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International Journal of Advanced Science and Technology
Vol. 28, No. 16, (2019), pp. 1649-1663

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATIRX TABLET OF VILDAGLIPTIN USING NATURAL AND SYNTHETIC POLYMERS

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Abstract
The aim of this paper was to evulate vidagliptin matrix tablet of 50 mg. Vildagliptin is an anti diabetic drug of new dipeptidylpeptidase – 4 (DPP-4) inhibitor class of drug Vildagliptin is one of the best passed relefing and short acting drug. Medication is developed in such a way that will provide the full advantage of SR formulations. The natural polymer like pectin was utilized in the formulation of the matrix tablet with the help of wet granulation technique we can find out the characteristics and evaluation of drug containing vildagliptin. Pectin is one of the hydrophilic polymer was utilized in the formulation of these tablets and all the formulation showed the pharmacopeian standard. There are six different types of formulation of drugs with polymer concentration, first three drugs contain pectin polysaccharide and the other three contain polymers combination of pectin HPMC K100M- F1 (1:1), F2 (1:2), F3 (1:3) F4 (1:1), F5 (1:2) and F6 (1:3). Some all the above formulation F6 is the best and show best result up to 12 hrs. It is also absorbed that F6 with pectin combination shows better sustain effect. These result shows that drug release kinetic was absorbed by increasing their polymer concentration. The data which was collected was fitted to various models (mathematical model) like higuchi, first- order and zero order, to find out the mechanism of drug release. F6 shows higuchi model. So the present study evaluate the drug release (vitro) by interchanging are changing the amount of polymer according to patient compliance and improvement.

Keywords:
Tablet, Solubility, Drugs, Vildagliptin, Parameters, higuchi, Evulation

Introduction

Sustained release dose are made up in such a way to get long therapeutic result over a long period of time after the release of single dose. Various dosage are focused, filtered, modify, arrange, to enhance the drug time of act[1]. Conventional drug needs periodic dosage of therapeutic agents. these agents are designed to get maximum stability, availability, activity. Various method for used to get the large and long therapeutic range, but only some drugs are not stable and so small therapeutic range. Few drugs have solubility issue, so in order to remove these issue various methods like continuous administration of therapeutic agent to get a fixed and stable plasma levels. To remove these problems a system was introduced called controlled drug delivery system. These systems have lot of uses over traditional system like reduced toxicity and improve patient convenience. The main aim of this system is to maintain and improve the effectiveness and uses of drug therapies. Oral dosage form is design in such a way so that it can release immediately to GI tract in a pre-determine fraction. This fraction of drug give desired pharmacological action. A maintained dose is release of the fraction in constant rate. The absorption rate should be equal to the removal rate of drug from body. After completing this a pharmacological response is needed so waited[2]. Vildagliptin is oral antidiabetic drug for type 2 diabetic patients; it is blocking the dipeptidyl peptidase 4 (DPP-IV). Vildagliptin 50mg twice daily is generally safe in patient with diabetic disorder. Vildagliptin have a very short half-life period and get

ISSN: 2005-4238 IJAST

fastly absorbed in gastrointestinal tract. So it is given via tablets, This process is not so good for the patient as the patient will come into trouble due to several administration. It may also cause fluctuation in plasma drug concentration result in side effects. To over come all this advantages a extended release formulation can be used with double combination of sulphonylurea.The recommended dose of vildagliptin is 50 mg once daily administered in the morning. Vildagliptin 100 mg daily was not so successful than vildagliptin 50 mg once daily. A lower dose of sulphonylurea, reduse the risk of hypoglycaemia.Vildagliptin is used for type 2 or non-insulin dependent diabetes. It can trigger the amount of insulin in the body it may also decrease the amount of glucagon in the body. Due to these effect the the vildagliptin help in controlling blood sugar levels in diabetes patient[3-4].

Materials and Method

vildagliptin was a gift sample from Bharat immunologicals and biologicals Corporation Bulandshahr.HPMCK100M & MCC form Kalpana polymer private limited Mumbai, pectin is extracted from orange peels, the fruit was purchased from the local market of Meerut.

