ISSN 2581-6217

World Journal of Pharmaceutical Science & Technology

Journal homepage: www.wjpst.com

Review Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION CHARACTERISTIC OF VILDAGLIPTIN BY USING SOLID DISPERSION TECHNIQUE

Gawande Rushikesh S.,*[1]Landage Dhananjay A.[2]

1. H.s.b.p.v.t's parikrama college of pharmacy, kashti, shrigonda
2. H.s.b.p.v.t's parikrama college of pharmacy, kashti, shrigonda

Address for correspondence:

Gawande Rushikesh S., H.s.b.p.v.t's parikrama college of pharmacy, kashti, shrigonda.
E-mail- **rushikeshgawande376@gmail.com**

Received: 15-3-2022, Revised: 29-3-2022, Accepted: 1-4-2022

ABSTRACT

Current study aim is to raise the dissolution rate of a water-soluble drug, Vildagliptin by the solid dispersion technique. Vildagliptin belongs to a class of orally active anti-diabetic drug which inhibits dipeptidyl peptidase-4 (DPP-4) and to raise the emission of insulin in the β-cells, thereby decreasing blood glucose level. Solid dispersion is the system made up of one or more active ingredients which are dispersed in inert carrier in a solid state. SD are classified as follows: first generation as crystalline carriers such as urea, second generation amorphous carriers which are generally polymers and third generation carriers with surface activity properties. Generally it contains surfactant or a mixture of surfactants. They are prepared by the fusion method, solvent method and fusion solvent-method. Eutectic mixtures are also form of solid dispersions which are also prepared by fusion method with the help of specific solvents on the basis of a formulation strategy to improve the physical properties of the active ingredient for the enhanced dissolution rate and solubility.

KEYWORDS – Vildagliptin, Vildagliptin Solid Dispersion, Solid Dispersion Methods

INTRODUCTION

Bioavaibility is the most important factors. This factor is used to achieve the optimal concentration of drug which reaches in systemic circulation. When a drug has a poor bioavaibility then it shows slow dissolution

rate, poor stability and solubility of drug and extensive first pass metabolism. Over the past thirty years, because the expense and complication concerned in new entities have hyperbolic with concomitant recognition of the medical aid benefits of controlled drug delivery, bigger attention has been centered on development of sustained or controlled drug delivery system.[1] Increase effectiveness of the drug at the targeted site of action and to reduce frequency of dosing or for providing uniform drug delivery is goal of the formulation. [2] The drug delivery systems(ideal) has require two things first is single dose, the treatment span is either weeks or days, as among infection, or for the life time of the patient, as in hypertension or diabetes. By minimizing side effects active entity directly deliver to the site of action. Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action. [3]

Techniques for improving bioavaibility

1. Enhancement of solubility and dissolution rate
2. Modification of partition coefficient
3. Avoidance of hepatic first pass metabolism
4. Avoidance of degradation in gastrointestinal tract
5. Novel Drug Delivery system.

Oral sustained release products give us benefit over conventional dosage forms which can optimize biopharmaceutics and pharmacokinetic property of drug when it is incorporated in Nanoparticulate system. Pharmacokinetic property includes Bioavaibility of drug. It includes drug delivery system which is achieves drug release over an elongate period of time, which not time dependent. Formulation of Sustained dosage form commonly used polymer matrix which is hydrophilic in nature. Role of ideal drug delivery system to provide proper amount of drug at regular time interval and at target site of action to maintain therapeutic effect of drug in blood plasma [4] Recently, nanoparticles production have been reported and modify to improve the dissolution rate of drugs for pharmaceutical applications which leads to substantial enhance in bioavailability [5]. Nanoparticles engineering enables poorly soluble drugs to be formulated as particles alone, or with a combination of pharmaceutical excipient. Increase in the surface area and related dissolution rate by decreasing the particle size from a micron to a nanometer [6]

