0.14	0.25 ± 0.14	25 ± 0.11	43 ± 0.11	99.44 ± 0.16
F3	102 ± 0.26	2.1 ± 0.09	3.2 ± 0.11	0.41 ± 0.21	26 ± 0.06	52 ± 0.19	98.64 ± 0.12
F4	102 ± 0.05	2.5 ± 0.07	3.0 ± 0.06	0.26 ± 0.16	30 ± 0.05	32 ± 0.21	100.2 ± 0.08
F5	99 ± 0.05	1.9 ± 0.24	3.0 ± 0.04	0.34 ± 0.08	17 ± 0.15	33 ± 0.24	99.49 ± 0.15
F6	100 ± 0.19	2.1 ± 0.18	3.1 ± 0.12	0.21 ± 0.04	21 ± 0.25	31 ± 0.15	99.85 ± 0.14
F7	100 ± 0.14	2.3 ± 0.15	3.0 ± 0.19	0.23 ± 0.09	23 ± 0.23	39 ± 0.11	98.80 ± 0.11
F8	101 ± 0.16	2.5 ± 0.11	3.0 ± 0.12	0.15 ± 0.12	22 ± 0.17	48 ± 0.09	99.12 ± 0.09
F9	100 ± 0.24	2.0 ± 0.23	2.9 ± 0.15	0.29 ± 0.15	26 ± 0.09	50 ± 0.17	99.42 ± 0.15
F10	99 ± 0.12	2.2 ± 0.14	3.0 ± 0.19	0.34 ± 0.14	28 ± 0.16	51 ± 0.15	99.74 ± 0.24

**Table 4:** Results of *In-vitro* drug dissolution studies

Time (min)	% Cumulative Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	32 ± 0.18	31 ± 0.06	36 ± 0.13	32 ± 0.16	34 ± 0.16	41 ± 0.21	39 ± 0.04	19 ± 0.09	39 ± 0.14	36 ± 0.18
10	51 ± 0.12	54 ± 0.09	49 ± 0.08	50 ± 0.21	52 ± 0.12	62 ± 0.24	59 ± 0.09	42 ± 0.12	52 ± 0.21	51 ± 0.13
15	76 ± 0.09	74 ± 0.12	66 ± 0.14	59 ± 0.29	68 ± 0.09	84 ± 0.19	63 ± 0.12	53 ± 0.19	61 ± 0.28	62 ± 0.09
20	88 ± 0.14	86 ± 0.17	79 ± 0.19	67 ± 0.16	84 ± 0.11	99 ± 0.16	81 ± 0.16	62 ± 0.08	74 ± 0.09	70 ± 0.11
30	92 ± 0.22	91 ± 0.08	89 ± 0.11	81 ± 0.11	90 ± 0.16	--	92 ± 0.21	86 ± 0.13	89 ± 0.16	88 ± 0.14

## Stability data

**Table 5:** Physical and chemical parameters of Candesartan tablets of formulation F6 after one month at 25 °C / 60% RH

Parameter	Initial	After 1 Month
Description	White colored round shaped tablets	White colored round shaped tablets
Avg. weight (mg)	100 ± 0.19	100 ± 0.19
Hardness (Kg/Cm <sup>2</sup> )	3.1 ± 0.12	3.1 ± 0.12
Thickness (mm)	2.1 ± 0.18	2.1 ± 0.18
Friability (%)	0.21 ± 0.04	0.21 ± 0.04

**Table 6:** Physical and chemical parameters of Candesartan tablets of formulation F6 after one month at 40 °C / 75% RH

Parameter	Initial	After 1 Month
Description	White colored round shaped tablets	White colored round shaped tablets
Avg. weight (mg)	100 ± 0.19	100 ± 0.19
Hardness (kp)	3.1 ± 0.12	3.1 ± 0.12
Thickness (mm)	2.1 ± 0.18	2.1 ± 0.18
Friability (%)	0.21 ± 0.04	0.21 ± 0.04

## CONCLUSION

From all the above observations, it was concluded that the formulation F6 containing 4% of Crospovidone XL 10 was found to be better formulation in terms of rapid disintegration and maximum percentage drug release when compared with all other formulations. Prepared tablets disintegrate within few seconds without need of water; thereby enhance absorption leading to increase

bioavailability. Thus, the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and increased patient compliance.

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