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FORMULATION AND EVALUATION OF BILAYER ANTI DIABETIC TABLETS

Correspondence author's: [1]Sandesh Kumar, [2]Yograj Mahajan, [3]Vishal Gupta, [4]Harish kumar Singh [5]Kumar Abhishek

1. Research Scholar, Faculty of Pharmacy, Mansarovar Gloval University, Bhopal
2. Associate Professor, Faculty of Pharmacy, Mansarovar Gloval University, Bhopal
3. Dean, Faculty of Pharmacy, Mansarovar Gloval University, Bhopal
4. Ph.D. Scholar, Faculty of Pharmacy, Mansarovar Gloval University, Bhopal
5. Assistant Professor, Government Pharmacy College Rohtas

ABSTRACT

Bilayer tablets of an Glimepiride hydrochloride is to formulate, and evaluate for oral sustained drug release, in pharmaceutical system to enhance its oral bioavailability, Reduction in drug toxicity, Reduction in dosing frequency of drug. Biphasic release is characterized by rapid initial release of the drug, followed by sustained rate of release. The drug released by the initial pulse, quickly attains the therapeutic plasma drug levels and ameliorates the slow onset of action of sustained release layer. This increases patient compliance as the patient is quickly relief. Such type of drug delivery systems is designed to deliver the drug in such a way that the drug level is maintained within the therapeutic window for a period as long as the system continues to deliver the drug and to avoid fluctuations in plasma drug level. The purpose of the research work was formulation development and evaluation bi-layer floating tablets of glimepiride to improve the oral therapeutic efficacy of these drugs exhibit pH dependent solubility and show good permeability from stomach and upper part of the small intestine into systemic circulation. Direct compression method form glimepiride was used to formulate bi-layer floating tablets.

Keywords: Glimeperide, Bilayer tablet, Xanthan gum, Magnesium Stearate Crospovidone, crosscarmellose sodium, microcrystalline cellulose

BILAYER TABLET

Bilayer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to

release drug, later, either as second dose or in an extended release manner. Bilayer 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.

Bilayer 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 loading dose and second layer is maintenance dose. In case of bilayered tablets drug release can be rendered almost unidirectional if drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity.

The immediate release layer of bilayer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time. This article explains why development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bilayer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc.

2. PREFORMULATION STUDY

A. Organoleptic Properties

Table 2.1 List of Sensory characters

S. No.	Sensory characters	Result
1.	Colour and Morphology	White to off white powder
2.	Odor	Odorless

B. Solubility Study

Table 2.2 Solubility of glimepiride

S. No.	Solvent used	Observation
1	Distilled Water	- - - -
2	0.1 N Hydrochloric acid	+ + - -
3	dimethylformamide	+ + ++
4	Methanol	+ - - -
5	0.1 N NaOH	+ - - -
6	Phosphate Buffer pH 7.2	++ - -

C. Melting point

Table 2.3 Melting point of the glimepiride

S. No.	Melting Point of Standard Drug	Melting Point of Sample Drug	Average Melting Point of Sample Drug
1.	207°C	207°C	207°C
2.		206°C	
3.		207°C	

D. Identification Test FT-IR Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 µ to 2.5 µ is called Near Infra-red and that from 15 µ to 200 µ is called Far infra-red region Approx 5 mg of drug was mixed with KBr and prepared their pallet. Pallet was analyse using FT-IR spectrophotometer.