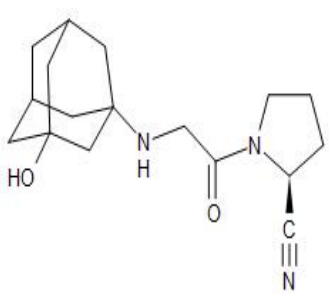


Fig No. 1 Chemical Structure of Vildagliptin

Vildagliptin is an anti-diabetic agent i.e. oral hypoglycemic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. The drug inhibits the inactivation of GLP-1[7] and GIP[8] by DPP-4, allowing GLP-1 and GIP to enhance the emission of insulin in the beta cells and also repress glucagon release by the Langerhans cells which is present in the pancreas (alpha cells).

MATERIAL AND METHOD

Material

Vildagliptin was gift sample from Chemicea Pharmaceuticals Pvt Ltd. Pune. Polymers like Thiourea, Chitosan Chlorhydrate, PVP procured from Thermosil fine chem. Pune.

Methods

EXPERIMENTAL WORKS

DEVELOPMENT OF CALIBRATION CURVE:

Preparation of Buffer Solution (pH-1.2)

250 ml of 0.2M Potassium chloride solution (14.911 gm of KCL in 1000ml) and 425ml of 0.2N Hydrochloric acid (7.292 gm in 1000ml) were mixed properly and the volume was made up to 1000 ml with distilled water.

Preparation of Standard Solution of Vildagliptin

A Solution of 5mg Vildagliptin was prepared by dissolving in 100 ml methanol, from which 1ml was withdrawn in separate volumetric flask and diluted to 10ml with HCl buffer to produce 5µg/ml concentration and absorbance at 240 nm.

Preparation of Working Solution:

From standard solution, 0.5, 1, 1.5, 2, 2.5, and 3ml was withdrawn in six 10ml volumetric flasks and diluted to 10ml with HCL buffer pH 1.2 to produce concentration 2.5, 5, 7.5, 10, 12.5 and 15 respectively. The solutions were analyzed by U.V. spectrophotometer at 240nm and results were recorded. The calibration graph was plotted as concentration on X-axis Vs absorbance on Y-axis

PRILIMINARY INVESTIGATIONS:

a. Screening of Carrier

Carriers used for study were PEG-6000, Thiourea and Chitosan Chlorhydrate. The Solid dispersion of PEG6000, Thiourea and Chitosan Chlorhydrate were prepared by physical mixing method using ratio 1:1 of Drug: Carrier and were screened for yield, texture and color, physical characteristics and suitability in preparation.

b. Effect of Carriers solubility:

Known amount of samples of solid dispersion was added in 50 ml of distilled water and kept for 24 hrs occasional stirring. After 24hrs contents were filtered by the wattman filter paper, and appropriate dilutions

were made with 0.2N HCl buffer and absorbance of the resultant solution was measured at 245nm and extrapolated on standard graph to determine the concentration.

c. Loss on drying:

Procedure: Loss on drying is directly measured by IR moisture balance. Firstly calibrated the instrument by knob then taken 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

d. FTIR Studies:

To know about the interaction between the drug and carriers used in the formulation, the IR analysis was carried out. The IR spectra of pure Vildagliptin, was studied by FTIR it is scanned over the Frequency range of 4000-400 cm^{-1}.

e. Compatibility Studies of Drug and Excipients

In the compatibility testing program, blends of drug and excipients are prepared by triturating the drug with Individual excipients.

Procedure: Taken 50mg accurately weigh of Vildagliptin dry powder and 50mg of excipients and mix the blend of drug and excipients and binary/tertiary blends of extract and excipients were prepared and transferred to inert glass vials.The mouths of the vials were covered with rubber closures followed by the aluminum seal caps. Binary/tertiary blends of extract and excipients, Vildagliptin neat and excipients were stored at $4^{\circ}C$ (refrigerator) as control and at $40^{\circ}C$/75%RH for accelerated stability studies for 4 weeks. The visual observations (color, flow, & sticking) were recorded after one month. Therefore formulation remains stable for sufficient time.

