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Research Article

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Formulation and Evaluation of Fast Dissolving Delivery System of Saxagliptin

Jyothi Rani L*[1], K. Abbulu[2]

[1]*Mallareddy Institute of Pharmaceutical Sciences, Dhulapally, Secunderabad-14, India*
[2]*Professor & Principal, Nova college of pharmaceutical education and research, Hyderabad, India*

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Abstract

The Fast Dissolving Drug Delivery Systems was an advancement that came into existence in the early 1970's and combats over the use of the tablets, syrups, capsules which are the other oral drug delivery systems. Fast Dissolving Drug Delivery Systems serves as a major benefit over the conventional dosage forms since the drug gets rapidly disintegrated & dissolves in the saliva without the use of water. In spite of the downside i.e, lack of immediate onset of action; these oral dosage forms have beneficial purposes such as self medication, increased compliance, ease of manufacturing and lack of pain. A variety of FDDs like mouth dissolving tablets and fast dissolving film (FDFs) were commercialized. FDFs evolved over the past few years from by the confection and oral care market in the form of breath strips & became a novel & widely accepted form by consumers. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. Fast disintegrating tablets (FDTs) have received ever- increasing demand during the last decade and the field has become a rapidly growing area in the pharmaceutical industry because of such tablets readily dissolve or disintegrate in the saliva generally less than 60 seconds. The aim of the present study is to formulate and evaluate the mouth dissolving tablet and film of Saxagliptin with different ratios of polymeric combinations by the solvent evaporation technique. Saxagliptin is a new peptidase 4 (DPP-4) inhibitor and is used for the treatment of Diabetes mellitus. The drug is formulated as different formulations Tablet formulations named as F1 to F15, Film formulations named as F1 to F9 and studied for Thickness, mean weight(mg), drug content(mg),% hydration, %moisture loss , surface PH, Tensile strength, %elongation at break, folding endurance, mucoadhesion time, disintegration time. And these are also studied for *In vitro* dissolution studies. Among all the film and Tablet formulations F5 film formulation with combination of polymers (1:1) showed maximum release of 98 % in 15min emerging to be ideal formulations.

Keywords: Fast dissolving drug delivery system, fast dissolving oral tablet, fast dissolving oral film, PVP K 30,Polyvinyl alcohol, Saxagliptin.

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***Corresponding author**
Jyothi Rani L
Mallareddy Institute of Pharmaceutical Sciences, Secunderabad-14, India
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1. Introduction

A vast variety of pharmaceutical research is directed at developing new dosage forms. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists [1]. Fast dissolving dosage forms are useful in patients[2,3,4] such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup, leading to ineffective therapy[5] with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style[6].In disease conditions such as motion sickness, sudden episodes of attacks of coughing and repeated emesis and swallowing[7], conventional tablets become difficult. Orally disintegrating dosage forms can serve as an effective alternative mode of drug delivery in such situations.

Fast dissolving Oral Films (FDOF) are a solid single-unit dosage form which are made of a water dissolving polymer, allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue in the oral cavity to provide local or systemic drug delivery[8]. The large surface area available in the film dosage form allows rapid wetting by saliva, quick disintegration, dissolution and absorption of drug directly enter into the systemic circulation without undergoing first-pass hepatic metabolism with increased bioavailability [9]. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [10].

Improved patient compliance is the primary benefit of fast dissolving films. Oral films as dosage form are getting more attention for the delivery of active pharmaceutical ingredients (API). In oral cavity films offers distinct advantages like an easy application, no degradation of API by gastrointestinal fluids, bypassing the first-hepatic metabolism and potentially improved bioavailability ensuring rapid invasion and fast onset. Many advantages of this route have been recently recognized and various products are under development [11, 12, 13].

Saxagliptin[14] is an oral antidiabetic drug belongs to the class of gliptins and is a dipeptidyl peptidase enzyme inhibitor. It is a competitive inhibitor of DPP4 enzyme causes inactivation of the incretin hormones thereby increasing their blood stream concentrations & reducing fasting and postprandial glucose concentrations in a glucose dependent manner in patients with Type II diabetes mellitus.

2. Materials and Methods

2.1 Materials

Saxagliptin was obtained as a gift sample from Ranbaxy Pvt Ltd, Gurgaon, Croscarmellose sodium, PVP K 30, PVA, Mannitol, Glycerol, Sodium starch glycolate, Sodium saccharine were obtained as gift sample. All other chemicals and reagents were of analytical grade.