Standardization of drug

UV Spectrophotometric method for Vildagliptin:-

The drug vildagliptin was analyzed by using LAB INDIA UV-1800 spectrophotometer having double beam detector configuration. Calibration curve of vildagliptin was plotted in 0.1N hydrochloric acid at the maximum wavelength of 273nm[5].

Micrometry Study

A) Angle of repose powder

Mostly funnel is used find out The angle of repose of powder, in this method firstly weight of the powder and it taken in a funnel, the height (h) funnel is place in a stand the funnel was set such a way that tip of the funnel is just touches the apex of the mass of the powder, after the powder is place in the funnel to freely flow, then the angle of repose of the powder is find out. Range of repose cans zero degree. The angle of repose of the powder is found out the following formula[6].

Tan θ= h/r (1) ..... (1)

Therefore, θ = tan height/ radios

Here, θ = angle of repose

h = height of the pile

r = radius of the pile base

B) Bulk density

Bulk density is formulated by adding a known mass powder to a cylinder. The density is formulated as mass.

Tapped density in this method firstly we have to weigh the known powder and then the known powder transfer in a 10 ml mechanically tapping cylinder. The tapping is started until the little further volume changed is observed[7].

C) Bulk density calculated by following equation

Loosen bulk density = total mass of powder /volume of powder

Tapped bulk density = powder wt. / tapped volume

D) Carr's index

Carr's help in measuring the power need to breakdown the friction into the particle & the hopper. Carr's index > 25 % is carefully to be a sign of low flow capability, and under 15, of good flow property It can be calculated by following equation[8-9].

Carr's index (%) = [(total bulk density –loosen bulk density) ×100]/TBD

Where TBD = tapped bulk density ..... (2)

E) Fourier transformation infra –red analysis

Drug- excipients compatibility studies the infra red absorption spectra of unmixed drug & with unalike ingredient were hold in the scale of four hundred thousand to four hundred **cm-1** using KBr dise procedure, 1-2 milligram of material to be analyse was mixed with 300-400 mg, specified quantity of minute powder & dried KBr these sum are mainly enough to give a circle of 10-15 diameter and pellet of right strength by a hydraulic press[10].

Prepration Of Vildagliptin Matrix Tablets

Method of preparation

Vildagliptin 50 mg tablet were prepared by using different polymer as pectin HPMC with their different concentration like 50, 100, 150, 25,75mg and make different formulation with different polymer by using different ratio. The weight quantity of drug and polymer were mixed well in mortar pastle and passed through sieve no 40. Starch solution was used as a binding agent with water. The granules of produced were dried at 50**°C** for 30 min. After this process of drying the granules were transferred via sieve 22-25. Magnesium stearate add to the granules. And then compress 16 station rotation tableting machine[11].

Formulation series

Table 1: Formulation series of vildagliptin sustained release matrix tablets

Formulation code	Drug	Pectin	HPMC	MCC	Mg stearate	Total
F1	50	100	-	97.5	2.5	250
F2	50	50	-	147.5	2.5	250
F3	50	150	-	47.5	2.5	250
F4	50	50	50	97.5	2.5	250
F5	50	25	25	147.5	2.5	250
F6	50	75	75	47.5	2.5	250

Evaluation parameters of matrix tablet

Physiological parameter or post compressional parameters of all formulations

A) Tablet hardness

Tablet hardness is laboratory techniques in this technique we have check the hardness of tablets in case of storage and handling before usage. The hardness of the tablets we can perform by using the hardness taster like Monsanto hardness taster, 6 tablets each batch crushing with known weight was recorded in kg/cm2 and average weight was calculated[12].

B) Tablet thickness

Tablet thickness is done for equality of tablet size. Tablet thickness would be control within a 5% difference of standard value. 20 tablets taken from the batch and individual tablet thickness was measured with using digital vernier[13].

C) Friability of tablets

Friability is defined as it is capacity of a solid material break into smaller pieces in case of transportation. Friability follows the following procedure. Firstly 20 tablet taken and weight accurately and place in a plastic chamber and set the chamber at 25 rpm for 4 minutes, after the 4 min and 100 revolutions stop the Roche apparatus and reweight the 20 tablets and Calculate the loss in tablet weight by the following formula[13].