FORMULATION OF SOLID DISPERSION

Preparation of solid dispersion by Physical mixture method

Physical Mixture of drug with PEG6000, Thiourea and Chitosan Chlorhydrate were prepared by separately at three different ratios 1:1, 1:2 and 1:3. Accurately weighed 100mg drug was taken and mixed with 100, 200 and 300mg of PEG6000, Thiourea and Chitosan Chlorhydrate Physical mixture were prepared by triturating the powder mix in pestle mortar for 3 to 5 minutes. Subsequent to this the mixture was passed through sieve number 60 having mesh size of 250µm. Then accurately weighed 50mg of physical mixture of Vildagliptin was used sprinkled directly to surface of the dissolution medium and dissolution studies were carried out with TYPEII (LABINDIA, DISSO 2000) dissolution apparatus at a stirring speed of 100 rpm and 0.2 M hydrochloric acid at (pH 1.2) 37 ± 0.5°C as the dissolution medium.

EVALUATION OF SOLID DESPERSION

Estimation of Drug Content

The drug contents in solid dispersion were determined by the UV- spectroscopic method. An accurately weighed quantity of solid dispersion and nanoparticles equivalent to 5 mg of VLBM was transferred to a 100 ml volumetric flask containing 100 ml of methanol and dissolved. The solution was then filtered through the filter paper. 1 ml of this solution was diluted 10 times with 0.2 M HCL buffer solutions and the absorbance was measured at 240nm.

Particle size analysis of solid dispersion

An ordinary compound microscope was used for this purpose. The ordinary microscope is used for the measurement of particle size in the range of 0.2 to 100µm. Test material, diluted or undiluted is mounted on a slide and placed on a mechanical stage. The eyepiece of the microscope is fitted with a micrometer, using which the sizes of particles are determined. Eyepiece micrometer should be calibrated using a standard stage micrometer. In this, one millimeter is divided into 100 equal divisions and hence, each division is equal to 10 µm. The eyepiece micrometer, which is linear, consists of 100 divisions. Calibration is undertaken to find out the measure of each division.

IN- VITRO RELEASE STUDIES

IN-VITRO dissolution studies of all formulations were carried out using 900 ml of 0.2 M hydrochloric acid at (pH 1.2) 37 ± 0.5°C as the dissolution medium in a Type II apparatus (LABINDIA,DISSO 2000) at a stirring speed of 100 rpm. Accurately weighed pure Vildagliptin solid dispersions and nanoparticles containing 50 mg of GB was used sprinkled directly to surface of the dissolution medium. Five milliliter sample solution of dissolution medium were withdrawn at the time interval 10, 20, 30, 40, 50 and 60 min and immediately replaced with an equal volume of the dissolution medium (maintained at 37 ± 0.5°C) in order to maintain constant volume of dissolution medium. The withdrawn samples were filtered and analyzed for drug content at 240 nm and cumulative percentage of drug dissolved was calculated. The amount of drug removed in each sample was compensated in the calculations. All experiments were performed in triplicate. Drug release kinetics was also determined for Different kinetic models (zero-order and first-order).

KINETIC ANALYSIS OF DISSOLUTION DATA

Drug release kinetic mechanism

To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches were fitted to zero order and first order to ascertain the kinetic modeling of drug release.

Zero order:

In many of the modified release dosage form particularly controlled or sustained release dosage form (those dosage forms that release the drug in planned, predictable and slower than normal manner) is zero order kinetics.

$$Q=K_0t$$

Were, Q is the amount of drug release at time, t and K_0 is the release constant.

