World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

FORMULATION AND IN VITRO EVALUATION OF VILAZODONE ORAL THIN FILMS

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Received: 29-11-2025 / Revised Accepted: 01-12-2025 / Published: 04-12-2025

ABSTRACT:
Fast dissolving medication delivery systems provide a solution for individuals who have difficulties swallowing tablets/capsules. The current study aims to generate oral thin films of Vilazodone utilizing the solvent casting process. Oral thin films were created by combining several super disintegrants such as Lycoat and Ludiflash in varying concentrations with PVA and Gelatin as film formation agents. The film formulations were tested for film thickness measurement, folding endurance, in-vitro disintegration time, and in-vitro drug release pattern (in pH 6.8 phosphate buffer). Drug content and drug-polymer interaction analysis (IR spectroscopy). The formulation (F12) containing 45 mg of Ludiflash demonstrated effective drug release (99.28±1.46%) within 10 minutes.

Keywords: Vilazodone, Gelatin, Ludiflash, oral thin films and FTIR.

INTRODUCTION

Under these conditions, oral thin film (OTF) drug delivery systems are the better option. The oral bioavailability of many medications is insufficient due to the enzymes, common firstpass metabolism, and pH of the stomach. Such conventional medications have been delivered parenterally and have exhibited low patient compliance. Situations like this have paved the door for the pharmaceutical industry to develop alternate mechanisms for medication transportation by manufacturing thin dispersible/dissolving films in the mouth.[1,2,3] Fear of drowning, which may be a risk with ODTs, has been connected with these patient groups. Rapid dissolution/disintegration of OTF drug delivery systems is a superior option to ODTs in patients with fear of asphyxiation. When they are placed on the tongue, OTFs are immediately wetted with saliva. In order to release the medication for systemic and/or local absorption, they are distributed and/or dissolved. ODTs are brittle and may shatter while being transported. Therefore, oral rapid disintegrating/dissolving OTF drug delivery devices are created as an alternative Oral disintegrating/dissolving films or strips can be defined as follows: "These are drug delivery systems that, when placed in the mouth cavity or on the tongue, quickly release the drug by dissolving or adhering in the mucosa with saliva within a few seconds because they contain water-soluble polymers." Because of its thin membrane structure and strong vascularization, the sublingual mucosa has a high membrane permeability. Due to its quick blood flow, it gives very excellent bioavailability.[4,5] Enhanced systemic bioavailability is attributed to bypassing the first pass effect and greater permeability is owing to enhanced blood flow and lymphatic circulation. Additionally, due to its wide surface area and simplicity of application for absorption, the oral mucosa is a particularly effective and selective route of systemic drug administration.[6] In general, OTFs are described as a thin and flexible polymer layer, with or without plasticizers in their composition. They can be argued to be less distracting and more agreeable to patients, as they are thin and flexible in their natural shape. Thin films are polymeric systems that satisfy many of the requirements needed of a drug delivery device. In studies, thin films have proven their abilities such as improving the initial effect of the medicine and duration of this impact, lowering the frequency of dosage, and boosting the efficacy of the treatment. With thin-film technology, it can be advantageous to remove the negative effects of medications and lessen common metabolism generated by proteolytic enzymes. Ideal thin films should possess the desired properties of a drug delivery system, such as a suitable drug loading capacity, rapid dispersion/dissolution, or

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How to Cite this Article: S.Sridevi, FORMULATION AND IN VITRO EVALUATION OF VILAZODONE ORAL THIN FILMS. World J Pharm Sci 2025; 13(04): 200-208; https://doi.org/10.54037/WJPS.2022.100905

prolonged application and reasonable formulation stability. They must also be biocompatible, biodegradable, and harmless.[6]

