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Research Article

FORMULATION AND IN VITRO EVALUATION OF EZOGABINE ORAL THIN FILMS

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ABSTRACT:

Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets/capsules. The present research work is to develop oral thin films of Ezogabine by using solvent casting method. Oral thin films were developed by using various super disintegrants like Lycoat and Ludiflash in different concentrations with Gelatin, Poly vinyl alcohol as a film forming agents. The prepared formulations of films were evaluated for film thickness measurement, folding endurance study, in-vitro disintegration time, in-vitro drug release pattern (in pH 6.8 phosphate buffer). Drug content, and drug-polymers interaction study (IR spectroscopy). Among all formulations, the formulation (F12) prepared by 450mg of Lycoat show good drug release (99.37±1.45%).

Keywords: Ezogabine, Poly vinyl alcohol, Lycoat, oral thin films and FTIR.

INTRODUCTION

EZG was effective in a wide variety of animal models when tested in the NIH antiepileptic drug development (ADD) program and by the original manufacturer. It is active against seizures in rodents induced by maximal electroshock, pentylenetetrazole, picrotoxin, NMDA[1], and amygdalar kindling[2]. Based on rotorod testing, it had a better protective index in these models than valproate or phenytoin[3]. Thus it appeared to be a broad-spectrum drug when it emerged from preclinical testing. Subsequently, it has been found to be effective in the amygdala-kindled lamotrigine-resistant rat model of drug-resistant epilepsy[4], a model which is also resistant to phenytoin and carbamazepine.

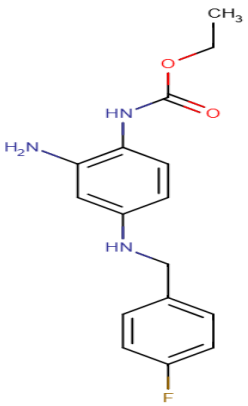

Figure No.1 Structure of Ezogabine

In modern era, the development of novel delivery system for oral route has grabbed a lot of attention due to its patient compliance[5]. Delivery through buccal route was considered as one of the important alternatives to administer the loaded drug through oral route, as it was considered as the most convenient, easiest, and the fastest route of drug absorption[6]. Stratified squamous epithelium which was separated by the wavy basement membrane, from the underlying tissue of lamina propria and submucosa was present in the surface of oral cavity which eases the delivery of administered drugs. Oral mucosa which is highly vascularized ensures better permeability of many drugs and thus the absorption of drugs is better at this site[7]. Therefore, bioavailability of

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drug can be improved by bypassing the first pass metabolism when administered through buccal cavity[8]. Among various formulations administered through buccal cavity oral films (OFs) have started to gain popularity and acceptance, due to their rapid disintegration or dissolution when placed under the tongue or buccal cavity, self-administration even without the use of water, the first kind of OFs were used for mouth freshening, sold as Listerine® pocket packs™ by the major pharmaceutical company Pfizer.

MATERIALS & METHODS USED: Ezogabine API was procured from Kekule Pharma Limited, and Propylene Glycol, Citric acid, Ludiflash, Gelatin and Aspertame were procured from S.D Fine Chemicals, P.V.A were procured from INR chem. Mumbai and Vanilla Flavor were procured from International flavours of fragnance India Ltd.

Preparation Method:

Formulation of Oral Thin Films of Ezogabine:

The oral thin films of Ezogabine was prepared by solvent casting technique. The Oral Thin Films were prepared using polymers like Gelatin, PVA. Propylene glycol is used as a plasticizer and super disintegrants like Ludiflash and Lycoat. The calculated amount of polymer was dispersed in the three-fourth volume of with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. The calculated amount of Ezogabine was incorporated in the polymeric solutions after levitation with required volume of Propylene Glycol and Aspartame and Vanilla Flavor. The solution was cast onto Glass Plate then kept in hot air oven at 400c. The films were punched into size of 4cm2 containing 50mg of Ezogabine. By carrying out the trial and error method different concentrations for a film forming polymers were used like Gelatin, PVA. It has been found that 500mg of gelatin, 500 mg of PVA shows better films. Which these concentrations of films were prepared by dissolving different quantities of film forming polymers in required amount of water.