First Order:

The dissolution data was fitted to first order equation

$$In(100-Q) = In100 = k_1t$$

Were k_1 is the release rate constant

Preformulation Studies:

Development of Calibration Curve:

Table No: 2 Standard Calibration Curve of Vildagliptin

Sr. No	Concentration	Absorbance
1	0	0
2.	5	0.098
3.	10	0.203
4.	15	0.306
5.	20	0.399
6.	25	0.501

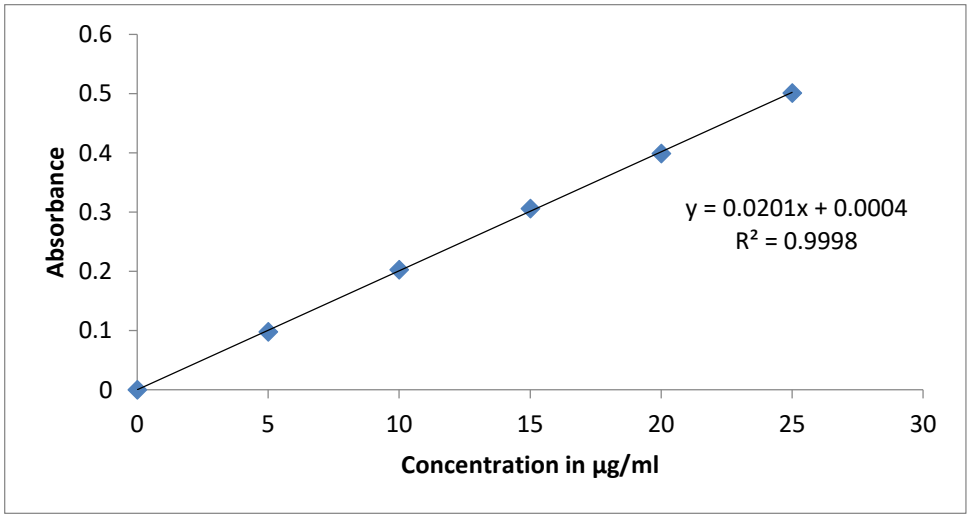


Figure No. 2: Standard calibration curve of Vildagliptin

PRILIMINARY INVESTIGATIONS:

a) Screening of Carriers:

For the screening study, the carriers PEG 6000, Thiourea, Chitosan Chlorhydrate were used to prepare solid dispersion of Vildagliptin. The observations of the screening study are shown in Table No: 6.3. From

the screening studies, it was possible to prepare the solid dispersion system of Vildagliptin by physical mixing method using PEG6000, Thiourea, Chitosan Chlorhydrate.

Table No 3: Screening of Carriers (Drug: Polymer = 1:1)

Carrier	Miscibility	Decolourization	Final Appearance	Colour Appearance	Yield %
PEG600	Miscible	No	Crystalline Solid	White	96.7
Thiourea	Miscible	No	Crystalline Glassy Solid	White	98.9
Chitosan Chlorhydrate	Miscible	No	Fine Solid	Pale Yellow	94.3

b) Effect of Carriers on Solubility of Vildagliptin

To find out the effect of carriers on solubility of pure drug (Vildagliptin), solubility study was carried out using 1:1 solid dispersion in distilled water. The results are shown in Table No: 6.4

