EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 7
502-513
Year: 2020

FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF VILAZODONE SOLID DISPERSIONS

Ch. Anusha*, A. Naganjaneyulu, P. Sreenivasa Prasanna and K. Thejomoorthy

Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101.

***Corresponding Author: Ch. Anusha**
Department of Pharmaceutics, M.L. College of Pharmacy, S. Konda-523101.
Email id: mlcollegeofpharmacy@gmail.com,

Article Received on 03/05/2020 **Article Revised on 23/05/2020** **Article Accepted on 13/06/2020**

ABSTRACT
Vilazodone is used to treat depression. It is an SSRI (selective serotonin reuptake inhibitor) and partial serotonin receptor agonist. Main disadvantage with Vilazodone is it belongs to BCS class II drug having 25hrs half-life. So to improve its aqueous solubility it has been formulated as solid dispersions. The main aim of present work is to formulate solid dispersions of improve the solubility and rapidly increases bioavailability of and Vilazodone by using HP β Cyclodextrin and β Cyclodextrin to improve patient compliance, improve the solubility and rapidly increases bioavailability of and Vilazodone. Results of prepared solid dispersions of Vilazodone by Solvent Evaporation method and physical mixture were discussed which includes solubility, melting point determination, percentage yield and *in vitro* dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR studies. Finally by comparing all the formulations (SF1-SF6) SF3 containing Vilazodone + HP β cyclodextrin (1:1.5) shows better results by solvent evaporation method at the end of 60 min with drug release of 88.86%, hence it was selected as the best formulation. By compairing the release kinetics studies of best formulation of Vilazodone with zero order and first order we can say that the best formulation follows first order release kinetics studies.

KEYWORDS: Vilazodone, HP β cyclodextrin, β Cyclodextrin, solid dispersions, FT-IR.

INTRODUCTION
A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980).[1]

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excepient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs. changes in the hydrodynamics are difficult to invoke *in-vivo* and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the luminal Fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media.[3,4]

The approaches that have commonly been used to overcome drawbacks associated with poorly watersoluble drugs, in general includes micronization, salt formation, use of surfactant and use of pro- drug.[5]

Vilazodone is approved for treatment of acute episodes of major depression (Major Depressive Disorder (MDD). It is a BCS Class – II drug[6], offer challenges in developing a drug product with adequate bioavailability. It is an SSRI (selective serotonin reuptake inhibitor) and partial serotonin receptor agonist the chemical name**:** 5-{4-[4-(5-cyano-1H-indol-3-yl)

butyl]piperazin-1-yl}-1-benzofuran-2-carboxamide the molecular formula $C_{26}H_{27}N_5O_2$. Vilazodone selectively inhibits serotonin reuptake in the central nervous system as well as acting as a partial agonist of 5HT-1A receptors. The exact mechanism for how these effects translate to its antidepressant effects are not known Label, though there is an association between these effects and antidepressive activity.

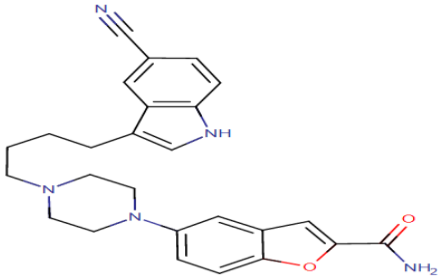

Figure 1: Chemical structure of Vilazodone.

EXPERIMENTAL WORK[7-12]

MATERIALS AND METHODS

Vilazodone was gifted by B.M.R. Chemicals, Hyderabad, Hyderabad, HP β Cyclodextrin, β Cyclodextrin purchased from S.D. Fine Chemicals Ltd. All other chemicals used were of analytical grade and procured from commercial sources.

Preformulation studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.

The following preformulation studies were carried out for Vilazodone

a) Determination of melting point of Vilazodone
b) Solubility studies
c) Drug– excipient compatibility studies

a) Determination of melting point

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was noted.

b) Solubility studies: Solubility of Vilazodone was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Vilazodone was determined spectrophotometrically at suitable nm.

c) Drug–polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Vilazodone, and the selected polymers. The pure drug and drug with excipient were scanned separately.

FT-IR studies

The FT IR studies were performed to the pure and drug complex to know the compatibility of drugs with polymers and ingredients used in the formulation.

Experimental Methods

Preparation of Buffers and Reagents

0.1N HCL Solution

Dissolve 8.5ml of Concentrated HCL in 1000ml volumetric flask with distilled water and the final volume was made up to the mark with distilled water.

Phosphate buffer solution (pH 6.8)

50 ml of 0.2 M potassium dihydrogen ortho phosphate was taken in a 200 ml volumetric flask, to which 22.4 ml of 0.2 M sodium hydroxide was added and volume was made up to the mark with distilled water.

Analytical method development by U.V. Spectroscopy

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution.

Scanning of λ_{max} of Vilazodone

Preparation of Stock Solution: 10 mg of Vilazodone was taken in a 10 ml volumetric flask. To that 5 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 0.1 N HCL to give 1000 µg /ml concentration.

