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BILAYER TABLET OF GLIMEPERIDE AND METFORMIN: A IDEALISTIC WAY TO IMPROVE PATIENT COMPIENCE.

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Abstract:

sustained release bilayer tablet containing metformin and glimeperide in which metformin is in the form of sustained release layer and Glimeperide is in the form of immediate release layer gives fast release. The aim and objective of present study is to design and prepare oral dosage form able to deliver a first impulse of the dose in the shorten time possible and a second fraction of dose in the prolonged time at a constant rate. This combination of drugs used in Diabetes Mellitus type 2 which shows potent effect. Metformin tablet were prepared by using tablet compression technique. different grades of HPMC were used. HPMC used as a matrix forming polymer for the metformin layer enables drug release for up to 9-10hour. Glimeperide tablet are prepared by using solvent evaporation method of solid dispersion technique is PEG6000.The formulated Metformin Hydrochloride & Glimeperide tablets were evaluated for thickness, hardness, weight variation, friability, drug contents & in vitro drug release .

Keywords : Metformin, Glimeperide,Impulse,Substained Relese bilayer Tablet.

General Introduction

Unit solid dosage form containing drug with excipients prepared by compression machinery by use of compaction phenomenon. Conventional tablets- Generally conventional dosage forms delays the release of therapeutic system layers & do not provide rapid onset of action.

Immediate release tablets- Gives fast release to provide rapid onset of action but fails to provide longer duration of action Improved compliance/added convenience. Allows high drug loading.

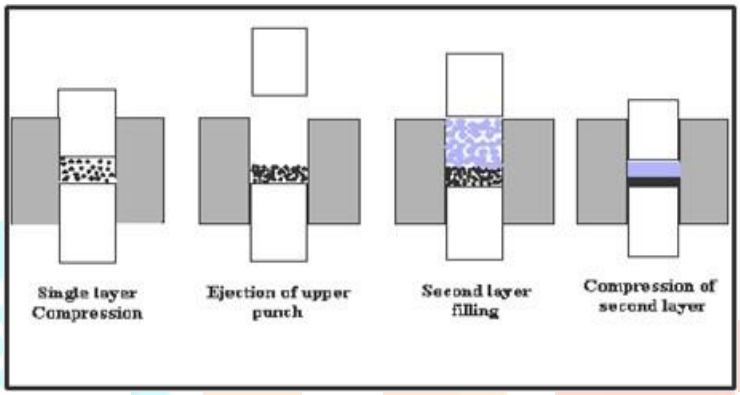
Extended release tablets- For some drugs (such as NSAIDs, antihypertensive, antihistaminic, antidiabetic, antiallergic) extended release formulations generally lead to a delayed appearance of effective plasma levels & they can't provide a prompt disposition of the dose immediately after administration. modify and improve the drug performance by the duration of drug action. Decreasing the To frequency of dosing. Decreasing the required dose employed.Providing uniform drug delivery

Bilayer Tablet-

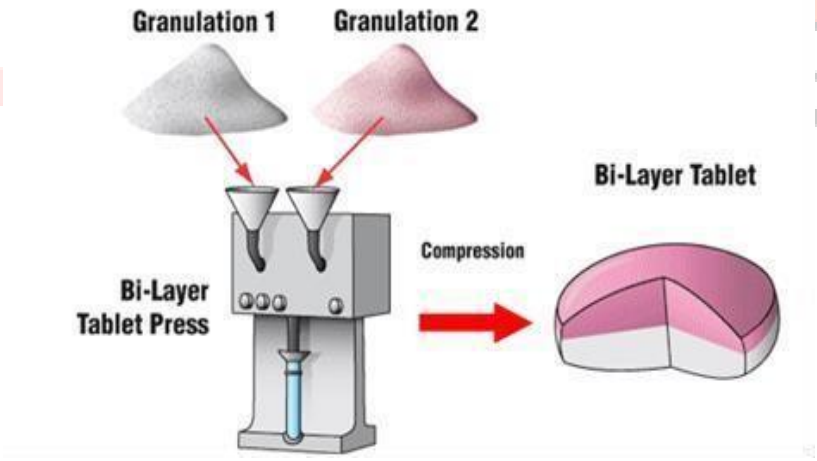
On the basis of these considerations, we have proposed anew oral delivery device in the form of a double component tablet in which -

- First layer is formulated to obtain a prompt release of the drug, with the aim a short period of time (called as loading dose).
- The second layer is a prolonged released hydrophilic matrix, which designed to maintain an effective plasmalevel for a prolonged period of time (called as maintenance dose).
- This concept can be used to produce a biphasic delivery system combining a fast release together with theslow release period of the drug.

Compression cycle of bilayer tablet



General concept of Bilayer tablets



Advantages of bilayer tablets

Dosing frequency is reduced.

Improved patient compliance.

Drug administration can be made more convenient.

Reduction in drug level fluctuation in blood, more even blood level maintained.

Better control of drug absorption can be attained since the high blood level peaks that may be observed after administration of dose of a high availability drug.