Table.1 Formulation details of Ezogabine Oral thin films

Formulation Code / Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ezogabine	450	450	450	450	450	450	450	450	450	450	450	450
Gelatin	500	500	500	500	500	500	-	-	-	-	-	-
PVA	-	-	-	-	-	-	500	500	500	500	500	500
Ludiflash	200	250	300	350	400	450	-	-	-	-	-	-
Lycoat	-	-	-	-	-	-	200	250	300	350	400	450
Aspartame	20	20	20	20	20	20	20	20	20	20	20	20
Vanilla Flavor(mg)	20	20	20	20	20	20	20	20	20	20	20	20
Propylene Glycol(ml)	30	30	30	30	30	30	30	30	30	30	30	30
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 Ezogabine:

The dose of Ezogabine is 450 mg. Therefore, amount of Ezogabine required in 4 cm2 film is 50 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 50 mg of drug
- 9 films contain 450 mg drug (9*50).
- So, the Labelled claim of drug = 50 mg

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[9]

Three films of the size 4cm square were weighed individually using digital balance and the average weights were calculated.

c) The thickness of films[10]

The thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

d) Folding endurance of films[11]

The flexibility of films can be measured quantitatively in terms of folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 4 cm^2) at the same place till

it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

e) Surface pH of films[12]

Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min.

f) In vitro disintegration time of films[13]

Disintegration test was performed in the USP disintegration time testing apparatus. 0.1N HCl solution used as a medium. The films were placed in the tubes of the container and disintegration time was recorded.

g) Drug content uniformity study of films[14]

The films were tested for drug content uniformity by a UV-Spectrophotometric method. Films of 2 cm diameter were cut from three different places from the casted films. Each film was placed in 100 ml volumetric flask and dissolved in 6.8 pH Buffer solution and 0.2 ml is taken and diluted with Buffer up to 10 ml. The absorbance of the solution was measured at 218 nm using UV/visible spectrophotometer (Shimadzu UV-1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films**.**

h) In-vitro Dissolution Study[15]

In vitro dissolution of Ezogabine Oral thin films was studied in USP XXIV dissolution test apparatus 900ml 6.8 pH Buffer solution was used as dissolution medium. The stirrer was adjusted to rotate at 50rpm.The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One film was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of a syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 218 nm. The volume withdrawn at each time interval was replaced with the fresh quantity of dissolution medium. Cumulative percent Ezogabine released was calculated and plotted against time.

i) Drug Release Kinetics[16]

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)

RESULTS AND DISCUSSIONS

Solubility

Solubility of Ezogabine was carried out in different buffers.

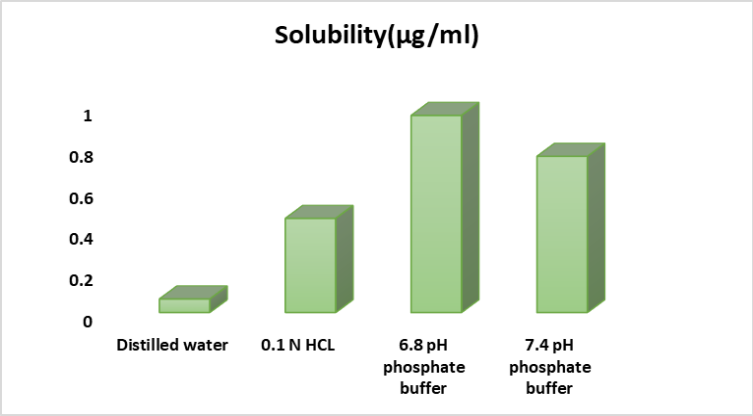

Figure.No.2 Solubility Studies

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.

Flow properties of the pure drug:

Table.2 Flow properties of the pure drug

Angle of repose	**25.02±0.92**
Bulk density	0.48±0.24
Tapped density	0.53±0.28
Carr's index	14.28±0.37
Hausner's ratio	1.15±0.08

Discussion: From the above flow properties of the pure drug, it was concluded that the all the parameters are within the limits indicating the free flow of drug. Total 10 formulations were prepared and three different film forming polymers without disintegrants and complete composition of all batches. The films were then characterized by various physicochemical parameters.