From the above solution 1 ml is diluted to 10 ml with 0.1 N HCL to give 100 µg /ml concentration. From the above solution, take 1ml, and diluted to 10 ml with 0.1 N HCL, to give 10 µg /ml concentration. The prepared solution i.e., 10 µg/ml concentration was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

Calibration curve of Vilazodone in 0.1N HCL: Preparation of stock solution

10 mg of Vilazodone was taken in a 10 ml volumetric flask. To The solution was made up to the mark with 0.1N HCL to give 1000 µg /ml concentration. From this Solution 1 ml is diluted to 10 ml with, 0.1N HCL to give 100 µg /ml concentration. From the above stock solution subsequent dilutions containing 2 to 12 µg/ml solutions were prepared. The absorbance of each test solution was measured at λ_{max} i.e. 238 nm of Vilazodone in UV/Visible spectroscopy against blank.

PREPARATION OF SOLID DISPERSIONS OF VILAZODONE

There are several carriers, which have been reported for the preparation of solid dispersions by using HP β Cyclodextrin various methods of preparation.

a. Physical mixture method

Drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use.

Table 1: formulation of Vilazodone: HP β Cyclodextrin using Physical methods.

Formulation code	Drug : polymer ratio (Vilazodone: HP β Cyclodextrin)
PF1	1:0.5
PF2	1:1
PF3	1:1.5

Table 2: formulation of Vilazodone: β Cyclodextrin using Physical methods.

Formulation code	Drug : polymer ratio (Vilazodone: β Cyclodextrin)
PF4	1:0.5
PF5	1:1
PF6	1:1.5

b. Solvent evaporation

Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved.

Table 3: Formulation of Vilazodone: HP β Cyclodextrin using Solvent evaporation method.

Formulation code	Drug : polymer ratio(Vilazodone: HP β Cyclodextrin)
SF1	1:0.5
SF2	1:1
SF3	1:1.5

Table 4: formulation of Vilazodone: β Cyclodextrin using Solvent evaporation method.

Formulation code	Drug : polymer ratio (Vilazodone: β Cyclodextrin)
SF4	1:0.5
SF5	1:1
SF6	1:1.5

Evaluation of Solid Dispersions

Prepared polymer drug conjugates were evaluated by

1) Estimation of drug content
2) Entrapment efficiency
3) *In- vitro* dissolution studies

Estimation of Drug Content

A quantity, which was equivalent to 50 mg of drug, was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, 0.1 N HCL buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10 mg of standard drug in 0.1 N HCL buffer. For both the sample and standard solutions absorbance was measured at 238 nm for Vilazodone in UV-Visible spectrophotometer.

Percentage Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation.

$$\textbf{Percentage Yield} = \frac{Practical\ mass}{Theoeitical\ mass} X\ 100$$

***In vitro* dissolution study**[9]

The prepared solid dispersions containing 10 mg weight equivalent of Unifenovir was placed in a capsule and subjected to *in vitro* dissolution. Dissolution test was carried out using USP type 1 Basket method [apparatus I]. The stirring rate was 50 rpm, 0.1 N HCL buffer was used as dissolution medium and dissolution medium was maintained at 37±1^{0}C. Samples of 5 ml were

withdrawn at regular intervals of time, filtered and replace with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Vilazodone at 238 nm by using UV-visible spectrophotometer.

KINETICS OF DRUG RELEASE[10]

The mechanism of drug release for the Vilazodone solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

- **Zero Order Kinetic**

It describes the system in which the drug release rate is independent of its concentration.

$Qt = Qo + Ko\ t$

Where,

Qt= Amount of drug dissolved in time t

Qo = Initial amount of drug in the solution, which is often zero and

Ko = zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of Qt versus t will give a straight line with a slope of Ko and an intercept at zero.

- **First Order Kinetic**

It describes the drug release from the systems in which the release rate is concentration dependent.

$Log\ Qt = log\ Qo + kt/\ 2.303$

Where,

Qt = amount of drug released in time t.

Qo = initial amount of drug in the solution k = first order release constant If the first order drug release kinetic is obeyed, then a plot of log (Qo- Qt) versus t will be straight line with a slope of kt/ 2.303 and an intercept at t=0 of log Qo.

RESULTS AND DISCUSSION

Preformulation Studies

Determination of melting point

The melting point of Vilazodone was found to be 205^{O}C which was determined by capillary method and complies with IP standards.

Solubility

Solubility of Vilazodone was carried out at 25^{0}C using 0.1 N HCL, 6.8 phosphate buffer, and purified water.

Table 5: Solubility of Vilazodone.

S.NO	MEDIUM	SOLUBILITY(mg/ml)
1	water	0.106
2	0.1 N HCL	0.326
3	6.8 PH buffer	0.522

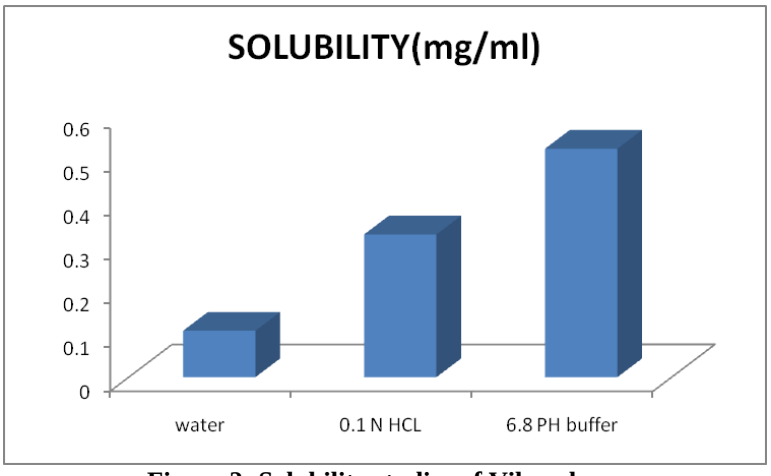

Figure 2: Solubility studies of Vilazodone.