Incompatible substance can be separated

Drug selection for oral sustained release drug delivery system

Physicochemical parameters for drug selection

Parameter	PREFERED VALUE
Molecular weight/Size	<1000
Solubility	>0.1mg/ml for PH 1 to PH 7.8
Apparent partitio ncoefficient	High
Absorption mechanism	Diffusion
General absorbability	For all GI segments
Release	Should not be influenced by PH and enzyme.

DIABETES MELLITUS

- The name “diabetes”, meaning “syphon” or “running through”.
- The name ”mellitus” from Latin meaning “sweetened with honey”.
- Refers to presence of sugar in urine of patients having disease. Mellitus distinguishes this disease from diabetes insipidus, which is caused by impaired renal reabsorption of water.
- Diabetes Mellitus, disease in which the pancreas produces insufficient amounts of insulin, or in which the body’s cells fail to respond appropriately insulin.

Solubility Enhancement

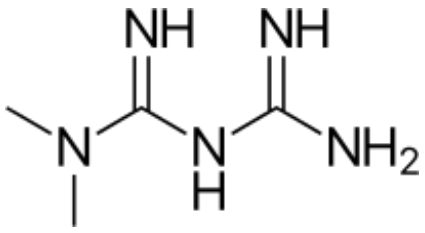
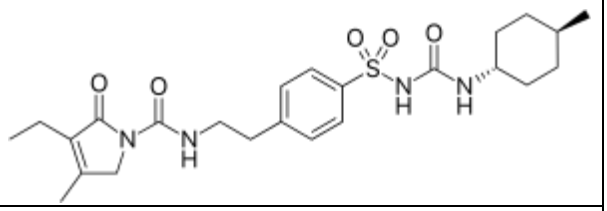
Glimepiride is a poorly soluble in water as well as gastric fluids. Due to the solubility problem, the solubilityof glimepiride can be increased by using solubility enhancement technique like solid dispersion.

Solid dispersion

A solid dispersion is "the dispersion of one or more active ingredients in an inert carrier at solid state prepared by melting (fusion), solvent or the melting- solvent method".

Solid dispersion of glimepiride in Polyvinylpyrrolidone (PVP K30) with water soluble polymers were prepared by solvent evaporation method and then formulating solid dispersion (SDs) tablets of the best formulation of SDs .

DRUG, POLYMER & EXCIPIENTS PROFILE (Short) Drug Profile

Parameter	Comments on Metformin hydrochloride	Comments on Glimeperide
Structure		
Molecular Formula	**C4H11N5**	**C24H34N4O5S**
Molecular weight	129.16 g/mol (free) or 165.63g/mol (Hcl)	490.617 g/mol
Melting point	: 223 – 226oC	207-0C
Mechanism of action	Decrease blood glucose level by decreasing hepatic glucose production, increase insulin sensitivity by increasing peripheral glucose uptake	Selectively bind to sulfonylurea receptors on the surface of the pancreatic beta cells.
Absorption	About 50 – 60% dose of metfomin Hydrochloride absorbed throughout GIT	Rapidly & well absorbed
Half life	1.2 Hrs	5-8hrs
Solubility	Freely soluble in water, ethanol	Soluble in dimethylformamide , Slightly soluble in dichloromethane, very slightly soluble in methanol
Dose	500 mg to 3.5g daily.	1 to 2 mg (once a day) 30 mg to 60 mg in modified release

Polymer Profile

Sr. No.	Polymer	Use
01	**HPMC (K4M, K15M, K100M)**	**Rate controlling polymer for sustained release, Coating agent, Film former,Viscosity increasing agent.**

