IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 13, Issue 2 Ver. V (Mar. – Apr. 2018), PP 16-30
www.iosrjournals.org

Formulation and In Vitro Evaluation of Anti Diabetic Bi-Layered Tablet-Metformin and Ezetimibe

Asfia Kauser *, Fatima Nasreen , Nida Samar , Sania Samreen , Syeda Ibtesam Fatima, Syeda Arshiya Tasleem , Zaara Majeed , Ayesha Haseeena
**Assistant Professor, Shadan Women's College Of Pharmacy, Khiartabad, Hyderabad.*
Department Of Pharmaceutics
Corresponding Author: Asfia Kauser

Abstract: *The Combination Of Metformin Hcl And Ezetimibe Is Used For The Management Of Type Ii Diabetes Mellitus. The Present Research Work Was Carried Out To Develop A Bilayer Tablet Of Metformin Hcl As Extended Release Layer Which Was Prepared By Using Hydrophilic Matrix Polymers Such As Eudragit Rs100, Peo And Carbapol And Ezetimibe As Immediate Release Layer.Drug Release From The Matrix Was Found To Decrease With Increase In Polymer Concentration.Er6 Gave Better Release When Compared To All Formulations. The Angle Of Repose, Bulk Density, Tapped Density And Compressibility Index Results Has Shown That The Formulation Is Suitable For Wet Granulation Method.The Drug Release Kinetics Of The Optimized Bi-Layered Tablets Corresponded Best To Korsmeyer- Peppas Model And The Drug Release Mechanism As Per ' N' Value Of Korsmeyer - Peppas Is Anomalous (Nonfickian) Diffusion And The Tablets Showed No Significant Change In Physical Appearance, Drug Content Or In Vitro Dissolution Pattern.*

Date of Submission: 09-04-2018 Date of acceptance: 23-04-2018

I. Introduction

1.1 Tablet- A Conventional Dosage Form

Tablet Is A Solid Dosage Form In Which Powder, Crystalline Or Granular Form Of Drug Is Compressed In A Disk Or Molded. It Is The Most Frequently Used Means Of Administering A Drug. Most Of The Tablet Is Administered Orally. However, The Tablet For Application As Implant, Solution, Vaginal Use, And External Use Are Also Available.

Oral Tablet Is Designed To Release The Drug Within The Gastrointestinal Tract For Absorption Into The Circulation Or More Rarely For A Local Effect. It Is Usually Swallowed Or Dissolved In Water Before Taking.

The Molded Tablet Is Softer Than The Compressed Tablet. The Molded Tablet Dissolves Rapidly When Administered By Placing Under The Tongue. The Compressed Tablet Offers Many Advantages To The Patient, The Prescriber And The Manufacturer. There May Be Single Or Multiple Compressed Drug Following Oral Administration.

To Make The Tablet Well Acceptable To The Patient And Easier To Swallow, The Tablet Is Prepared In Different Shapes And Sizes. The Tablet Is Usually Discoid In Shape. It May Be Available In Other Shapes Such As Round; Oval, Triangular Or Elliptical .The Upper And Lower Surfaces Of A Tablet May Be Flat Or Convex. The Tablet May Be Marked With A Line Across The Surface So That It Can Be Broken Into Halves Easily. Sometimes The Tablet May Be Marked With Trade Name With Or Without The Amount Of The Active Ingredient.

Types Of Tablet:

Tablet May Be Uncoated Or Coated. Uncoated Tablets Are Chewable Tablet, Effervescent Tablet, Lozenge Tablet, Soluble Tablet, And Sublingual Tablet. Coated Tablets Are Enteric Coated Tablet, Film Coated Tablet, Implant, Sugar Coated Tablet, And Modified-Release Tablet. A Broken Section Of A Coated Tablet Shows A Core Which Is Surrounded By A Continuous Layer Of A Different Texture. The Reasons For Coating A Tablet Are:

A) For Protection Of The Active Ingredients From Air, Moisture, Light,
B) To Mask The Unpleasant Tastes And Odour; And
C) To Improve The Appearance

Chewable Tablet:

The Tablet Which Is Intended To Be Broken And Chewed In Between The Teeth Before Ingestion. Antacid And Vitamin Tablets Are Usually Prepared As Chewable Tablets. It Is Given To The Children Who Have Difficulty In Swallowing And To The Adults Who Dislike Swallowing.

Effervescent Tablet:

The Tablet That Contains Acid Substances And Carbonate Or Hydrogen Carbonate That React Rapidly In The Presence Of Water To Release Carbon Dioxide. Sodium Bicarbonate, Citric Acid And Tartaric Acid Are Added To The Active Ingredients To Make The Tablet Effervescent. This Preparation Makes The Tablet Palatable.

Lozenge Tablet:

The Tablet That Is Intended To Produce Continuous Effect On The Mucous Membrane Of The Throat. There Is No Disintegrating Agent. The Quality Of The Binding Agent Is Increased So As To Produce Slow Dissolution. Suitable Sweetening (Sugar), Coloring And Flavoring Agents Must Be Include In This Formulation. Gum Is Used To Give Strength And Cohesiveness To The Lozenge And Facilitating Slow Release Of The Active Ingredient.

Soluble Tablet:

The Tablet That Dissolves Completely In Liquid To Produce Solution Of Definite Concentration. Mouth Wash, Gargle, Skin Lotion, Douche; Antibiotic, Certain Vitamins, And Aspirin Are Given In This Formulation.

Sublingual Tablet:

The Drug Which Is Destroyed Or Inactivated Within The Gastrointestinal Tract But Can Be Absorbed Through The Mucosal Tissue Of The Oral Cavity Is Usually Given In This Formulation. The Tablet Is Required To Be Placed Below The Tongue For The Slow Release Of Drug. But For Immediate Effect, Some Medicaments Are Formulated In Such A Way That They Are Dissolved Within 1 To 2 Minutes. For Example, Nitroglycerin Is Prepared In This Formulation.