Table No 4: Effect of Carriers on Solubility of Vildagliptin

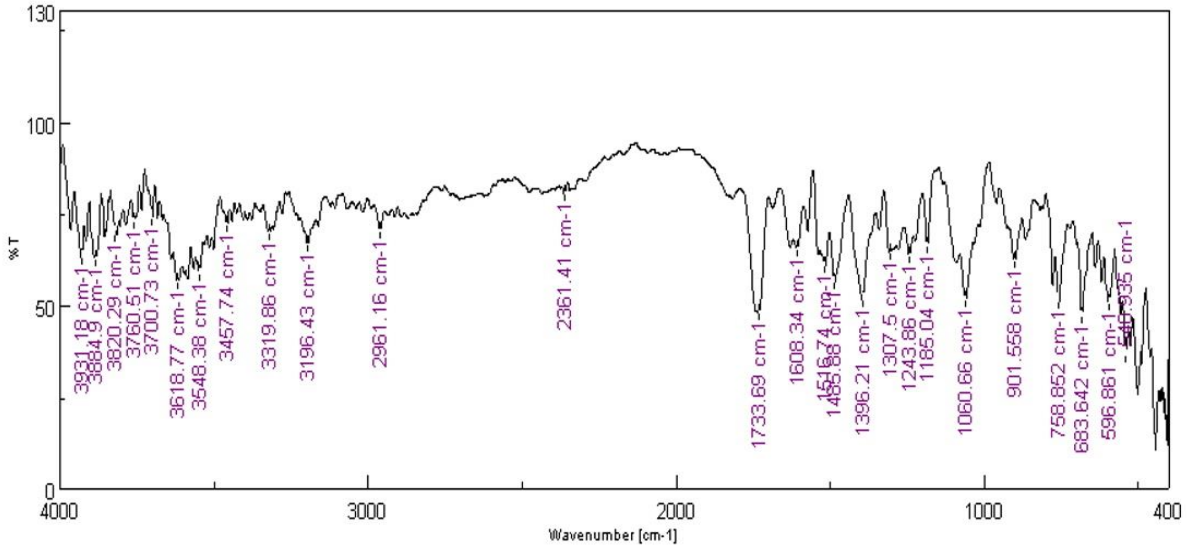
Sr. No	Formulation Code	Solubility mg/ml
1.	**VLG**	1.72
2.	**VLPP1**	1.96
3.	**VLTUP1**	2.21
4.	**VLCCP1**	1.91

c) Loss on Drying:

Table 5: Loss on Drying for Vildagliptin

Test	Specification	Observations
Loss on drying	Not more than 0.2 %	0.1%

d) FTIR Studies:



Compatibility Studies of Drug and Excipients:

Table No.6 Physical Compatibility Drug and Excipients

S. No.	Physical Mixture	Status After 1 Month kept at 25ºC /60%RH & 40ºC /75%RH
1	Vildagliptin + PEG 6000	No Change
2	Vildagliptin + Thiourea	No Change
3	Vildagliptin+ Chitosan Chlorhydrate	No Change

EVALUATION OF SOLID DESPERSIONS:

Estimation of Drug Content

All the Solid dispersions and nanoparticles were extracted with Methanol and the extract was suitably diluted with 0.2N HCl buffer pH 1.2. The Vildagliptin content was estimated spectrophotometrically 245nm. The formulation PEG6000 physical mixing: (VLPP1) 96.9%, (VLPP2) 97.9% and (VLPP3) 98.0%, the formulation Thiourea physical mixing: (VLTUP1) 97.2%, (VLTUP2) 96.1% and (VLTUP3)98.3%, the formulation Chitosan Chlorhydrate physical mixing: (VLCCP1) 95.8%, (VLCCP2) 95.7% and (VLCCP3) 96.5%, The results are presented in Table No: 6.6 and it showed that the percentage of Vildagliptin was ranging from 95-98% in all formulations it reveals that the drug, in all dispersed and conforms homogeneous mixing of drug and carriers. However slight variation of Vildagliptin may be due to physically loss of drug and instrumental or handling error.

Particle size analysis of solid dispersion

Particle size of best releasing formulations were analyzed by using compound microscope the obtained values can be followed: VLPP3 (165.64µ), VLTUP3 (158.42µ), VLCCP3 (162.93µ), results are shown in Table no.6.7

Table No. 7: Particle size of ideal batches of best releasing solid dispersion formulations

Formulations	**Average particle size(µm) ± SD**
VLPP3	165.64±0.31
VLTUP3	158.42±0.51
VLCCP3	162.93±0.43

IN-VITRO RELEAE STUDIES:

In the batches of solid dispersions prepared (Physical mixture) with PEG6000, the maximum dissolution of Vildagliptin, at the end of 1 hour, was observed with 1:3 combination of Physical mixture. At the end of 1 hour, this combination was able to release 27.12% of drug. The least dissolution of Vildagliptin was observed with 1:1 combination, which able to release only 25.23% of Vildagliptin .Whereas, the other combination s 1:2 has released 26.16% of drug after1hr mentioned in table no. 6.8.