Analytical method development by U.V. Spectroscopy

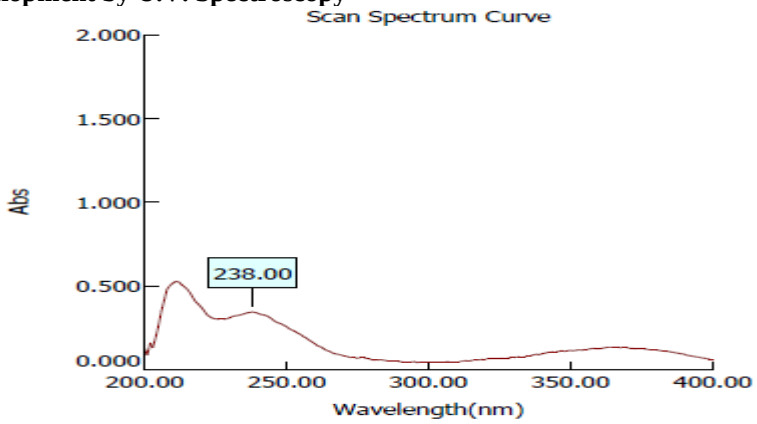

Figure 3: Uv Scan Spectrum of Vilazodone.

Table 6: Calibration curve data of Vilazodone.

Concentration (µg/ml)	Absorbance
0	0
2	0.112
4	0.242
6	0.357
8	0.471
10	0.574
12	0.685

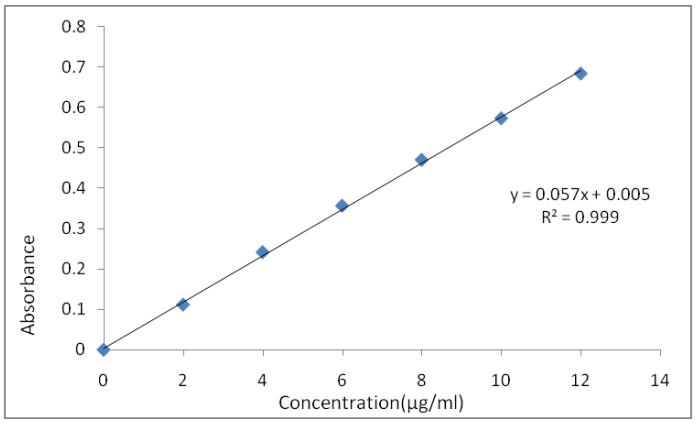

Figure 4: Calibration curve of Vilazodone.

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation. From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Vilazodone) and optimized formulation (Vilazodone: excipients) which indicates there are no physical changes.

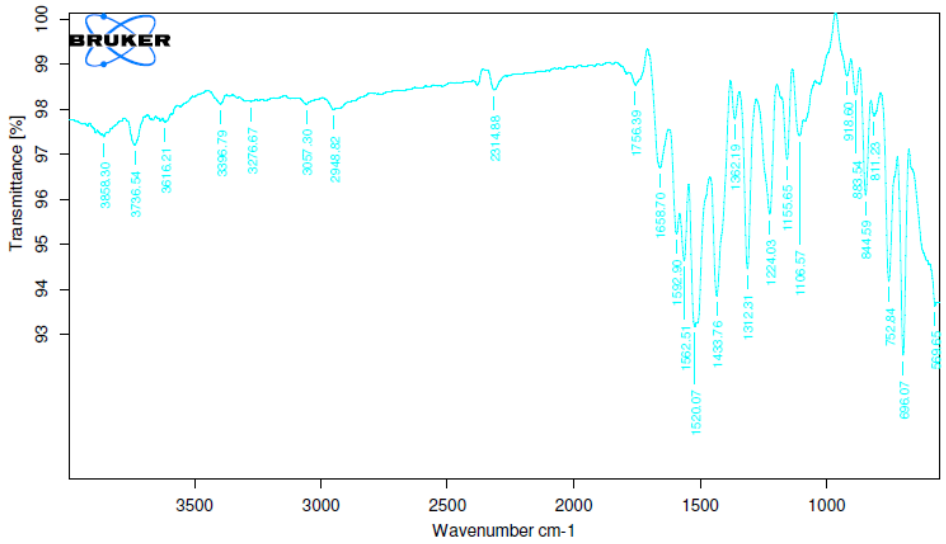

Figure 5: IR spectrum of pure Vilazodone.