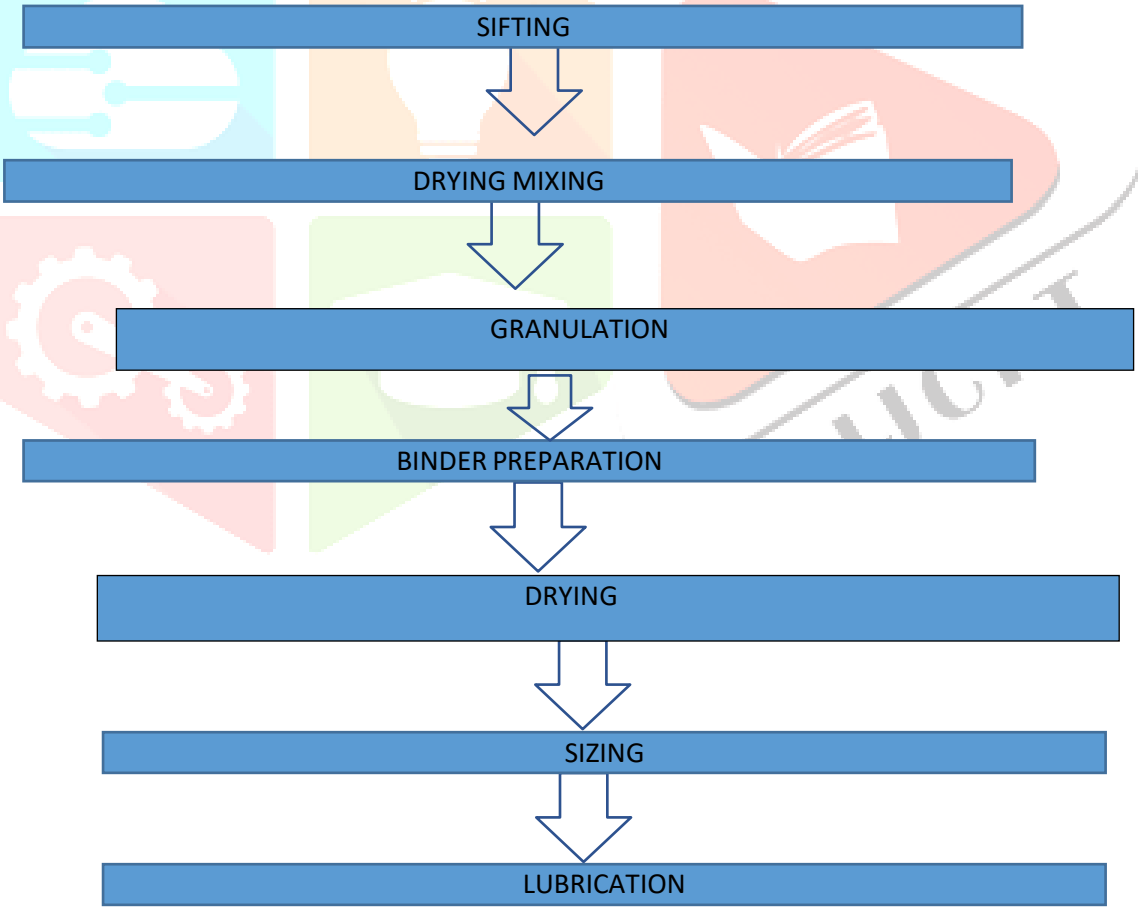
Polymer Profile

EXPERIMENTAL PROFILE

Sr. No.	Excipients	Use
01	Lactose monohydrate	Diluent
02	Cross carmellose Sodium	Superdisintegrant
03	Magnesium stearate	Lubricant
04	Starch	Binder

FORMULATION DEVELOPMENT

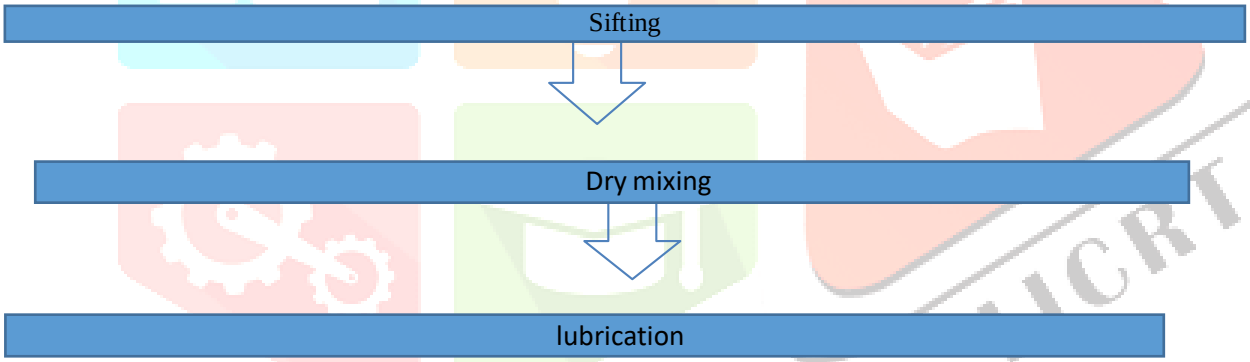
1. Formulation of sustained release layer granules (Metformin HCL)



Formula for sustained release layer

Ingredients(mg)	M1	M2	M3	M4	M5	M6	M7	M8	M9
Metformin HCl	500	500	500	500	500	500	500	500	500
HPMC K4M	110	-	-	130	-	-	150	-	-
HPMC K15M	-	110	-	-	130	-	-	150	-
HPMC K100M	-	-	110	-	-	130	-	-	150
MCC	113	113	113	93	93	93	73	73	73
Starch	20	20	20	20	20	20	20	20	20
Mg Stearate	7	7	7	7	7	7	7	7	7
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	750	750	750	750	750	750	750	750	750

2. Formulation of immediate release layer granules (glimepiride)



Formula for immediate release layer

Ingredients(Mg)	G1	G2	G3
Glimepiride	240	240	240
Cross carmellose Na	8	12	15
MCC	52	48	45
Mg Stearate	5	5	5
Total	305	305	305

PRECOMPRESSIONAL STUDY OF GRANULES (Chart)

1. Angle of Repose
2. Bulk density & Tapped density
3. Compressibility Index
4. Hausners Ratio

COMPRESSION OF BILAYER TABLETS

1. Filling of first layer.
2. Compression of first layer.
3. Ejection of upper punch.
4. Filling of second layer.
5. Compression of both layer together.
6. Ejection of bilayer tablet.