UV spectrum of Ezogabine:

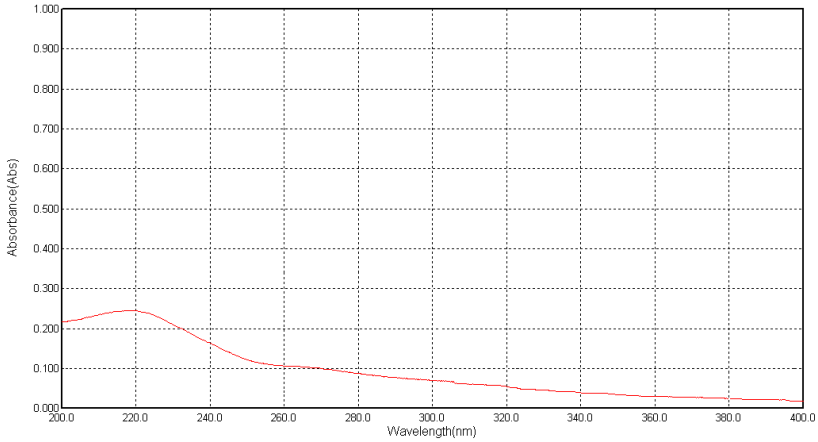

Figure.No.3 Absorption maxima of Ezogabine in 6.8 pH phosphate buffer

Discussion: The maximum absorbance of the Indomethacin in 6.8 pH phosphate buffer was found to be 218 nm as shown in Fig. Hence, the wavelength of 218 nm was selected for analysis of drug in dissolution media.

Standard Calibration Curve of Ezogabine In 6.8 pH Phosphate Buffer:

Standard calibration curve of Ezogabine was drawn by plotting absorbance vs concentration. The λmax of Ezogabine in 6.8 pH phosphate buffer was determined to be 218 nm as shown in Fig. The absorbance values are tabulated in Table. Standard calibration curve of Ezogabine in the Beer's range between 0-30 µg/ml is shown in Fig.

Table.3 Calibration data of Ezogabine in 6.8 pH Phosphate Buffer at λ max 218 nm

Concentration (µg/ml)	Absorbance*
0	0
5	0.125
10	0.249
15	0.37
20	0.489
25	0.597
30	0.722

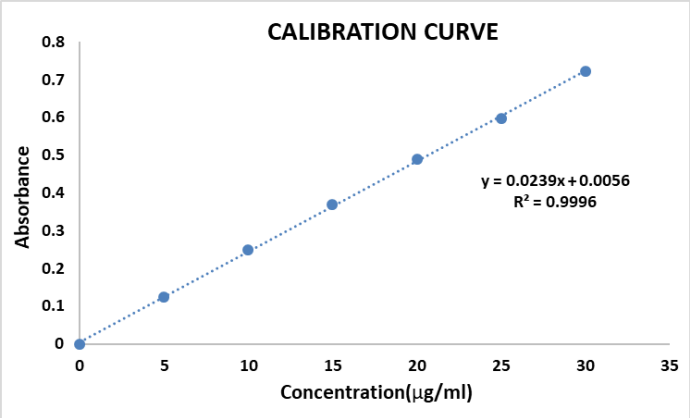

Figure.No.4 Standard calibration curve for Ezogabine 6.8 pH Phosphate Buffer at λmax 218 nm.

Discussion: The standard calibration curve shown 0.999, through that the drug obeys Beers and Lamberts law in the concentration range of 5 to 30 µg/mL. A standard graph was plotted by keeping the known concentration on X – axis and obtained absorbance on Y – axis.

Compatibility Study: FTIR

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic absorption peaks of Ezogabine were obtained at different wave numbers in different samples.

