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# FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF SAXAGLIPTIN

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**ABSTRACT**

The present work aimed at formulation and evaluation of a taste masked Fast dissolving tablets of Saxagliptin. Saxagliptin is an anti-diabetic drug which belongs to BCS Class III drug, having a bad and metallic taste. So by formulating it as fast dissolving tablet the absorption and the bioavailability of the drug will fasten and hence the action of the drug will be faster. The mode of action of Saxagliptin is mainly by inhibition of dipeptidyl peptidase enzyme. Three superdisintegrants were used namely sodium starch glycolate, crospovidone, crosscarmellose sodium in combination with Kollidon CL, as novel super disintegrant and Pearlitol as a taste masking agent. The tablets were formulated and evaluated for various parameters like weight variation, hardness, friability, drug content, disintegration and in vivo dissolution. Among all the formulations F5 showed 99% drug release within 15 min. So it was considered as best formulation. Finally stability studies were done for the F5 formulation as per the ICH guidelines at 40º C & 75 % RH for 3 months and there are no changes in the drug content, disintegration, *in vitro* dissolution.

**Key Words**: Saxagliptin, Pearlitol, Fast dissolving tablets, Super disintegrants.

## INTRODUCTION

Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been used for the systemic delivery of drugs via various pharmaceutical products of different dosage forms (Ved Parkash *et al*., 2011). The reason for that the oral route achieved such popularity mainly be due to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs ingested daily (Ashish P *et al*., 2011). In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form within the inherent constraints of GIT physiology. The active ingredients from the fast dissolving tablets are absorbed through the mucous membranes in mouth, GIT and finally enter into the blood stream.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules. Apart from that drinking water plays an important role in the swallowing of oral dosage forms (Abdul Sayeed & Mohd.Hamed Mohiuddin, 2011; Suresh B *et al*., 2008).

The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts, and mouth disintegrating tablets. However of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has

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used the term "orodispersible tablet" for tablets that disperse readily and within three minutes before swallowing (Indurwade NH *et al*., 2002; Ashish P *et al*., 2011).

United States Food and Drug Administration (USFDA) defined ODT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The disintegration time for ODTs generally ranges from several seconds to about a minute.

Diabetes mellitus (DM) or simply diabetes is a group of metabolic diseases in which a person has high blood sugar. There are three main types of diabetes mellitus called Type I, Type II and Gestational diabetes. Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity. As of 2010 there were approximately 285 million people diagnosed with the disease compared to around 30 million in 1985 (Centers for Disease Control and Prevention, 2011). Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor blood flow in the limbs leading to amputations. DPP-4 (Dipeptidyl Peptidase enzyme) inhibitors or gliptins are a class of oral anti-diabetic drugs that block DPP-4. They can be used to treat diabetes mellitus type II.

Saxagliptin is the drug which is mainly used for the treatment of type II Diabetes Mellitus (Anonymous 1; Atlanta GA, 2011). Saxagliptin is a new oral hypoglycemic (anti-diabetic drug) of dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. It is superior to the other gliptins with an oral bioavailability of 67% due to its poor permeability. This drug belongs to the class of BCS III, highly soluble and is rapidly absorbed by oral route (Dave DJ, 2011).

Many studies were conducted on Saxagliptin as formulation in tablets such as film coated tablets, bilayered tablets. However this study mainly based on the formulation of Saxagliptin as fast dissolving tablets. The prepared tablets were evaluated for various *In-vitro* dissolution studies to show that the bioavailability of drug can be enhanced by formulating it as fast dissolving tablets.

## MATERIALS AND METHODS

### *Chemicals*

Saxagliptin was obtained as a gift sample from Ranbaxy Pvt Ltd, Gurgaon, Avicel 200, Qualigen fine chemicals , Bombay, India; Magnesium stearate , Oxford laboratory, Mumbai, India; $Na_2HPO_4$, $KH_2PO_4$, FINAR reagents, Ahmadabad, India; Aerosil, Yarrow chem. products, Mumbai, India; SSG, CCS , CP, Kollidon CL, Pearlitol, A to Z chemicals, Chennai, India.