Major depressive disorder (MDD) affects about 350 million individuals globally and is a primary source of disability and economic burden. [7,8,9] Fortunately, the symptoms of depression may be treated with suitable medication and psychosocial interventions. Ten Initial and subsequent choices of antidepressants are based on a comprehensive consideration of a variety of factors including symptom profile, patient choice, outcomes of previous trials, adverse effect profiles, drug interactions, treatment cost, product availability, and differential effectiveness, although there is little evidence of clinical superiority of one antidepressant over the others. [11,12] However, the clinical response to antidepressants is very varied and, for far too many people with MDD, symptomatic improvement and restoration of normal functioning is inadequate or absent following numerous therapy attempts. [13,14,15] Furthermore, rates of non-adherence to antidepressants range from 50% to 75%, mainly owing to side effects.[16] These data underscore the need of having a broad spectrum of antidepressants for treating MDD in adults. Vilazodone is a selective serotonin reuptake inhibitor and serotonin 5-HT1A receptor partial agonist that received US Food and Drug Administration (FDA) approval in 2011 for the acute treatment of MDD in adults.[17] Based in part on its combined serotonin reuptake inhibition and 5-HT1A partial agonist effects, there has been interest in the potential advantages of vilazodone over other antidepressants, including selective serotonin reuptake inhibitors (SSRIs), with respect to efficacy (faster onset, broader symptomatic effectiveness) and tolerability. [18,19] If true, such advantages might potentially justify vilazodone's greater expense as a relatively younger arrival into the competitive antidepressant market, compared to other antidepressants for which generic versions are available.

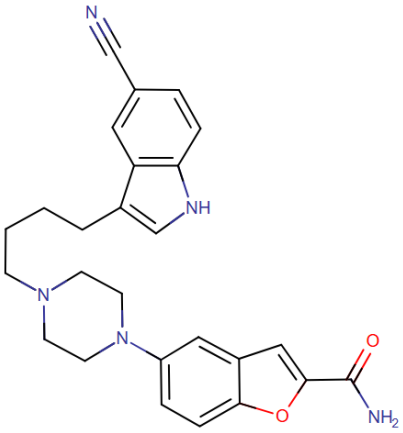

Figure .1 Structure of Vilazodone

MATERIALS

Vilazodone procured from Kekule Pharma Limited, Gelatin, Propylene Glycol, Citric acid, Ludiflash, Aspertame from S D fine chemical Ltd, Mumbai, P.V.A from INR chem. Mumbai, Lycoat from Signet Chemical Corp., Mumbai, Vanilla Flavor from International flavours of fragnance India Ltd.

METHODOLOGY

Solubility studies:

Vilazodone's solubility was tested in several buffers. Saturated solutions were generated by adding an excess medication to the vehicles and shaking on the shaker for 24 hours at 25°C under continual vibration. Filtered samples (1ml) were diluted adequately with acceptable buffer and solubility of Vilazodone was evaluated spectrophotometrically at suitable nm.

Flow properties of the pure drug:

Angle of repose

The funnel technique is used to calculate the angle of repose. A funnel is filled with the precisely weighed mixture. The height of the funnel is regulated in such a way that the tip of the funnel just reaches the apex of the heap of the mix. The drug-excipient combination is allowed to run through the funnel freely onto the surface. The following formula is used to determine the angle of repose and measure the diameter of the powder cone. The Angle of Repose less than 30° demonstrates the free flowing of the material.

$$\theta = \tan^{-1} (h / r)$$

Bulk density

Pouring a weighed amount of mix into a graduated cylinder and measuring the volume and weight yields the apparent bulk density.

The bulk density was estimated by applying the below-mentioned formula

$$Db=M/Vo$$

Where M is the mass of powder, V0 is the bulk volume of the powder

Tapped density:

It is calculated by filling a graduated cylinder with a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from a height of 10 cm at 2-second intervals. The tapping is repeated until no additional volume change is seen.

The tapped density was computed using the following formula:

$$DT=M/Vt$$

Where M is the mass of powder, VT is the tapped volume of the powder

Compressibility index:

The simplest method for measuring free flow of powder is compressibility, which indicates the ease with which a material may be induced to flow. The compressibility index (I) is determined as follows:

Carr's Index (I) = (Tapped Density- Bulk Density)/(Tapped Density) x100

A value between 13 and 19% indicates a powder with good flow characteristics, whereas a value greater than 21% indicates poor flow ability.