Compatability studies:

The compatability of Saxagliptin drug with different excipients was tested using FTIR and DSC studies. Film formulation was also studied by SEM analysis.

2.2 Method

2.2.1 Preparation of Oral Dispersible Film:

Fast dissolving film was prepared by solvent evaporation method. It was prepared by dissolving required amount of PVA and PVP K30 polymers in water and ethanol stirred continuously for one hour to get polymeric solution. Then required amount of drug was dissolved in water followed by the addition of plasticizer, sweetener and flavoring agent. The drug solution was then added to the polymeric solution and stirred by using a magnetic stirrer and finally the solution was poured into petriplate and dried at 60ºC for 24 hrs. Then the film was carefully removed from petriplate and cut into desired size and evaluate the films for physical and chemical properties.

3. Evaluation

3.1 Evaluation of Oral Dispersible Film:

a. **Physical appearance:** All the prepared Films were visually inspected for colour, clarity, flexibility and smoothness.

b. **Thickness Uniformity**
The thickness of the formulated film was measured at 3 different places and average thickness of three readings was calculated.

c. **Weight Uniformity**
For each formulation, there randomly selected films were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

d. **Folding endurance**

e. The folding endurance was measured manually for the prepared films. A film (2X2 cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking give the value of folding endurance.

f. Percentage moisture absorption

The films were weighed accurately and placed in the dessicator containing 100ml of saturated solution of potassium chloride, which maintains 80-90% RH. After 3days, the films were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

g. **Percentage moisture loss**

The films were weighed accurately and kept in a dessicator containing anhydrous calcium chloride. After 3 days the films were taken out and weighed. The moisture loss was calculated using the formula:

$$\% \text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

h. Tensile Strength

Tensile strength of the film was determined with Universal strength testing machine (Hounsfiled, UK). The sensitivity of the machine was 1gm. It consists of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (2X 2 cm) was fixed between these cell grips and force was gradually applied till the film broke. It can be calculated from the formula:

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

i. Drug content uniformity of films

The films ($2cm^2$) were cut and added to a beaker containing 100ml of phosphate buffer pH 6.8. The medium was stirred with magnetic bead. The contents were filtered using Whatman filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films at 208 nm spectrophotometrically. The experiment was repeated to validate the result.

j. *In vitro* drug release studies

The *In vitro* drug dissolution of films were performed using phosphate buffer pH 6.8 at 37 ± 5^0C. 5ml of Sample was withdrawn periodically for every 10min upto 30min by replacing with same amount of dissolution medium. And these samples were again diluted and examined spectrophometrically at 208 nm. The values obtained were shown in **Table no 4 and Graph no: 1**

The physical and chemical parameters of different formulations of Saxagliptin from F1 to F9 studied are represented in **Table 2& 3.**

4. Results and Discussion

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 5 & Fig 6 & 7.** All the prepared films were transparent, smooth, uniform and flexible. The thickness of the formulated film were varies from 0.120± 0.09mm to 0.138±0.023mm. Low standard deviation values ensured uniformity of the patches. The weights ranged between 100.3 to 109.4mg. The folding endurance was found to be < 100 which was sufficient.

The films were % of moisture loss found to between 1.774 ± 0.09 to 2.945±0.01 and it increases with increasing concentration of hydrophilic polymers. Water vapour transmission rate for prepared films were found to be 0.363± 0.01 to 0.708 ± 0.03 as mentioned in **Table No2**. The Tensile strength of films is found to be in order F2>F6>F9>F8>F3>F4>F1>F5>F7. It was found to be in **Table No.3**. Drug content was found to be 81.34% to 99.51%. The result indicated that the release of drug from films having SSG F5 shows better dissolution. The cumulative percentage of immediate release Oral Dispersible Film was 98% in 15min for formulation F5 and minimum was 70% from F1 formulation**.**