Enteric Coated Tablet:

Some Drugs Are Destroyed By Gastric Juice Or Causes Irritation To The Stomach. These Two Factors Can Be Overcome By Coating The Tablet With Cellulose Acetate Phthalate. This Polymer Is Insoluble In Gastric Contents But Readily Dissolves In Intestinal Contents. So There Is Delay In The Disintegration Of Dosage Form Until It Reaches The Small Intestine. Like Coated Tablet, Enteric Coated Tablet Should Be Administered In Whole Form Broken Or Crushed Form Of The Enteric Coated Tablet Causes Destruction Of The Drug By Gastric Juice Or Irritation To The Stomach. Enteric Coated Tablet Is Comparatively Expensive.

Film Coated Tablet:

The Tablet That Is Covered With A Thin Layer Or Film Of Polymeric Substance Which Protects The Drug From Atmospheric Conditions And Mask The Objectionable Taste And The Odor Of Drug.

Implant:

A Small Tablet That Is Prepared For Insertion Under The Skin By Giving A Small Surgical Cut Into The Skin Which Is Stitched After The Insertion Of The Tablet. This Tablet Must Be Sterile One. The Drug Used In This Preparation Is Usually Water Insoluble And The Tablet Provides A Slow And Continuous Release Of Drug Over Prolonged Period Of Time Ranging From 3 To 6 Months Or Even More Contraceptive Tablet Is Formulated As Implant.

Sugar Coated Tablet:

The Tablet That Contains Active Ingredient(S) Of Unpleasant Taste May Be Covered With Sugar To Make It More Palatable. This Type Of Tablet Should Be Administered In Whole Form, Otherwise The Patient Will Experience The Unpleasant Taste Of The Active Ingredient.

Modified Release Tablet:

Modified-Released Tablet Is Either Uncoated Or Coated. This Contains Special Additives Or Prepared By Special Procedure Which, Separately Or Together, Is Intended To Modify The Rate Of Release Of The Drug Into The Gastrointestinal Tract. It Prolongs The Effect Of Drug And Also Reduces The Frequency Of Administration Of Drug. Several Drugs Are Available In Modified Release Tablet Such As Indomethacin.

Advantages

1. Tablets Are Elegant In Appearance And Convenient To Use.
2. The Tablets Dosage Forms Are Simple, Economical In Manufacturing, Most Stable And Most Convenient In Packaging, Shipping And Transportation.
3. These Can Be Manufactured To Show Product Identification, E.G. Exhibiting The Required Markings On The Surface.
4. A Wide Range Of Tablet Types Is Available, Offering A Range Of Drug Release Rates And Durations Of Clinical Effect. Tablets May Be Formulated To Offer Rapid Drug Release Or Controlled Drug Release, The Latter Reducing The Number Of Daily Doses Required (And In So Doing Increasing Patient Compliance).
5. Tablets May Be Formulated To Contain More Than One Therapeutic Ingredients Showing A Combination Thus Reducing Multiple Tablets Use.

Disadvantages

1. Its Manufacturing Involve Several Unit Operation Thus At Each Step There Is Loss Of Ingredients Of Tablets.
2. Finding Of Good Compatibility Between Active And Inactive Ingredients For Tablets Formulation Require Huge Hit And Tial Experimentation.
3. The Absorption Of Therapeutic Agents From Tablets Is Dependent On Physiological Factors, E.G. Gastric Emptying Rate And Shows Interpatient Variation.
4. May Be Problematic For Children And Elders Due To Difficulties In Swallowing.

.

1.2 Introduction Of A Bilayer Tablet:

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.

Usually Conventional Dosage Form Produce Wide Ranging Fluctuation In Drug Concentration In The Blood Stream And Tissues With Consequent Undesirable Toxicity And Poor Efficiency. This Factor Such As Repetitive Dosing And Unpredictable Absorption Led To The Concept Of Controlled Drug Delivery Systems. The Goal In Designing Sustained Or Controlled Delivery Systems Is To Reduce The Frequency Of The Dosing Or To Increase Effectiveness Of The

Drug By Localization At The Site Of Action, Reducing The Dose Required Or Providing Uniform Drug Delivery. The Primary Objective Of Sustained Release Drug Delivery Is To Ensure Safety And To Improve Efficacy Of Drugs As Well As Patient Compliance.

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. 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.

Advantages Of Bilayer Tablet

The Advantages Of The Bilayer Tablet Over The Other Conventional Preparations Of Oral Solid Dosage Forms Include:

1. When The Two Different Layers Of The Tablet Content Two Different Drugs, Then The Tablet Can Be Easily Used In Combination Therapy.
2. Frequency Of The Dose Administration Is Reduced Which Ultimately Improve The Patient Compliance.
3. This Formulation Can Be Use To Deliver Separate Two Incompatible Substance.
4. In Case Of Drugs Having A Low Half Life, Each Of The Two Layers Of The Tablet Respectively Content A Loading Dose And Maintenance Dose Of The Same And Thus Increase The Bioavailability Of The Drug.
5. In Case Of A Conventional Dosage Form Due To Fluctuation Of The Dose Interval The Plasma Drug Concentration May Differ (Under Medication Or Over Medication), But In This Dosage Form The Plasma Drug Concentration Is Always Constant, Which Ultimately Provide A More Effective Action Of The Drug.

Gmp Requirements For Bilayertablet

To Produce A Quality Bi-Layer Tablet, In A Validated And Gmp-Way, It Is Very Important To Follow The Following Criteria For The Selection Of Bilayer Press. These Requirements Seem Obvious But Are Not So Easily Accomplish. The Press Should Be Capable Of:

1. Preventing Capping And Separation Of The Two Individual Layers That Constitute The Bi-Layer Tablet;
2. Preventing Cross-Contamination Between The Two Layers;
3. Providing Sufficient Tablet Hardness;
4. Accurate And Individual Weight Control Of The Two Layers;
5. Producing A Clear Visual Separation Between The Two Layers;
6. Manufacturing Products Of High Yield.

A. Floating Drug Delivery System:

These Are Designed To Have A Low Density And Thus Float On Gastric Contents After Administration Until The System Either Disintegrates Or The Device Absorbs Fluid To The Point Where Its Density Is Such That It Loses Buoyancy And Can Pass More Easily From The Stomach With A Wave Of Motility Responsible For Gastric Emptying. The Bilayer Tablet Is Designed In Such A Manner That, One Layer Gives The Immediate Dosing Of The Drug Which Gives Faster Onset Of Action While Other Layer Is Designed As A Floating Layer Which Floats In The Stomach (Gi-Fluid).