FORMULATION/ FORMULA FOR BILAYER TABLET

Sr.No	Ingredient(mg)	M7	M8	M9	Ingredients(mg)	G3
1	Metformin Hcl	500	500	500	Gliclazide	240
2	HPMC K4M	150			Cross. Carm. Sod.	15
3	HPMC K15M		150		MCC	45
4	HPMC K100M			150	Mag. Stearate	05
5	MCC	73	73	73		
6	Starch	20	20	20		
7	Mag. Stearate	07	07	07		
8	Water	q.s.	q.s.	q.s.		

POST- COMPRESSIONAL STUDIES OF BILAYER TABLETS

1. Shape of tablets
2. Tablet dimensions
3. Weight variation test
4. Hardness test
5. Friability test
6. Uniformity of content

7. Dissolution studies

DISSOLUTION STUDY

	Glimeperide	**Metformin Hydrochloride**
Dissolution medium	0.1N Hcl (pH 1.2)	0.1N Hcl (pH 1.2)
Dissolution medium volume	900 ml	900 ml
Apparatus	IP- II (Basket type)	IP- II (Basket type)
Temperature	37±0.5ºC	37±0.5ºC
Basket shaft speed	50 rpm	50 rpm
Sample volume withdrawn	5 ml	5 ml
Sampling intervals	5 min interval for each sample	5 min interval for each sample
Absorbance measured at	225nm	234 nm

2. Metformin Hydrochloride

KINETIC RELEASE PROFILE OF BILAYER TABLTS

The kinetic release profile of bilayer tablets was determined by design expert software.

RESULT & DISCUSSION PREFORMULATION STUDY

Preformulation Study of Pure Drug

a. Identification of pure drug

The IR spectrum of pure drug was found to be similar to the reference standard IR spectrum of Metformin Hydrochloride & Glimeperide given in British pharmacopoeia.

b. Organoleptic properties

1. Metformin Hydrochloride

Test	**Specification**	**Observations**
Colour	White crystalline powder	White crystalline powder
Taste	Bitter	Bitter
Odour	Odourless	Odourless

1. Glimeperide

Test	Specification	Observations
Colour	White or almost white powder	White crystalline powder
Taste	Bitter	Bitter
Odour	Odourless	Odourless

c.Solubility determination

It was found that Metformin Hydrochloride was insoluble in chloroform & ether, and freely soluble in water, ethanol, methanol and Glimeperide was slightly soluble in alcohol, soluble in methanol, Dichloromethane and poorly soluble in water. Solubility of glimepiride can be increased by using solubility enhancement technique like solid dispersion.

d. Melting point determination

The melting point of Glimeperide and Metformin Hydrochloride was found to be in the range of 181-183 °C and 223-226 °C respectively.

e. Micrometric study

1. Metformin Hydrochloride

Property Studied	Loose Bulk Density (g/ml)	Tapped Bulk Density(g/ml)	Carr's Index (%)	Hausner's Ratio (%)	Angle of Repose (ϕ)
Result	0.416±0.006	0.50±0.05	16.80±0.41	1.20±0.01	25.31±0.01

2. Glimeperide-

Property Studied	Loose Bul kDensity(g/ml)	Tapped Bul kDensity(g/ml)	Carr's Index(%)	Hausner's Ratio (%)	Angle of Repose (ϕ)
Result	0.403±0.01	0.490±0.02	17.75±0.12	1.22±0.02	27.34±0.57

ANALYTICAL METHOD OR CALIBRATION CURVEs Metformine Hydrochloride

1. Calibration curve in Phosphate buffer (pH 7.4)

Parameters	**Value**
Λmax	234nm
R2	0.996
Equation ofline	Y = 0.091*+0.009
Con. Range	1 – 10 µg/ml

3. Calibration curve in 0.1N Hydrochloric acid

Parameters	**Value**
Vλmax	234 nm
R2	0.9998
Equation ofline	Y = 0.0802 *- 0.0077
Con. Range	0 – 12 µg/ml

Glimepride:

