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Formulation and Evaluation of Gliclazide Immediate Release and Metformin Sustain Release Bilayer Tablet

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ABSTRACT

The aim of the present work is to formulate and evaluate a bilayer tablet (BT) of Metformin HCl as Sustained release and Gliclazide as Immediate release (IR). The polymer used in sustained release is HMPC K100M and the super disintegrant used in immediate release in proportion of Gum Karaya & Croscarmellose sodium by Direct compression method. The Preformulation studied, Bulk density, Tapped density, Housner's ratio, Carr's index, Angle of repose and UV of Metformin HCl and Gliclazide is performed. In this study, a bilayer tablet containing gliclazide in IRL and metformin in SRL was made using the direct compression method, with the goal of making the formulations IRL as small as possible. Will release gliclazide as soon as possible to combat postprandial hyperglycaemic level, followed by steady-state plasma glucose management by Metformin with a long-term release. The hardness of the different formulations ranged from 7.5-8.5 kg/cm. All the formulations exhibited less than 1% friability. The drug content analysis of Metformin and Gliclazide in all formulations was found within the I P limits (±5%) which indicate that the drug was uniformly distributed in the tablets. The in-vitro dissolution study was performed for layer I (Metformin) up to 12 hrs (after every 1hour intervals) and for layer II (Gliclazide) up to 40 min (after every 5 min interval). The bilayer tablet contributing initial loading dose and dissolves rapidly, the remainder of the drug in the extended release was constant rate till the end of the dissolution process. The DSC & I.R spectra proved that there was no interaction between the polymer/ excipients and Metformin, Gliclazide. The stability study of Formulation F4 showed after three months that there was no degradation and the drug was stable under accelerated and real time stability conditions.

KEYWORDS: *Bilayer tablet, Immediate release layer, Sustain release layer*

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1. INTRODUCTION

The goal of any delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Oral drug administration has been the predominant route for drug delivery; numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. [1] The Metformin is used as an antidiabetic in treatment of diabetes mellitus. Due to short half- life Metformin requires frequent administration so to avoid this there is requirement of two layers of immediate as well as sustained action of drug so bilayer tablet can deliver the drugs in both manners.

The present research is based on formulation of bilayer tablet of Gliclazide and Metformin by using different polymers for sustained released action and various concentration of super disintegrants for immediate released action. Bi-layer tablet is suitable for sequential release of two drugs together, separate two incompatible substances and also for sustained release tablet during which one layer is immediate

release as initial dose and second layer is maintenance dose.

The primary objective of Bilayer tablet system is to make sure safety and to enhance efficacy of medicine also as patient compliance.

2. Materials and Methods

Materials: -

Metformin HCl and Gliclazide were purchased from Arti distributor, Mumbai, India and Gum Karaya, HPMC K100M purchased from Research lab Fine chem. Industries, Mumbai. Similarly Starch, Micro crystalline cellulose, Croscarmellose, Magnesium stearate and were obtained from pharmaceutical department.

Methods

DSC

Differential scanning calorimetry is the thermo-analytical techniques. Heat input or output of a sample was measured with the help of calorimeter. DSC thermograms of Metformin HCl and Gliclazide were established by analysing the drug. The drug component was placed in an aluminium pan and subjected to DSC instrument (METTLER, STARESW 12.10.) Indium was used as reference standard. During heating the sample from 250^0C to 300^0C at a rate of 10^oC/ min the DSC spectrum were recorded.

FTIR

Fourier Transform Infrared Spectroscopy was carried out for solid samples to identify the presence of various functional groups present in drug. The samples were prepared by the potassium bromide disc method. Powders (20mg drug in 280mg KBr) were triturated in agate mortar and pestle to produce fine and uniform mixture. Prepared sample disc was placed in a sample holder and transferred to sample compartment. Samples were scanned in the region of 4000-400 cm^{-1} using a Bruker FTIR spectrometer and it was compared with standard.

3. Formulation of Sustained Release Tablet Metformin

The sustained release tablets were formulated by direct compression method. Polymers such as HPMC-K100M, with addition of Microcrystalline cellulose, Starch are used. Total 4 batches (SR1 to SR4) were prepared by varying the concentration of HPMC-K100M. Magnesium Stearate was used to improve flow property and provide lubrication during compression of tablets by adding Starch a filler.

