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Formulation and Evaluation of Bilayer Tablet of Saxagliptin

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ABSTRACT
In the present study Saxagliptin 60mg tablets have been formulated and developed using direct compression and dry granulation technique, to provide a safe, highly effective method for treating congestive heart failure, edema and kidney disorder, while reducing undesirable adverse effects. Pre and post formulation parameters were studied for the formulated batches. The result of all the physical and in-vitro dissolution data concluded that bilayer tablet (I3,S9) was the most promising formulation. The trial conducted with the consecutive three batches for immediate release and sustained release revealed relative standard deviation below 2 %, indicative the insignificant batch-to-batch variation that can be overcome if processes are run out in a controlled manner. Using Crosspovidone as super disintegrate and HPMC as sustained release polymer blend would be cost effective and dissolution mediums 0.1N HCl would the ideal media for conducting dissolution studies. It was concluded that the bilayer tablet formulation can be act as a better tool for the successful administration of two or more drug which will remain stable for longer period of time.
Keywords: Bilayer Tablet, Saxagliptin, sustained release polymer, super disintegrate, drug released.

1. INTRODUCTION

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor antidiabetic for the treatment of type 2 diabetes. DPP-4 inhibitors are a class of compounds that work by affecting the action of natural hormones in the body called incretins. Incretins decrease blood sugar by increasing consumption of sugar by the body, mainly through increasing insulin production in the pancreas, and by reducing production of sugar by the liver.

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The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bi- layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.

The main objective of my research work is to develop a bilayer tablet of Saxagliptin, in which one layer is immediate layer for immediate action and second layer is the sustain release layer for maintaining the dose of the drug.

The major objective of the work is following:

- Saxagliptin is frequently administered up to 3 times in a day so the reducing dosing frequency by sustainer release tablet.
- Long term effect can be achieved by this dosage form.
- This drug help full in reducing high blood pressure and as a diuretic.
- With the help of reduced fluctuation in plasma drug concentration, Reduction in side effect and dose related toxicity.
- Patient compliance.

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2. EXPERIEMENTALS

2.1 Physical Description:

2.1.1 Organoleptic properties

Colour

Small quantity of drug powder was put on butter paper and observed.

Taste

Small quantity of drug was taken to taste with tongue.

Odour

Very less quantity of drug was taken and smelled for determination of its odour.

Table 1 physical properties of Saxagliptin

Test	Standard	Observation
Colour	White crystalline	White
Odour	Odour less	Odour less
Taste	Bitter	Bitter

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2.2. Solubility Analysis

A Qualitative determination was done by adding a solvent to a fixed amount of solute to a test tube

Procedure: By adding a solvent to a fixed amount of solute to a test tube. After each addition test tube was shaken and visually observed. Solubility Profile of Saxagliptin in various solvents are shown in Table:

Table 2 Solubility profile of drug

S. No.	solvent	Solubility
1	Water	Sparingly soluble
2	Phosphate buffer 5.8	Soluble
3	methanol	Soluble
4	0.1 N HCl	Soluble

2.3 MELTINGPOINT:

Melting Point

It is one of the methods to check the purity of crude drugs. In pure chemicals or photochemical, melting points are very sharp and constant. Since the crude drugs contain the multiple of chemicals which have fixed range of melting point.

Procedure: Capillary Method

Capillary melting-point apparatus, are basically used for the detection of the melting point of a solid. A small quantity of sample was added to a thin walled capillary tube 5-10 cm long and 1 mm in diameter, and closed at one end. Then this capillary was placed with a thermometer and, was heated evenly and slowly. The temperature was noted at which sample get liquefied.