Pure Drug

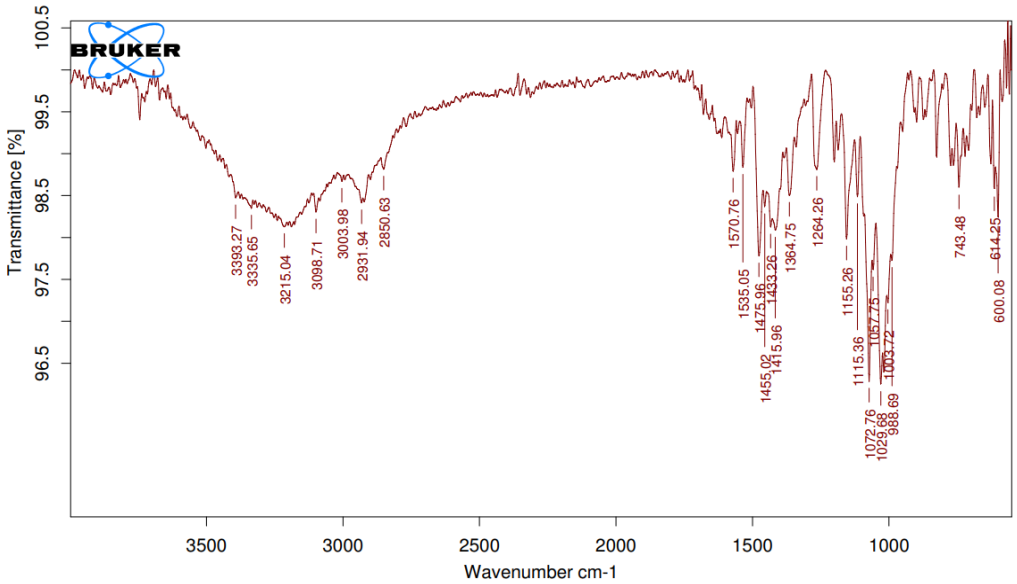

Figure.No.5 I.R. Spectra of pure drug

Optimized Formulation

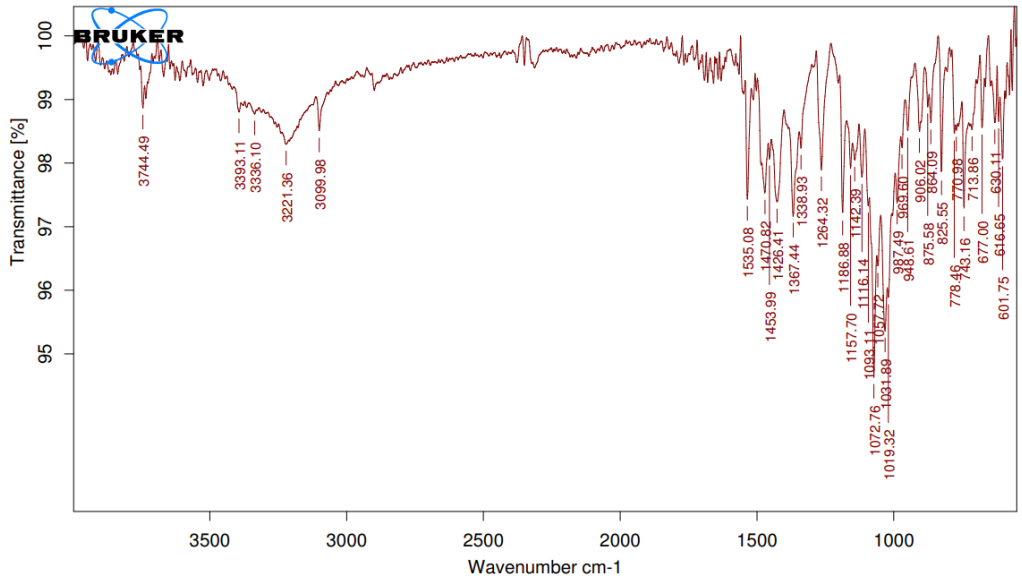

Figure.No.6 I.R. Spectra of optimized formulation

Discussion: From the drug excipients compatibility studies we observe that there are no interactions between the pure drug and (drug+ excipients) which indicates there are no physical changes.

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.4 Evaluation of Oral Thin Films of Ezogabine

Formulation Code	Avg. Weight of Film (mg)	Avg. Thickness (mm)	Avg. Folding Endurance
F1	132.48±1.20	0.27±0.02	195±2
F2	141.07±1.51	0.29±0.01	214±1
F3	145.39±1.69	0.30±0.02	226±2
F4	150.97±1.45	0.31±0.03	239±1
F5	158.41±1.27	0.33±0.01	251±2
F6	162.45±1.16	0.34±0.02	267±1
F7	131.49±1.37	0.29±0.01	203±1
F8	140.45±1.42	0.31±0.02	224±1
F9	147.68±1.10	0.32±0.03	236±2
F10	153.16±1.38	0.34±0.01	245±1
F11	160.74±1.24	0.35±0.02	258±2
F12	164.48±1.15	0.37±0.02	271±1

Discussion: The average weight the film was found in between 131.49±1.37-164.48±1.15. The average thickness of the films was found in between the range of 0.27±0.02-0.37±0.02. The average folding endurance of the films was been found in between the ranges of 195±2-271±1.

Table.7 Evaluation of Oral films of Ezogabine.