Hausner's Ratio :

The Hausner's ratio is an indirect indicator of the ease of powder flow. It is calculated by the following formula

$$\text{Hausner's Ratio} = \frac{\text{BulkDensity}}{\text{Tapped Density}}$$

Preparation of Standard Stock Solution:

10 mg of Vilazodone was carefully weighed into a 10 mL volumetric flask and dissolved in a tiny amount of 6.8 pH buffer solution. To achieve a concentration of 1000 µg/ml, the volume was increased to 10 ml using the 6.8 pH Buffer solution. To get a concentration of 100 µg/ml SS-II, 1 ml was removed and diluted to 10 ml with 6.8 pH buffer solution.

Determination of UV spectrum:-

To achieve a concentration of 10 µg/ml, 1 ml was taken from the stock solution (SS-II) and added to 10 ml of 6.8 pH buffer solution. The UV scan range was collected between 200 and 400 nm. The peak at 239 nm was selected as the λmax for Vilazodone.

PREPARATION OF CALIBRATION CURVE OF VILAZODONE

Procedure for standard curve in pH 6.8:

To dissolve 10 mg of Vilazodone in 10 ml of pH 6.8 solution, shake gently (1000 µg/ml). To create a stock solution with a concentration of 100 µg/ml, 1 ml of this solution was added to 10 ml of pH 6.8 water. The stock solution was used to create concentrations of 5, 10, 15, 20, 25, and 30 µg/ml at pH 6.8. The absorbance of diluted solutions was measured at 239 nm, and a standard plot was created using the results.

Drug-excipient compatibility study.

FTIR spectroscopy

Infrared (IR) spectroscopy was utilized to determine the physical compatibility of the pure medication and the polymers employed in the study. FTIR absorption spectra of pure drug and physical combination were acquired in the 400-4000cm-1 range using the KBr disc technique and an FTIR spectrophotometer.

Preparation Method:

Formulation of Oral Thin Films of Vilazodone:

Vilazodone oral thin films were produced using the solvent casting process. Oral thin films were created utilizing polymers such as PVA and gelatin. Propylene glycol is utilized in plasticizers and super disintegrants such as Ludiflash and Lycoat. The determined amount of polymer was dispersed in a three-fourth volume with continuous stirring using a magnetic stirrer, and the final volume was adjusted with distilled water. Following levitation, the determined quantity of Vilazodone was introduced into the polymeric solutions together with the appropriate volume of Propylene Glycol, Aspartame, and Vanilla Flavor. The solution was cast onto a glass plate and heated in a hot air oven at 400 degrees Celsius. The films were punched to a size of 4 cm2 and contained 10mg of Vilazodone. Using the trial and error approach, various concentrations of film-forming polymers such as PVA and gelatin were utilized. It has been discovered that 180mg of gelatin and 180mg of PVA produce superior films. These film concentrations were achieved by dissolving varying amounts of film-forming polymers in the appropriate amount of water.

Table.1 Formulation details of Vilazodone Oral thin films

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Vilazodone	90	90	90	90	90	90	90	90	90	90	90	90
PVA	180	180	180	180	180	180	-	-	-	-	-	-
Gelatin	-	-	-	-	-	-	180	180	180	180	180	180
Lycoat	20	25	30	35	40	45	-	-	-	-	-	-
Ludiflash	-	-	-	-	-	-	20	25	30	35	40	45
Citric Acid	5	5	5	5	5	5	5	5	5	5	5	5
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5
Vanilla Flavor(mg)	5	5	5	5	5	5	5	5	5	5	5	5
Propylene Glycol(ml)	20	20	20	20	20	20	20	20	20	20	20	20
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Calculation of dose for Vilazodone:

The dose of Vilazodone is 90 mg. Therefore, amount of Vilazodone required in 4 cm2 film is 10 mg.

- Length of glass plate =6 cm.
- Width of glass plate =6 cm.
- Area of the plate =36 cm2.
- No. of 4 cm2 films present whole plate =36/4 =9 films.
- Therefore, Each films contains 10 mg of drug
- 9 films contain 90 mg drug (9*10).