%weight loss = initial of tablet – final weights of tablets/ final weights ×100 ..... (4.3)

D) Weight variation

Weight variation is define as to ensure that each of tablet carry proper amount of drug. This method is performed as, weight of 20 individual tablet using analytical balance, after that calculate the average weight of tablet, and after that calculate the individual tablet weight to the average[14].

% of weight Variation = average wt–average wt individual wt / average wt×100 ..... (4.4)

E) Uniformity of drug content

We have taken 10 tablets into a mortar and make a fine powder of tablets; exactly weight portion of powder equal to 50mg of vildagliptin was taken to 100ml volumetric flask hold 70 ml of 0.1N HCL. And then shake for 1 hrs by mechanical then it was fitted by filtered by a whatman filter paper and diluted to 100ml with pH 6.8 phosphate buffer. 1 ml was taken by this solution, diluted to 50 millilitres by 6.8 buffers and 273nm absorbance was measure against blank 273nm[15].

F) Dissolution studies

Drug release was estimated by dissolution test by following n=3, united state pharmacopoeia type 2 dissolution equipment (paddle method) at 50 rpm in 900 millilitres of 0.1N HCl and for 1 to 12 hrs, keep at 37±.5°°C a hole (5 millilitre) was introverted at identified time interval & restore with the same volume of pre heat (37 °C ± 0.5°C**)** fresh dissolution way, the sample was analyzed by UV-visible spectrophotometer at 273nm[16].

Kinetic parameters of all formulations

The dissolution view of main acceptable preparation is provide to zero order, 1st order & higuchi model to know the mechanism modelling of liberate the model was adopted for determining the proper model.

1. Cumulative percent drug released v/o time (zero order kinetic models)
2. Log cumulative percent drug released v/s time (1st order kinetic model)
3. Cumulative percent drug released v/o square root time (higuchi model)
4. Cumulative log c v/o log T drug (peppas model)

1) Zero order

A zero order response in few reactions, the measure is adequately equivalent of the reactant concentration the rate of zero order reaction dose not very neither grater nor lowering reactants alternativeness means equal to the rate continual, (k) of the reaction.

2) First order reaction

First order reaction is defined as that proceeds at a rate on rectilinear on single reactant concentration.

3) Higuchi model

A huge number of modified release formulation have few sort matrix system in such instances, the moiety dissolve from the matrix, the dissolution pattern of drug is dictated by H2O perforation, in this higuchi method, a plot of cumulative % moiety released v/o square root of time is linear.

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4) Krosmeyer-Peppas model

The Krosmeyer peppas model empirical related the function of time for diffusion controlled mechanism; it is given as followed:

$$Mt / M\infty = ktn \quad \text{..... (4.5)}$$

Here

Fraction of drug release time = $Mt/M\infty$

Release rate constant = Kt

The release exponent = n

Stability Studies:

Stability studies are one of the most vital and precious part for the improving of the life of pharmaceutical dosage form. They allow the evaluation of active pharmaceutical ingredient (API) Drug product stability studies is finding out of the main acceptable preparation as per international conference of harmonization guideline at 40**±2°C/** 75± 5%. There is a no major change in the physical and chemical properties of tablet of formulation F6 after 3 months. Table 5.8 showing the all parameters at various time intervals[17].

