e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

Research article

FORMULATION AND EVALUATION OF BILAYER TABLETS METFORMIN HYDROCHLORIDE AND EZETIMIBE

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ABSTRACT

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience. The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period.

Key Words:- Modified release dosage forms, Metformin, Ezetimibe.

Access this article online

Home page: http://ijptjournal.com/

DOI: http://dx.doi.org/10.21276/ijpt.2017.8.4.8

Quick Response code

Received:25.10.17 **Revised**:12.11.17 **Accepted**:15.09.17

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INTRODUCTION

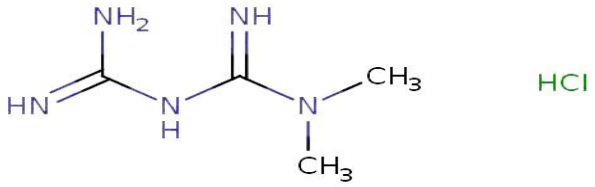
Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose (Chinam NP *et al*., 2007). There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

AIM AND OBJECTIVE

The primary objective was to formulate & evaluate bilayer tablets of Ezetimbe and Metformin by using different polymers in different ratios. When administrated as bilayer tablet containing sustained release and immediate release parts, immediate release act as a loading dose and sustained release as maintenance dose for prolonged period such as one day. This attempt is to improve patient's compliance by reducing the inconvenience caused by the frequent dosing of conventional tablets.

METFORMIN HYDROCHLORIDE

Chemical structure:

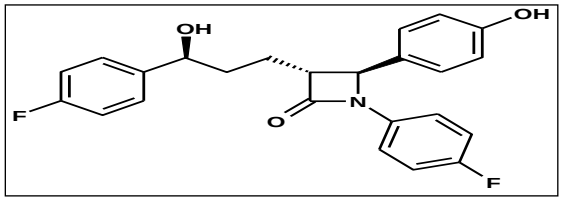


IUPAC NAME: 1-carbamimidamido-N,N-dimethylmethanimidamide hydrochloride

Categories: Anticholesteremic Agents and Hydroxymethylglutaryl-CoA Reductase Inhibitors
Chemical Formula: $C_4H_{11}N_5$ • HCl
Molecular weight: 165.625g/mol
Melting point: 222-226 °C
Solubility: Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.

EZETIMIBE
IUPAC Name
(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3hydroxypropyl]-4-(4 hydroxyphenyl) azetidin-2-one.
CAS Registry No: 163222-33-1
Molecular formula: $C_{24}H_{21}F_2NO_3$
Molecular Weight: 409.42
Melting Point: 164°C- 166 °C
Description: It is a white, crystalline powder.
Solubility: Practically insoluble in water and is freely to very soluble in ethanol, Methanol, and acetone.

Structural formula



Indications: Hypercholesterolemia, Homozygous sitosterolemia (phytosterolemia)
Dosage and administration: It is given by mouth in a usual dose of 10 mg once daily.

MATERIALS AND METHODS
Analytical Method Development in 0.1N HCL buffer
Preparation of 0.1 N Hydrochloric Acid (pH 1.2)
8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml.

Determination of λ_{max} of Ezetimibe in 0.1N HCL
Working standard: 100mg of Ezetimibe was weighed and dissolved in 10ml mithanol and then make up to the volume of 100ml with 0.1N HCL it give 1000µg/ml concentrated stock solution.
Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 0.1NHcl it will give 100 µg/ml concentrated solution.
Dilution 2: From the dilution1, 10ml solution was diluted to 100ml with 0.1NHcl it will give 10 µg/ml concentrated solutions.
This solution was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as λ_{max}.

Construction of calibration curve of Ezetimibe in 0.1N HCL
Working standard: 100mg of Ezetimibe was weighed and dissolved in 10ml mithanol and then make up to the volume of 100ml with 0.1N HCL it give 1000µg/ml concentrated stock solution.
Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 0.1NHcl it will give 100 µg/ml concentrated solution.
From dilution 1, take 0.2, 0.4, 0.6, 0.8, and 1ml of solution was diluted up to mark in 10ml volumetric flask to obtain 2, 4, 6, 8 and 10µg/ml concentrated solutions. This solutions absorbance was noted at 265nm.

Analytical Method Development in 0.1N HCL
Preparation of 0.1 N Hydrochloric Acid (pH 1.2)
8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml.