B. Polymeric Bioadhesive System:

These Are Designed To Imbide Fluid Following Administration Such That The Outer Layer Becomes A Viscous, Tacky Material That Adheres To The Gastric Mucosa/Mucus Layer. This Should Encourage Gastric Retention Until The Adhesive Forces Are Weakened. These Are Prepared As One Layer With Immediate Dosing And Other Layer With Bioadhesive Property.

Disadvantages: The Success Seen In Animal Models With Such System Has Not Been Translated To Human Subjects Due To Differences In Mucous Amounts, Consistency Between Animals And Humans.

The System Adheres To Mucous Not Mucosa. The Mucous Layer In Humans Would Appear To Slough Off Readily, Carrying Any Dosage Form With It. Therefore, Bioadhesive Dosage Form Would Not Appear To Offer A Solution For Extended Delivery Of Drug Over A Period Of More Than A Few Hours.

C. Swelling System:

These Are Designed To Be Sufficiently Small On Administration So As Not To Make Ingestion Of The Dosage Form Difficult (E.G., Less Than Approximately 23 Mm Long And Less Than 11 Mm Wide For An Oval Or Capsule – Shaped Tablet Whereas 10- 12mm In Diameter For Round Tablets). On Ingestion They Rapidly Swell Or Disintegrate Or Unfold To A Size That Precludes Passage Through The Pylorus Until After Drug Release Has Progressed To A Required Degree. Gradual Erosion Of The System Or Its Breakdown Into Smaller Particles Enables It To Leave Stomach. The Simple Bilayer Tablet May Contain An Immediate Release Layer With The Outer Layer As Extended Release Or Conventional Release.

II. Materials

S.No	Ingredients
1	Ezetimibe
2	Metformin Hcl
3	Eudragit Rs 100
4	Peo
5	Carbapol
6	Mcc
7	Pvp K30

8	Ipa
9	Lactose
10	Talc
11	Magnesium Stearate
12	Aerosil

III. Methodology

I. Analytical Method Development In 0.1 N 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:

Procedure:

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 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 Ezetimibe In 0.1n Hcl:

Procedure:

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.

Ii. 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:

Procedure:

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:

Procedure:

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.

Iii. Analytical Method Development 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:

Procedure:

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:

Procedure:

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 $\Lambda_{max=232}$

Iv. 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.

Table 5: 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

V. 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.

Table 6: 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
Eudragit 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

Iv. Evaluation Of Tablets

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.

$\theta = Tan^{-1} (H/R)$

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.

Table 7: Angle Of Repose Limits
Flow Properties And Corresponding Angles Of Repose

Flow Property	Angle Of Repose (Degrees)
Excellent	25–30
Good	31–35
Fair—Aid Not Needed	36–40
Passable—May Hang Up	41–45

Flow Property	Angle Of Repose (Degrees)
Poor—Must Agitate, Vibrate	46–55
Very Poor	56–65
Very, Very Poor	>66

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.

Bulk Density = Weight Of Powder/ Bulk Volume.

$$D_b = M / V_0$$

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[18].

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[19]. The Formula For Carr's Index Is As Below:

$$\text{Compressibility Index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. Hausner's Ratio:

Hausner's Ratio Is A Number That Is Correlated To The Flow Ability Of A Powder[19] .

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

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.

$$Average\ weight = weight\ of\ 20\ tablets/20$$

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

Table 9: 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

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%.

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

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.

Calculate The Quantity In Mg Of Drug In The Portion Taken By The Formula

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

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 $37^0c\pm0.5^0c$. 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).

Table 10: 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
Time Points	5, 10, 15, 30, 45 And 60
Analytical Method	Ultraviolet Visible Spectroscopy
Λ_{max}	265nm

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 $37^0c\pm0.5^0c$. 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).

Table 11: 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

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

Log C= Log C_o-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[20].

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).

$Mt/ M_\infty = K.T^n$

Where, Mt Is The Amount Of Drug Released At Time T

M_α Is The Amount Released At Time A,

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 12: 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

IV. Results And Dicussion

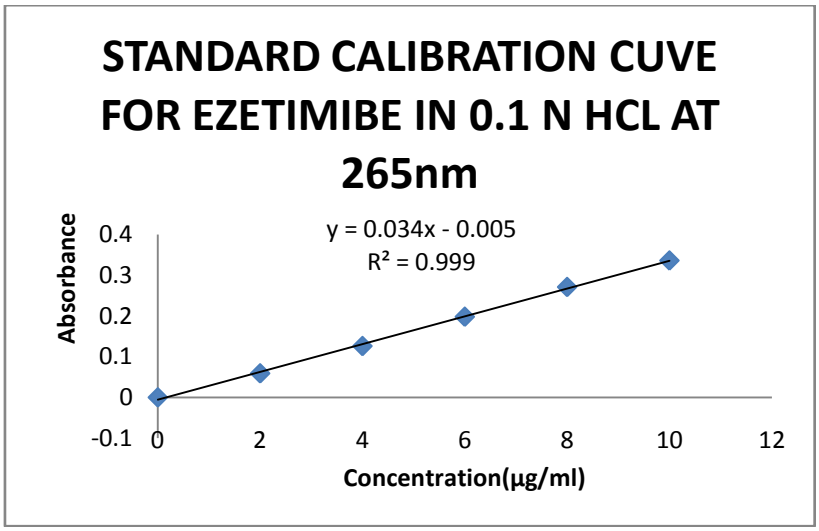
1. Construction Of Standerd Caliberation Curve Of Ezetimibe In 0.1n Hcl:

The Absorbance Of The Solution Was Measured At 265nm, Using Uv Spectrometer With 0.1n Hcl As Blank. The Values Are Shown In Table. 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.