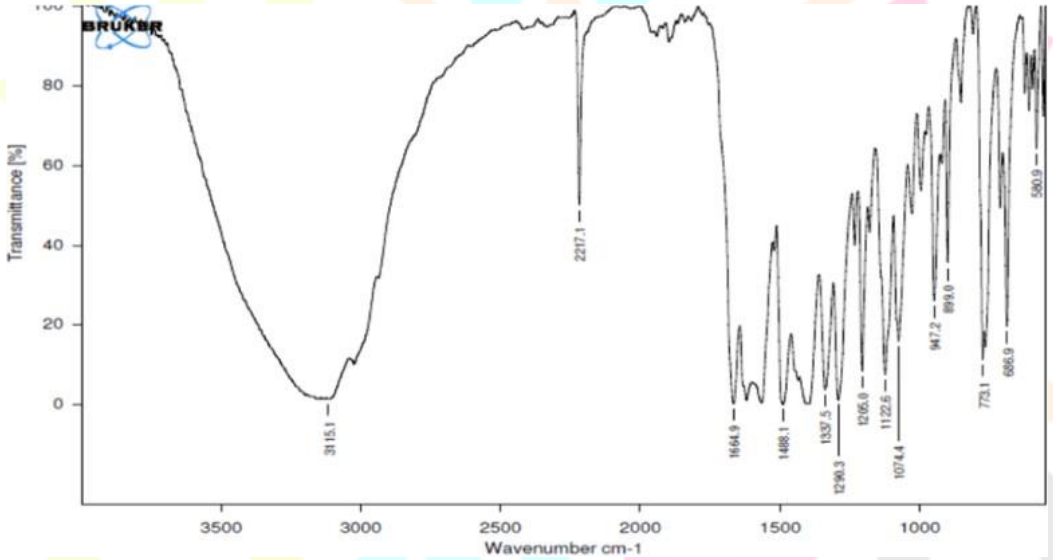

Figure 2.1: FT-IR Spectrum of glimepiride

E. Determination of moisture content

The amount of consumed electric charge is used to calculate the consumption of iodine and therefore the amount of water in the sample.

Moisture content in mg = K.F factor x KF consumed

Table 2.4 Determination of moisture content

S. No.	Drug	KF Factor	Amount of KF Reagent consumed	Moisture content (mg)
1	Glimepiride	0.394	0.12ml	0.047

F. Determination of λ max of glimepiride

The λ_{max} of Glimepiride was determined by analyzing the drug solution in double beam ultraviolet spectrophotometer. This solution was scan at wavelength 400-200 nm on UV spectrophotometer. The higher absorption peak was obtained at 238 nm which was the λ_{max} of drug.

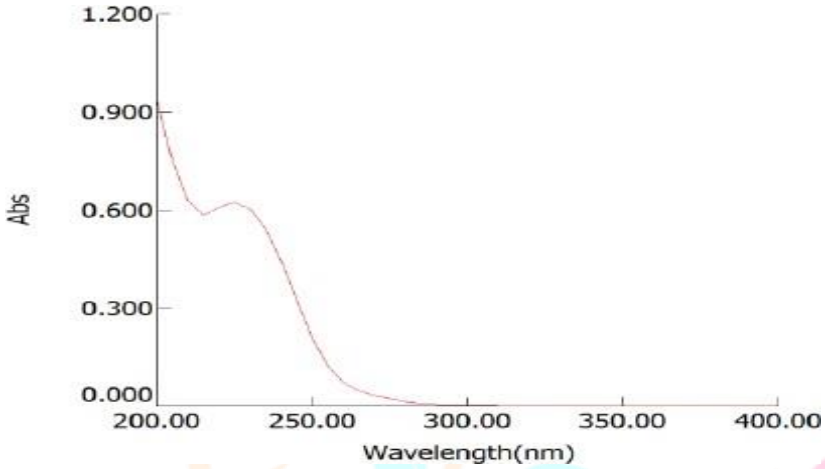

Figure 2.2: λ max scan graph of glimepiride in phosphate buffer pH 7.2.

3. PREPARATION AND CHARACTERIZATION

3.1 Formulation Development

Fast dissolving tablets of Glimepiride were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium, crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio.The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Eight formulations of Glimepiride hydrochloride granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 150mg, were obtained. Composition of tablets is mentioned in Table.

Table 3.1 Composition of Glimepiride Fast Dissolving Tablets

Ingredients(mg)	Formulation code							
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8
Glimepiride	100	100	100	100	100	100	100	100
Sodium Starch Glycolate	10	15	20	-	-	-	-	-

Croscarmellose Sodium	-	-	-	10	15	20	-	-
Crospovidone	-	-	-	-	-	-	10	15
Microcrystalline Cellulose	25	20	15	25	20	15	25	20
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Total weight	150	150	150	150	150	150	150	150

3.2 Evaluation of Precompression Parameter

1. **Bulk density:** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

$$\text{Volume of Packing}$$

2. **Carr's Compressibility index**: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Table 3.2 Grading of the powders for their flow properties according to Carr'sIndex