In the batches of solid dispersions prepared (Physical mixture) with Thiourea, the maximum dissolution of Vildagliptin, at the end of 1 hour, was observed with 1:3 combination of Physical mixture. At the end of 1 hour, this combination was able to release 42.5% of drug. The least dissolution of Vildagliptin was observed with 1:1 combinations, which able to release only 38.45% of Vildagliptin .Whereas, the other combinations 1:2 have released 40.57% of drug after1hr.

In the batches of solid dispersions prepared (Physical mixture) with Chitosan Chlorhydrate, the maximum dissolution of Vildagliptin, at the end of 1 hour, was observed with 1:3 combination of Physical mixture. At the end of 1 hour, this combination was able to release 31.59% of drug. The least dissolution of Vildagliptin was observed with 1:1 combination, which able to release only 24.63% of Vildagliptin .Whereas, the other combination s 1:2 has released 28.57%of drug after1hr.

It was observed that solid dispersion of drug with Thioura in a ratio of 1:3 showed highest dissolution (42.5%) followed by PEG6000 and Chitosan Chlorhydrate solid dispersion by physical mixing method.

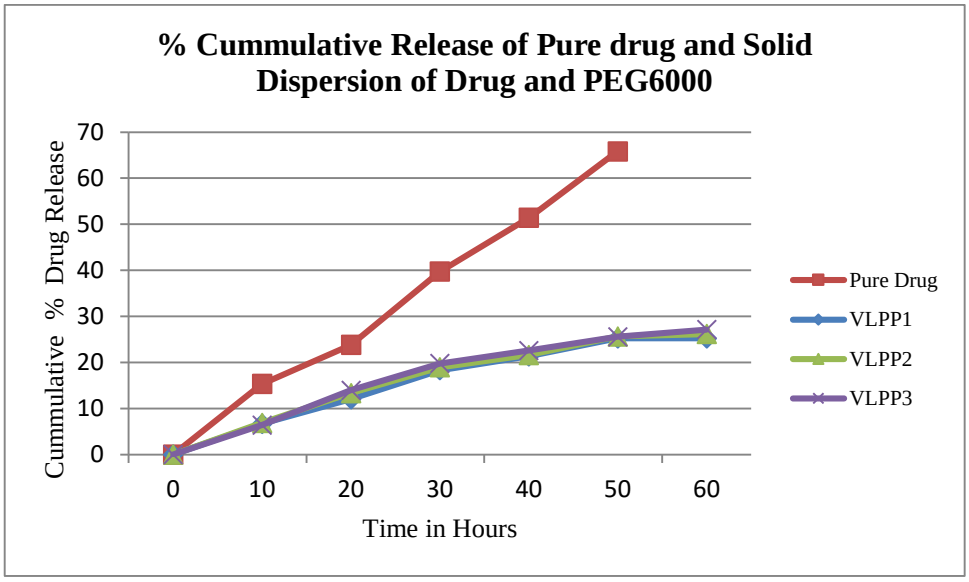


Figure No. 4: Cumulative % drug Release vs. time plot Vildagliptin solid dispersion by physical mixture with PEG6000