Ingredients (mg per tablet)	SR1	SR2	SR3	SR4
Metformin HCl	500	500	500	500
HPMC-K100M	80	90	100	110
Microcrystalline cellulose	93	83	73	63
Magnesium Stearate	7	7	7	7
Starch	20	20	20	20
Total Weight	700	700	700	700

Table No 1: - Formulation of sustained released tablet by direct compression method with different drug: polymer ratios.

4. FORMULATION OF IMMEDIATE RELEASE TABLET OF GLICLAZIDE.

The Second layer of bilayer tablet is immediate layer, which provides initial loading for Gliclazide. Superdisintegrants were added to get faster disintegration and ultimately faster dissolution of Gliclazide so two superdisintigrants Gum karaya, Croscarmellose Sodium in different ratios (2%, 4% Conc.) were taken for tableting. Total four formulations (IR1 – IR4) were prepared.

Ingredients (mg per tablet)	IR1	IR2	IR3	IR4
Gliclazide	80	80	80	80
Gum Karaya	5	6	7	8
Croscarmellose Sodium	5	5	5	5
Microcrystalline cellulose	102	101	100	99
Colour	0.5	0.5	0.5	0.5
Mg. Stearate	7.5	7.5	7.5	7.5
Total wt.	200	200	200	200

Table No 2: - Formulation of Immediate Release Tablet of Gliclazide

5. FORMULATION OF BILAYER TABLETS OF GLICLAZIDE AND METFORMIN.

The Immediate released powder of batch IR4 and Sustained released powder of batch SR4 were found better in performance hence both batches were selected for preparation of bilayer tablets.

6. Evaluation of pre-compression flow properties of powder blend.

Organoleptic properties

Organoleptic properties of drug like colour, odour and solubility were observed and recorded. Solubility was observed in Water and Ethanol.

Bulk Density

Bulk density was measured using bulk density apparatus. Fixed weight of powder was poured in the measuring cylinder and volume was recorded.

Bulk density = Bulk weight/Bulk volume

Tapped Density

Fixed weight of powder was poured in the measuring cylinder and tapped 50 cycles multiple times. Volume was recorded after each 50 tapping cycles until fixed (concurrent) reading was obtained. The tapped density was obtained by using following equation:

Tapped Density = Bulk weight/Tapped volume

Carr's Index

Carr's index was obtained by using following equation:

$$\text{Carr's index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{Tapped Density}} \cdot X100$$

Tapped density Value less than 1.25 indicate good flow (= 20% Carr), where greater than 1.25 indicates poor flow.

Angle of Repose

Fixed weight of powder was poured through funnel. The height and diameter of the power pile was noted. Angle of repose was obtained by using following equation:

Angle of repose $\theta = \tan^{-1}(2h/d)$

Where, h = maximum height
D = Average diameter

Hausner's ratio

Flow properties of the powder can also be examined using hausner's ratio. Hausner's ratio was obtained by using following equation:

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

The value of ratio below 1.25 indicates good flow while above 1.35 indicates the poor flow

7. Post Compression Studies

Weight variation

For each batch, 20 tablets were taken and weighed for weight of each tablet using a digital balance. The average weight of tablet for was determined and minimum and maximum deviation was calculated for each batch.

Thickness

Dimension of 10 tablets for each batch was determined using vernier calliper and the average diameter and thickness was determined.

Hardness

Using Monsanto Hardness tester, the hardness of 10 tablets was measured and average hardness of tablets was determined.

Friability

The weight of tablets equal to 6.5 grams were taken and rotated for 100 cycles in a friabilator. After 100 revolutions, the tablets were weighed and percentage loss was calculated.

8. In Vitro Dissolution Test of Bilayer Tablet

The in vitro release of sustained release layer was carried out for 12 hours using USP type-II apparatus at 50 rpm for the first 40 minute in 900 ml 0.1N HCL maintaining at 37 $\pm 0.5^0$C and then at phosphate buffer pH 7.4 in 900 ml for another 12 hours. A 5 ml was withdrawn at different time intervals and replaced with an equal volume of

fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analysed on UV spectrophotometer at 233 nm.