1. Calibration curve in 0.1N HCl (pH 1.2)

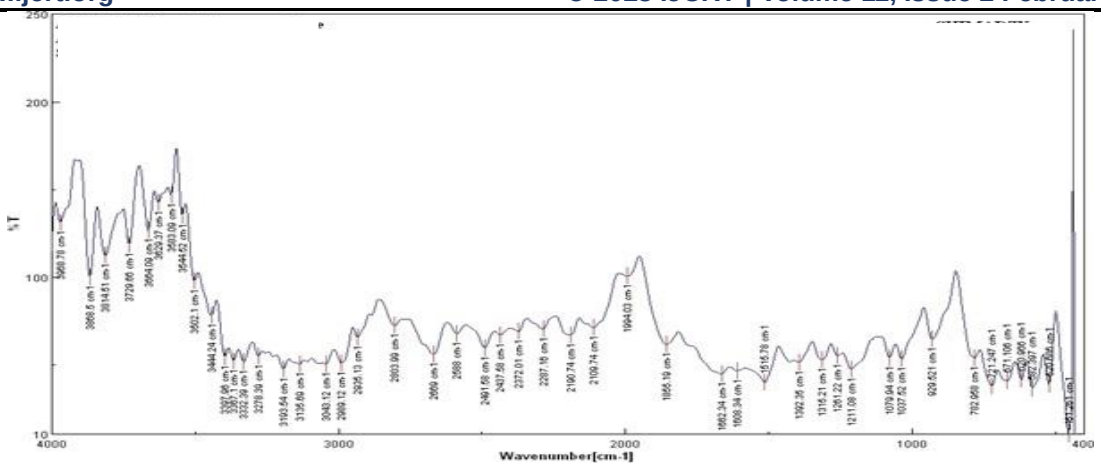
Parameters	Value
Λmax	225
R2	0.9993
Equation ofline	Y = 0.0599x +0.0003
Con. Range	0 – 10 µg/ml

COMPATIBILITY STUDY OF INGREDIENTS (DRUG & EXCIPIENTS) FTIR STUDY

1. Sustained release layer

a. Metformin Hydrochloride

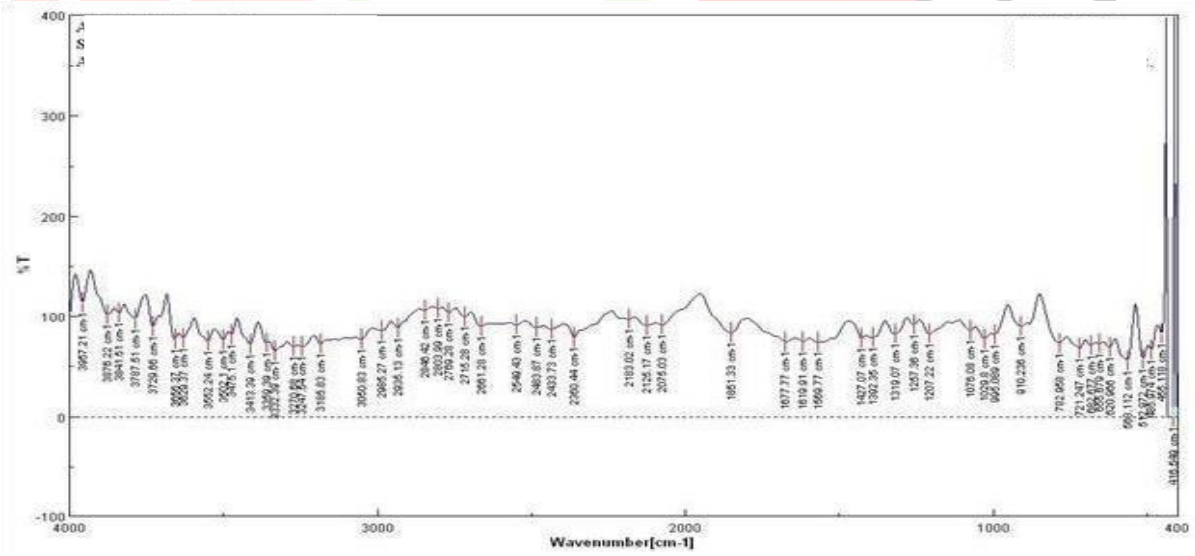
Range (cm^{-1})	Functional gr. Present
782-929	C-N
1037-1261	C-N
1515-1662	N-H deformation
3267-3378	NH_2
3502-3729	-NH stretching



Ranges of Fun. Group of Metformin Hcl

b. Physical mixture (Metformin Hydrochloride & other excipients)Physical mixture

Range (cm^{-1})	**Functional group present**
782 – 929	C – N
1037 – 1261	C – N
1515 – 1662	N – H deformation
3367 – 3278	-NH_2
3502 – 3729	-NH stretching