Table 13: 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



2. Construction Of Standerd 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. 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

Table 14: 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

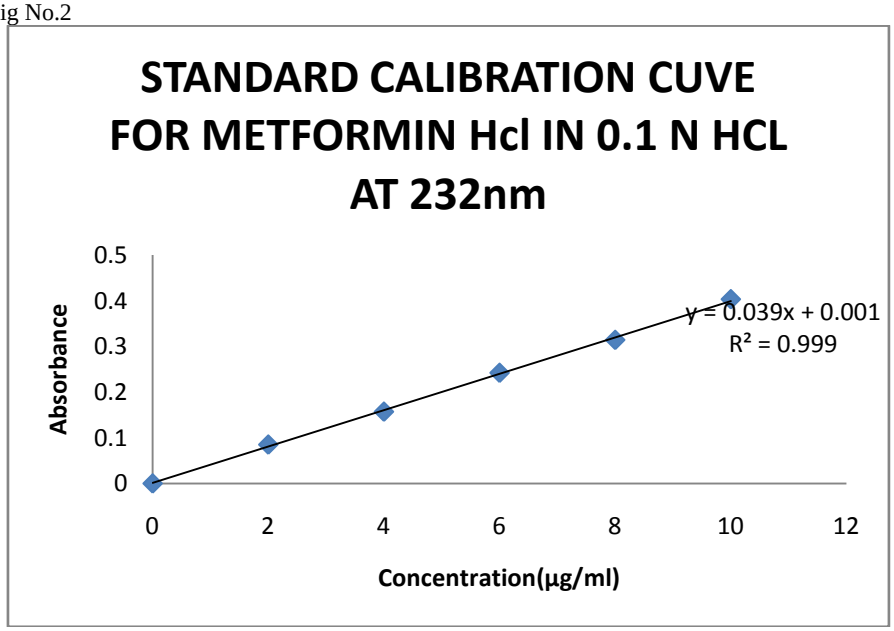


Figure 2: Standard Calibration Curve Of Metformin Hcl In 0.1n Hcl

3. Construction Of Standerd Caliberation 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. 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

Table 15: 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

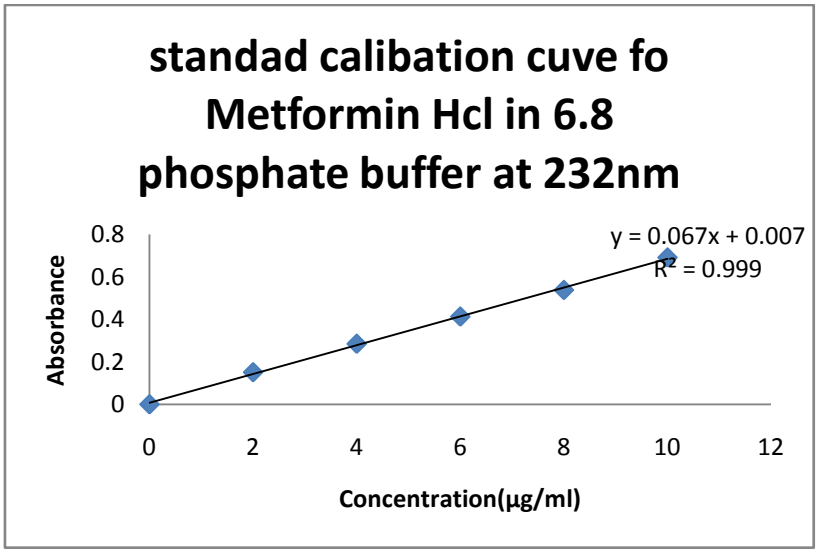


Figure 3: Standard Calibration Curve Of Metformin Hcl In 6.8 Phosphate Buffer

3. Evaluation Of Tablets:

Table 16: 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 17: 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

*Test For Friability Was Performed On Single Batch Of 20 Tablets

Table 18: 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	-

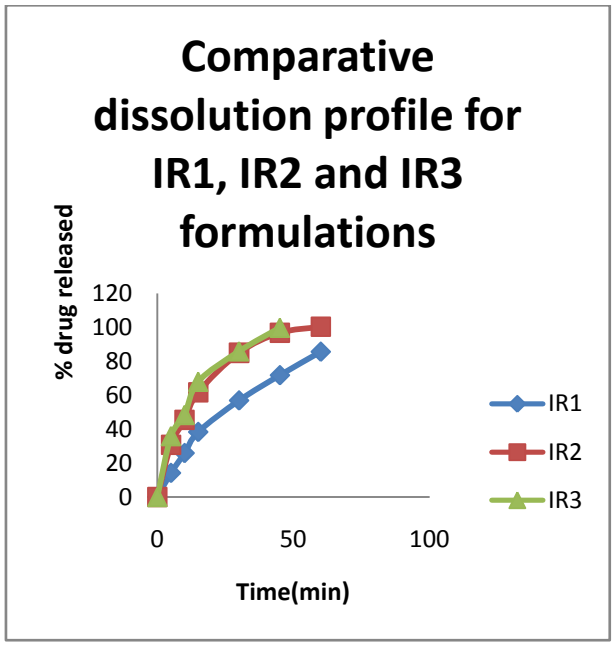


Figure 4: Comparative Dissolution Profile For Ezetimibe Ir Tablets

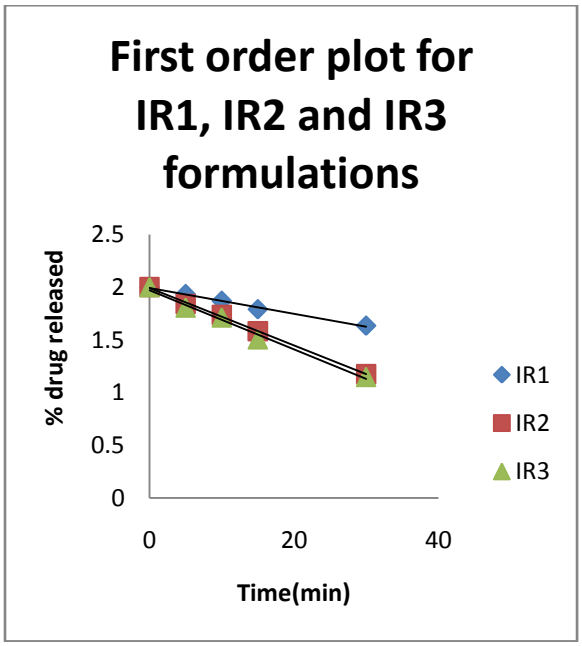


Figure 5: First Order Plots For Ezetimibe IrTablets

Table 19: 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 20: 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 21: 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 22: 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