S. No.	Carr's Compressibility index	Flow
1.	5 – 15	Excellent
2.	12 – 16	Good
3.	*18 – 21	Fair to passable
4.	*23 – 35	Poor
5.	33 – 38	Very poor

6.	>40	Very very poor

***Adding glidant E.g. Talc should improve the flow properties**

3. **Hausners ratio:** It is determined by comparing tapped density to the bulkdensity by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Table 3.3 Results of pre-compressional parameters of Glimepiride

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.412	0.533	20.857	1.265
IF2	0.415	0.536	20.771	1.252
IF3	0.442	0.536	19.323	1.244
IF4	0.435	0.532	20.552	1.249
IF5	0.441	0.539	19.928	1.253
IF6	0.432	0.535	18.527	1.231
IF7	0.436	0.535	18.257	1.236
IF8	0.439	0.532	18.125	1.226

3.3 Evaluation of post compression Parameter

1. Shape and colour of tablets:

Uncoated tablets were examined under a lens for the shape of the tablet andcolour was observed by keeping the tablets in light.

2. Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

3. Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a

little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Table 3.4 Percentage deviation in weight variation

S.no.	Average weight of a tablet	Percentage deviation
1.	130 mg or less	10
2.	More than 130 mg and less than 324mg	7.5
3.	324 mg or more	5

In all the formulations the tablets weight is more than 130 mg and less than 324 mg, hence 7.5% maximum difference allowed.

4. Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

5. Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not loose more than 1% of their weight

6. Uniformity of drug content:

The test is mandatory for tablets with 10mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at

238.0 nm for Glimepiride.

Table 3.5 Results of Post-Compression parameters of all formulations

F. Code	Hardnesstest (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.1	0.492	153	2.33	99.57
IF2	3.3	0.496	155	2.45	98.84
IF3	3.2	0.761	152	2.37	99.39

IF4	3.1	0.655	151	2.34	98.84
IF5	3.3	0.693	154	2.31	99.47
IF6	3.2	0.469	149	2.37	98.95
IF7	3.4	0.563	145	2.23	99.79
IF8	3.5	0.475	148	2.27	99.62

Table 3.6 Results of post-compressional parameters of all formulations

Formulation code	Disintegration Time (sec.) (n=3) Mean ± SD
IF1	109±3
IF2	96±4
IF3	84±5
IF4	113±6
IF5	101±5
IF6	97±6
IF7	102±4
IF8	79±3