***Compatability studies:*** The compatability of Saxagliptin drug with different excipients was tested using FTIR and DSC studies.

### Preformulation studies

***Evaluation of parameters for powdered blend***

*Bulk density*

Density is defined as weight per unit volume. Bulk density is defined as the mass of the powder divided by the bulk volume. Apparent bulk density was determined by pouring pre- sieved drug-excipients blend into a graduated cylinder and measuring the volume and weight as it is. It is expressed in g/cm3 and is given by

$$Db = M / V0$$

M - Mass of powder

V0 - Bulk volume of the powder.

*Tapped density:*

It was determined by placing a graduated cylinder, containing a known mass of drug excipient blend on mechanical tapping apparatus which is operated for a fixed number of taps. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

$$Dt = M / Vt$$

M - Mass of powder

Vt- Tapped volume of the powder.

*Angle of repose*

Angle of repose is used for the measurement of frictional force in a loose powder. Angle of repose was determined by using funnel method suggested by Newman. Powder was poured from a funnel that can be raised vertically until a maximum cone height (h) was obtained. Diameter of heap (D) was measured. The angle of repose ( Θ) was calculated by using the formula

$$\text{Tan } \Theta = h / r, \ \Theta = \tan^{-1} (h / r)$$

Θ - Angle of repose

h - Height in cm

r - Radius.

Angle of repose < 30 shows the free flowing of the material.

*Carr's index*

The measurement of free flow property of powder is called as compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility .It can be calculated by the following formula

$$C = ( \rho t - \rho b) \rho t \times 100$$

ρt - Tapped density

ρb - Untapped bulk density

*Hausner ratio*

It is calculated by using the following formula .

$$H = Dt / Db$$

Dt - tapped density of the powder , Db - Bulk density of the powder.

***Formulation of fast dissolving tablets of Saxagliptin***

*Method*

Fast dissolving tablets of Saxagliptin were prepared by direct compression technology. The various disintegrants like crospovidone, crosscarmellose and sodium starch glycolate were used. Required quantity of each ingredient is taken for each specified formulation and all ingredients were mixed. Aerosil and magnesium stearate were then passed through mesh no.60 and mixed with initial mixture. The resulting mixture was compressed into tablet by using 16 station tablet punching machine (cadmach) using 8 mm punch size.

***Post formulation studies***

*Weight variation*

As per USP weight variation test twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. The weight variation test was performed by calculating the average weight of tablet. As the weight of the tablet is 100 mg, the weight variation limit is ± 7.5% (Ashish P *et al*., 2011).

*Hardness, Friability and Thickness*

Hardness or tablet crushing strength is the force required to break a tablet in a diametric compression, measured using Monsanto tablet hardness tester. In this test the tablet was placed between two plungers, the lower plunger was placed in contact with the tablet and upper plunger was forced against a spring. It was measured in Kilograms.

The friability was tested using a Roche friabilator. The tablets were weighed and then placed in a friabilator and rotated for 100 revolutions at 25 rpm. Then the tablets were dusted and weighed.

The thicknesses of the tablets were measured by using Vernier callipers.

*Content uniformity*

Ten tablets were randomly selected and tested for their drug content. Each tablet was powdered and dose of the drug equivalent was taken and to it 10 ml of 6.8 pH phosphate buffer was added and the resulting solution was diluted appropriately and measured for its absorbance at 208 nm using a UV-Visible spectrophotometer.

*Disintegration time*

Tablet was placed in the disintegrating apparatus having pH 6.8 phosphate buffer solution (1000 ml) at 37 ± $0.5^{o}$ C. Time required for complete dispersion of a tablet was measured.

*Wetting time or water absorption Ratio*

The water uptake characteristic of the loose disintegrant powder allows evaluation of both the intrinsic swelling and the wettability of the super disintegrants .Water uptake test was performed at room temperature. Water absorption ratio R was determined by using the following formula.

Water absorption = [Wa-Wb / Wb] *100

Wa and Wb are the tablet weights after and before wetting.