Determination of λ_{max} of Metformin Hcl in 0.1N HCL
Working standard: 100mg of Metformin Hcl was weighed and dissolved in 10ml mithanol and then make up to the volume of 100ml with 0.1N HCL it give 1000µg/ml concentrated stock solution.
Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 0.1NHcl it will give 100 µg/ml concentrated solution.
Dilution 2: From the dilution1, 10ml solution was diluted to 100ml with 0.1NHcl it will give 10 µg/ml concentrated solution.
This solutions was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as λ_{max}.

Construction of calibration curve of Metformin Hcl in 0.1N HCL
Working standard: 100mg of Metformin Hcl was weighed and dissolved in 10ml mithanol and then make up to the volume of 100ml with 0.1N HCL it give 1000µg/ml concentrated stock solution.
Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 0.1NHcl it will give 100 µg/ml concentrated solution.
From dilution 1, take 0.2, 0.4, 0.6, 0.8, and 1ml of solution was diluted up to mark in 10ml volumetric flask to obtain 2, 4, 6, 8 and 10µg/ml concentrated solutions. This solutions absorbance was noted at 232nm.

Analytical Method Development in 6.8 phosphate buffer
Preparation of 6.8 phosphate buffer
6.8gms of potassium di hydrogen ortho phosphate was taken in a 1000ml volumetric flask and dissolved with distilled water and make up to 1000 ml with distilled water and adjust pH upto 6.8 with Sodium hydroxide solution.

Determination of λ_{max} of Metformin Hcl in 6.8 phosphate buffer

Working standard: 100mg of Metformin Hcl was weighed and dissolved in 10ml mithanol and then make up to the volume of 100ml with 6.8 phosphate buffer it give 1000µg/ml concentrated stock solution.

Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 6.8 phosphate buffer it will give 100µg/ml concentrated solution.

Dilution 2: From the dilution-1, 10ml solution was diluted to 100ml with 6.8 phosphate buffer it will give 10µg/ml concentrated solution.

This solution was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as $\lambda_{max.}$

Construction of calibration curve of Metformin Hcl 6.8 phosphate buffer

Working standard: 100mg of Metformin Hcl was weighed and dissolved in 10ml mithanol and then make up to the volume of 100ml with 6.8 phosphate buffer it give 1000µg/ml concentrated stock solution.

Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 6.8 phosphate buffer it will give 100 µg/ml concentrated solution.

From dilution 1, take 0.2, 0.4, 0.6, 0.8 and 1ml of solution and was diluted up to mark in 10ml volumetric flask to obtain 2, 4, 6, 8 and 10µg/ml concentrated solutions. This solutions absorbance was noted at $\lambda_{max=232}$

Formulation of Ezetimibe IR tablets by direct compression method

Processing steps involved in direct compression method

The Ezetimibe tablets were prepared by following the General Methodology as given below:

All ingredients (Ezetimibe + Avicel PH 102 + SSG + Lactose + MCC + Red oxide of Iron) were weighed accurately and co sifted by passing through #40 sieve, blended in a Poly Bag for 15 min. The above blend were lubricated with # 40 Sieve passed Aerosil and Magnesium stearate. The final blend was then compressed into tablets using single station tablet compression machine with an average hardness of 3.5kg/cm^2, by using 8mm-12mm dies.

Formulation of Metformin Hcl ER tablets by Wet granulation method

Processing steps involved in Wet granulation method:

The Metformin Hcl ER tablets were prepared by following the General Methodology as given below:

1. All ingredients (Metformin Hcl + polymer) were weighed accurately and co sifted by passing through #22 sieve, blended in a Poly Bag for 5 min.
2. Above blend were granulated with PVP K30w/v solutiion in Iso propyl alcohol.
3. The above granules were lubricated with # 40 Sieve passed Magnesium stearate and Talc.
4. The final blend was then compressed into tablets using single station tablet compression machine with hardness of 7.0-8.0kg/cm^2,by using 8mm-12mm dies.

EVALUATION OF TABLETS

FT-IR Spectroscopic Analysis

Drug polymer interactions were studied by FT-IR spectroscopy. Ten milligrams of drug alone, mixture of drug and polymer were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 450-4000cm-1 was recorded taking air as the reference and compared to study any interference (Defang O *et al*., 2005).

A) Pre Compression studies

1. **Angle of Repose:** It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation (Deshpande RD *et al*., 2011).

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

Where:

θ = angle of repose

h = height in cms

r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

2. Density

a) **Bulk density (BD):** It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula (Divya A *et al*., 2011).

Bulk density = weight of powder/ Bulk volume.

$$D_b = \frac{M}{V_0}$$

M = mass of the powder

V_0 = bulk volume of the powder.

b) Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder

Weigh accurately 25 g of granules, which was previously passed through 40# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula (Gohel MC *et al*., 2010; Kumar BV *et al*., 2010).

Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f)$$

M = mass of the powder

V_f = tapped volume of the powder.

3. Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down (Kumar KK *et al*., 2010). The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tappeddensity} - \text{Bulk density}}{\text{Tappeddensity}}$$

4. Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flow ability of a powder (Panchal HA *et al*., 2012).

$$\text{Hausner's Ratio} = \frac{\text{TappedDensity}}{\text{Bulk Density}}$$

B) Post compression studies

1. **General appearance:** The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.
2. **Average weight/Weight Variation:** 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\boldsymbol{Average\ weight = weight\ of\ 20\ tablets/20}$$

$$\%\ \boldsymbol{weight\ variation} = \frac{\boldsymbol{Average\ weight - weight\ of\ eact\ tablet}}{\boldsymbol{Average\ weight}} * \mathbf{100}$$

3. Thickness: Thickness of the tablets (n=3) was determined using a Vernier calipers

4. Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

5. Friability test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min.

The difference in the weight is noted and expressed as percentage.

It should be preferably between 0.5 to 1.0%.

$$\%\text{Friability} = [(W_1 - W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test,

W_2 = weight of tablets after test

6. Content uniformity test

Drug content estimation: Ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of Drug was transferred to a 100 ml volumetric flask and 10 ml methanol is added. The drug is dissolved in methanol by vigorously shaking the volumetric flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the solution is filtered. From prepared solution take 0.1ml solution in 10ml volumetric flask and make up to mark with distilled water. The Drug content was determined by measuring the absorbance at suitable wavelength after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations (Shiyani B *et al*., 2008; Sonar SG *et al*., 2007).

Calculate the quantity in mg of drug in the portion taken by the formula

$$\boldsymbol{Assay} = \frac{\boldsymbol{Test\ Absorbance}}{\boldsymbol{Standard\ Absorbance}} * \frac{\boldsymbol{Standard\ Concentration}}{\boldsymbol{Sample\ Concentration}} * \frac{\boldsymbol{Average\ weight}}{\boldsymbol{Label\ claim}} * \frac{\%\ \boldsymbol{Purity\ of\ drug}}{\mathbf{100}} * \mathbf{100}$$

7. In vitro Dissolution Study for Ezetimibe

900 ml of 0.1N HCL was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37^0C±0.5^0C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 60minutes at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were

analyzed spectrophotometrically at λ_{max} =265nm using a UV-spectrophotometer (Lab India).

8. In vitro Dissolution Study for Metformin Hcl

900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. A tablet was placed in the vessel and was covered; the apparatus was operated up to 2hours at 50 rpm. After completion of 2hours remove the 0.1N HCL and add 6.8 phosphate buffer then continue the apparatus up to 12hours. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =232 nm using a UV-spectrophotometer (Lab India).

C) In vitro Release Kinetics Studies

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from ER was described by using zero order kinetics or first order kinetics. The mechanism of drug release from ER was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time.

$$\mathbf{Q=k_0t.}$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{Log\ C= Log\ C_o\text{-}kt/2.303}$$

Where C is the amount of drug dissolved at time t,

C_o is the amount of drug dissolved at t=0 and

k is the first order rate constant.

A graph of log cumulative of log % drug remaining Vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

3. Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q=K_2t^{1/2}$$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent (Uttam Mandal *et al.*, 2008).

4. Peppa's-Korsemeyer equation (Power Law)

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law).

$$Mt/\ \mathbf{M}_\infty = K.t^n$$

Where, Mt is the amount of drug released at time t

M_α is the amount released at time α,

M_t/M_α is the fraction of drug released at time t,

K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value[21].the kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL.

Table 1. List of equipments and Companies

S.No	Name of the Equipment	Model
1	Electronic weighing balance	Scale-tec
2	Friabilator	Roche Friabilator Electrolab, Mumbai
3	Laboratory oven	Dtc-00r
4	Compression machine	Cmd(Cadmach)
5	Tablet hardness tester	Pfizer Hardness Tester, Mumbai
6	UV	Labindia Uv 3000+
7	Dissolution apparatus	Electrolab TDT-08L
8	Vernier calipers	Cd-6"Cs

Table 2. Formulation of Ezetimibe IR tablets by direct compression method

Ingredients	IR1	IR2	IR3
Ezetimibe	10	10	10
Sodium starch glycolate	3	6	9
Lactose	50	50	50
MCC	80	77	74
Aerosil	3	3	3
Mg. Stearate	3	3	3
Red oxide of iron	1	1	1
Total weight (mg)	150	150	150