So, the Labelled claim of drug = 10 mg

Evaluation of Oral Thin Films:

Post formulation studies:

Vilazodone Oral Thin Films were examined for the following properties:

a) Physical appearance and surface texture of film:

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

b) Weight uniformity of films

Three 4cm square films were individually weighed using a digital scale, and their average weights were computed.

c) The thickness of films

The thickness of the films was measured using a screw gauge with a minimum count of 0.01mm at various locations on the films. The thickness was measured at three distinct locations on the films, and the average was calculated.

d) Folding endurance of films

The flexibility of films may be objectively assessed via folding endurance. Folding endurance of the films was tested by repeatedly folding a tiny strip of film (about 4 cm2) at the same location until it broke. The number of times a film can be folded in the same location without breaking determines its folding endurance.

e) Surface pH of films

The surface pH was evaluated by placing the films in contact with 1ml of distilled water. The surface pH was determined by placing a combination glass electrode or pH paper near the surface of the films and allowing it to equilibrate for 1 minute.

f) In vitro disintegration time of films

The disintegration test was conducted using the USP disintegration time testing instrument. 6.8 pH Buffer solution was utilized as a medium. The films were inserted in the container's tubes, and the time of disintegration was recorded.

g) Drug content uniformity study of films

The films were analyzed for drug content homogeneity using a UV-Spectrophotometric technique. Films with a diameter of 2 cm were cut from three separate locations on the casted films. Each film was put in a 100 ml volumetric flask and dissolved in 6.8 pH buffer solution, with 0.2 ml collected and diluted with buffer to 10 ml. The absorbance of the solution was measured at 239 nm with a UV/visible spectrophotometer (Shimadzu UV-1700). The % drug content was calculated using the usual graph, and the operation was repeated for three films.

h) In-vitro Dissolution Study

In vitro dissolution of vilazodone Oral thin films were examined in a Type II dissolving test device using a 900ml 6.8 pH buffer solution as the dissolution medium. The stirrer was set to revolve at 50 rpm.The dissolving media temperature remained at 37±0.5ºC throughout the experiment. Each test utilized a single film. At

predetermined intervals of time, samples of dissolving media (5ml) were withdrawn using a syringe equipped with a pre-filter and tested for drug release by measuring absorbance at 239 nm. The amount extracted at each interval was replaced with a new quantity of dissolving medium. The cumulative % release of Vilazodone was computed and shown against time.

i) Drug Release Kinetics

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as:

1) Cumulative percentage drug released Vs time (In-Vitro drug release plots)

2) Log cumulative percentage drug remaining Vs Time (First order plots)

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K.t$$

First Order Kinetics:

A first order release would be predicted by the following equation

$$\text{Log } C = \log Co \quad Kt\ 2.303$$

RESULTS AND DISCUSSION

Solubility studies of pure drug:

Solubility

The solubility of Vilazodone was carried out at 250C using 0.1 N HCl, 6.8 pH phosphate buffer, and purified water

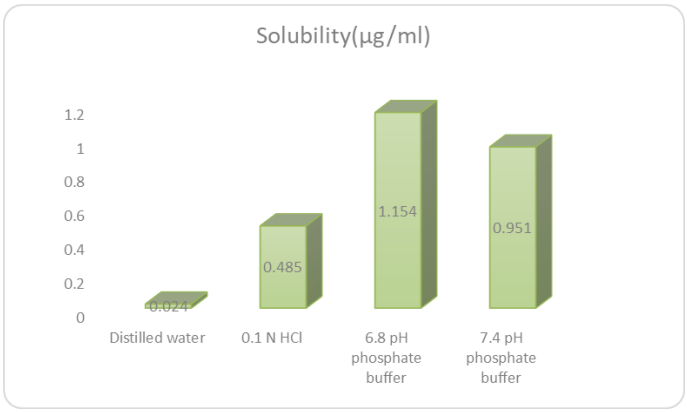

Figure .2 Solubility studies

Discussion:

From the conducted solubility studies in various solutions, we can say that 6.8 pH phopshate Buffer solutions have more solubility when compared to other buffer solutions.