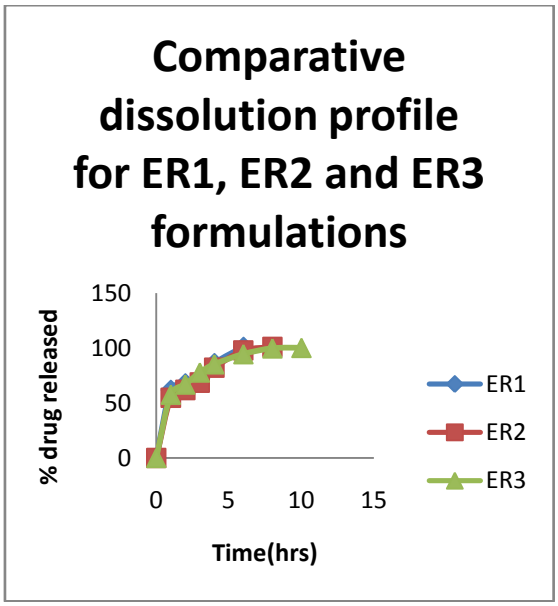


Figure 6: Comparative Dissolution Profile For Er1, Er2 And Er3 Formulations

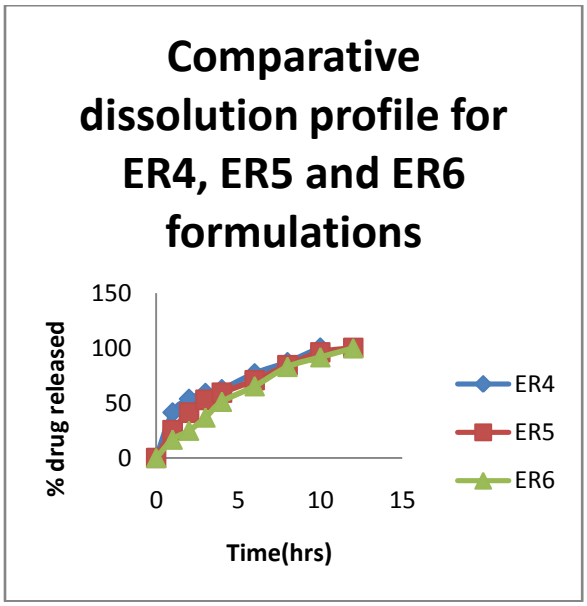


Figure 7: Comparative Dissolution Profile For Er4, Er5 And Er6 Formulations

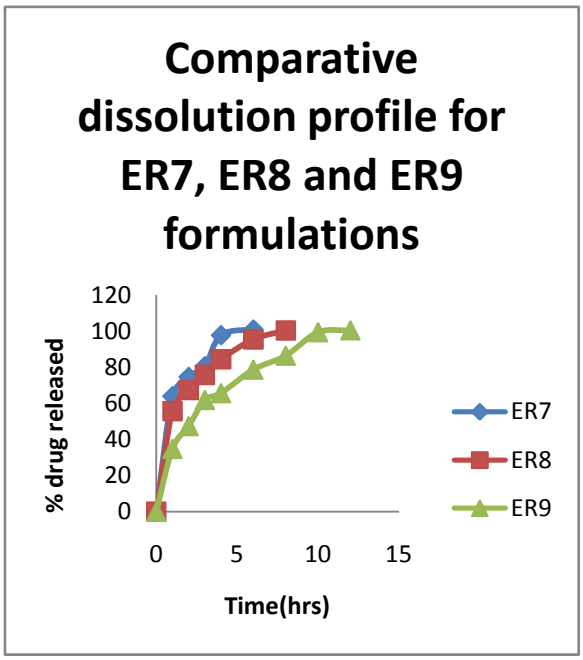


Figure 8: Comparative Dissolution Profile For Er7, Er8 And Er9 Formulations

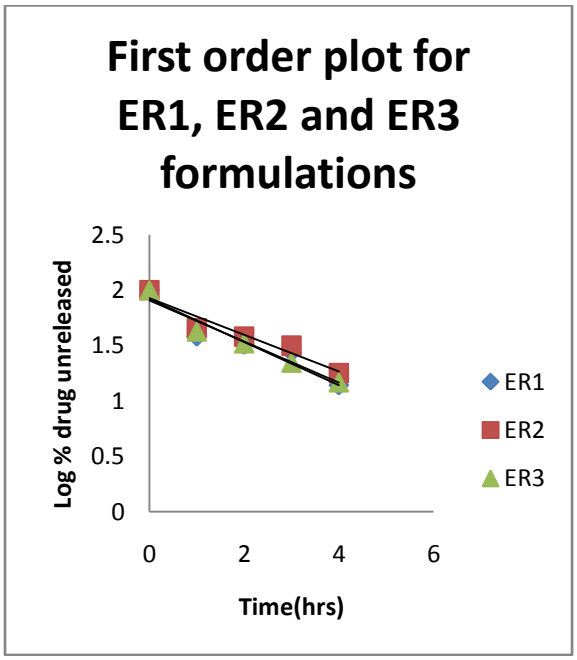


Figure 9: First Order Plot For Er1, Er2 And Er3 Formulations

ss

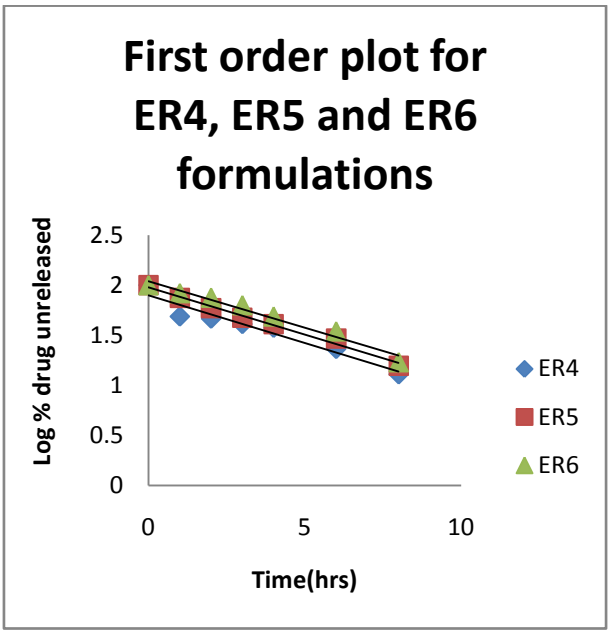


Figure 10: First Order Plot For Er4, Er5 And Er6 Formulations

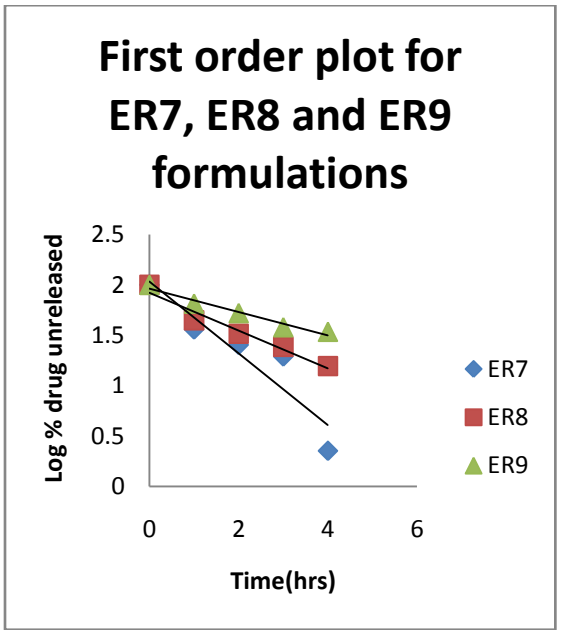


Figure 11: First Order Plot For Er7, Er8 And Er9 Formulations

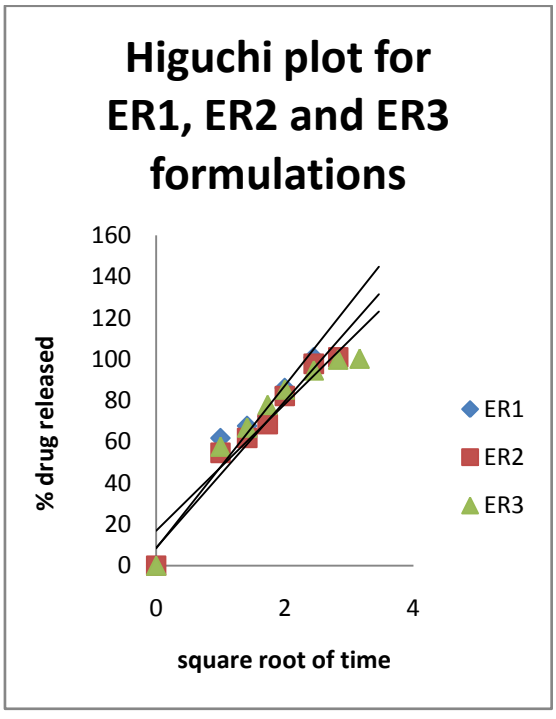


Figure 12: Higuchi Plot For Er1, Er2 And Er3 Formulations

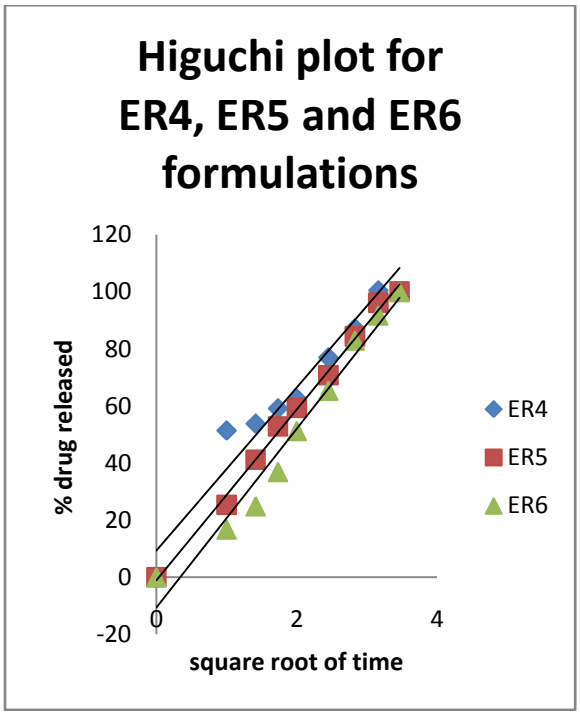


Figure 13: Higuchi Plot For Er4, Er5 And Er6 Formulations

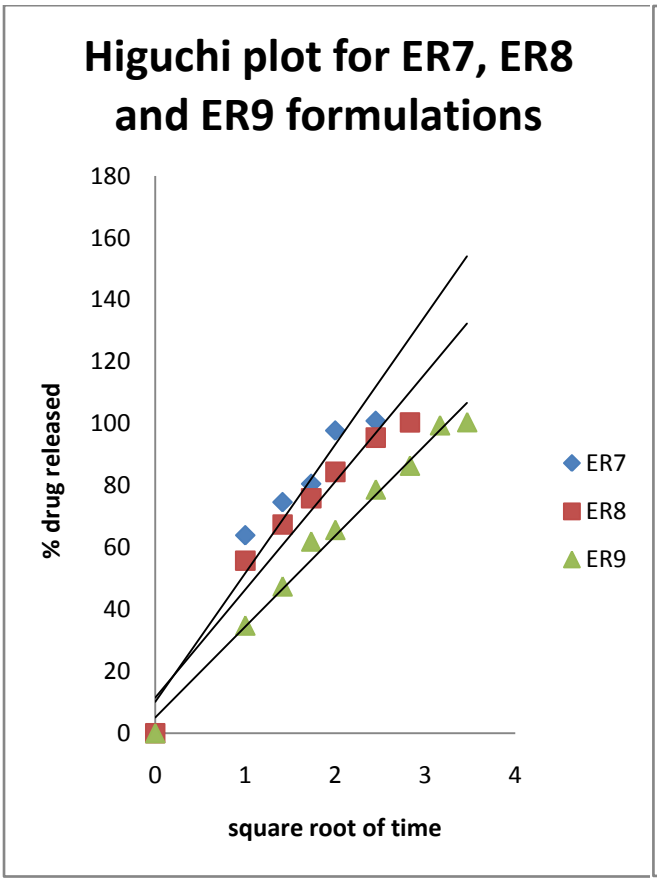