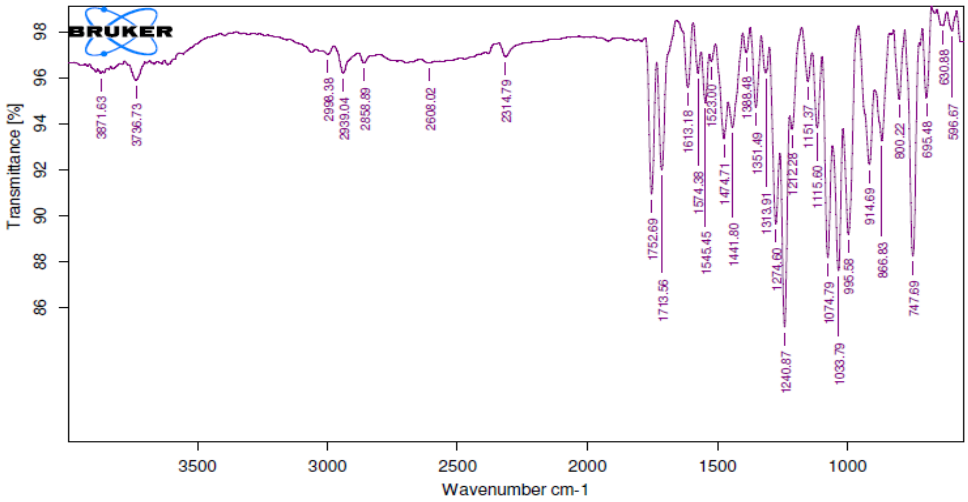

Figure 6: IR spectrum of Vilazodone Optimised Formulation.

Drug content uniformity of Vilazodone solid dispersions

Table 7: Drug content uniformity for solid dispersions by physical mixture method.

Formulation code	%Drug content	Formulation code	%Drug content
PF1	64.28	SF1	72.64
PF2	70.12	SF2	79.51
PF3	78.16	SF3	89.32
PF4	62.10	SF4	69.82
PF5	69.52	SF5	80.20
PF6	72.19	SF6	79.12

% Drug content values of all the formulation (PF1-PF6) formulated by using physical mixture technique were in the range of 62.10-72.19%. The % Drug content values of all the formulation (SF1-SF6) formulated by using Solvent evaporation technique were in the range of 72.64 – 89.32%.

Percentage yield of Vilazodone solid dispersions

Table 8: Percentage yield of solid dispersions by physical mixture method.

Formulation code	%Yield	Formulation code	%Yield
PF1	68.12	SF1	68.02
PF2	75.12	SF2	75.54
PF3	80.22	SF3	78.16
PF4	71.26	SF4	65.82
PF5	72.54	SF5	71.22
PF6	79.82	SF6	76.42

The % Drug content values of all the formulation (PF1-PF6) formulated by using physical mixture technique were in the range of 68.12-79.82%. The % Drug content values of all the formulation (SF1-SF6) formulated by using Solvent evaporation technique were in the range of 65.82 – 78.16%.

INVITRO DRUG RELEASE STUDIES OF SOLID DISPERSIONS

Physical mixture method (PF1-PF6)

In vitro drug release of Vilazodone solid dispersions with H P β Cyclodextrin in various ratios were observed which shows at the end of 60 mins, the formulation PF1 releases 65.26, formulation PF2 releases 68.86, PF3 releases 79.91, formulation PF4 releases 64.96, formulation PF5 releases 69.71, and frormulation PF6 releases 74.18%.

Table 9: In vitro drug release studies for formulations (PF1-PF6).

Time (Min)	Percentage drug release					
	Vilazodone:HP β Cyclodextrin			Vilazodone: β Cyclodextrin		
	1:0.5 (PF1)	1:1(PF2)	1:1.5 (PF3)	1:0.5 (PF4)	1:1 (PF5)	1:1.5(PF6)
0	0	0	0	0	0	0
5	23.28	25.28	34.26	26.42	29.46	31.26
10	29.82	32.32	39.42	36.82	38.32	39.69
15	43.62	46.21	46.42	41.26	44.28	47.22
30	54.21	58.42	57.82	54.98	55.21	59.25
45	61.86	64.36	68.26	61.86	65.32	69.26
60	65.26	68.86	79.91	64.96	69.71	74.18