Table 3. Formulation of Metformin Hcl ER tablets by wet granulation method

Ingredients	ER1	ER2	ER3	ER4	ER5	ER6	ER7	ER8	ER9
Metformin Hcl	500	500	500	500	500	500	500	500	500
Eudra gir RS 100	25	50	75	-	-	-	-	-	-
PEO	-	-	-	25	50	75	-	-	-
Carbapol	-	-	-	-	-	-	25	50	75
MCC	215	190	165	215	190	165	215	190	165
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight	750	750	750	750	750	750	750	750	750

Table 4. Angle of repose limits

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 5. Compressibility index limits - Scale of Flow ability (USP29-NF34)

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table 6. Weight variation tolerance for uncoated tablets
Acceptance criteria for tablet weight variation (USP 29-NF 34)

Average Weight of Tablet (mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table 7. Dissolution parameters for Ezetimibe

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1 N HCL
Volume	900 ml

Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
ime points	5, 10, 15, 30, 45 and 60
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	265nm

Table 8. Dissolution parameters for Metformin Hcl

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1 N HCL and 6.8 Phosphate buffer
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1, 2, 3, 4, 6, 8, 10 and 12hrs
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	232nm

Table 9. Drug release kinetics mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

RESULTS AND DICUSSION

Table 10. Standard Calibration graph values of Ezetimibe in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.059
4	0.126
6	0.198
8	0.271
10	0.336

Standard plot of Ezetimibe plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig No.1.

Table 11. Standard Calibration graph values of Metformin Hcl in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.085
4	0.157
6	0.242
8	0.314
10	0.403

Standard plot of Metformin Hcl plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig No.2.

Table 12. Standard Calibration graph values of Metformin Hcl in 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.151

4	0.285
6	0.413
8	0.538
10	0.691

Standard plot of Metformin Hcl plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig No.3.

Table 13. Pre compression studies of Ezetimibe IR tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
IR1	0.49	0.52	5.76	1.06	26.82
IR2	0.41	0.47	12.76	1.14	33.13
IR3	0.43	0.49	12.24	1.13	32.68

Table 14. Post compression studies of Ezetimibe IR tablets

Formulation Code	% Weight Variation	Thickness (mm)	% Friability	% Drug Content	Hardness (Kg/cm^2)
IR1	pass	3.01±0.10	0.213	100.5 ±1.5	3.56 ±0.17
IR2	pass	3.07±0.14	0.158	99.8 ±1.2	3.45 ±0.15
IR3	pass	3.03±0.09	0.211	100.2 ±1.4	3.53 ±0.1

Table 15. *In-vitro* Dissolution results for Ezetimibe formulations

Time (mins)	IR1	IR2	IR3
0	0	0	**0**
5	14.15	30.76	**35.89**
10	25.87	45.38	**48.37**
15	38.32	61.73	**67.95**
30	56.89	84.97	**85.88**
45	71.78	96.73	**99.79**
60	85.63	100.32	-

Table 16. R^2 table for Ezetimibe IR formulations

Formulation Code	R^2 values	
	Zero order	First order
IR1	0.957	0.997
IR2	0.841	0.986
IR3	0.854	0.877

Table 17. Pre compression studies of Metformin Hcl ER tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
ER1	0.54	0.61	11.47	1.12	31.26
ER2	0.52	0.59	11.86	1.13	32.31
ER3	0.45	0.50	10	1.11	30.42
ER4	0.44	0.51	13.72	1.15	33.81
ER5	0.4	0.45	11.11	1.12	32.14
ER6	0.48	0.55	12.72	1.14	34.38
ER7	0.50	0.56	10.71	1.12	31.75
ER8	0.45	0.53	15.09	1.17	37.83
ER9	0.46	0.51	9.80	1.10	29.32

Table 18. Post compression studies of Metformin Hcl ER tablets

Formulation Code	% Weight Variation	Thickness (mm)	% Friability	% Drug Content	Hardness (Kg/cm^2)
ER1	pass	4.92±0.05	0.120	101.2± 1.7	7.61 ±0.1
ER2	pass	5.12±0.1	0.312	101.5± 1.4	7.43 ±0.04
ER3	pass	5.02±0.2	0.13	99.2±1.1	7.69 ±0.05
ER4	pass	5.02±0.15	0.123	99.9 ±2.3	7.48 ±0.05
ER5	pass	4.93±0.05	0.110	100.2± 1.7	7.7 ±0.1
ER6	pass	5.1±0.1	0.133	100.5± 1.4	7.53 ±0.04
ER7	pass	5.03±0.05	0.132	99.6±1.5	7.63 ±0.03
ER8	pass	5.03±0.15	0.143	98.9 ±2.3	7.5 ±0.05
ER9	pass	5.03±0.057	0.62	100.1 ±1.2	7.85 ±0.1