Figure 14: Higuchi Plot For Er7, Er8 And Er9 Formulations

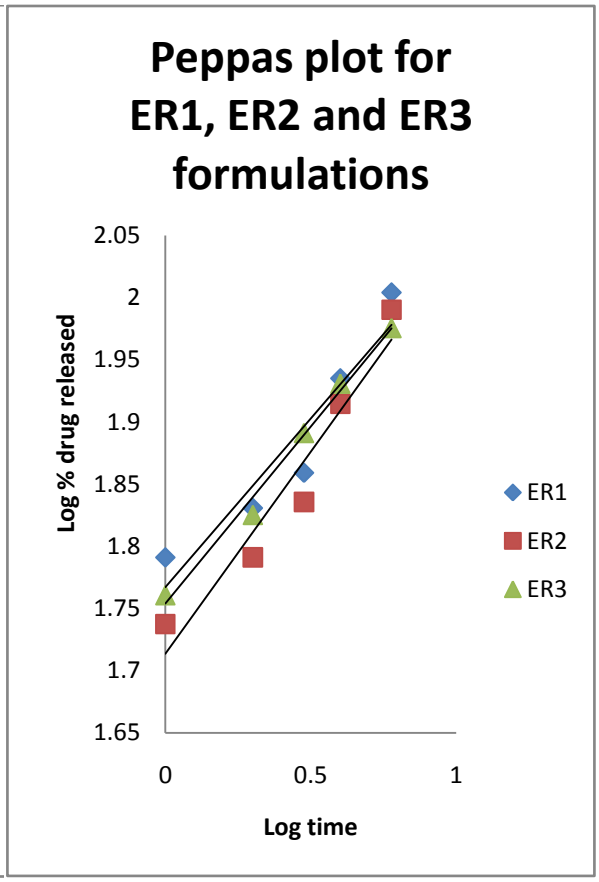


Figure 15: Korsmayers Pepas Plot For Er1, Er2 And Er3 Formulations

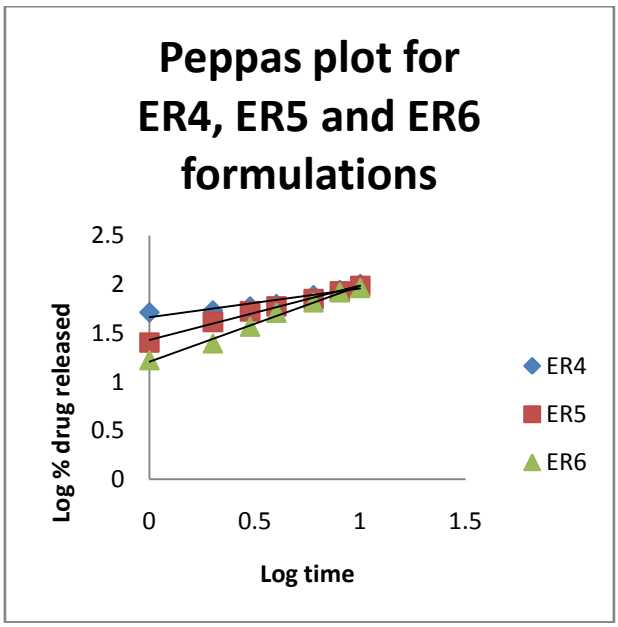


Figure 16: Korsmayers Pepas Plot For Er4, Er5 And Er6 Formulations

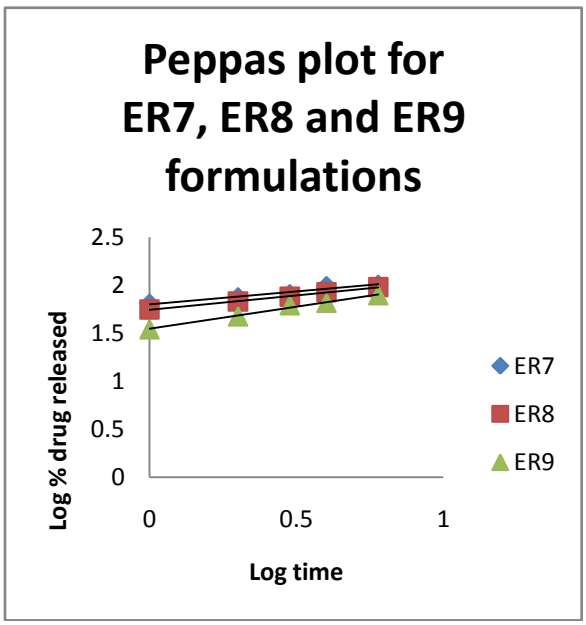


Figure 17: Korsmayers Pepas Plot For Er7, Er8 And Er9 Formulations

Table 23: 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

Inference

- Among The Different Control Release Polymers Peo Were Showing Highest Drug Release Retarding Capacity
- Er6 Was Showing The Satisfactory Results.
- For The Er6 Formulation Diffusion Exponent N Value Is In Between 0.45 To 0.89 So They Are Following Non Fickian Anomalous Diffusion Modeol.
- Higuchi Plots For Er6 Formulations Are Having Good Correlation Values So The Drug Is Releasing Diffusion Mechanism

V. Conclusion

- The Present Research Work Was Carried Out To Develop A Bilayer Tablet Of Metformin Hcl As Extended Release Layer Was Prepared By Using Hydrophilic Matrix Polymers Such As Eudragit Rs100, Peo And Carbapol And Ezetimibe As Immediate Release Layer Was Prepared.
- Combination Of Metformin Hcl And Ezetimibe For The Management Of Type Ii Diabetes Mellitus.
- Drug Release From The Matrix Was Found To Decrease With Increase In Polymer Concentration.
- Er6 Gave Better Release When Compared To All Formulations.
- The Angle Of Repose, Bulk Density, Tapped Density And Compressibility Index Results Shown That The Formulation Is Suitable For Wet Granulation Method.
- The Drug Release Kinetics Of The Optimized Bilayered Tablets Correspond Best To Korsmeyer- Peppas Model And The Drug Release Mechanism As Per N Value Of Korsmeyer - Peppas Is Anomalous (Nonfickian) Diffusion And The Tablets Showed No Significant Change In Physical Appearance, Drug Content Or In Vitro Dissolution Pattern .