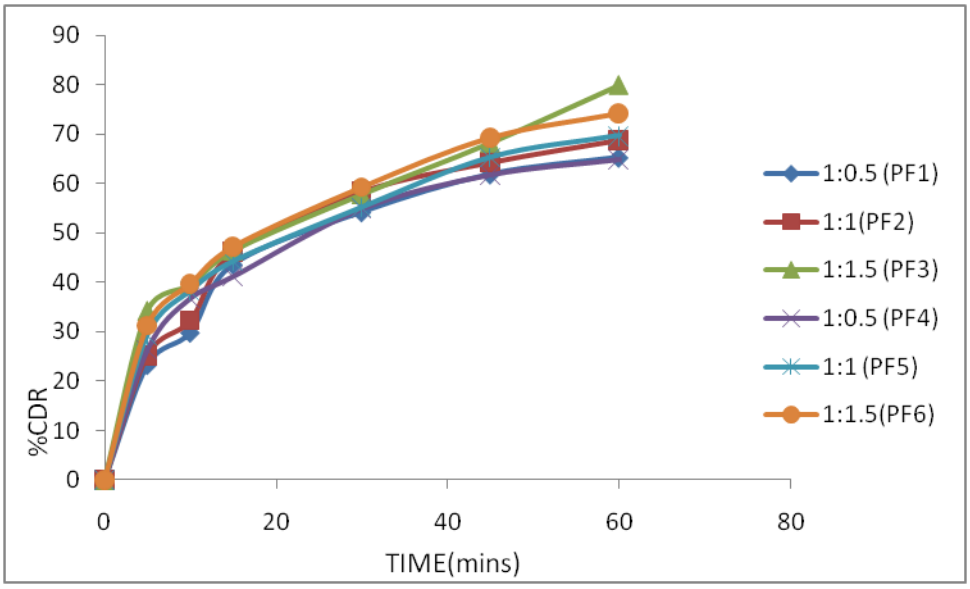

Figure 7: *Invitro* drug release profile for (PF1-PF6).

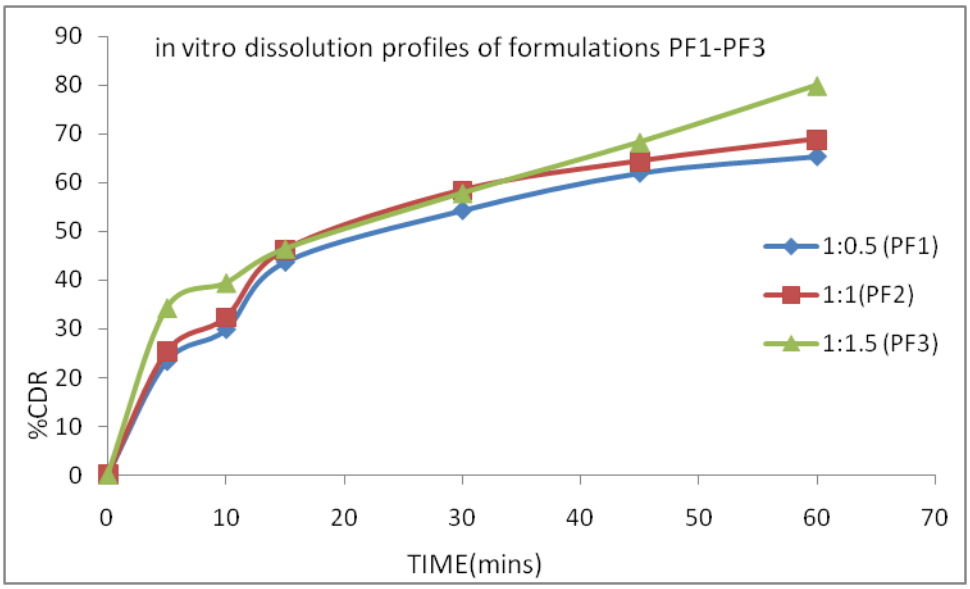

Figure 8: *Invitro* drug release profile for (PF1-PF3).

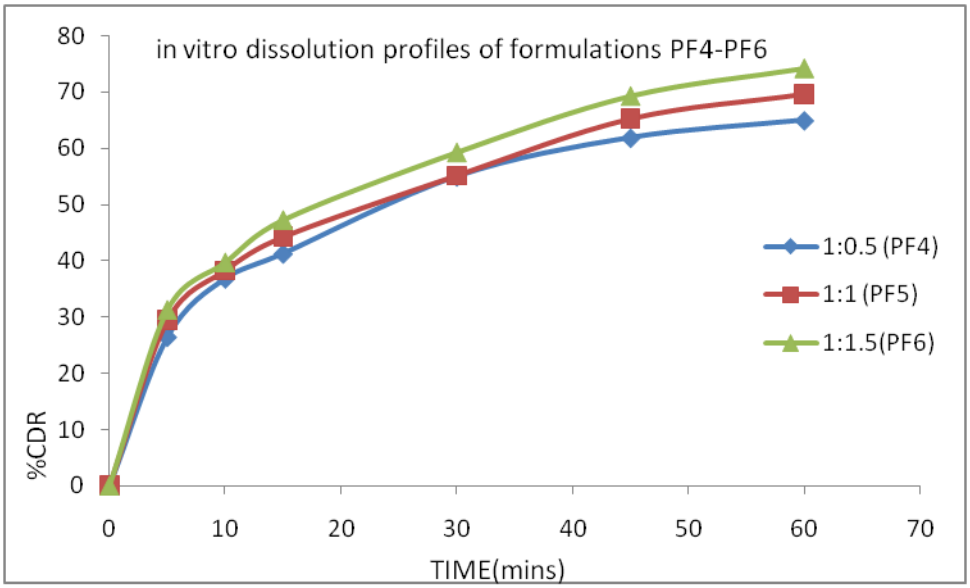

Figure 9: *Invitro* drug release profile for (PF4-PF6).

Fusion Method

***Invitro* drug release studies for formulations (SF1-SF6)**

The *Invitro* drug release of Vilazodone solid dispersions with H P β Cyclodextrin in various ratios were observed which shows at the end of 60 mins the formulation SF1 releases 79.82, formulation SF2 releases 82.84, formulation SF3 releases 88.86, formulation SF4 releases 64.26, formulation SF5 releases 76.56, formulation SF6 releases 79.21%.