Table 1. Formulation table for Saxagliptin films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Mg/film								
Saxagliptin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Polyvinyl alcohol	30	30	30	30	30	30	30	30	30
PVP K30	15	15	15	15	15	15	15	15	15
Mannitol	10	10	10	10	10	10	10	10	10
Glycerol	10	10	10	10	10	10	10	10	10
Mint flavor	10	10	10	10	10	10	10	10	10
Sodium Saccharin	10	10	10	10	10	10	10	10	10
SSG	-	5	10	15	20	-	-	-	-
CCS	-	-	-	-	-	5	10	15	20
Purified water	50	50	50	50	50	50	50	50	50
Ethanol	50	50	50	50	50	50	50	50	50

Table 2.Thickness, Mean weight (mg), Drug content(mg), % Hydration ratio, %Moisture loss , Surface pH

Formulation Code	Thickness(mm)	Mean weight(mg)	Drug content (%)	%Hydration ratio	% Moisture loss	Surface pH
F1	0.120	104.1	95.54	0.446	1.774	6.65
F2	0.123	105.4	94.45	0.534	2.087	6.63
F3	0.127	106.4	95.13	0.623	2.567	6.45
F4	0.131	107.3	81.34	0.708	1.243	6.34
F5	0.135	109.4	93.36	0.524	2.945	6.81
F6	0.122	102.4	85.23	0.405	2.542	7.03
F7	0.128	100.3	91.34	0.363	2.116	6.61
F8	0.137	106.6	99.51	0.553	2.113	6.34
F9	0.139	104.4	98.45	0.445	1.189	6.67

Table 3.Tensile strength, %Elongation at break, Folding endurance, Mucoadhesion time, Disintegration time

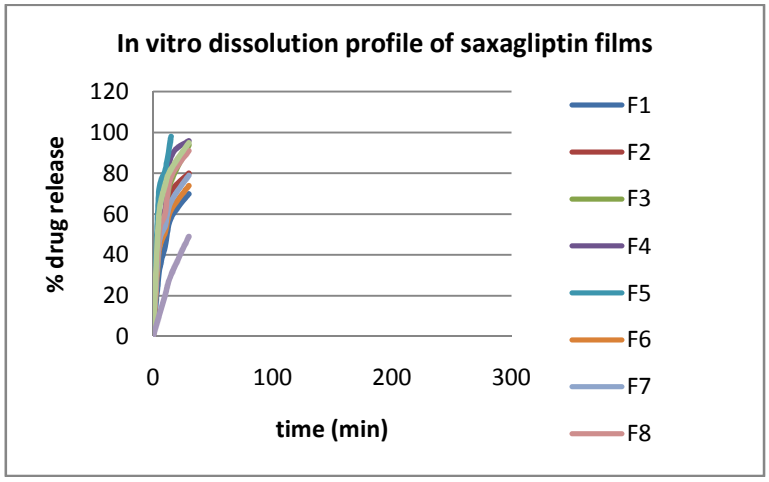
Formulation	Tensile strength	%elongation at break	Folding endurance	Mucoadhesion time(SEC)	Disintegration time(s)
F1	0.606	5.34	56	120	41
F2	0.807	6.21	67	100	34
F3	0.716	6.13	65	110	38
F4	0.617	5.34	53	133	36
F5	0.601	4.34	50	118	26
F6	0.787	5.12	55	125	34
F7	0.563	5.08	49	220	28
F8	0.678	6.23	56	210	26
F9	0.778	6.16	58	167	27

Table 4. *In vitro* dissolution profile

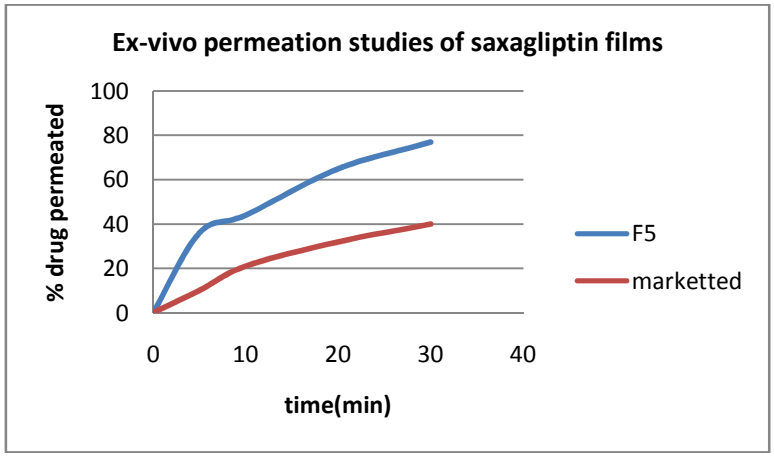
Time/ Formulation Code	5 min	10 min	15 min	30 min
	Time			
F1	31	44	58	70
F2	50	60	71	80
F3	52	61	76	94
F4	57	62	88	96
F5	72	81	98	-
F6	42	51	62	74
F7	46	54	66	79
F8	51	60	78	91
F9	60	74	82	95
Marketted	10	22	30	49