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Table 3. Melting point of drug

Drug	Specified	Observations
Saxagliptin	210^0C	207^0C

2.4 IDENTIFICATION OF DRUG BY INFRAREDSPECTROSCOPY

Infrared spectroscopy is widely used analytical technique which provides information about the structure of molecule. Infrared spectrum of chemical substances is fingerprint for its identification. An infrared spectrum of drug was taken using KBr pellets. Small quantity of drug was mixed with oil and one drop was placed between KBr pellets. The pellets were in holder and infrared spectrum was interpreted for presence of different group in the structure of drug. The Fourier transform infrared spectra of showed Saxagliptin all characteristic peaks of Saxagliptin Figure No .4 IR spectra of Drug

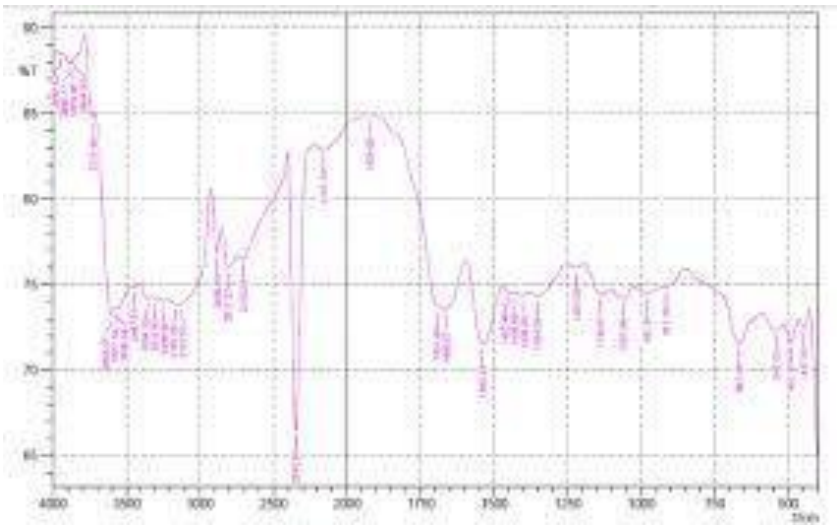

Figure No. 4 I R spectra of drug

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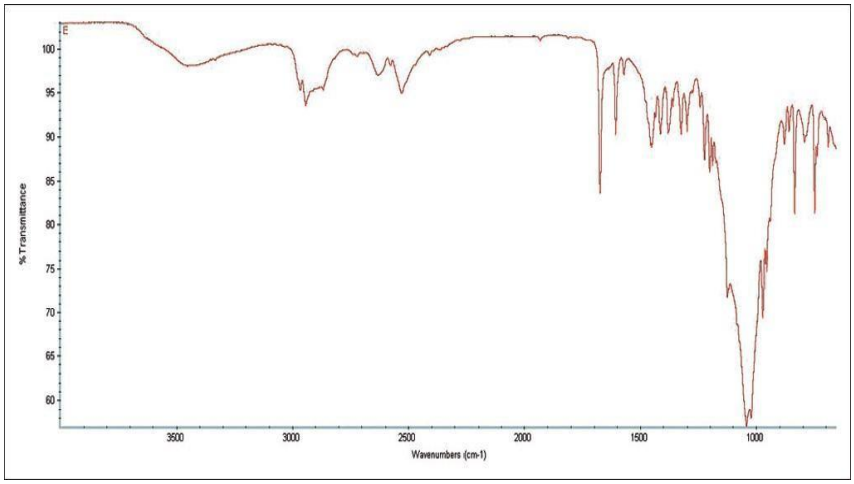

Table 6 Infrared characteristics of Saxagliptin drug sample

S. No.	Wave no.(cm^{-1})	Interpretations
1.	700-800	Alkanes (C-C Stretching)
2.	1015	C-H Bending Vibrations
3.	1120	Alcoholic C-O Stretching
4.	1150	Methylene Group
5.	1720	C=O Stretching
5.	3200-3400	C-H Stretching of Alkynes

2.5 IDENTIFICATION OF DRUG BY ULTRAVIOLETSPECTROSCOPY

Organic molecules when exposed to light in UV region they absorb light of particular wavelength depending on the type of electron transition associated with the absorption. The absorption maximum of drug was determined by running the spectrum of drug solution in double

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beam ultraviolet spectrophotometer. 10 mg of drug was weighted accurately and dissolved in water in 100 ml of volumetric flask and suitable stock was prepared. The spectrum of this stock solution was run in 200-400 nm range in ultra visible spectrophotometer. (Shimadzu 1700, ml of water in 100 ml of volumetric flask and suitable stock was prepared. The spectrum of this stock solution was run in 200-400 nm range in ultra visible spectrophotometer. (Shimadzu 1700, Japan)