Table 10: Invitro drug release studies for formulations (SF1-SF6).

Time (Min)	Percentage drug release					
	Vilazodone:HP β Cyclodextrin			Vilazodone: β Cyclodextrin		
	1:0.5 (SF1)	1:1 (SF2)	1:1.5 (SF3)	1:0.5 (SF4)	1:1 (SF5)	1:1.5(SF6)
0	0	0	0	0	0	0
5	36.46	35.24	42.82	20.86	32.26	41.12
10	49.82	47.29	55.86	32.21	45.29	52.27
15	54.23	53.86	61.89	41.26	52.02	59.86
30	66.52	64.28	73.21	53.81	64.39	68.71
45	73.26	69.85	79.91	60.92	71.98	72.65
60	79.82	82.84	88.86	64.26	76.56	79.21

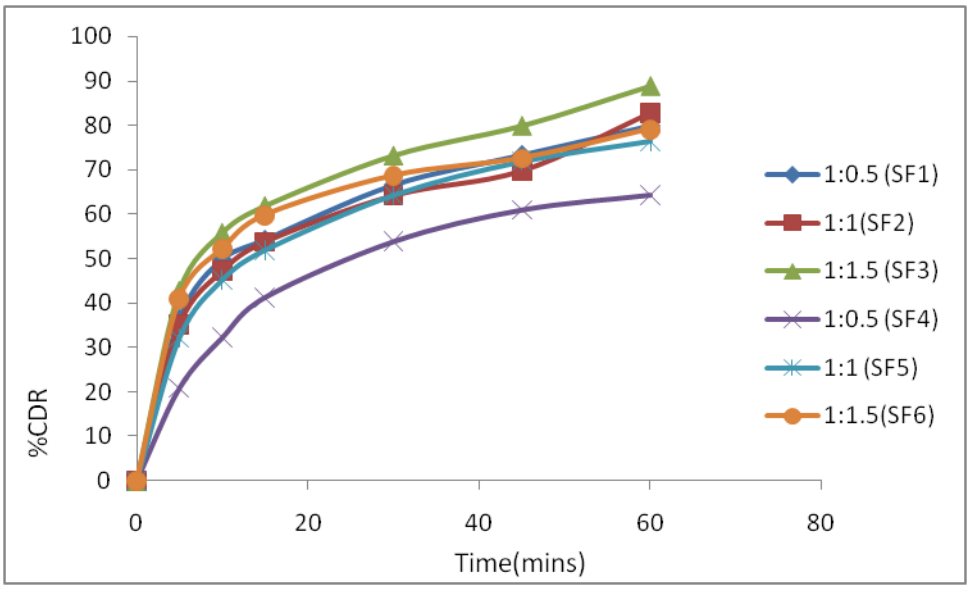

Figure 10: *Invitro* drug release studies for formulations (SF1-SF6).

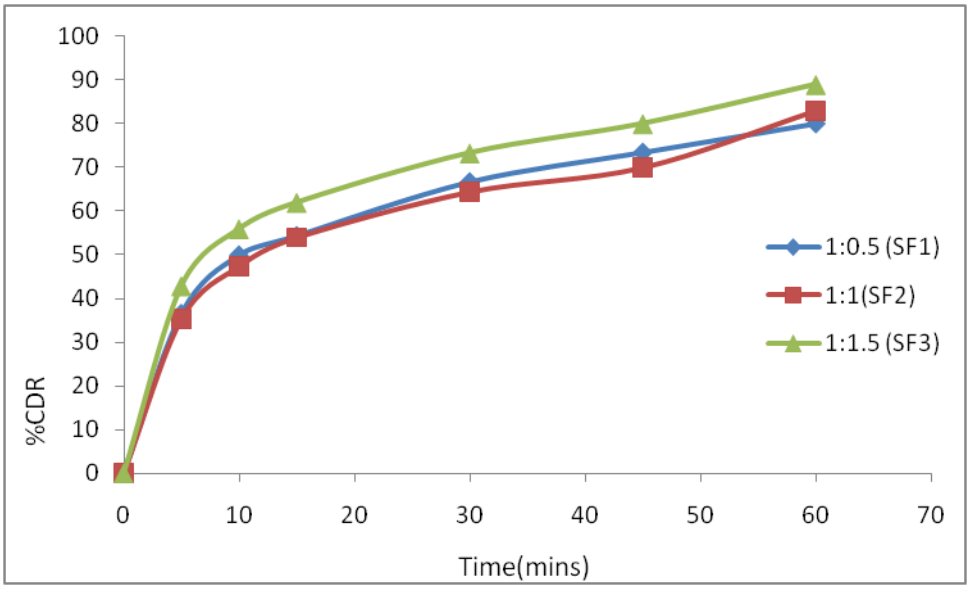

Figure 11: *Invitro* drug release studies for formulations (SF1-SF3).