Formulation Code	Avg. Drug Content Uniformity (%)	Avg. In Vitro Disintegration (sec)	Avg. Surface pH
F1	92.14±1.19	35±2	6.7±0.1
F2	94.29±1.26	32±1	6.6±0.2
F3	95.38±1.37	30±1	6.8±0.1
F4	96.46±1.20	27±2	6.6±0.1
F5	97.51±1.14	26±2	6.5±0.2
F6	98.36±1.37	24±1	6.5±0.2
F7	94.68±1.20	27±1	6.6±0.1
F8	95.35±1.95	24±1	6.7±0.2
F9	96.42±1.26	21±2	6.8±0.2
F10	98.69±1.56	18±1	6.7±0.1
F11	98.76±1.37	15±1	6.6±0.2
F12	99.52±1.18	13±1	6.8±0.2

Discussion: The average content uniformity of the formulations from F1 to F12 was found in between 92.14±1.19%-99.52±1.18%. The Disintegration time of the films from F1 to F12 was in between the range of 35±2- 13±1. The average surface pH of the films was in the range of pH 6.6±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.8 In vitro dissolution studies

Time(min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	37.15 ±1.45	41.24 ±1.16	45.12 ±1.34	52.26 ±1.48	57.12 ±1.45	65.55 ±1.54
10	49.20 ±1.17	50.39 ±1.45	59.45 ±1.20	60.45 ±1.14	65.37 ±1.45	73.43 ±1.28
15	61.46 ±1.52	65.58 ±1.15	70.46 ±1.75	74.26 ±1.48	79.69 ±1.52	80.45 ±1.42
20	73.13 ±1.27	77.37 ±1.45	79.69 ±1.15	82.20 ±1.15	85.43 ±1.27	92.37 ±1.45
25	80.46 ±1.24	83.26 ±1.95	86.24 ±1.45	89.24 ±1.17	93.45 ±1.32	98.16 ±1.27
30	88.16 ±1.20	90.25 ±1.16	93.57 ±1.45	98.49 ±1.10	99.42 ±1.87	
35	98.18 ±1.16	98.67 ±1.59	99.57 ±1.59			

Table.9 In vitro dissolution studies

Time(min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	34.15 ±1.45	42.17 ±1.47	47.37 ±1.25	55.45 ±1.28	62.45 ±1.22	73.14 ±1.52
10	51.35 ±1.45	57.65 ±1.45	64.15 ±1.45	69.45 ±1.35	75.15 ±1.26	85.35 ±1.45
15	58.15 ±1.42	69.38 ±1.47	76.37 ±1.45	76.67 ±1.27	87.45 ±1.18	90.19 ±1.69
20	65.25 ±1.45	75.45 ±1.28	82.48 ±1.57	89.45 ±1.18	94.45 ±1.97	95.56 ±1.51
25	77.67 ±1.45	83.34 ±1.45	89.48 ±1.34	93.42 ±1.35	98.75 ±1.52	99.37 ±1.45
30	88.48 ±1.51	92.67 ±1.12	98.45 ±1.28	99.45 ±1.12		
35	98.13 ±1.46	99.14 ±1.45				

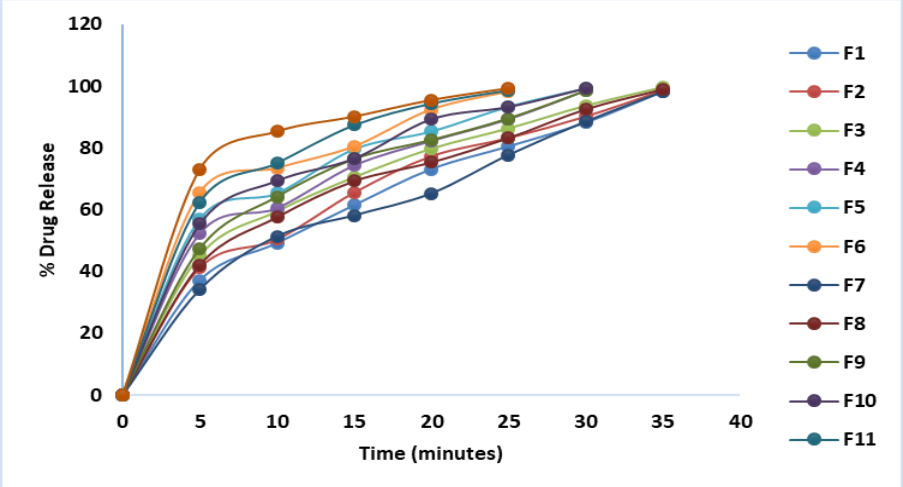

Figure.No.7 In-vitro drug release of formulations (F1-F12)