Hence, It Is Finally Concluded That, The Bilayer Tablet Technology Can Be Successfully Applied For Sustained Release Of Metformin Hcl And Immediate Release Of Ezetimibe.

Bibliography

[1] Nagaraju, R., Rajesh Kaza. Ijps. 2009, 2(3), 638 - 946.
[2] Remya P.N., Damodharan, N., Sulakshan Kumar C.V., International Journal Of Pharm Tech Research 2010, 2 (2), 1250-1255.
[3] Jadhav, R.T., Payal, H., Patil And Pratibha, R. Patil., J. Chem. Pharm. Res., 2011, 3(3), 423.
[4] Wilding Ir, Coupe Aj, Davis Ss. The Role Of Gamma Scintigraphy In Oral Drug Delivery. Adv. Drug Deliv. Rev.1991; 7:87–117.
[5] Chien Yw. Fundamentals Of Controlled-Release Of Drug Administration In: J. Swarbrick (Ed.), Novel Drug Delivery System Marcel Dekker, New York, 1982, Pp. 465–574.
[6] Lee L. Diffusion-Controlled Matrix Systems, In: A. Kydonieus (Ed.), Treatise On Controlled Drug Delivery, Marcel Dekker, New York, 1992, Pp. 155– 198.
[7] Kumar Kk, Mahesh M, Sasikanth K. Design, Development And Characterization Of Sustained Release Of Metformin Hydrochloride And Gliclazide Bilayered Tablets By Wet Granulation Method. Int J Biopharm 2010; 1(2):67-71.
[8] Shiyani B, Gattani S, Surana S. Formulation And Evaluation Of Bi-Layer Tablet Of Metoclopramide Hydrochloride And Ibuprofen. Aaps Pharm Sci Tech 2008 ; 9(3):818-27
[9] Deshpande Rd, Gowda Dv, Mahammed N, Deepak N. Maramwar. Bi-Layer Tablets- An Emerging Trend: A Review. Ijpsr 2011; 2(10): 2534-2544.
[10] Panchal Ha, Tiwari Ak. Novel Approach Of Bilayer Tablet Technology: An Review. Journal Of Pharmaceutical Science And Technology 2012; 4(4): 892–904.
[11] Divya A, Kavitha K, Kumar Mr, Dakshayani S, Jagadeesh Ssd. Bilayer Tablet Technology: An Overview. Journal Of Applied Pharmaceutical Science 2011; 01(08): 43-47.
[12] Patel M, Ganesh Ns, Kavitha, Tamizh M. Challenges In The Formulation Of Bilayered Tablets: A Review. Ijprd 2010; 2(10): 30–42.
[13] Panchal Ha, Tiwari Ak. Novel Approach Of Bilayer Tablet Technology: An Review. Journal Of Pharmaceutical Science And Technology 2012; 4(4), 892–904
[14] Aithal Ks Et Al., 1996; Akihiko I. Et Al 1996.
[15] K. Mounika Saranya, P. Lakshmana Rao, M. Prasada Rao And M. Rama Kotaiah, Formulation And Evaluation Of Bilayer Tablets Of Metformin Hcl And Ezetimibe, World Journal Of Pharmacy And Pharmaceutical Sciences, Volume 3, Issue 12, 777-790.
[16] Chinam Np, Arethi Bk, Hemant Kp, Prakash S, Vimala Dm. Design And Evaluation Of Sustained Release Bilayer Tablets Of Propranolol Hydrochloride**.** Acta Pharm.2007; 57:479–89.
[17] Kumar Bv, Prasad G, Ganesh B, Swathi C, Rashmi A, Reddy Ag. Development And Evaluation Of Guaifenesin Bilayer Tablet. Int J Pharm Sci 2010; 3(3):1122-28.
[18] Sonar Sg, Jain Dk, More Dm. Preparation And In Vitro Evaluation Of Bilayer And Floating-Bioadhesive Tablets Of Rosiglitazone Maleate. Asian. J. Pharma Sci. 2007; 2(4): 161-69.
[19] Gohel Mc, Parikh Rk, Nagori Sa, Jethwa Ba. Fabrication And Evaluation Of Bilayer Tablet Containing Conventional Paracetamol And Modified Release Diclofenac Sodium. Ind. J. Pharm Sci, 2010; 72(2):191-199.
[20] Uttam Mandal , Tapan Kumar Pal El Al, Formulation And In Vitro Studies Of A Fixed-Dose Combination Of A Bilayer Matrix Tablet Containing Metformin Hcl As Sustained Release And Glipizide As Immediate Release, Drug Dev. Ind. Pharm , 2008, 34 (3), 305 –313.
[21] Jitendra R. Amrutkar, Mohan. G.Kalaskar, Varsha. G. Shrivastav, P.G. Yeole., Bilayer Tablet Formulation Of Metformin Hydrochloride And Gliclazide: A Novel Approach In The Treatment Of Diabetes. Int. J. Pharm Res And Dev. 2009, 1, 1- 11.
[22] Ramesh D. Sathis Kumar, Guruviah, A.Harani., Formulation And Evaluation Of Bilayered Sustained Release Matrix Tablets Of Metformin Hcl Sr And Pioglitazone. Int. J. Sci Res. 2010, 5(3) 176- 182.
[23] Defang O, Shufang N, Wei L. In Vitro And In Vivo Evaluation Of Two Extended Release Preparations Of Combination Metformin And Glipizide. Drug Dev. Ind. Pharm. 2005, 31:677-685.
[24] Galeone F, Fiore G, Arcangeli A, Mannucci E. Gliclazide And Metformin Combination In Patients With Type 2 Diabetes. Preliminary Data. Minerva Endocrinol 1998; 23: 71-75.
[25] N. Patel, R. Natarajan, N.N. Rajendran And M. Rangapriya, Formulation And Evaluation Of Immediate Release Bilayer Tablets Of Telmisartan And Hydrochlorothiazide, Int.J. Pharm Sci And Nanotech.(4),2011:1477-1482.