***In-vitro 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 Phosphate buffer with a pH of 6.8.The volume of the medium in the dissolution apparatus was maintained at 900ml.The stirring rate was 50 rpm and the temperature was maintained at 37± $0.5^{0}$C. Aliquots of dissolution medium were withdrawn at predetermined time intervals 5, 10,15,30 min and the same volume of medium was replaced to maintain the constant volume (Leon Lachman *et al*., 1987).

## RESULTS AND DISCUSSIONS

***Compatability studies***

From the FT-IR and DSC study the drug was found to be compatible with all the excipients. Refer Fig 1 to Fig 8.

***Precompresional parameters***

Saxagliptin powder blends were free flowing as indicated by the values of bulk density(0.39 to 0.53gm/cc),Tapped density( 0.34 to 0.54 gm/cc), Hausner's ratio(1.11 to 1.26), Compressibility index (11.24 to 20.39%) and the Angle of repose ranged from 21.02 $^{0}$ to 28.48$^{0.}$ The values are given in Table 2.

***Post Compressional Evaluation parameters of formulated ODT's***

Saxagliptin tablets were uniform in weight (99.5to 100.1mg), the thickness (0.210 to 0.243 mm) of all tablets were uniform. The hardness of all the tablets was found to be between 2.00 to 3.41kg/cm$^{2}$ , While the friability of the ODT'S ranged from 0 .13 to 0.34%.The content uniformity of all the formulations were ranged from 97.3% to 100.11% w/w .The disintegration time of all the formulations ranged from 10 to 48 seconds, the modified disintegration test values ranged from 14 to 28 seconds and the wetting time values ranged from 10 to 42 seconds. Fifteen formulations (F1-F15) were made by taking different superdisintegrants with different concentrations. The post compressional parameters were shown in the Table 3.

***In-vitro release study of the tablets***

F1 to F15 formulations were prepared by using Pearlitol as a taste masking agent. F1 to F5 formulations were prepared using crospovidone as the superdisintegrants at a concentration of 2, 3, 4, 5 and 7.5%. F6 to F10

formulations were prepared using cross carmellose sodium as the superdisintegrants at a concentration of 2, 3, 4, 5 and 7.5%. F11to F15 formulations were prepared using croscarmellose sodium as the superdisintegrants at a concentration of 2, 3, 4, 5, and 7.5%. It was observed that all the formulations showed a gradient and proportional increase in the drug release. Among all the formulations F5 showed better results. The Formulation F5 results compared with the marketed formulation (ONGLYZA-2.5 mg) which is a conventional film coated tablet. Among these two F5 formulation showed better results. The results were tabulated in Table 4 and 5. Refer Fig 9 and 10 for comparative dissolution profiles.

**Table 1. Formulation design of an oral disintegrating tablet**

| Ingredients / Formulation | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (mg) | | | | | | | | | | | | | | |
| Saxagliptin | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Kollidon CL | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Pearlitol | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Crospovidone | 2 | 3 | 4 | 5 | 7.5 | - | - | - | - | - | - | - | - | - | - |
| Crosscarmellose sodium | - | - | - | - | - | 2 | 3 | 4 | 5 | 7.5 | - | - | - | - | - |
| Sodium starch Glycolate | - | - | - | - | - | - | - | - | - | - | 2 | 3 | 4 | 5 | 7.5 |
| Avicel PH 200 | 38.3 | 37.3 | 36.3 | 35.3 | 32.8 | 38.3 | 37.3 | 36.3 | 35.3 | 32.8 | 38.3 | 37.3 | 36.3 | 35.3 | 32.8 |
| Aerosil | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| Magnesium stearate | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| Peppermint Flavor | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Total Wt in mg | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 2. Preformulation studies**