UV Spectrum of Vilazodone:

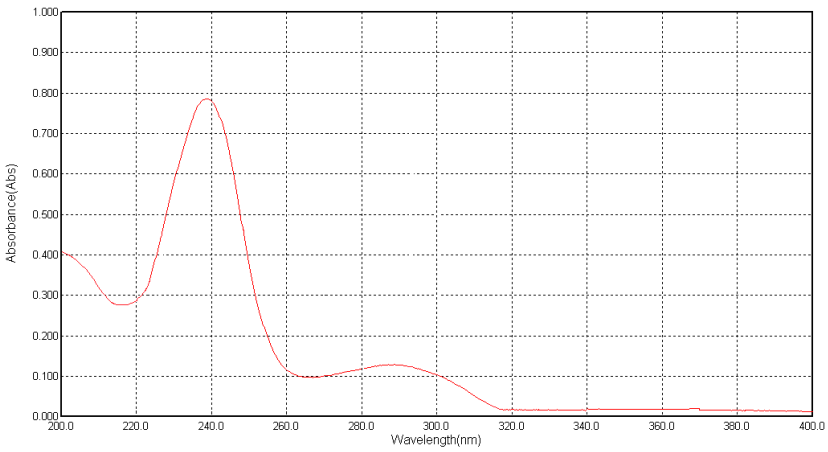

Figure .3 Absorption maxima of Vilazodone in 6.8 pH phosphate buffer

Discussion: The maximum absorbance of the Vilazodone in 6.8 pH phosphate buffer was found to be 239 nm as shown in Fig. Hence, the wavelength of 239 nm was selected for analysis of drug in dissolution media.

Evaluation of Oral Thin Films Formulations:

Physical appearance and surface texture of films:

These parameters were checked simply with visual inspection of films and by feel or touch. The observation suggests that the films are having the smooth surface and they are elegant enough to see.

Table.2 Evaluation of Oral Thin Films of Vilazodone

Formulation Code	Avg. Weight of Film (mg)	Avg. Thickness (mm)	Avg. Folding Endurance
F1	36.17±1.57	0.10±0.02	159±2
F2	36.62±1.81	0.11±0.01	163±1
F3	37.26±1.45	0.13±0.01	166±2
F4	37.70±1.96	0.15±0.01	170±1
F5	38.37±1.23	0.17±0.02	174±1
F6	38.75±1.45	0.18±0.01	178±1
F7	36.19±1.58	0.10±0.02	162±2
F8	36.37±1.14	0.12±0.01	165±1
F9	37.20±1.46	0.14±0.02	169±2
F10	37.75±1.25	0.16±0.01	173±1
F11	38.30±1.67	0.18±0.01	176±2
F12	38.81±1.45	0.19±0.02	181±2

Discussion:

- The average weight the film was found in between 36.17±1.57-38.81±1.45.
- The average thickness of the films was found in between the range of 0.10±0.02-0.19±0.02.
- The average folding endurance of the films was been found in between the ranges of 159±2-181±2.

Table.3 Evaluation of Oral films of Vilazodone

Formulation Code	Avg. Drug Content	Avg. In Vitro Disintegration(sec)	Avg. Surface pH
F1	92.17±1.17	28±2	6.7±0.1
F2	94.69±1.45	25±1	6.8±0.2
F3	96.37±1.95	23±1	6.8±0.1
F4	97.46±1.20	21±2	6.7±0.2
F5	93.57±1.46	19±1	6.8±0.1
F6	95.25±1.58	16±1	6.8±0.1
F7	96.49±1.12	25±2	6.7±0.2
F8	98.30±1.47	22±2	6.8±0.2
F9	95.45±1.58	19±1	6.7±0.1
F10	97.16±1.10	17±1	6.8±0.1
F11	98.20±1.42	14±2	6.7±0.2
F12	99.75±1.95	12±1	6.8±0.1

Discussion:

- The average content uniformity of the formulations from F1 to F12 was found in between 92.17±1.17%-99.75±1.95%.
- The Disintegration time of the films from F1 to F12 was in between the range of 28±2- 12±1.
- The average surface pH of the films was in the range of pH 6.7±0.1-6.8±0.2.