Result and Discussion

Preformulation studies

UV Spectrophotometric method for vildagliptin

Preparation of calibration curve in 0.1N hydrochloric acid

Table 2: calibration curve data of vildagliptin in 0.1N hydrochloric acid

Concentration (µm/ml)	**Absorbance**
2	0.07
4	0.13
6	0.21
8	0.274
10	0.351

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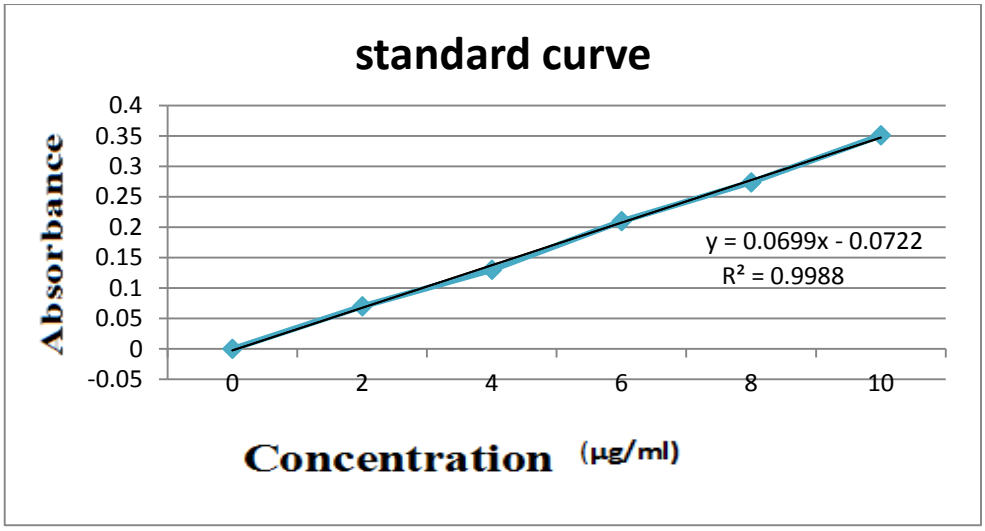

Figure 1: vildagliptin in 0.1N HCL

MICRCOMETRY STUDY:-

Micrometrics properties like tapped density, bulk density, Carr's index etc of whole formulation of sustained release matrix tablet (SRMT) of Vildagliptin were performed & found the relevant data, shown in below table.

Table 3: Micrometrics properties of sustained release matrix tablet of vildagliptin

Formulation code (F)	**Angle of repose (Ɵ)**	**Bulk density (gm / cm3)**	**Tapped density (gm/ cm3)**	**Carr' index**
F1	25.10±0.7	0.44±0.04	0.52± 0.03	1.18± 0.02
F2	26.79±0.16	0.42±0.03	0.49±0.04	1.17±0.04
F3	24.54±0.06	0.42±0.03	0.51±0.06	1.19±0.02
F4	25.38±0.7	0.44±0.08	0.52±0.09	1.18±0.03
F5	**27.56±**0.04	0.41±0.09	0.48±0.04	1.17±0.04
F6	28.10±0.05	0.43±0.03	0.50±0.04	1.16±0.03

Mean± SD (n=3)