9. Disintegration test

For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type sustained release tablets are tested for disintegrating time.

10. Results and Discussion

➢ **PRE-FORMULATION STUDY**

The results of physicochemical evaluation are as follows.

Identification and Characterization of Metformin.

Characteristics Test	Standards as per IP (Metformin)	Observation
Appearance	Microcrystalline Powder	Complies
Color	White	Complies
Taste	Bitter	Complies

Table.3: Organoleptic Characteristics of Metformin

Melting Point Melting point of Metformin was found to be 227±2°C, which complies with standards given in IP indicating purity of the drug sample.

Determination of Solubility:

Solvent	Solubility (mg/ml)
Water	0.100
Methanol	0.243

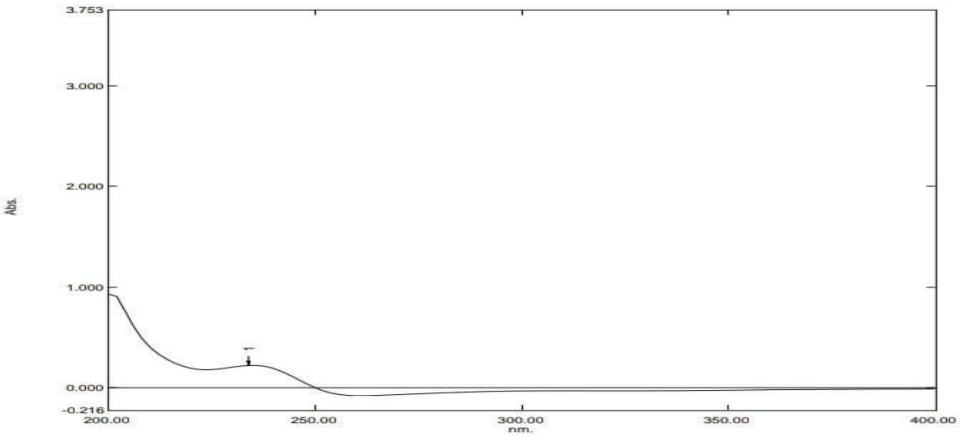
Table. 4. – Solubility Data of Metformin in Various Solvent

*Metformin was highly soluble in water and methanol.

UV-Spectroscopic Analysis of Drug for Determination of Absorption Maxima.

The Metformin was scanned in UV Spectrophotometer to detect the λ max of drug in 0.1 N HCl. The Metformin showed λmax at 233 nm

Fig.1: UV Spectrum of Metformin in 0.1N HCl



Standard Calibration Curve of Metformin in 0.1N HCl

Standard Calibration Curve of Metformin was determined by plotting Absorbance Vs Concentration at 233 nm using 0.1N HCl

Sr. No	Concentration (µg/ml)	Absorbance
1	2	0.22
2	4	0.63
3	6	0.98
4	8	1.29
5	10	1.72