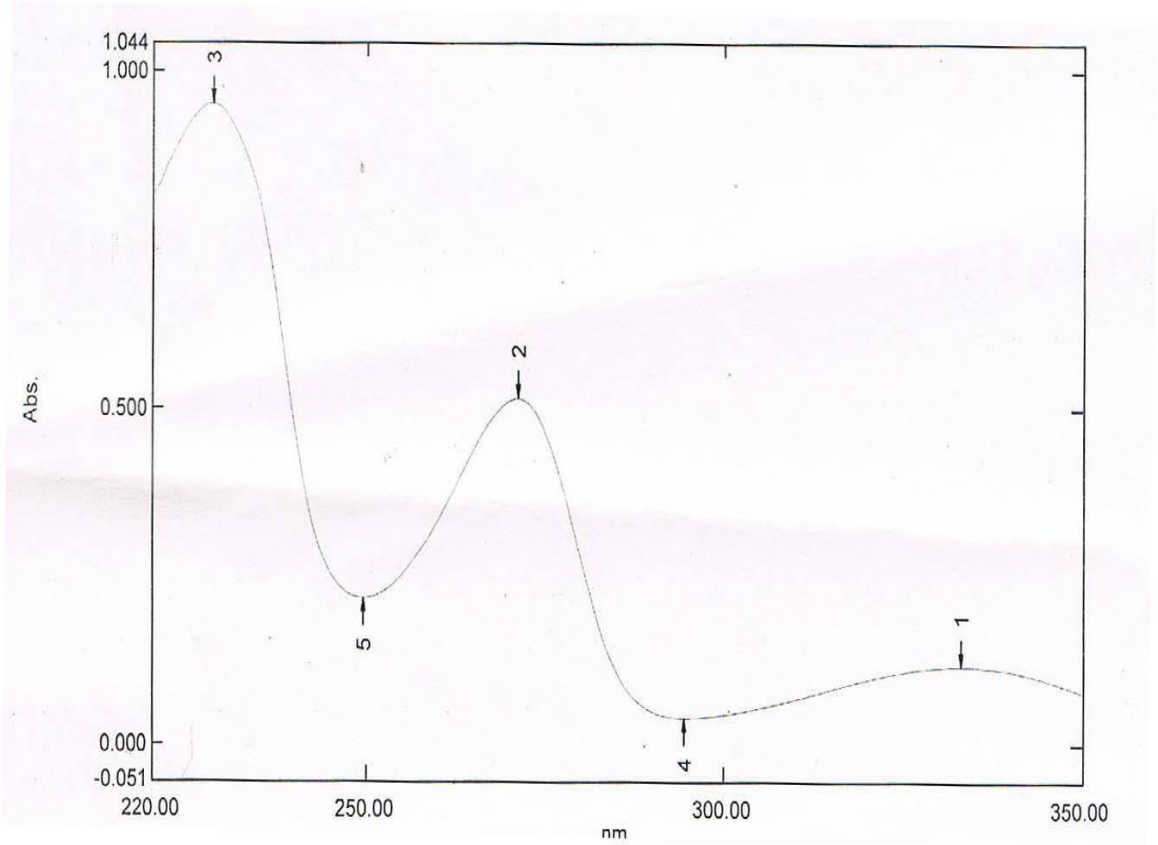

Figure No. 7 UV spectra of the sample drug

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2.6 Quantitative Estimation of Drug(Saxagliptin)

Standard curve of Saxagliptin Method:

100mg of Saxagliptin was weighed and poured into 100ml volumetric flask. It was dissolved and volume made up with 0.1N HCl to give 1000µg/ml sol..