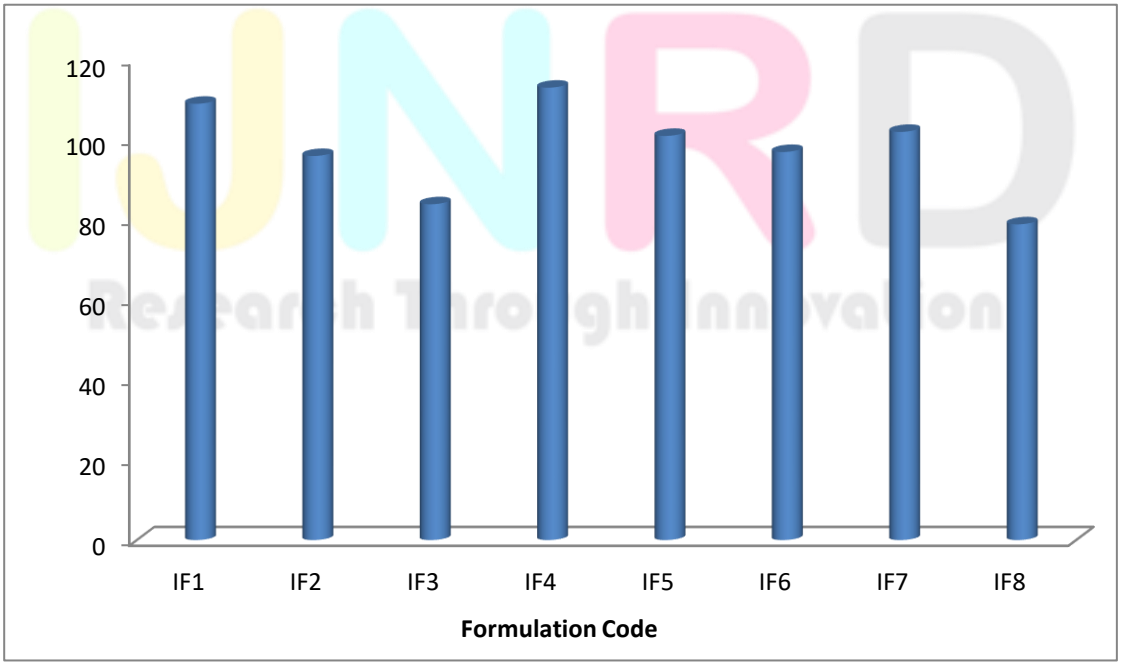

Figure 3.1: Graphical Representation of Disintegration Time

3.4 Method for Preparation Glimepiride tablets

Direct compression was followed to manufacture the tablets of Glimepiride. Eight different formulations (F1, F2, F3, F4, F5, F6, F7& F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table and all the formulation were used for further evaluations parameters.

Polymers selected for tablets are:

- Xanthan gum,
- Gaur gum,
- Karaya gum

Optimization of tablets of Glimepiride

Table 3.7 various formulations of Glimepiride tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Glimepiride	300	300	300	300	300	300	300	300
Xanthan gum	90	120	-	-	-	-	30	40
Gaur gum	-	-	90	120	-	-	30	40
Karaya gum	-	-	-	-	90	120	30	40
PVP K30	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	80	50	80	50	80	50	80	50
Total Weight	500	500	500	500	500	500	500	500

Table 3.8 Result of Pre-Compression Properties of Glimepiride

Material	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.484	0.582	16.480	1.194
F2	0.485	0.587	16.823	1.202
F3	0.481	0.585	17.713	1.214
F4	0.479	0.589	18.607	1.232

F5	0.483	0.582	17.519	1.213
F6	0.480	0.581	17.331	1.217
F7	0.483	0.585	17.319	1.211
F8	0.487	0.582	16.775	1.205

3.5 Evaluation of tablets:

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually.

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCL and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and reacts with dye and analyzed for drug content by UV spectrophotometer at a λ max of 238.0 nm using of 0.1 N HCL as blank.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Table 3.9 Results of Post Compression Properties of Glimepiride Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.4	5.3	497	0.758	98.87
F2	3.5	5.4	496	0.858	99.86
F3	3.7	5.2	499	0.589	98.88
F4	3.5	5.3	503	0.458	99.59
F5	3.4	5.4	506	0.558	99.41
F6	3.6	5.1	503	0.792	99.39
F7	3.7	5.3	505	0.472	99.29
F8	3.4	5.2	501	0.712	99.17

Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50ºc and rpm of 75. One Glimepiride tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 238nm using spectroscopy.

***In vitro* drug release study of tablet**

Table 3.10 *In-vitro* Drug Release Study of Tablets

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	52.56	47.54	45.23	40.30	37.89	32.14	31.31	30.74
1	73.56	55.89	57.56	54.34	46.65	41.43	44.47	39.83
1.5	82.56	86.89	82.25	72.65	65.89	63.15	58.54	54.47
2	99.78	98.71	88.98	83.65	76.38	71.43	70.65	63.84

3	-	-	98.90	91.25	84.56	77.36	76.73	71.62
4	-	-	-	98.85	89.23	83.69	81.45	77.91
6	-	-	-	-	99.59	89.23	87.91	83.38
8	-	-	-	-	-	95.37	93.47	89.42
12	-	-	-	-	-	99.19	98.82	94.71

3.5 Formulation development of bilayer tablet

Optimized formulation IF-6 of Instant release layer and optimized formulation of F- 6 for control release used for formulation of Bi-layer tablet.

3.5.1 Evaluation of bilayer tablets

All the tablets were evaluated for following different parameters which includes;

a. General Appearance

Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually.

b. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

c. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

d. Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

e. Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

f. Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 5mg of Glimepiride was transferred to 10ml standard flask. The powder was dissolved in 10 ml of 0.1 N HCL and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.2 ml to 10

ml suitably 10 ppm solutions and determines the Conc. of drug at 264nm.

g. Dissolution rate studies

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for Glimepiride bilayer tablets using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested.

The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5◦C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Labindia 3000 plus) spectrophotometer at λ max 238nm.