*Test for Friability was performed on single batch of 20 tablets

Table 19. *In-vitro* Dissolution results for Metformin Hcl ER formulations

Time (hrs)	ER1	ER2	ER3	ER4	ER5	ER6	ER7	ER8	ER9
0	0	0	0	0	0	**0**	0	0	0
1	61.82	54.63	57.63	41.37	25.32	**16.72**	63.92	55.71	34.78
2	67.74	61.81	66.87	53.76	41.15	**24.85**	74.61	67.35	47.42
3	72.31	68.48	77.83	59.13	52.81	**36.87**	80.53	75.83	61.92
4	86.13	82.13	85.28	62.54	59.29	**51.23**	97.74	84.40	65.67
6	100.97	97.75	94.53	76.98	70.71	**65.37**	100.87	95.43	78.73
8	-	100.91	99.76	87.17	84.36	**82.96**	-	100.34	86.42
10	-	-	100.23	100.47	96.14	**91.75**	-	-	99.46
12	-	-	-	-	100.09	**99.94**	-	-	100.47

Table 20. R^2 value and n result table

Formulation code	R^2 values				"N" values
	Zero order	First order	Higuchi	Peppas	
ER1	0.760	0.900	0.947	0.897	0.271
ER2	0.777	0.927	0.960	0.933	0.324
ER3	0.849	0.963	0.986	0.988	0.461
ER4	0.804	0.933	0.950	0.893	0.296
ER5	0.911	0.987	0.996	0.991	0.558
ER6	0.965	0.971	0.970	0.990	0.777
ER7	0.660	0.957	0.902	0.990	0.284
ER8	0.717	0.868	0.936	0.948	0.270
ER9	0.724	0.956	0.944	0.997	0.301