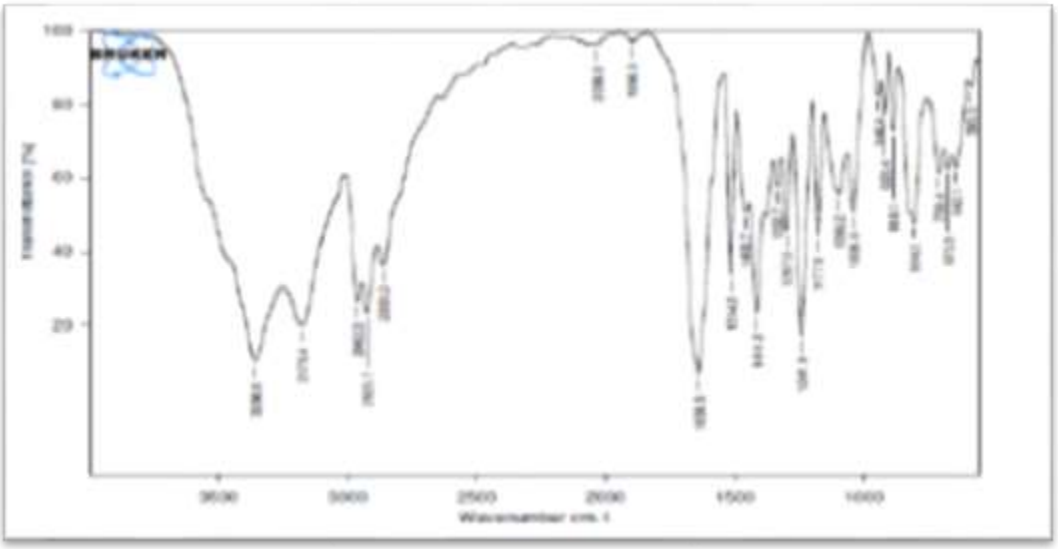

Fig 2: spectra of vildagliptin

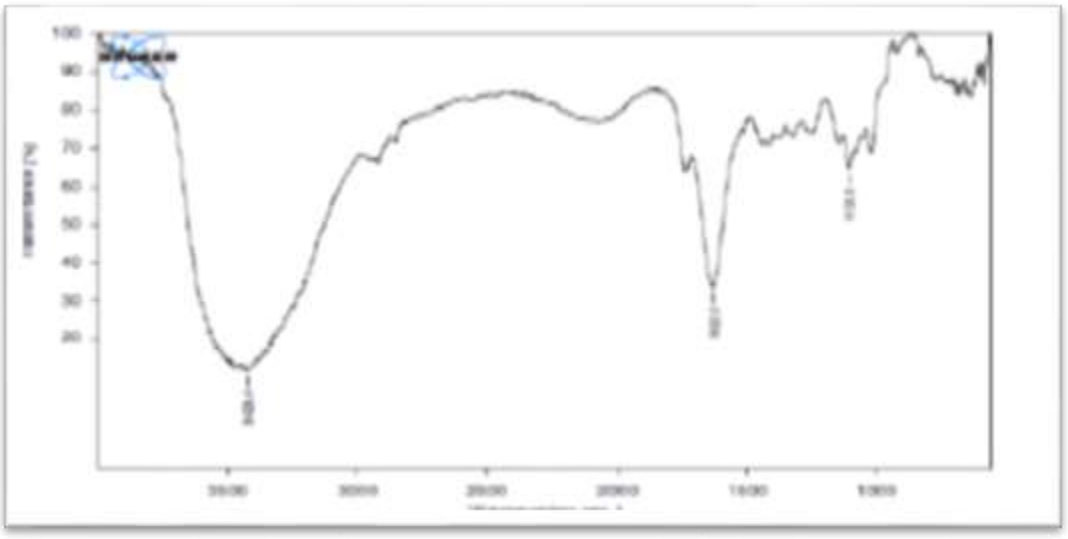

Fig 3: Spectra of pectin

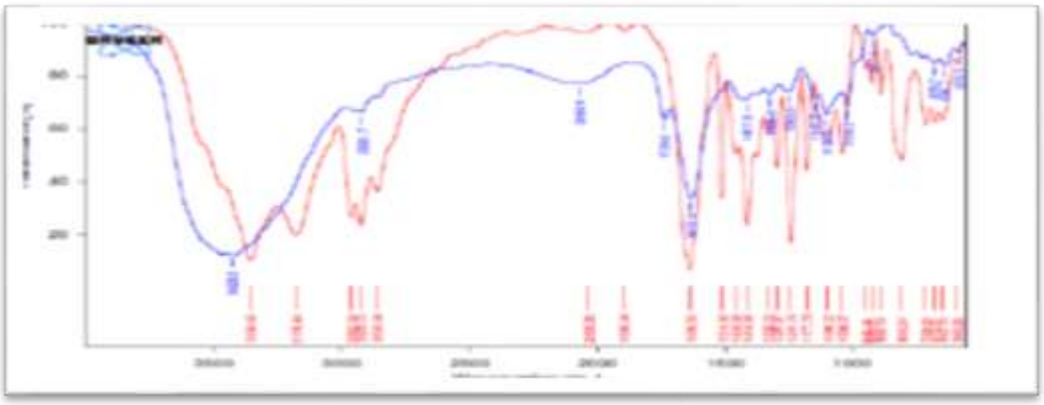

Figure 4: FTIR spectrum of drug+ pectin and optimized formula

Fourier transformation infra –red (FTIR) analysis

Table 4: FTIR spectrum analysis

S. No	Frequency, cm -1	Bond	Functional group	Pure drug (vildagliptin)	Drug +pectin
1	3300-3500	=CH- stretch	Alcohol	3356.6	3423.4
2	1680-1620	C=O	Alkenyl	1639.53	1637.4
3	920-675	C-H	Aromatics	917.5	946.44

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EVALUATION PARAMETERS:-

Post compression or physical parameters as (hardness test, weight variation, friability thickness and drug content) of vildagliptin tablet performed and found the relevant data shown in below table.