Table 5. Ex-vivo permeation studies

Formulation code	5min	10 min	20 min	30 min
	Time			
F5	36	45	64	77
Marketed	10	21	32	40



Graph 1



Graph 2

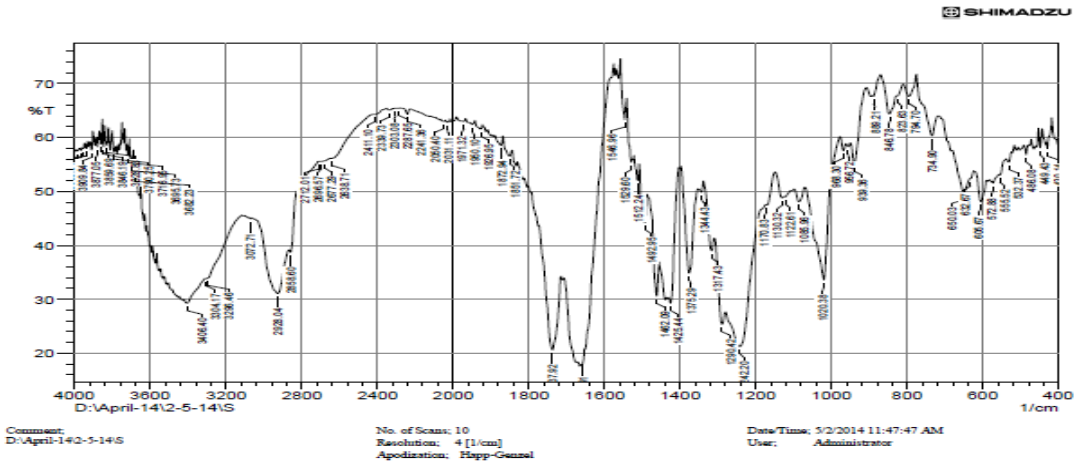


Figure 1. FTIR Spectra Saxagliptin

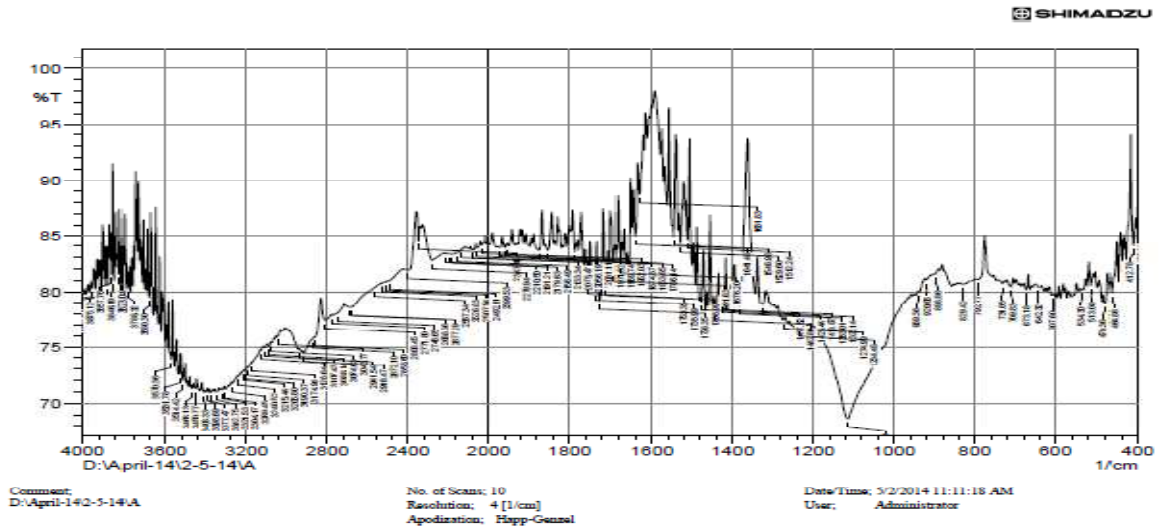


Figure 2. FTIR Spectra of Polyvinyl Alcohol

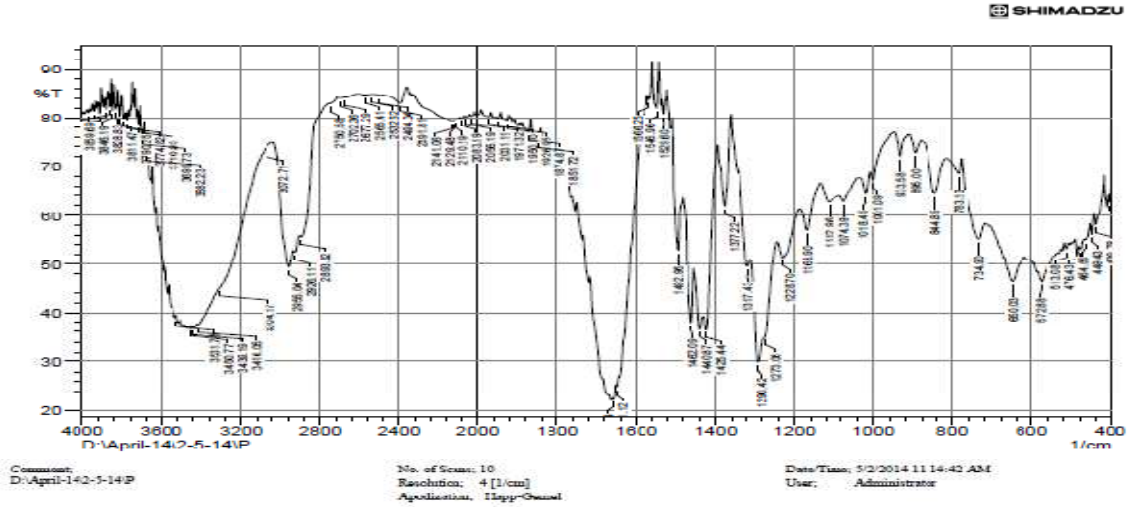


Figure 3. FTIR Spectra of PVP K30