Figure 1. Standard calibration curve of Ezetimibe in 0.1N HCL

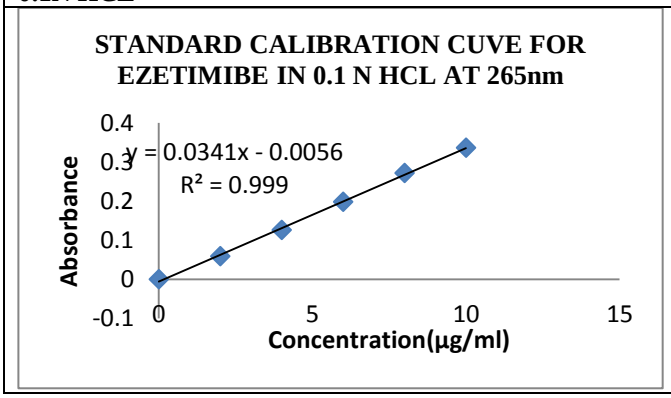


Figure 2. Standard calibration curve of Metformin Hcl in 0.1N HCL

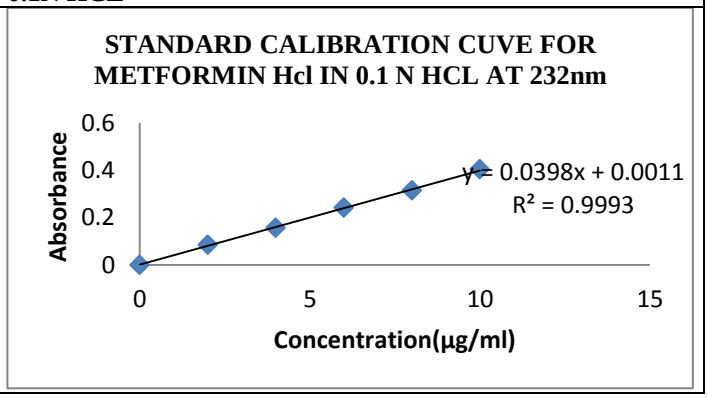


Figure 3. Comparative dissolution profile for Ezetimibe IR tablets

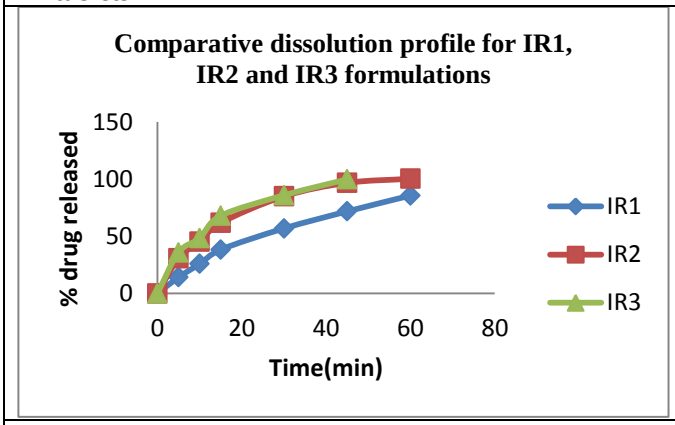


Figure 4. Comparative dissolution profile for ER1, ER2 and ER3 formulations

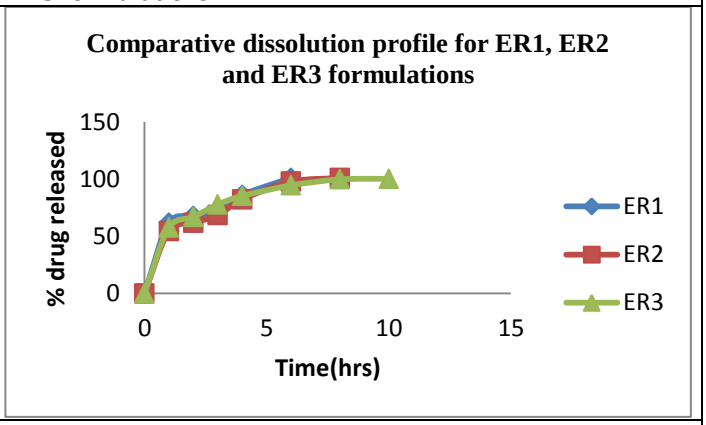