Table.5. Standard Calibration Curve of Metformin in 0.1N HCl

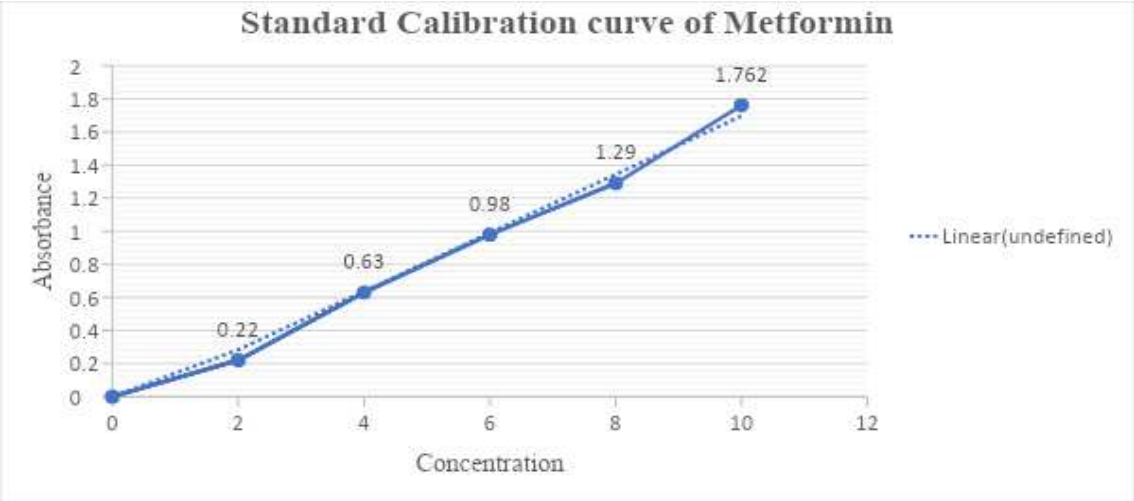


Fig:2 Standard Calibration Curve of Metformin

Chemical Compatibility Study.

FT-IR spectrum of Metformin HCl

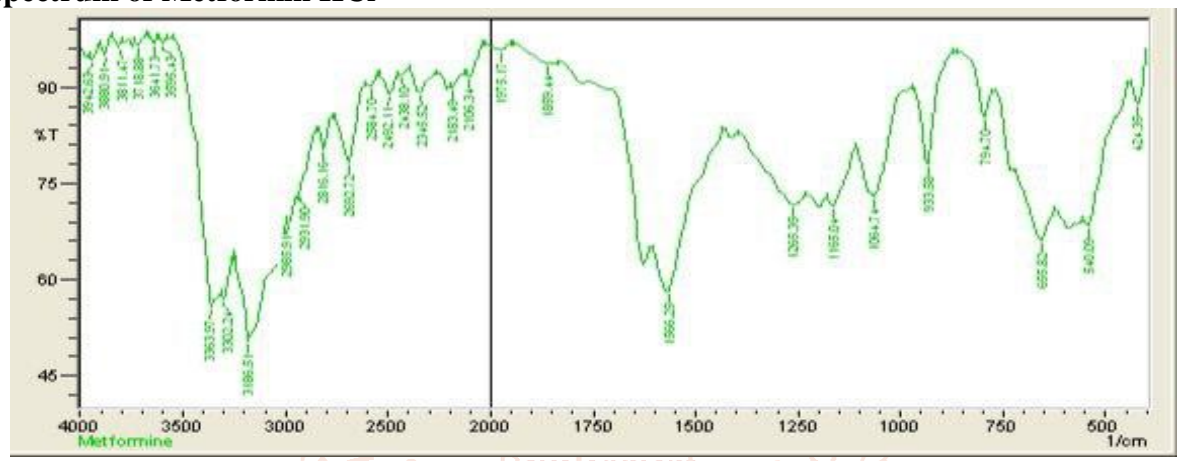


Fig.3: FT-IR spectrum of Metformin HCl

Functional Group	Characteristic wavenumber or frequency cm^{-1}	Metformin observed wavenumber or frequency cm^{-1}
NH stretching	3300-3400	3363.97
NH bending	1500-1700	1566.25
C=O stretching	1650-1600	1635.64
OH bending	1200-1350	1265.35
C_6H_5 stretching	700-650	655.82