Ranges of fun. Group of Physical mixture

2. Immediate release layer

a. Glimeperide

Ranges of fun. Group of Glimeperide

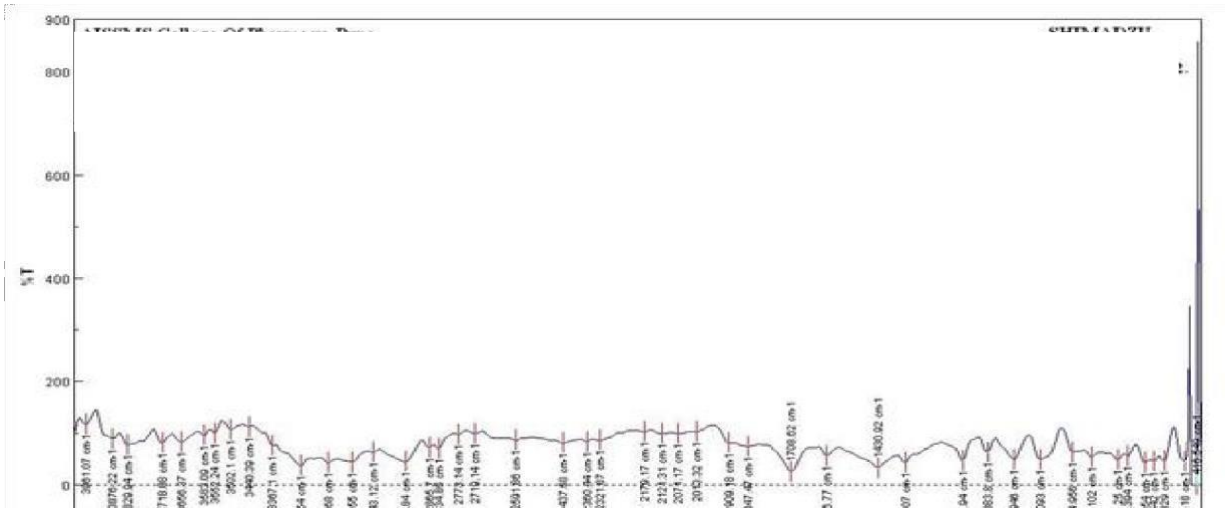
b. Physical Mixture (Glimeperide & other excipients)

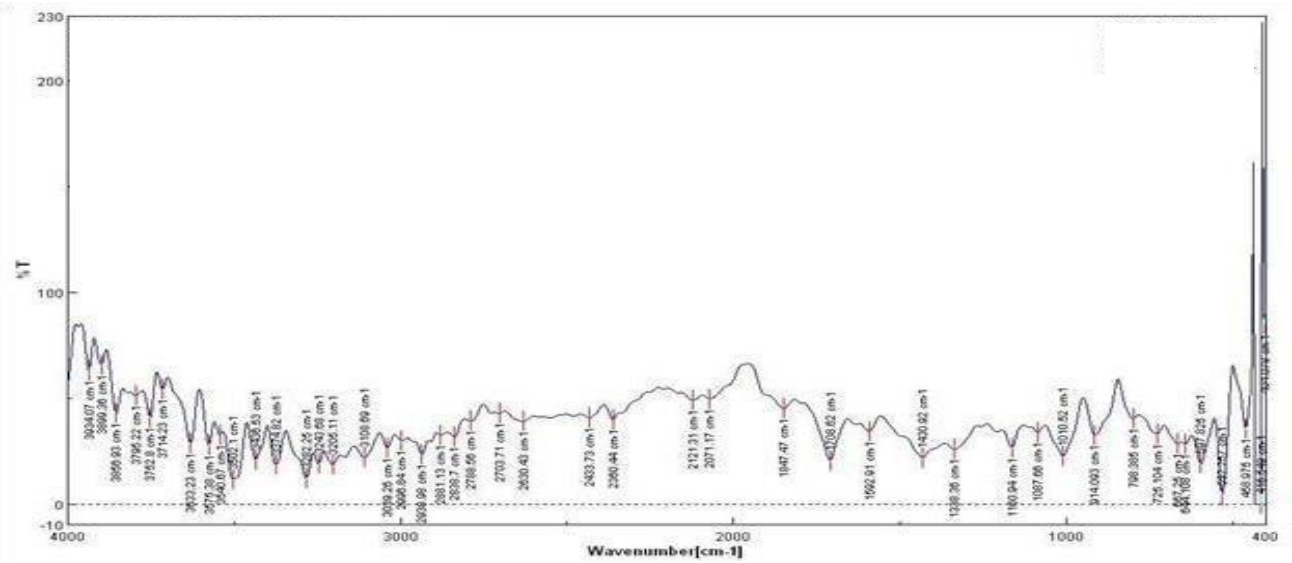
Ran e (cm^{-1})	**Functio al group present n**
800 914 –	-NH
1160 – 1349	C – H aromatic
1700 – 1800	Sulphonyl urea
1706 – 1780	C = O aromatic
3000 – 3100	C – H

Physical mixture

Ranges of fun. Group of Physical mixture

Range (cm^{-1})	**Functional group present**
800 – 914	-NH
1160 – 1349	C – H aromatic
1700 – 1800	Sulphonyl urea
1706 – 1780	C = O aromatic
3000 – 3100	C – H