Figure 5. Higuchi plot for ER4, ER5 and ER6 formulations

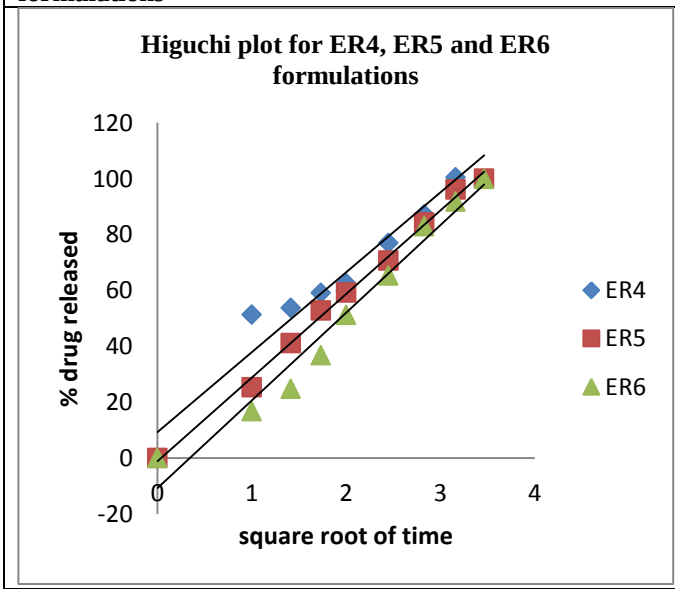


Figure 6. Higuchi plot for ER7, ER8 and ER9 formulations

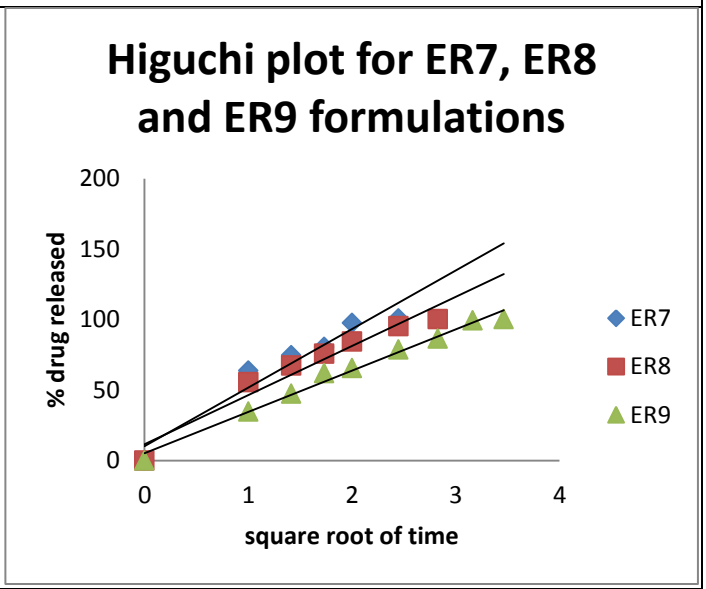


Figure 7. FT IR graph for Ezetimibe

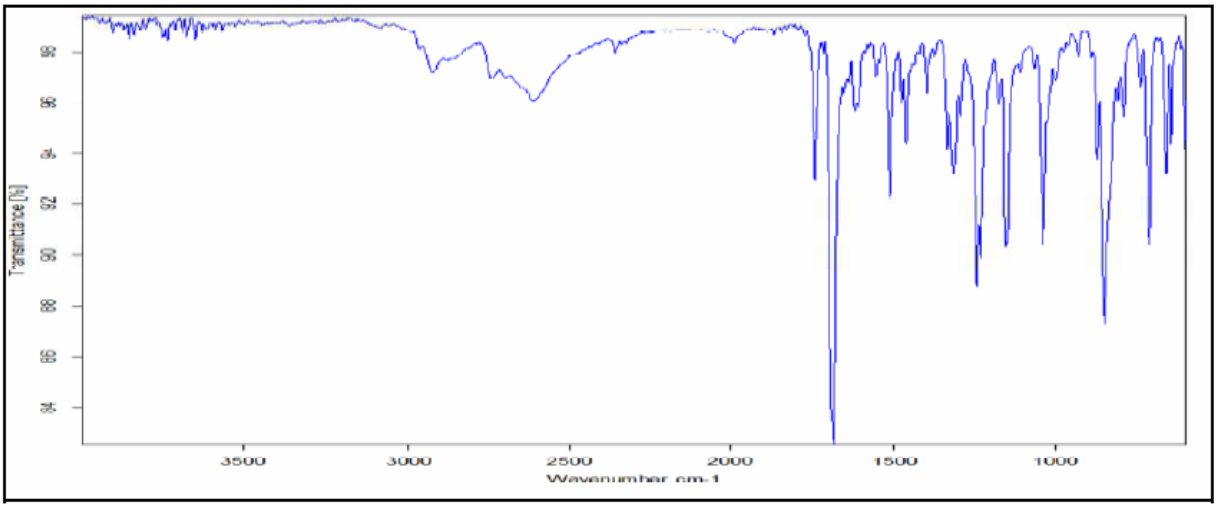


Figure 8. FT IR graph for Metformin Hcl

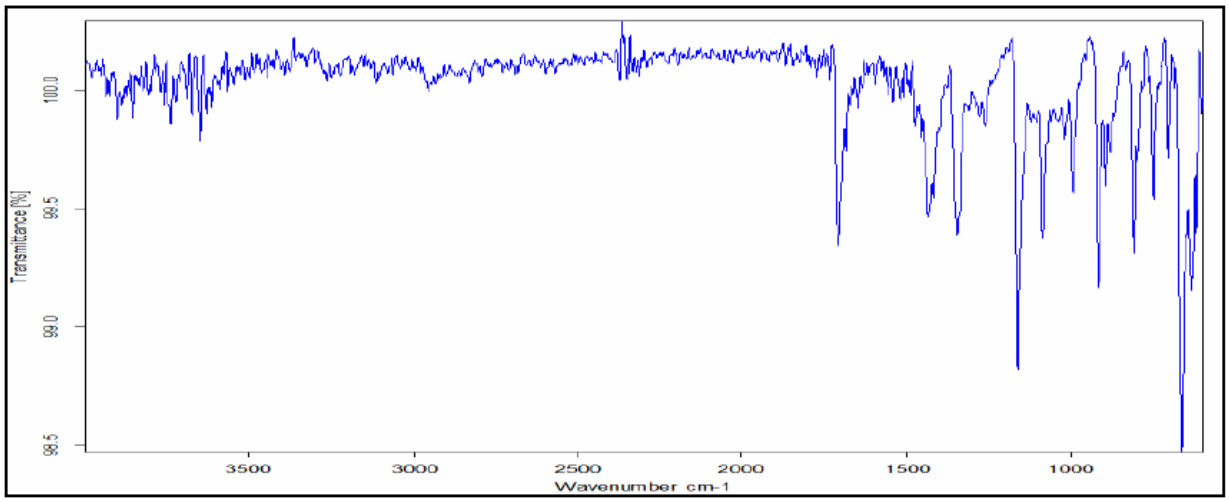
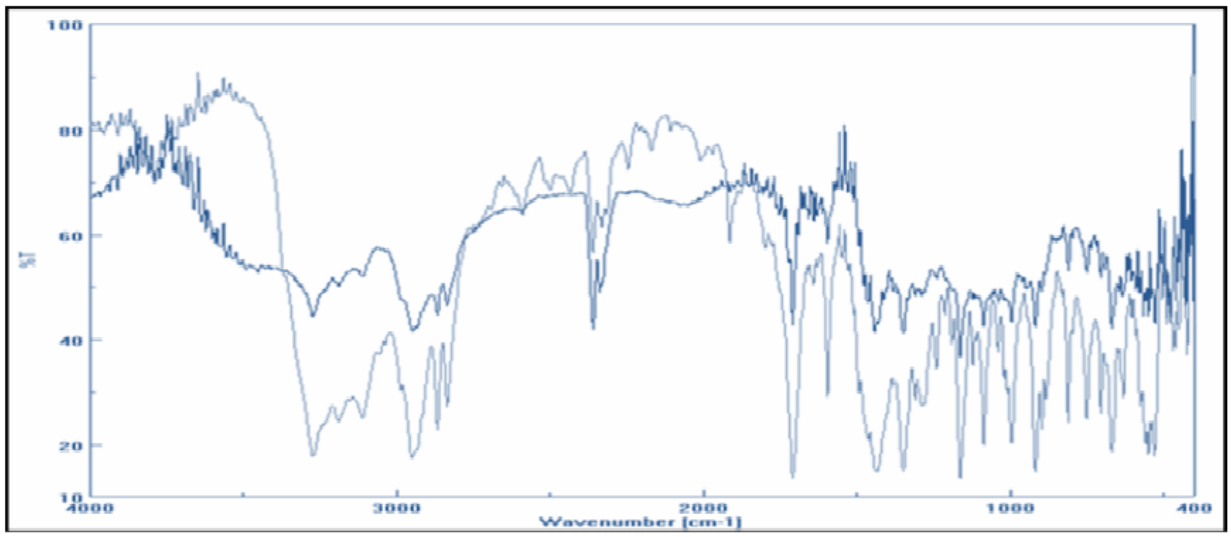