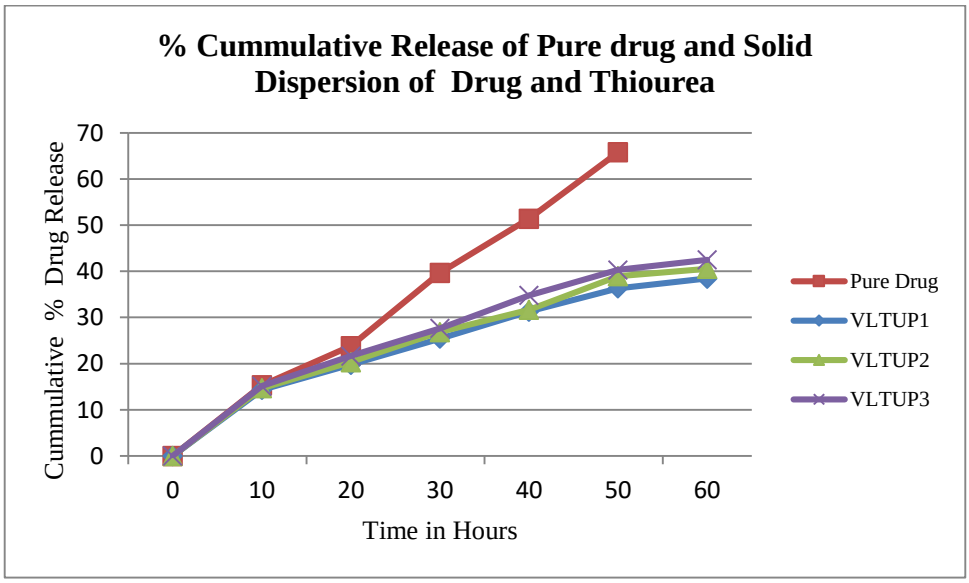


Figure No. 5: Cumulative % drug Release vs. time plot Vildagliptin solid dispersion by physical mixture with Thiourea

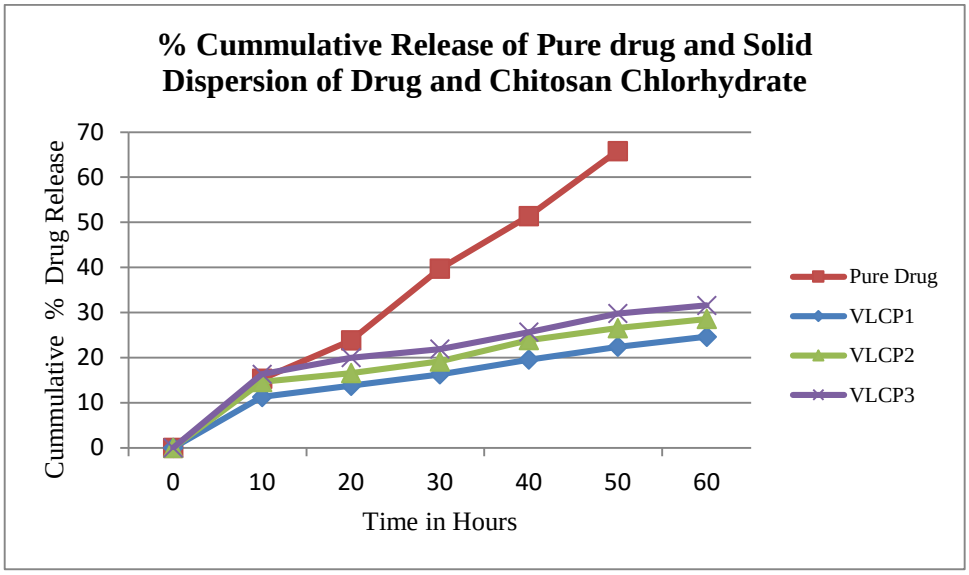


Figure No. 6: Cumulative % drug Release vs. time plot Vildagliptin solid dispersion by physical mixture with Chitosan Chlorhydrate

CONCLUSION:

The Vildagliptin was evaluated for preformulation parameters. All the parameters are within the limit as per standards. The solid dispersion of drug was prepared by using Physical mixing method with PEG6000, Thioura and Chitosan Chlorhydrate. The Vildagliptin content was estimated spectrophotometrically at 245nm. The formulation PEG6000 physical mixing: (VLPP1) 96.9%, (VLPP2) 97.9% and (VLPP3) 98.0%, formulation Thiourea physical mixing: (VLTUP1) 97.2%, (VLTUP2) 96.1% and (VLTUP3) 98.3%, formulation Chitosan Chlorhydrate physical mixing: (VLCCP1) 95.8%, (VLCCP2) 95.7% and (VLCCP3) 96.5%. The results showed that the percentage of Vildagliptin was ranging from 95-98% in all formulations. The average mean particle size of best formulation according to drug release was found VLPP3 (165.64µm), VLTUP3 (158.42µm) and VLCCP3 (162.93µm). The solid dispersion prepared by physical mixing in the ratio of 1:3 with PEG6000, Thioura and Chitosan Chlorhydrate shows better drug release than other combination. The formulation VLTUP3 shows higher drug release in 1hr i.e. 42.5%.