Table.6: IR frequencies of Metformin HCl

Differential Scanning Calorimetry (DSC) of Metformin

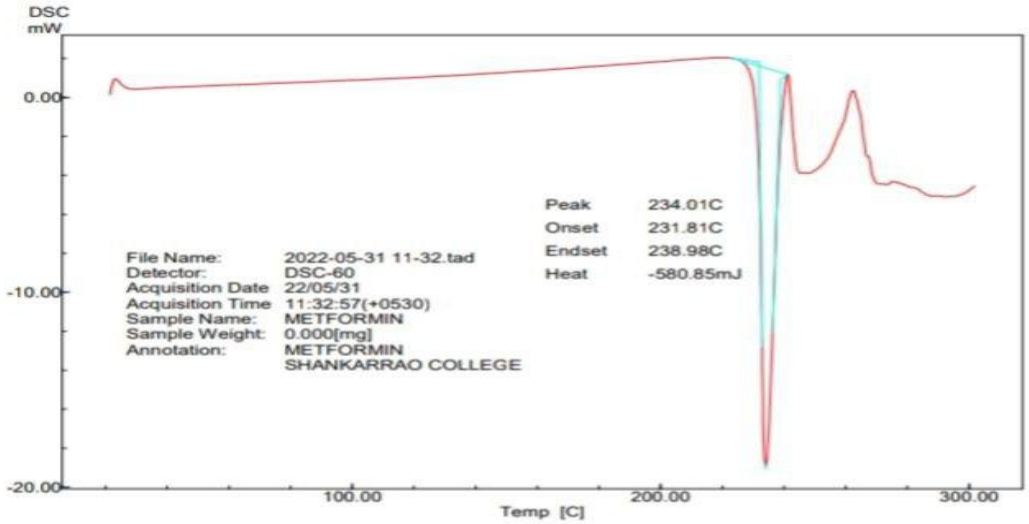


Fig.4: DSC of Metformin HCl

Physical Mixture Metformin + HPMC K-100M

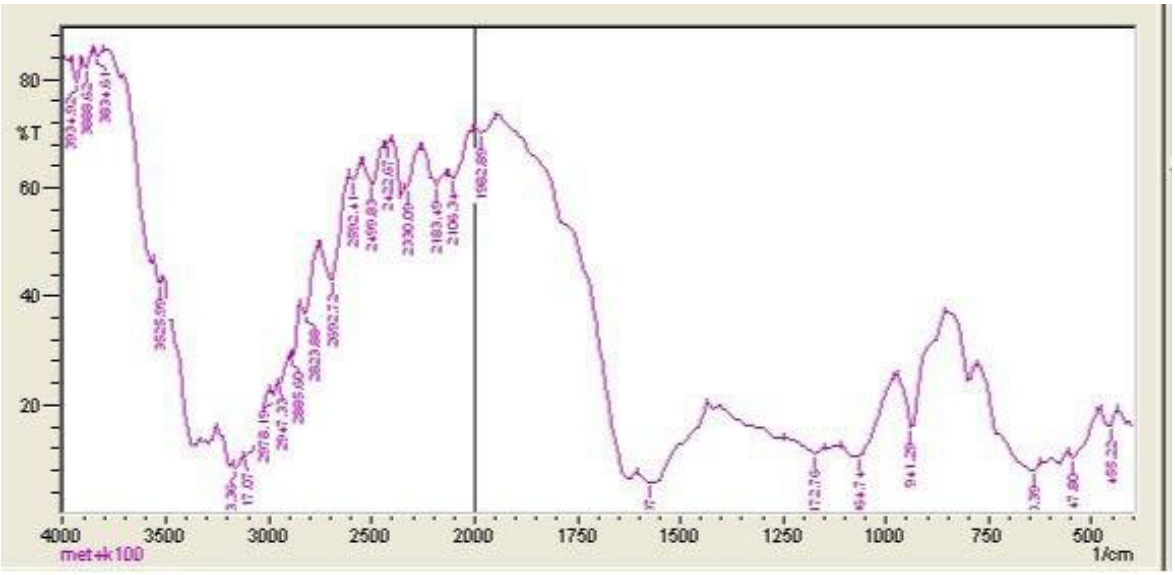


Figure.5: FTIR Spectrum of Physical Mixture of Metformin + HPMC-K100M

Table.7. IR frequencies Physical Mixture of Metformin + HPMC K-100M

Functional group	Characteristic wave number or frequency cm^{-1}	Metformin + HPMC K100M mixtures wave number cm^{-1}
NH stretching	3300-3400	3335.92
NH bending	1500-1700	1573.97
C_6H_5 stretching	700-650	639.66

The IR spectra did not show any significant difference from those obtained for their physical mixture. The obtained results indicate that there was no positive evidence for interaction between Metformin +HPMC K100M. These results clearly indicate that the above excipient can be used without any interaction for preparation of Bilayer tablet.

Identification and Characterization of Gliclazide.