3.5.2 Evaluation of bilayer tablets (Post-Compressional Parameters)

Table 3.11 Post-Compressional Parameters of Optimized Formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.4±0.1	0.862	Passes	5.31

1. Drug content

Table 3.12 Results of Drug content analysis

Formulation	Glimepiride (% Label Claim)
In-house Bilayer tablet	99.19

2. Dissolution rate studies of Instant layer

Table 3.13 Results of Dissolution rate studies of Instant layer

Time (min)	% Drug Release of Instant layer
30	32.14

3. Dissolution rate studies of bilayer tablets

Table 3.14 Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release
0.5	32.14±0.62
1	41.43±0.48
1.5	63.15±1.25
2	71.43±1.31
4	77.36±1.41

6	83.69±1.27
8	89.23±0.82
10	95.37±0.37
12	99.19±0.52

Graph of Release of Bilayer tablets

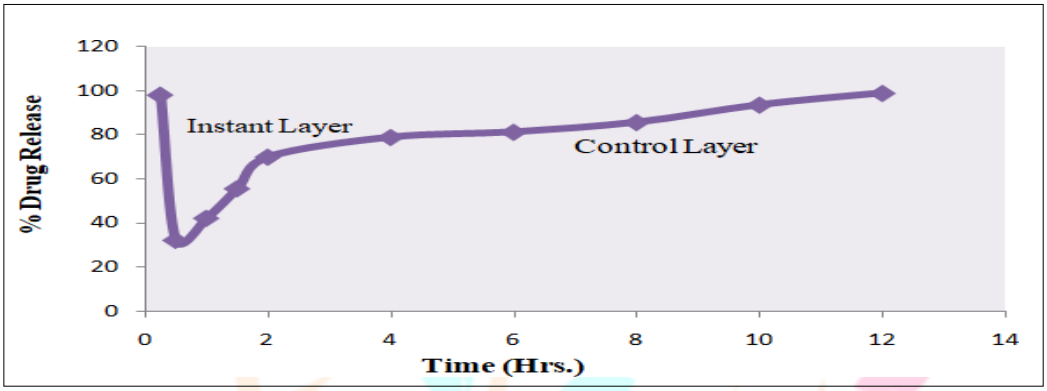

Figure 3.2: Graph of Release of Bilayer tablets

A dissolution study shows the release of Glimepiride. The Instant layer of Glimepiride release approx 32.14percent drug within 30 minutes and control floating layer Glimepiride shows release up to 12 Hours Approx 99.19±0.52 percent of Drug release in 12 hours.

CONCLUSION

The preliminary study showed that Glimepiride is White to off white and Odorless powder. Glimepiride is insoluble in water but it is soluble in dimethylformamide, slightly soluble in methylene chloride and very slightly soluble in methanol. Glimepiride is polymorphic and known to have two forms of polymorphs, form I and form II. The form I is more stable compared to form II, and it is useful in the treatment of diabetes mellitus. The melting point was in the range of 207ºC which is compliance with the standard value. Identification of Glimepiride was performed by UV/VIS Spectroscopy. The 10 µg/ml solutions of Glimepiride was scanned in the range of 200-400nm to determine the λ_{max} for drug. The λ_{max} of Glimepiride was found to be 238nm. From the respective stock solution (1mg/ml) different concentration of 5, 10, 15, 20 and 25µg/ml Glimepiride was prepared and scanned in UV region. Their absorbances were noted at 238.0nm and calibration curve was plotted as absorbance vs concentration and their linearity range was determined.

From the FT-IR data of the physical mixture obviously functionalities of drug have stayed unaltered including forces of the peak. This proposes amid the procedure drug and excipient has not responded with the drug to offer ascent to reactant items. So there is no interaction between them which is in favor to proceed for formulation of vesicular drug delivery system. Preformulation studies reported that the formulation of floating of Glimepiride can be prepared with appropriate methods. A study involving preparation and evaluation of bilayer tablets of Glimepiride were made. Physicochemical parameters of bilayer tablets were performed using natural polymers. *In vitro* drug release profiles of bilayer tablets were performed. A dissolution study shows the release of Glimepiride. The Instant layer of Glimepiride release approx 32.14 percent drug within 15

minutes and control Glimepiride shows release up to 12 Hours Approx 99.19±0.52 percent of Drug release in 12 hours.

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