Discussion:

From the In vitro dissolution studies it was identified that the Formulations containing Ludiflash in the concentration of 200-450mg and Gelatin in concentration of 500mg i.e.,(F1-F3) shows 98.18±1.16%, 98.67±1.59%, 99.57±1.59% at the end of 35mins. Formulation F3 an F4 results 98.49±1.10%, 99.42±1.87%. While Formulation F6 contain 450mg of Crospovidone Shows 98.16±1.27% release at the end of 25 mins.

Formulations containing Lycoat in the concentration of 200-450mg and PVA in concentration of 500mg i.e, (F7, F8) shows 98.13±1.46%, 99.14±1.45% at the end of 35mins, F9, F10 results 98.45±1.28%, 99.45±1.12%, at the end of 30mins.While Formulation F11, F12 contain 450mg of Lycoat Shows 99.37±1.45% release at the end of 25 mins

This shows that effectiveness of super disintegrants is in the order of Lycoat>Ludiflash. The concentration of super disintegrant's in the formulations also increased the dissolution rates. In all the formulations up to 500mg concentration of PVA and 450 mg of Lycoat, there was linearly increase in dissolution rate. At higher concentration, all the formulations showed increase in dissolution rate.

Drug Release Kinetics of Ezogabine

Zero Order Release Kinetics

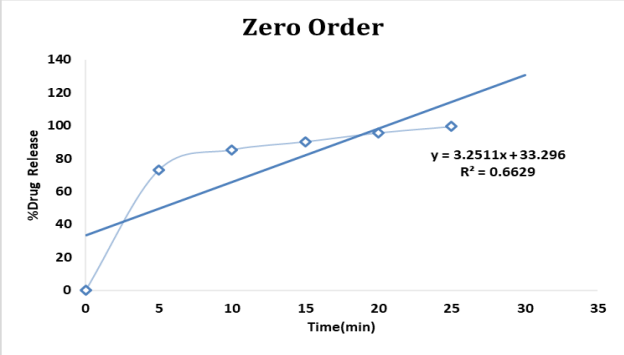

Figure.No.8 Zero order release profile of Ezogabine Best formulation (F12)

First Order Release Kinetics Data

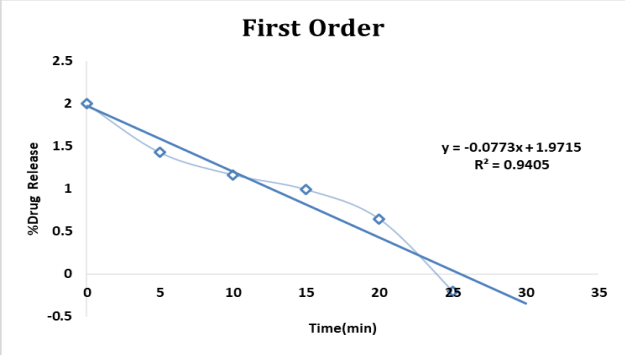

Figure.No.9 First order release profile of Ezogabine Best formulation (F12)

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.

CONCLUSION:

In the present study Oral drug delivery system of Ezogabine were successfully developed in the form of oral thin films which offers a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristics with increase bioavailability. Oral thin films of Ezogabine were prepared by using Ludiflash and Lycoat as super disintegrants.

Under the pre-formulation studies, API characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics.

The disintegrants and other excipients were selected based on the satisfying results produced during drug-excipient compatibility studies to develop the final formulation.

The final suitable formulation (F12) was achieved fruitfully by the solvent casting method using poly vinyl alcohol and Lycoat as super disintegrant which exhibited a rapid disintegration time (13±1 sec) and in vitro drug release (99.37±1.45%) ate the end of 25minutes.

Considering the results of batches containing lycoat and ludiflash as disintegrant it can be concluded that the formulation F12 was meeting the higher in-vitro correlation limits and in less instance of time when subjected to the comparison with other formulation with lycoat as the disintegrating agent. It was also observed that solvent casting method was the best suitable method used for immediate drug release.

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