In-Vitro Dissolution Study:

The in-vitro drug release study of oral thin films from each batch (F1 to F12) was carried out in 6.8 pH phosphate buffer solution for 30 mins and the values are shown in Table. The plot of % Cumulative drug release V/s time (mins) were plotted and depicted as shown in Fig & Table.

Table.4 In vitro dissolution studies

Time(min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	35.45±1.21	42.48±1.52	47.49±1.56	55.42±1.15	62.18±1.46	73.14±1.52
4	50.51±1.78	57.46±1.12	64.46±1.12	69.29±1.45	75.52±1.95	84.35±1.45
6	63.45±1.69	69.75±1.20	76.59±1.45	76.02±1.67	87.47±1.15	89.19±1.69
8	72.05±1.48	75.69±1.45	82.75±1.51	89.05±1.48	94.63±1.52	93.56±1.51
10	80.58±1.14	83.15±1.30	89.20±1.36	93.52±1.15	98.84±1.75	98.45±1.45
12	89.78±1.74	92.57±1.85	98.59±1.45	99.25±1.12		
14	98.45±1.46	99.49±1.51				

Table.5 In vitro dissolution studies

Time(min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
2	33.17±1.45	46.85±1.47	45.15±1.47	52.45±1.69	57.51±1.48	65.16±1.48
4	55.69±1.25	59.52±1.69	59.42±1.37	60.20±1.45	65.71±1.45	73.75±1.58
6	64.85±1.41	67.49±1.20	70.52±1.45	74.78±1.91	79.59±1.86	80.42±1.16
8	79.69±1.36	75.46±1.12	79.69±1.45	82.45±1.36	85.45±1.15	94.48±1.42
10	86.15±1.42	83.37±1.51	86.43±1.89	89.58±1.45	93.75±1.49	99.28±1.46
12	91.85±1.69	92.85±1.69	93.71±1.68	98.75±1.48	99.58±1.14	
14	98.75±1.95	98.64±1.75	99.81±1.72			

Discussion:

From the In vitro dissolution studies it was identified that the Formulations containing Lycoat in the concentration of 20-45mg and PVA in concentration of 180mg i.e.,(F1-F2) shows 98.45±1.46%, 99.49±1.51%, at the end of 14mins. Formulation F3 an F4 results 98.59±1.45%, 99.25±1.12% at the end of 12Minutes Formulation F5, F6 Shows 98.84±1.75%, 98.45±1.45% release at the end of 10 mins. Formulations containing Ludiflash in the concentration of 20-45mg and PVA in concentration of 180mg i.e, (F7, F8, F9) shows 98.75±1.95%, 98.64±1.75%, 99.81±1.72% at the end of 14mins, F10, F11 results 98.75±1.48%, 99.58±1.14%, at the end of 12mins.While Formulation F11, F12 contain 45mg of Lycoat Shows 99.28±1.46% release at the end of 10 mins. This shows that effectiveness of super disintegrants is in the order of Ludiflash>Lycoat. The concentration of super disintegrant's in the formulations also increased the dissolution rates. In all the formulations up to 180 mg concentration of Gelatin and 45 mg of Ludiflash, there was linearly increase in dissolution rate. At higher concentration, all the formulations showed increase in dissolution rate.