The Gliclazide was studied for physicochemical parameters such as color, taste and appearance. Sample of Gliclazide was found to be similar as in I.P. On the basis of physicochemical evaluation, it is concluded that the sample of Gliclazide complies with IP.

Table.11 : Organoleptic Characteristics of Gliclazide

Characteristics Test	Standards as per IP (Gliclazide)	Observation
Appearance	Amorphous Powder	Complies
Colour	White	Complies
Taste	Bitter	Complies

Melting Point Melting point of Gliclazide was found to be 181±2°C, which complies with standards given in IP indicating purity of the drug sample.

Determination of Solubility:

Solvent	Solubility (mg/ml)
Water	0.132
Methanol	0.182

Table 12 – Solubility Data of Gliclazide in Various Solvent

*Gliclazide was highly soluble in water and methanol.

UV-Spectroscopic Analysis of Drug Determination of Absorption Maxima.

The Gliclazide was scanned in UV Spectrophotometer to detect the λ max of drug in 0.1N HCl. The Gliclazide showed λmax at 224 nm.

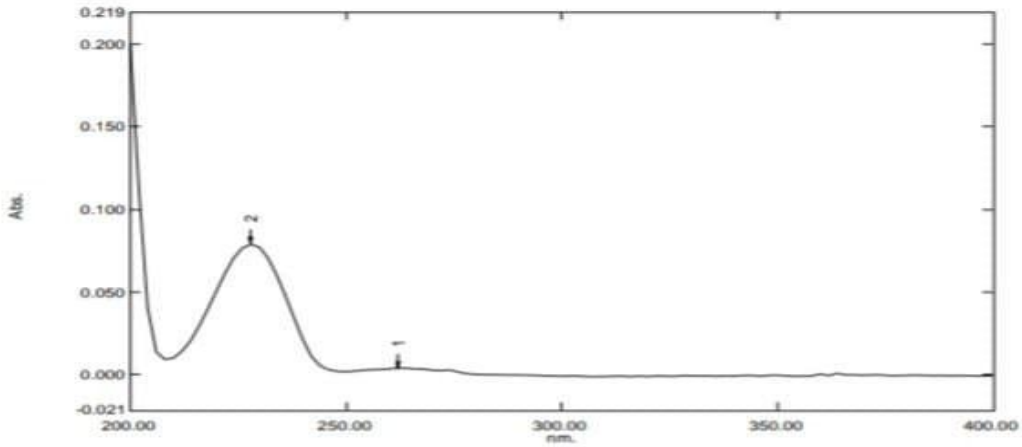


Fig.9: UV Spectrum of Gliclazide in 0.1 N HCl

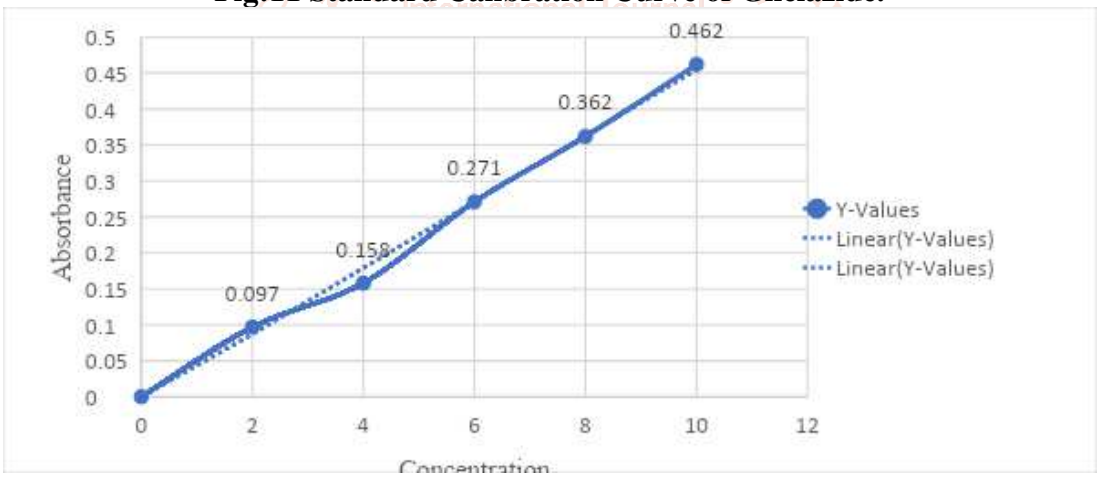
Standard Calibration Curve of Gliclazide in 0.1 N HCl

Standard Calibration Curve of Gliclazide was determined by plotting Absorbance Vs Concentration at 224 nm using 0.1 N HCl.