FORMULATION DEVELOPMENT

1. Precompressional Study of powder blend

a. Sustained release layer

Property / Batches	Bulk density(gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausners ratio	Angle of repose (ϕ)
M1	0.482±0.04	0.50±0.05	3.7±0.28	1.03±0.02	28.33±1.02
M2	0.513±0.05	0.533±0.04	3.8±0.3	1.04±0.5	26.12±1.08
M3	0.470±0.03	0.487±0.02	3.45±0.08	1.03±0.02	22.34±0.2
M4	0.457±0.06	0.467±0.03	2.20±0.1	1.02±0.01	24.37±0.2
M5	0.503±0.05	0.517±0.06	2.75±0.2	0.97±0.05	25.24±0.7
M6	0.498±0.05	0.511±0.02	2.6±0.1	0.97±0.05	23.01±0.01
M7	0.496±0.03	0.520±0.02	3.14±0.06	0.96±0.05	26.90±0.4
M8	0.505±0.05	0.520±0.02	3.0±0.1	0.96±1.05	24.53±0.4
M9	0.496±0.04	0.508±0.01	2.4±0.1	0.97±0.05	20.90±0.5

b. Immediate release layer

Property / Batches	Bulk density(gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausners ratio	Angle of repose (ϕ)
G1	0.414±0	0.450±0.02	8±0.5	1.08±0	28.45±0.5
G2	0.418±0.005	0.478±0.03	12.55±0.1	1.14±0.04	27.56±0.4
G3	0.421±0.01	0.487±0.02	13.55±0.4	1.156±0.05	25.21±0.8

2. Postcompressional study

a. Sustained release layer

Property / Batch	Diameter (mm)	Thickness (mm),	Hardness (kg/cm^2),	Weight Variation (mg)	Friability(%)	Drug Content (%),
M1	17	5.01±0.1	5.83±0.1	752.0±1	0.55	94.35±0.9
M2	17	5.2±0.17	5.63±0.3	751.85±0	0.79	94.01±0.005
M3	17	5.1±0.05	6.96±0.18	749.3±1	0.12	96.27±0.5
M4	17	5.00±0.64	6.7±0.15	751.6±2.8	0.20	94.92±0.13
M5	17	5.31±0.43	7.0±0.15	749.8±0.7	0.20	96.61±0.5
M6	17	5.42±0.32	5.86±0.11	750.95±0.9	0.11	95.37±0.61
M7	17	5.22±0.1	6.06±0.05	753.0±1.73	0.23	97.19±1.05
M8	17	5.19±0.2	6.53±0.17	754.6±1.28	0.31	95.82±0.6
M9	17	5.5±0.2	6.9±0.15	754.0±0.5	0.15	97.17±0.3

b. Immediate release layer

Property **Batch**	**Thickness (mm),**	**Hardness (kg/cm^2),**	**Weight Variation(mg)**	**Friability (%)**	**Drug Content(%),**
G1	2.45±0.01	4.1±0.2	304.55±0.5	0.132	96.05±0.72
G2	2.51±0.02	4.26±0.2	304.1±0.8	0.28	95.19±0.65
G3	2.57±0.03	3.96±0.2	305.8±0.3	0.28	97.16±0.72

In-vitro Disintegration test Immediate release layer

Batch code	Disintegrating time (min)
G1	2.46±0.65
G2	1.66±0.2
G3	1.45±0.35

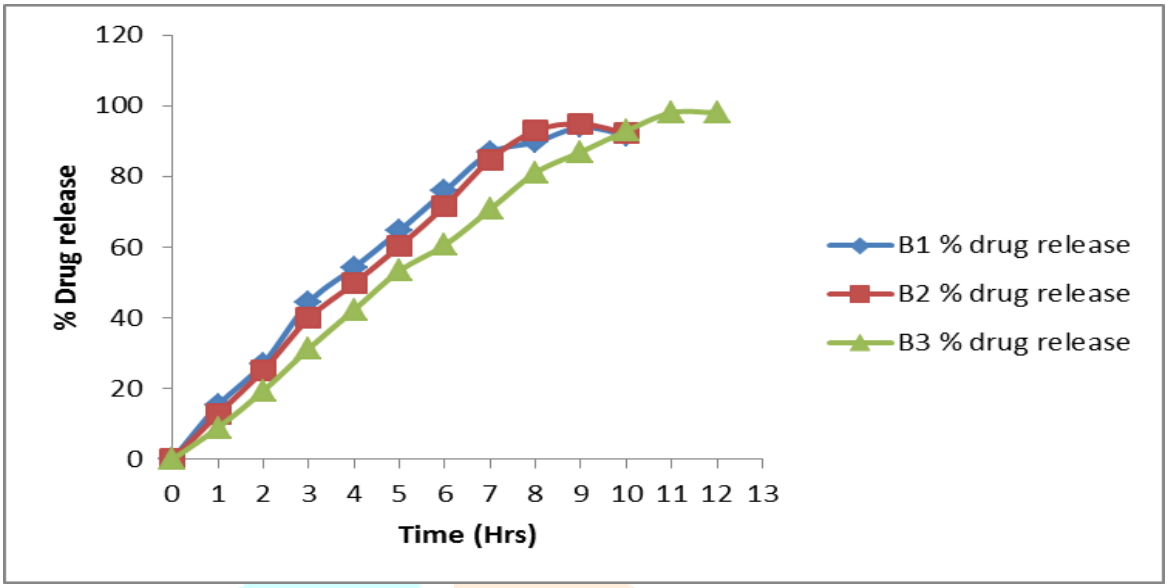
RESULTS & DISCUSSION In-Vitro Dissolution study