Table 5: Evaluation parameters

Formulation code (F)	**Hardness (kg/cm2)**	**Thickness (mm)**	**Friability (%w/w)**	**Drug uniformity (%)**	**Weight variation (mg)**
F1	**4.2**±0.08	3.82±0.02	0.26±0.03	99.6±0.25	248±4.1
F2	4.0±0.05	4.15±0.08	0.35±0.02	99.0±0.30	249±7.2
F3	4.3±0.07	4.20±0.02	0.28±0.02	99.4±0.25	252±4.1
F4	4.7±0.03	3.99±0.05	0.28±0.04	99.2±0.47	247±3.6
F5	4.5±0.03	3.97±0.06	0.33±0.03	99.3±0.37	249±2.7
F6	4.9±0.09	4.20±0.14	0.5±0.03	99.5±0.31	252±6.9

Mean± SD, n = 3

DISSOLUTION STUDY:-

In vitro, the percentage drug released study of vildagliptin tablet was performed with different polymers concentration at different intervals (1 to 12 hrs) & found the relevant data showing below.

Table 6: Percentage drug release in 12 Hours at 0.1N HCL Dissolution medium.

Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	34.2±0.12	31.5±0.11	27.1±0.12	37.3±0.12	32.4±0.09	19.5±0.09
2	62.3±0.12	55.1±0.09	47.4±0.14	63.3±0.12	53.2±0.07	30.6±0.29
3	63.7±0.14	60.5±0.14	50.6±0.11	69.4±0.09	61.3±0.08	35.2±0.19
4	77.4±0.17	68.4±0.17	58.8 ±0.15	75.6±0.11	69.1±0.05	43.4±0.08
5	85.3±0.16	81.5±0.13	69.9±0.14	76.9±0.12	76.3±0.06	56.8±0.15

ISSN: 2005-4238 IJAST

6	87.4±0.18	84.7±0.16	76.2±0.12	78.5±0.13	78.4±0.07	62.7±0.16
8	87.5±0.5	86.8±0.15	82.5±0.13	79.2±0.06	80.2±0.24	71.9±0.06
10	87.6±0.3	86.9±0.6	85.9±0.14	80.7±	83.3±0.07	88.3±0.14
12	87.7±0.4	87.1±0.9	86.4±0.5	83.4±0.8	84.4±0.8	95.1±0.03