Procedure: The standard stock solution was then serially diluted with 0.1N HCl to get 1 to 10µg/ml of Saxagliptin. The absorbance of the solution was determined against 0.1N HCl as blank at 271 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Table 8 : Standard calibration curve of Saxagliptin in 0.1N HCl (λ max = 271 nm)

S. No.	Concentration in (µg/ml)	Absorbance
1	0	0
2	2	0.111
3	4	0.165
4	5	0.210
5	8	0.279
5	10	0.349
7	12	0.419
8	14	0.480
9	15	0.539
10	18	0.590
11	20	0.549

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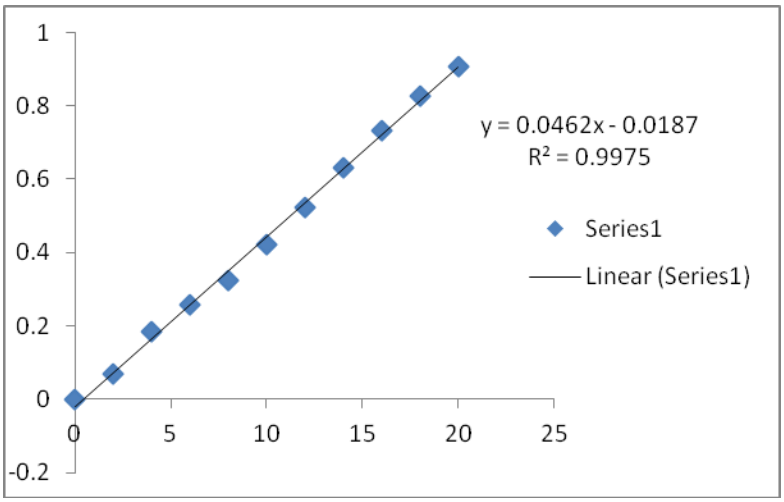

Figure 9 Calibration curve of drug in0.1 N HCl

3. FORMULATION OF COMPRESSED BILAYER TABLET

Table 10 Ingredients Used In Formulation of Compressed Bilayer Table

S. No.	Formula (In mg)	Formula for Bilayer tablet	
		I 3	S 9
1	Saxagliptin	20	40
2	Crosspovidone	10	-
3	Mannitol	86	15
4	Magnesium stearate	1.42	1.42
5	HPMC (K4M)	-	150
6	HPMC (K100M)	-	100
7	Talc	2.85	2.85

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4. EVALUTION PARAMETER FOR COMPRESSED BILAYER TABLET

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling and was determined using Monsanto hardness tester.

Procedure: Three tablets were randomly picked. The lower plunger was placed in contact with the tablet and a zero reading was taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. The force of fracture was recorded and zero force reading was deduced from it. Then average hardness (Kg/cm^2) and standard deviation was calculated.

Table: 11 Hardness test of bilayer tablet

Parameter	Observation (Kg/cm^2)
Hardness	7.3±0.19

Friability test

Roche friabilator used to determine tablet Friability. It is expressed in percentage (%).

Procedure: 10 tablets were initially weighed (W initial) and transferred in to the friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (W final). The % friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

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Table: 12 Friability of bilayer tablet

Parameter	Observation	Reference
% Friability	0.74±0.059	Not more than 1%

Where all values are mean ± S.D. forn=3

Weight variation test

The weight variation were done by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average.

Table: 13 Weight variation of bilayer tablet

Parameter	Observation(mg)	Reference(Lachman et al.,1991)
Weight Variation	415.8±4.077	±5%

Where all values are mean ± S.D. for n=3

Disintegration test

Dissolution and absorption of a drug from the gastrointestinal tract was done by this method.

Procedure: One tablet was kept in each tube and the basket rack was set in a 1 L beaker of simulated gastric fluid at 37 ± 2°C, such that the tablet remains 2.5 cm. below the surface of the liquid on their upward movement and descends not closer than 2.5 cm. from the bottom of the beaker. A standard motor driven device was used to move the basket assembly containing the tablets up and down through a distance of 5.to 6 cm. at the frequency of 28-32 cycles per minutes. Time at which there is no fraction of tablet present in tube was noted.

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Table: 14 Disintegration time for bilayer tablet

Parameter	Observation
Disintegration time (sec.)	28.16±1.47

Where all values are mean ± S.D. for n=3

Drug content

Procedure: Ten tablets were weighed and powdered in a pestle mortar to get fine powder; powder equivalent to weight of one tablet was dissolved in methanol & kept for 30 min and filtered through Whatman's filter paper and 1ml of this solution was taken in a test tube and volume made up to 10ml with methanol. The drug content was determined spectrophotometrically at 277 nm using an UV spectrophotometer.