POSTCOMPRESSION STUDY/ EVALUATION OF BILAYER TABLETS

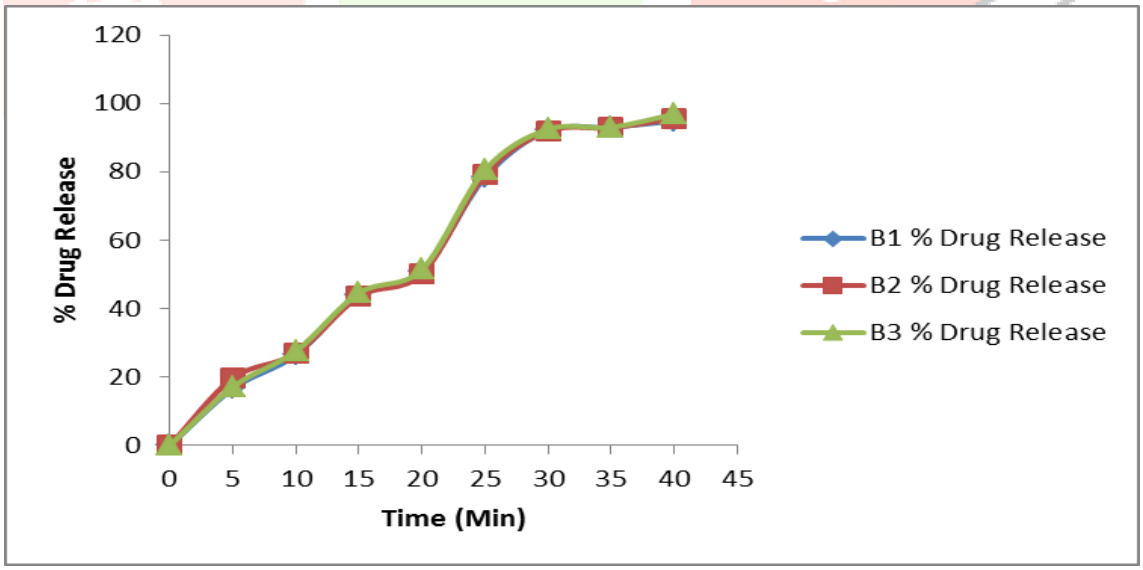
	B1	**B2**	**B3**
Thickness (mm)	7.37±0.05	7.52±0.11	7.63±0.2
Hardness (kg/cm^2)	5.84±0.5	6.01±0.01	6.3±0.1
Weight variation (mg)	1054.35±0.5	1055.15±0.8	1050.8±1.41
Friability (%)	0.592	0.471	0.50
Drug Content (%)Metformin Hcl Glimeperide	97.33±1 96.33±1	98.21±0.21 95.21±1.1	96.35±1 96.22±0.78

RESULTS & DISCUSSION

Iv – Vitro Dissolution Study for Bilayer TabletsMetformine Hcl (BatchB1 B2 B3)



In –Vitro DissolutIon study for Biayer tablet Glimeperide



Kinetic Relese Profile Of bIlayer Tablet (batch B3)

	Model	Batch B3	
		Metformin Hcl	Glimeperide
R2	Zero Order	0.978	0.957
	First Order	0.978	0.979
	Higuchi plot	0.906	0.917
	Korsmeyer plot	0.825	0.965

SUMMARY & CONCLUSION

The present study consist of two drugs one is Metformin Hydrochloride which is in the form of sustained release layer gives the release up to 10-11 hrs. Another drug is Glimeperide which is in the form of immediate release layer gives fast release.

Metformin tablets were prepared by using direct compression technique. Different grades of HPMC like HPMC K4M, HPMC K15M & HPMC K100M were used.

HPMC used as matrix forming polymer for the Metformin layers enables drug release for up to 9-10 hours. Among the different grades of HPMC there is a significant difference in the resulting Metformin release profiles from the SR layer of the tablets found. The formulation M9 can be preferred as integrity was maintained.

Glimeperide tablets are prepared by using solvent evaporation method of solid dispersion technique. The solubility enhancer used for the same technique is PEG6000.

The formulated Metformin Hydrochloride & Glimeperide tablets were evaluated for thickness, hardness, weight variation, friability, drug contents & *in vitro* drug release.

The in vitro drug release profiles of drug from the bilayer tablets could be best expressed by zero and first order release for Metformin Hydrochloride & first order for Glimeperide respectively.

- From the findings obtained, it can be concluded that:-
- The flow properties of polymer and drug were found within limit.
- The tablets prepared were found to be good without any chipping, capping and sticking.
- Formulated tablets gives satisfactorily result for various physicochemical evaluation of tablets like tablet dimension, hardness, friability, weight variation, *in vitro* dissolution study, and drug content.
- Based on *in vitro* dissolution study, formulation B3 was found to be promising.

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