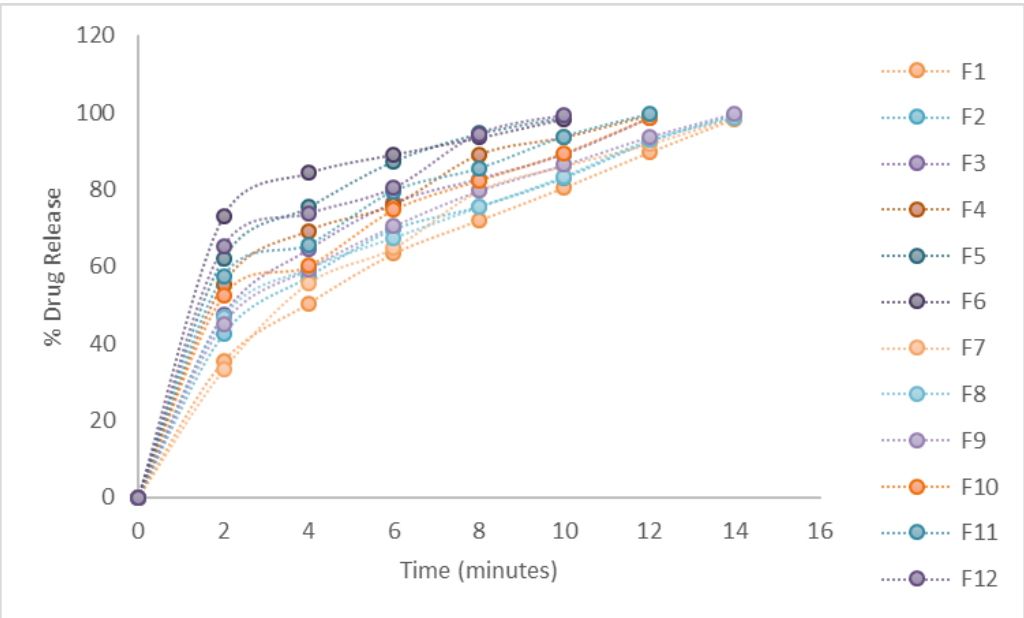

Figure.4 In-vitro drug release of formulations (F1-F12)

Drug Release Kinetics of Vilazodone
Zero Order Release Kinetics

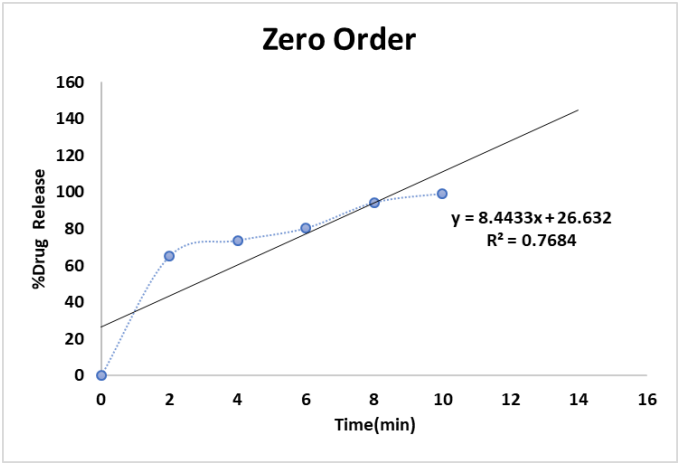

Figure.5 Zero order release profile of Vilazodone Best formulation (F12)

First Order Release Kinetics Data

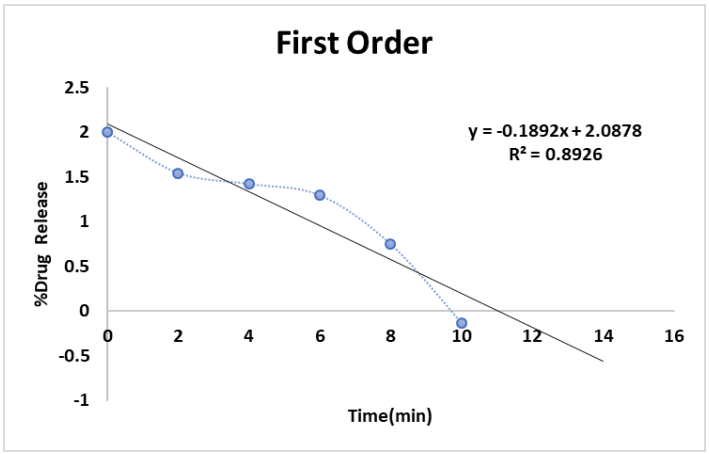

Figure.6 First order release profile of Vilazodone Best formulation (F12)

Table.6 Regression coefficients fit to different drug release kinetics models of Vilazodone Best formulation (F12).

Formulation code	Zero order	First order
	r2	r2
F12	0.768	0.892

Discussion: The in vitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order and first order. Optimized formulation F12 follows first order.

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