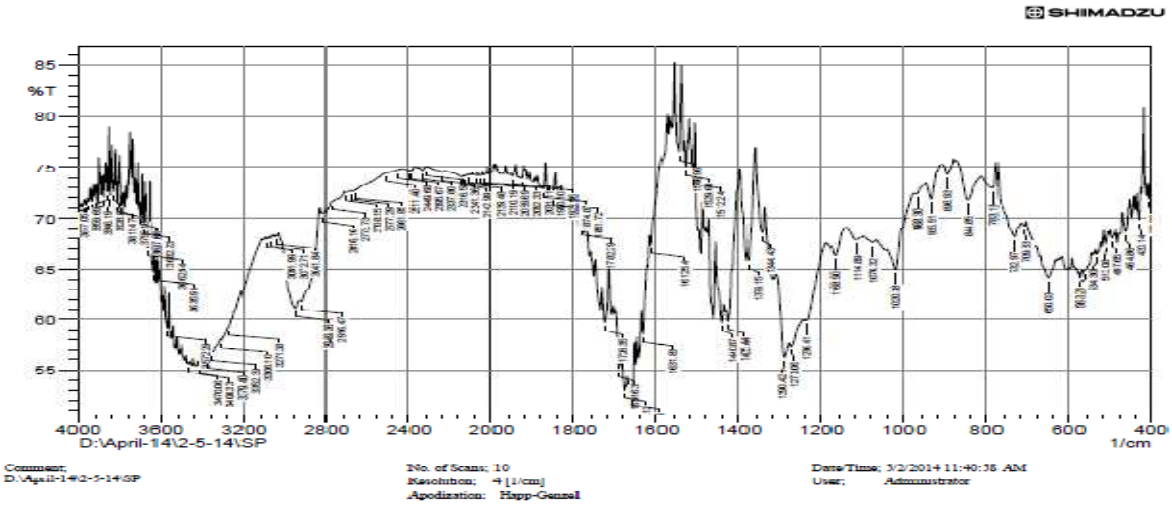


Figure 4. FTIR Spectra of Saxagliptin+ PVP K 30

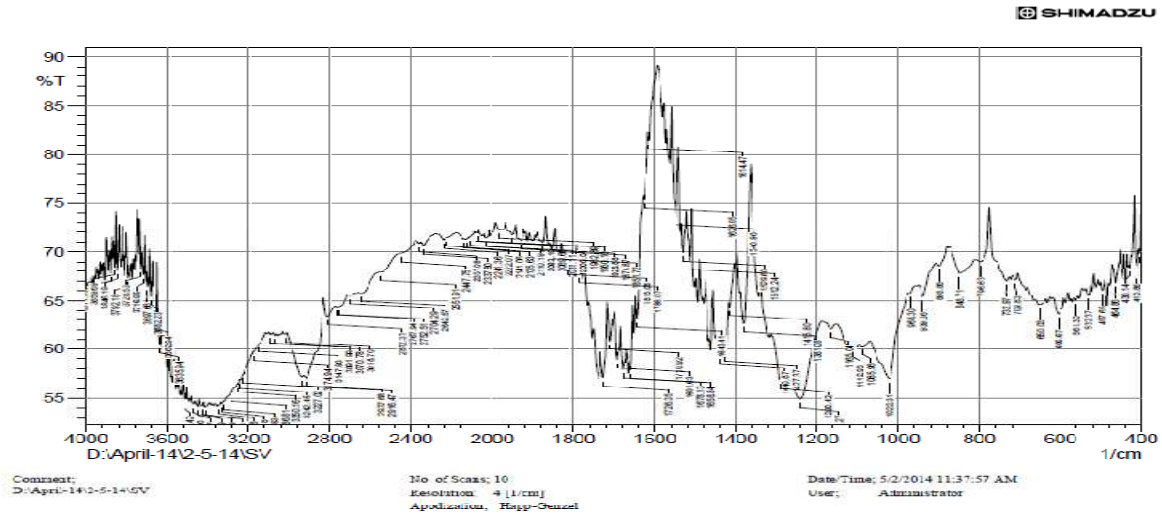


Figure 5. FTIR Spectra of Saxagliptin +PVA

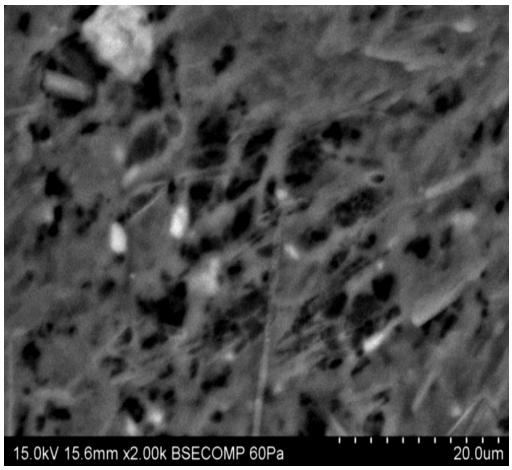


Figure 6. SEM of Saxagliptin film

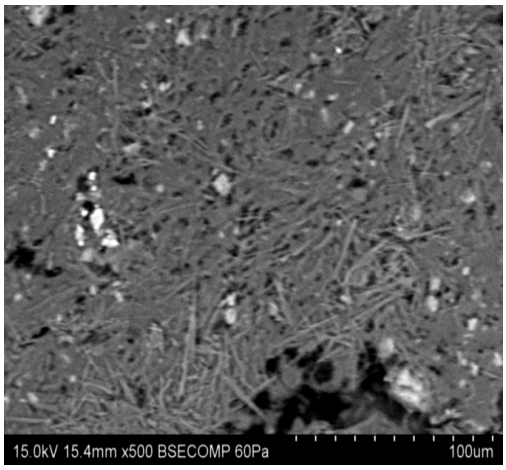


Figure 7. SEM of Saxagliptin film

5. Conclusion

The results obtained in the present study indicated that by using a combination of polymers like PVA and PVP K 30 fast dissolving oral film of Saxagliptin can be prepared. Formulation F5 have showed good in vitro dissolution and exvivo permeation. So film formulation F5 can be suitable for fast release of Saxagliptin for its use. Fast dissolving films of Saxagliptin can be considered suitable for clinical use in the treatment of diabetes.

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