Figure 9. FT IR graph for Ezetimibe and Metformin Hcl best formulation



1. Construction of Standard calibration curve of Ezetimibe in 0.1N HCL

The absorbance of the solution was measured at 265nm, using UV spectrometer with 0.1N HCL as blank. The values are shown in table no 12. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Inference: The standard calibration curve of Ezetimibe in 0.1N HCL showed good correlation with regression value of 0.999

2. Construction of Standard calibration curve of Metformin Hcl in 0.1N HCL

The absorbance of the solution was measured at 232nm, using UV spectrometer with 0.1N HCL as blank. The values are shown in table no 13. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Inference: The standard calibration curve of Metformin Hcl in 0.1N HCL showed good correlation with regression value of 0.999.

3. Construction of Standard calibration curve of Metformin Hcl in 6.8 phosphate buffer

The absorbance of the solution was measured at 232nm, using UV spectrometer with 6.8 phosphate buffer as blank. The values are shown in table no 14. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Inference: The standard calibration curve of Metformin Hcl in 6.8 phosphate buffer showed good correlation with regression value of 0.999.

Evaluation of Tablets

Pre compression studies of Ezetimibe IR tablets

Inference

- The Ezetimibe IR tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table 13.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.06 to 1.14 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 26.82-33.13˚ which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Post compression studies of Ezetimibe IR tablets

Inference

- The variation in weight was within the limit
- The thickness of tablets was found to be between 3.01 – 3.07 mm.
- The hardness for different formulations was found to be between 3.45 to 3.56 kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.

Pre compression studies of Metformin Hcl ER tablets

Inference

- The Metformin Hcl ER tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table:17.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.08 to 1.17 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 27.72-37.83˚ which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Post compression studies of Metformin Hcl ER tablets

Inference

- The variation in weight was within the limit
- The thickness of tablets was found to be between 4.93 – 5.12 mm.
- The hardness for different formulations was found to be between 7.43 to 7.93 kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.

CONCLUSION

The approach of the present study was to make a comparative evaluation among these polymers (Poly ethylene oxide, HPMC K15M and Ethyl cellulose) and to assess the effect of physico-chemical nature of the active ingredients on the drug release profile. The angle of repose, bulk density, tapped density and compressibility index results shown that the formulation is suitable for direct compression method. These dosage forms have the ability to reduce the dosing frequency. By increasing the polymer, release rate of the drug decreases. F4 gave better release when compared to all formulations. By the results we can confirm that order of drug release zero order.

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Cite this article:
Venkatesh R, Jaya Chandra Reddy P. Formulation and Evaluation of Bilayer Tablets Metformin Hydrochloride and Ezetimibe. *International Journal of Pharmacy & Therapeutics*, 8(4), 2017, 176-188.
DOI: **http://dx.doi.org/10.21276/ijpt.2017.8.4.8**