Kinetic parameters of optimized formulation

Fig 5: zero order release kinetics

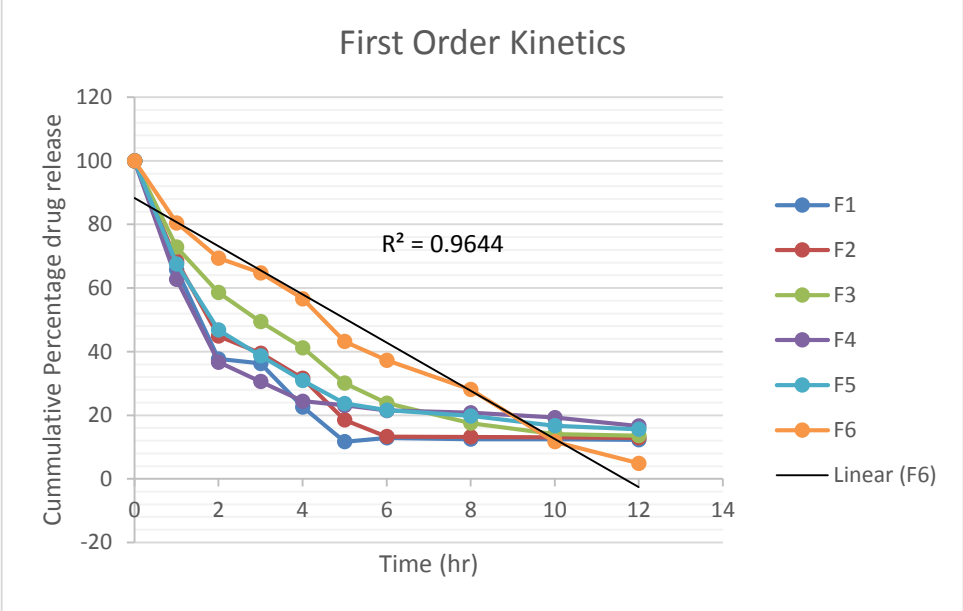

Fig 6: First order release kinetics

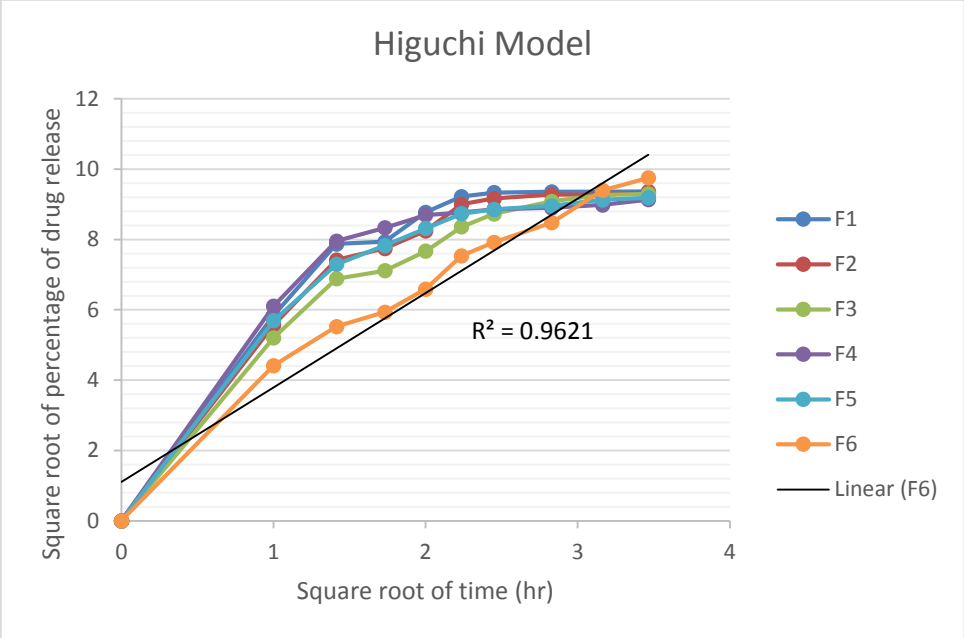

Fig 7: higuchi model

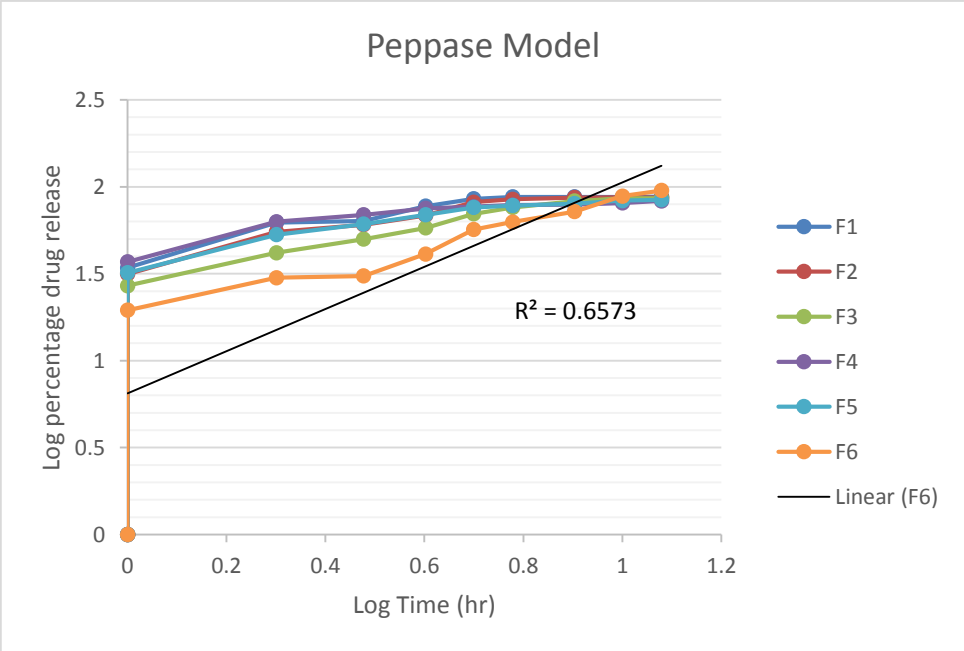

Fig 8: peppas model

Release kinetics parameter of vildagliptin tablet:-

Table 7: release kinetic for the optimized formulations

Formulation	Zero order	1st order	Higuchi model	Peppas model
	R^2	R^2	R^2	R^2
1	0.604	0.595	0.752	0.465
2	0.677	0.672	0.792	0.491
3	0796	0.811	0.853	0.547
4	0.542	0.542	0.699	0.427
5	0.668	0.668	0.776	0.479
6	0.668	0.964	0.962	0.657

STABILITY STUDY:-

Table 8: Stability study of best formulation F6

S.No	Parameter	Initial	1st month	2nd month	3rd month
1	Appearance	White	No change	No change	No change
3	Drug content	99.5	99.5	99.2	99
4	Hardness	4.9	4.9	4.7	4.5

5	Friability	0.5	0.5	0.6	0.8

Summary and conclusion

The main goal of these present research work was formulation and evaluation of sustained release vildagliptin matrix tablet by using natural and synthetic polymers. With the use of wet granulation process, Different studies such as preformulation, kinetics, stability studies were performed. It is widely used understand that which polymer were give the better matrix form to the tablets that help in sustained release of the tablets.The formulation developed by using different drug ration as pectin (100; 50; 150; 25; 75), HPMC K100M (50; 25; 75) uses for further examination. Vildagliptin tablet undergo the preformulation study with various formulation (F1-F6) to find out angle of repose, bulk density, tapped density and Carr's index. It shows the relevant data (F1-F6) angle of repose (25.10±0.13 to 28.10±38), Bulk density (0.44±0.002 to 0.43±0.003), tapped density (0.52±0.003 to 0.50±0.004), Carr's index (1.18±0.002 to 1.16±0.011). Characterization & evaluation is the most important part in the scheme, it helps to study the physical parameters of the tablet such as hardness test, friability weight variation, thickness. The founded data of different formulations (F1-F6) such as, hardness (4.2±0.08 to 4.9±0.09), thickness (3.82±0.02 to 4.20±0.14), and friability (0.26±0.03 