| Formulation code | Bulk Density(g/cc) | Tapped Density (g/cc) | Angle of Repose (degrees) | Carr's Index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| F1 | 0.39 | 0.54 | 22.40 | 13.04 | 1.14 |
| F2 | 0.38 | 0.52 | 24.06 | 11.72 | 1.16 |
| F3 | 0.46 | 0.43 | 23.38 | 12.20 | 1.14 |
| F4 | 0.42 | 0.43 | 22.72 | 11.24 | 1.12 |
| F5 | 0.45 | 0.45 | 25.94 | 11.76 | 1.11 |
| F6 | 0.49 | 0.34 | 28.48 | 12.36 | 1.14 |
| F7 | 0.53 | 0.54 | 23.21 | 13.06 | 1.16 |
| F8 | 0.43 | 0.51 | 23.74 | 12.11 | 1.14 |
| F9 | 0.40 | 0.48 | 21.02 | 13.79 | 1.15 |
| F10 | 0.43 | 0.46 | 22.51 | 12.50 | 1.13 |
| F11 | 0.37 | 0.44 | 24.68 | 13.96 | 1.16 |
| F12 | 0.47 | 0.365 | 22.45 | 14.03 | 1.13 |
| F13 | 0.43 | 0.46 | 22.61 | 13.28 | 1.12 |
| F14 | 0.45 | 0.52 | 24.34 | 19.17 | 1.26 |
| F15 | 0.42 | 0.53 | 22.42 | 20.39 | 1.11 |

**Table 3. Post formulation studies of the Formulated ODT**

| Formulation code | Weight Variation | Hardness ($Kg/cm^2$) | Thickness (mm) | Friability (%) | Content uniformity (%) | Disintegration time (sec) | Modified disintegration time (sec) | Wetting time (sec) |
|---|---|---|---|---|---|---|---|---|
| F1 | Passed | 2.00 | 0.230 | 0.14 | 98.92 | 34 | 28 | 38 |
| F2 | Passed | 2.01 | 0.243 | 0.16 | 97.3 | 30 | 27 | 34 |
| F3 | Passed | 2.02 | 0.242 | 0.15 | 100.11 | 26 | 28 | 10 |
| F4 | Passed | 3.01 | 0.202 | 0.29 | 99.24 | 12 | 17 | 27 |
| F5 | Passed | 3.02 | 0.203 | 0.34 | 99.28 | 10 | 14 | 16 |
| F6 | Passed | 3.30 | 0.212 | 0.29 | 99.52 | 48 | 21 | 22 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| F7 | Passed | 3.13 | 0.214 | 0.29 | 99.98 | 41 | 26 | 25 |
| F8 | Passed | 2.02 | 0.203 | 0.13 | 100.02 | 28 | 27 | 42 |
| F9 | Passed | 3.31 | 0.213 | 0.15 | 99.84 | 25 | 28 | 31 |
| F10 | Passed | 3.34 | 0.216 | 0.20 | 97.65 | 23 | 19 | 30 |
| F11 | Passed | 3.41 | 0.213 | 0.21 | 97.62 | 30 | 23 | 25 |
| F12 | Passed | 2.03 | 0.212 | 0.15 | 100.01 | 25 | 24 | 20 |
| F13 | Passed | 2.01 | 0.214 | 0.13 | 99.2 | 23 | 24 | 16 |
| F14 | Passed | 3.41 | 0.210 | 0.21 | 99.54 | 19 | 29 | 25 |
| F15 | Passed | 3.01 | 0.212 | 0.23 | 99.75 | 13 | 28 | 21 |

**Table 4. *In-vitro* dissolution studies of formulated ODT's**

| Tim | 5 min | 10 min | 15 min | 30 min |
|---|---|---|---|---|
| **Formulation** | **% Release** | | | |
| F1 | 40 | 58 | 69 | 78 |
| F2 | 49 | 56 | 71 | 81 |
| F3 | 52 | 61 | 76 | 90 |
| F4 | 60 | 70 | 85 | 91 |
| F5 | 66 | 83 | 98 | - |
| F6 | 32 | 41 | 52 | 64 |
| F7 | 40 | 54 | 61 | 71 |
| F8 | 46 | 54 | 62 | 88 |
| F9 | 55 | 67 | 76 | 92 |
| F10 | 61 | 72 | 84 | 96 |
| F11 | 31 | 43 | 51 | 60 |
| F12 | 46 | 59 | 61 | 76 |
| F13 | 51 | 64 | 78 | 86 |
| F14 | 59 | 67 | 71 | 88 |
| F15 | 61 | 70 | 88 | 97 |
| Market Formulation | 10 | 22 | 30 | 49 |