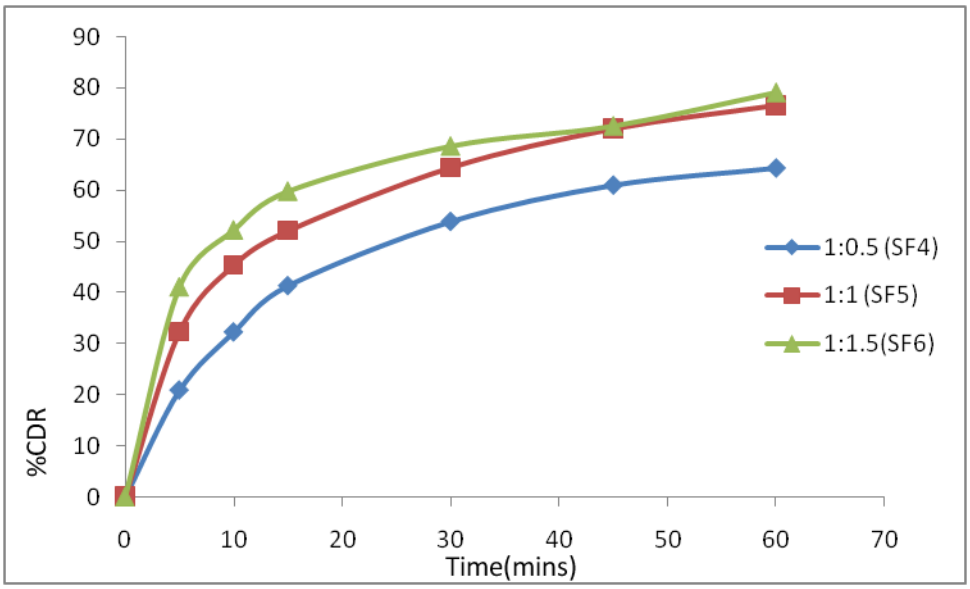

Fig: 12 *Invitro* drug release studies for formulations (SF4-SF6).

Finally by comparing all the formulations (PF1-PF6) (& (SF1-SF6) formulation SF3 containing Vilazodone: HP-β Cyclodextrin (1:1.5) shows better results at the end of 60 min with drug release of 88.86%, hence it was selected as the best formulation among all the formulations.

***In-vitro* drug release kinetics studies for best formulation SF3**

Zero order release kinetics studies

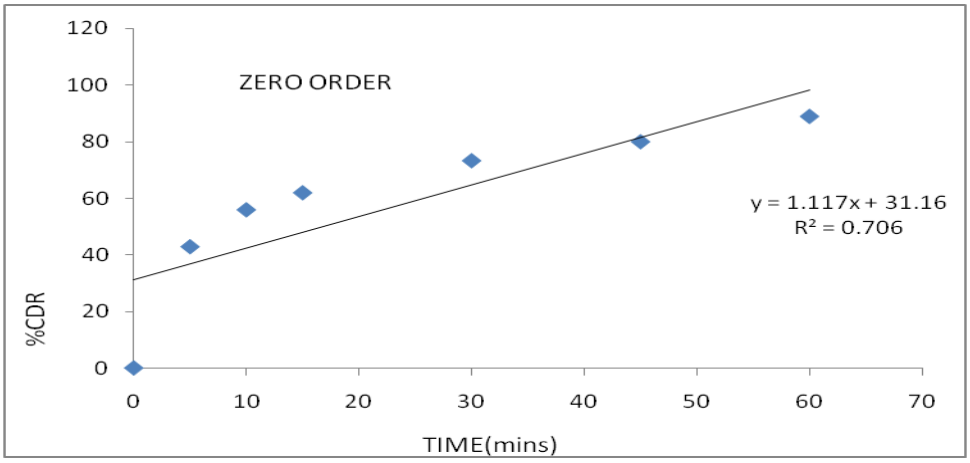

Figure 13: Zero order release profile for best formulation (SF3).

First order release kinetics studies

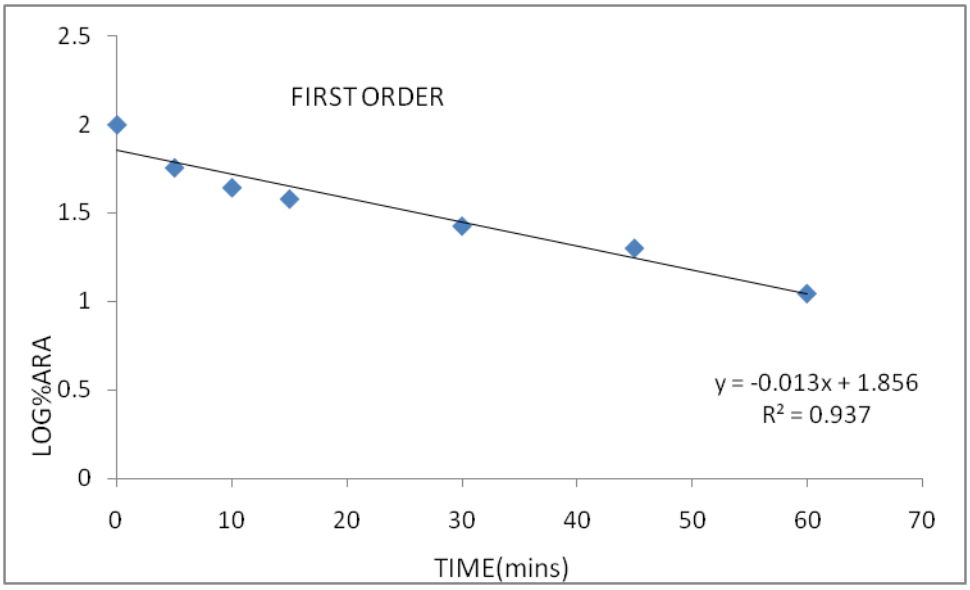

Figure 14: First order release profile for best formulation (SF3).