In the present investigation finally concluded that modified release dosage form of Vildagliptin can be prepared by using solid dispersion of drug and Thioura in ratio of 1:3 using physical mixing method which shows highest initial burst release from the formulation.

ACKNOWLEDGMENT:

The author is thankful to H.S.B.P.V.T'S Parikrama College of Pharmacy, Kashti, Shrigonda for providing all the facilities for conducting the research work.

REFERENCES

1. Khan A, Singh L, Various techniques of Bioavailability enhancement: A Review. Journal of Drug Delivery & Therapeutics.2016; 6(3):34-41.
2. Ahmed N, Bioavailability-A Pharmaceutical Review, International Journal of Novel Drug Delivery Technology.2011; 1(1):77-93.
3. Patel J, A Review on Bioavailability and Bioequivalence Trials and Its Necessity. International journal of pharmacy and pharmaceutical science, 2010; 2(3): 1-8.
4. Ratnaparkhi M P Sustained Release Oral Drug Delivery System An Overview. International Journal of Pharma Research & Review.2013; 2(3):11-21.
5. Mokarram A. Preparation and in-vitro evaluation of indomethacin nanoparticles. Journal of Pharmaceutical Sciences, 2010; 18(3), 185-192
6. Vikram M, Jayvadan K, Dhaval J. Effect of Different Stabilizer on the Formulation of Simvastatin Nanosuspension Prepared by Nanoprecipitation Technique. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2010; 1(4):910-17.
7. Ahren, B; Landin Olsson, M; Jansson, PA; Svensson, M; Holmes, D; Schweizer, A (2004). Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. The Journal of Clinical Endocrinology and Metabolism, 89 (5): 2078–84.
8. Mentlein, R; Gallwitz, B; Schmidt, WE (1993). Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36) amide, peptide histidine Methionine and is responsible for their degradation in human serum. European Journal of Biochemistry 214 (3): 829–35.
9. Dhaval J. Patel JK, Vikram M. Pandya, Rishad R. Jivani, Patel Rd. Optimization of Formulation Parameters on Famotidine Nanosuspension Using Factorial Design and the Desirability Function. International Journal of PharmTech Research, 2010; .2 (1):55-161.
10. Patle K, Bhowmick M, Rathi J. Formulation and Evaluation of Monolithic Matrix Transdermal therapeutic system of Vildagliptin using polymer Eudragit RSPO and RLPO. Pharma Research library 2018, 6 :(2), 50-61.
11. Awan, Ashraf A, Nazar M. Ranjha, and Farooq U. Design and optimization of extended release tablets of Vildagliptin by matrix diffusion system using directly compressible co-processed excipient. World Journal of Pharmacy and Pharmaceutical Science 2016, 5 :(3), 199-215.
12. Ponce G, Leticia W, Leticia S, Vásquez G, González-Barranco P, et al "In vitro evaluation of sustained released matrix tablets containing ibuprofen: a model poorly water-soluble drug. 2016; 52 (4):751-759.
13. Pradip Kumar, Sachin Kumar, Formulation and evaluation of sustained release matrix tablet of Vildagliptin using natural and synthetic polymers. International Journal of Advanced Science and Technology 2019; 28(16):1649-1663.

14. Marshall L. Lachman H A. Leon Liberman, JL Kanig. The Theory and practice of industrial pharmacy, Varghese publishing house, Bombay, 1987; 3:66-99.