**Fig 1. FTIR Spectra of Kollidon**

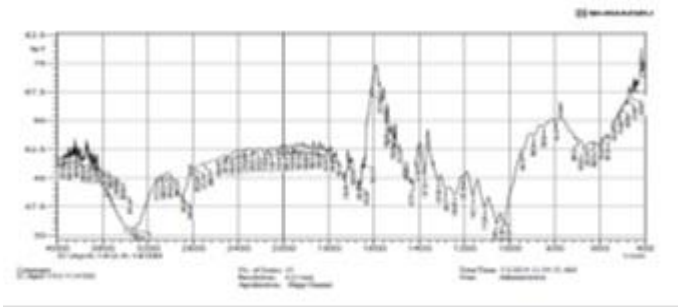


**Fig 2. FTIR Spectra of Pearlitol**

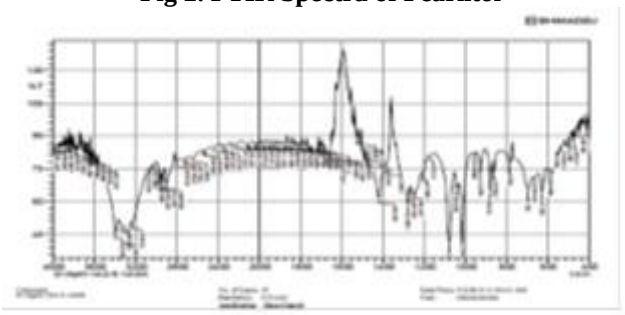


**Fig 3. FTIR Spectra of Saxagliptin +Kollidon CL**

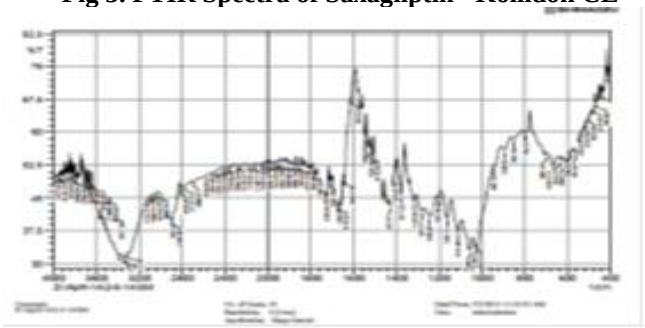


**Fig 4. FTIR Spectra of Saxagliptin+ Pearlitol**

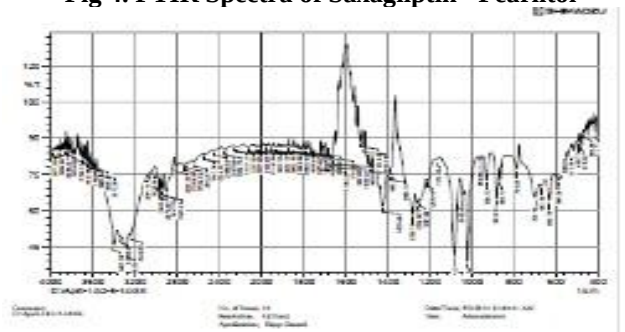


**Fig 5. FTIR Spectra of Saxagliptin**

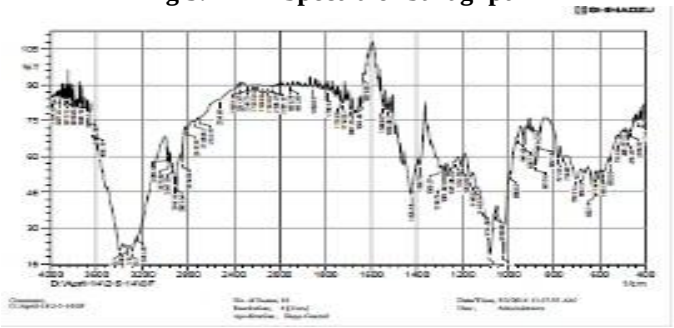


**Fig 6. FTIR Spectra of Saxagliptin Tablet Blend**

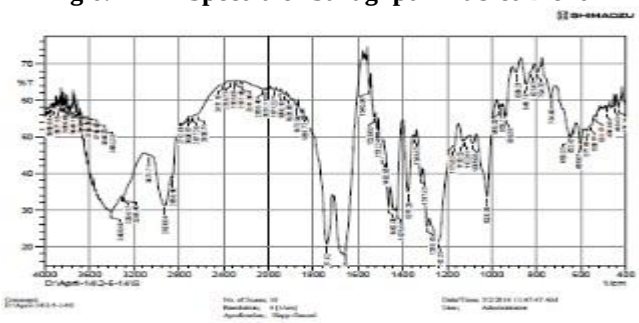


**Fig 7. DSC of Saxagliptin**

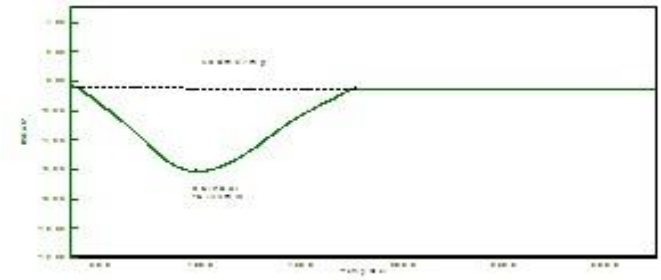


**Fig 8. DSC of Saxagliptin Formulation**

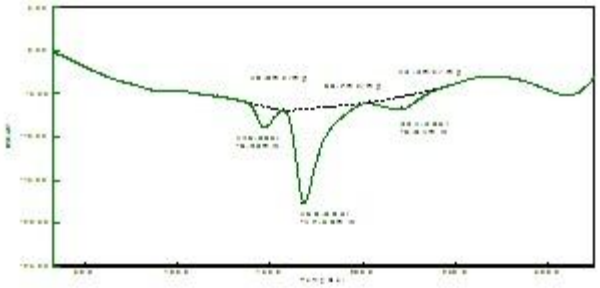
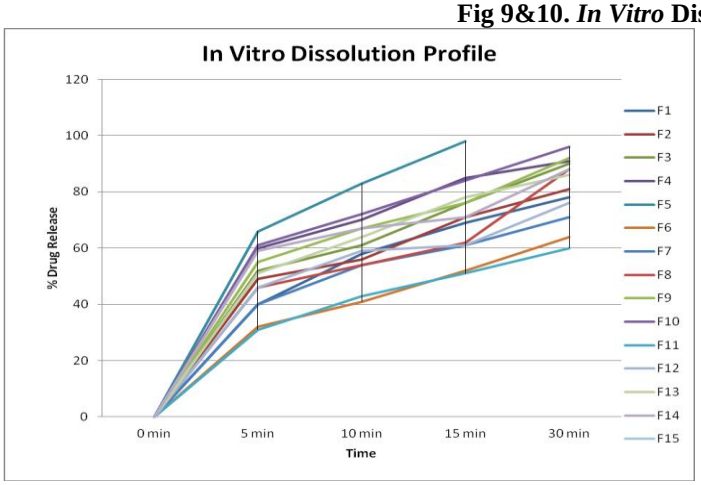


**Fig 9&10. *In Vitro* Dissolution Profiles**





## CONCLUSION

F1 to F5 batches were formulated using crospovidone as superdisintegrants at different concentrations of 2, 3, 4, 5% and 7.5% respectively. F5 batch with 7.5% crospovidone showed better results. Though the results indicate that crosspovidone showed concentration dependent disintegration and dissolution in which higher concentration of crosspovidone is responsible for faster water uptake. It facilitates wicking and welling action and brings about faster disintegration and dissolution when compared to other super disintegrants used like crosscarmellose sodium and sodium starch glycolate which acts by only swelling. By formulating Saxagliptin as fast dissolving tablet bioavailability of drug is increased with enhanced absorption of the drug. So it is an alternative to commercially available tablets and moreover the taste of the drug was masked which enhances better patient compliance.

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