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows first order release kinetics studies having R^2 value 0.937 were as zero order release kinetics studies having R^2 value 0.706, hence we can say that the best formulation follows first order release kinetics.

DISCUSSION

Solid dispersions of Vilazodone were prepared with polymers in different ratios of drug and carrier (1:0.5, 1:1, & 1:1.5). Results of prepared solid dispersions of Vilazodone by physical mixture mehod, and Solvent evaporation method were discussed which includes solubility, melting point determination, drug content uniformity, entrapment efficiency and *in vitro* dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR studies. Finally by comparing all the formulations (PF1-PF6), & (SF1-SF6) formulation(SF3) containing Vilazodone + HP β cyclodextrin (1:1.5) shows better results by solvent evaporation method at the end of 60 min with drug release of 88.86%, hence it was selected as the best formulation. By compairing the release kinetics studies of best formulation of Vilazodone with zero order and first order we can say that the best formulation follows first order release kinetics studies having R^2 value 0.937 were as zero order release kinetics studies having R^2 value 0.706.

CONCLUSION

HP β cyclodextrin, β cyclodextrin was used in the preparation of solid dispersions by physical mixture mehod, and Solvent evaporation method. By observing the dissolution studies the Solvent evaporation method shows good results for Vilazodone with HP β cyclodextrin (1:1.5). From the Solubility studies in various buffers we can say that 6.8pH buffer solution has more solubility when compared to other buffer solutions for Vilazodone. The melting point of Vilazodone was found to be 205°C which was determined by capillary method and which complies with IP standards. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes. All the formulations of Vilazodone were prepared physical mixture method, and Solvent evaporation method. All the prepared solid dispersions were evaluated for drug content and percentage yield. The invitro dissolution studies of Vilazodone was performed including the release kinetics studies, which shows that solubility of Vilazodone was increased by using Hp β cyclodextrin in 1:1.5 ratio using Solvent evaporation method for formulating solid dispersions than the physical mixture method.

REFERENCES

1. Noyes, A.A., and Whitney W.R., (1897). The rate of solution of solid substances in their own solutions, *J. Am. Chem. Soc*., 19: 930-934.
2. Van Drooge, D.J. et al. (2006). Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *Int. J. Pharm*,. 310: 220–229.
3. Galia, E., Nicolaides, E., HoÈrter, D., LoÈbenberg, R., Reppas, C., and Dressman, J.B., (1998). Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharm. Res*., 15: 698-705.
4. Sengodan guruswamy, V., and Mishra, D.N., 2006. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. *The Pharmaceutic. Soc. Jap*., 126(2): 93-97.

5. Hancock, B.C., and Zogra, G., (1997). Characteristics and significance of the amorphous state in pharmaceutical systems (review). *J. Pharm. Sci.*, 86: 1-12.
6. K. C Panda, A. V Reddy, N. Panda, MD Shamim, M. Habibuddin, K.N Jayaveera. Formulation and evaluation of vilazodone sublingual tablets by using lyophilization technique. Research J. Pharm. and Tech. 2018; 11(1): 267-274.
7. Sandrien Janssens, Clive Roberts, Emily F.Smith, Guy van den Mooter., Physical Stability Of Ternary Solid Dispersions Of Itraconazole Peg- 6000/Hpmc 2910 E5 Blends, *Int. J. Pharmaceutics*, 2008; 355: 100-107.
8. 59. Patel V.P., Patel N.M. and Chaudhari B.G., effect of water soluble polymers on dissolution profile of glipizide cyclodextrin complex, *Indian Drugs*, 2008; 45(1): 31-36.
9. 60. Phuong HA Lien Trana, Huyen Thi Thanh Trana and Beom Jin Lee, modulation of micro-environmental Ph and crystallinity of ionizable telmisartan using alkalizers in solid dispersion for controlled release., *Int. J. controlled release*, 2008; 129(1): 59-65.
10. 61. S.T. Prajapati, M.C.Gohel, L.D.Patel, studies to enhance dissolution properties of carbamazepine., Indian, J. Pharm. Sci., 2007; 69(3): 427-430.
11. 62. P.Srinivasa Babu., A.Ramu, R.Sasidhar, S. Vidyadhara, Enhancement Of Dissolution Rate Of Piroxicam By Solid Dispersions Using New Carriers, *The Pharma Review*, Aug 2007; 163-166.
12. 63. Asyaries., Rachmawati H., In vivo and In vitro evaluation of a solid dispersion system of gliclazide: PEG 6000. *J. Pharm. Sci. Technol.*, 2007; 61(5): 400- 410.