Table: 15 Percent Drug content in bilayer tablet

Drug	Observation (%)
Saxagliptin	96.22± 2.16%

Where all values are mean ± S.D. for n=3

In-vitro dissolution studies

Procedure: In-vitro dissolution of bilayer tablets containing Saxagliptin was performed using 0.1 N HCL as the dissolution media at 50 rpm using an USP Apparatus I. The dissolution study was carried out in a 900 ml volume of 0.1N HCL at 37°C (± 0.5) using the paddle apparatus method.10 ml of sample was withdrawn and replaced with fresh dissolution medium at the time intervals of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16 and 24 hrs for bilayer. l0ml sample was filtered through a 0.45 □m membrane filter. The concentration of Saxagliptin in samples was determined by taking UV absorbance method.

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Table: 17 Cumulative percentage drug release of bilayer tablet

Sr. No.	Time (hr.)	% Cumulative drug release
1	0	0
2	1	26.40
3	2	33.31
4	3	41.17
5	4	44.79
6	5	48.70
7	6	52.24
8	7	56.80
9	8	61.59
10	9	64.89
11	10	70.16
12	11	75.29
13	12	80.89
14	14	83.16
15	16	89.31
16	24	96.63

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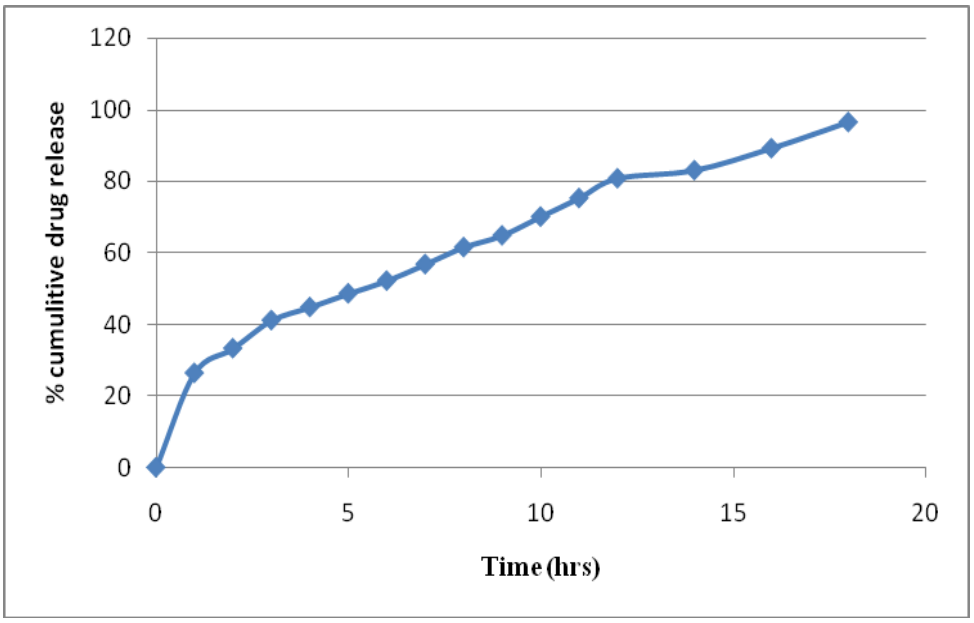

Figure: 18 Cumulative percent drug release of Saxagliptin bilayer table

5. CONCLUSION

The present study demonstrated the successful preparation of once daily conventional release bilayer tablet of Saxagliptin. The project work entitled, formulation development, and optimization of Saxagliptin bilayer tablet was carried out in the present study it was mainly concentrated on the optimization of the formulation based on compatibility study with IR as well as some other parameters. The Optimized formulation I3 and S9 was studied for the drug content and in-vitro drug release. Tablet blends were evaluated for various parameters such as bulk density, tapped density, and tablets were evaluated for thickness, drug content, hardness, and weight variation. It was revealed that the tablets of all batches had acceptable physical parameters. In the present study Saxagliptin 60mg tablets have been formulated and developed using direct compression and dry granulation technique, to provide a safe, highly effective method for treating congestive heart failure, edema and kidney disorder, while reducing undesirable adverse effects. Pre and post formulation parameters were studied for the formulated batches.

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