to 0.5±0.03), weight variation (248±4.1 to 252±6.9). *In vitro*, the % drug released study of vildagliptin tablet was performed with different polymers concentration (pectin -100,50mg 50,50mg 150,50mg 25,50mg 75,50mg HPMC- K100M 50,50mg 25,50mg 75,50mg) at the different intervals (1 to 12 hrs). During the each interval tablet show different percentage of drug release, after 12 hrs, formulation (F6) which was formulated with pectin 75mg and HPMC 75mg shown the batter sustained release of the (95,1±0.03). The kinetic property was necessary to find out the nature of the formulated tablet. In *vitro* drug release data of (F6) were fitted into various kinetics models.

Conclusion

It was concluded that the sustained release matrix tablets of Vildagliptin were successfully developed in order to get the drug release rate by using pectin as release retardant. The present work, "Formulation and Evaluation of Vildagliptin sustained Release Tablets" was undertaken with an aim to formulate Vildagliptin sustained Release tablets. During this phase of investigation various factors that affect the performance of the sustained release was examined. Wet granulation method was formulated. Granules were evaluated for tests such as bulk density, tapped density, Compressibility Index and Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness and friability, in-vitro dissolution test were performed & % drug release was studied. Dissolution tests were performed and percentage drug release was calculated. Dissolution profile of Formulation – F6 was optimized based on evaluation parameters. In the dissolution modelling all the developed formulations followed higuchi-peppas drug release. The optimized formulation F6 followed zero order drug release. The developed formulation was tested for its stability for three month and found to be stable. In this research, pectin was found to play a great role in controlling release of drug Vildagliptin sustained Release tablets from the matrix system. Accordingly, it can be concluded that the formulation is used in the performance is very less effected by different factors studied and examined.

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