Table.13. Standard Calibration Curve of Gliclazide in 0.1 N HCl

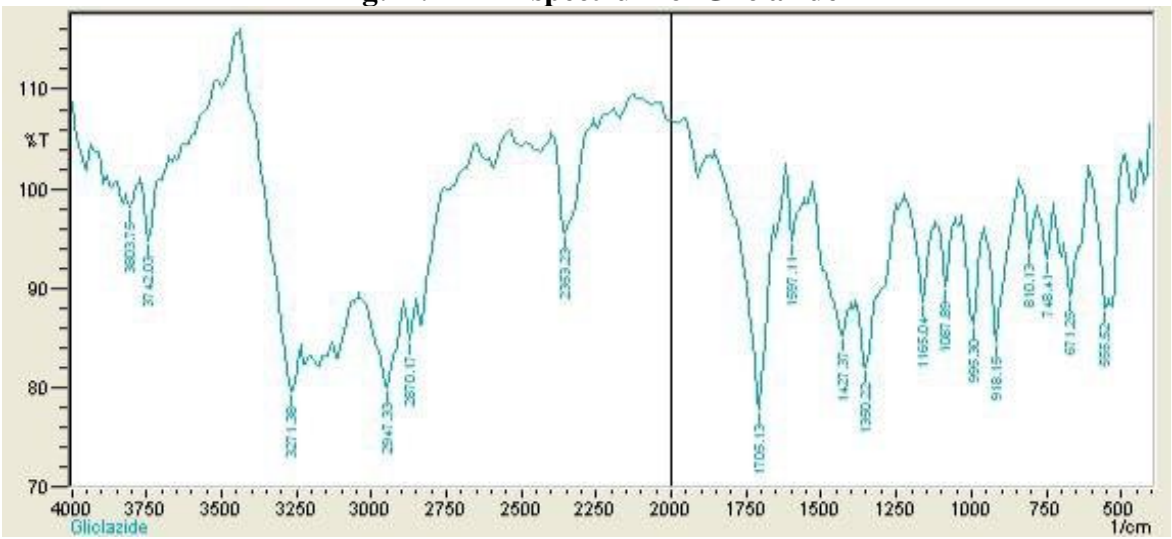
Sr. No	Concentration (mg/ml)	Absorbance
1	2	0.097
2	4	0.158
3	6	0.271
4	8	0.362
5	10	0.461

Fig:11 Standard Calibration Curve of Gliclazide.



Chemical Compatibility Study.

Fig:12. FT-IR spectrum of Gliclazide



Functional Group	Characteristic wavenumber or frequency cm^{-1}	Gliclazide observed wavenumber or frequency cm^{-1}
NH bending	1500-1700	1597.11
C-CH_3 stretching	1450-1400	1427.82
OH bending	1200-1350	1350.22
C_6H_5 stretching	700-650	671.25

Table.13: IR frequencies of Gliclazide

The FTIR spectrum for Gliclazide showed a weak peak at 3350 cm^{-1} due to the presence of a secondary amine. The broad band in the range of 3163-2900 cm^{-1} was due to the presence of –OH. The same also represents the intra- and intermolecular hydrogen bonding due to the – OH groups and also overlaps with the (–CH_3) group. The peak at 1650-1600 cm^{-1} was due to the presence of a C=O group. The presence of a peak at 665.44 cm^{1} indicates the presence of a phenyl group. The peaks analyzed in the table indicates that most characteristic wave numbers of functional group like NH, C=O, C-CH_3, OH and C_6H_5 etc. were matched and compared to the observed frequencies.

Differential Scanning Calorimetry of Gliclazide

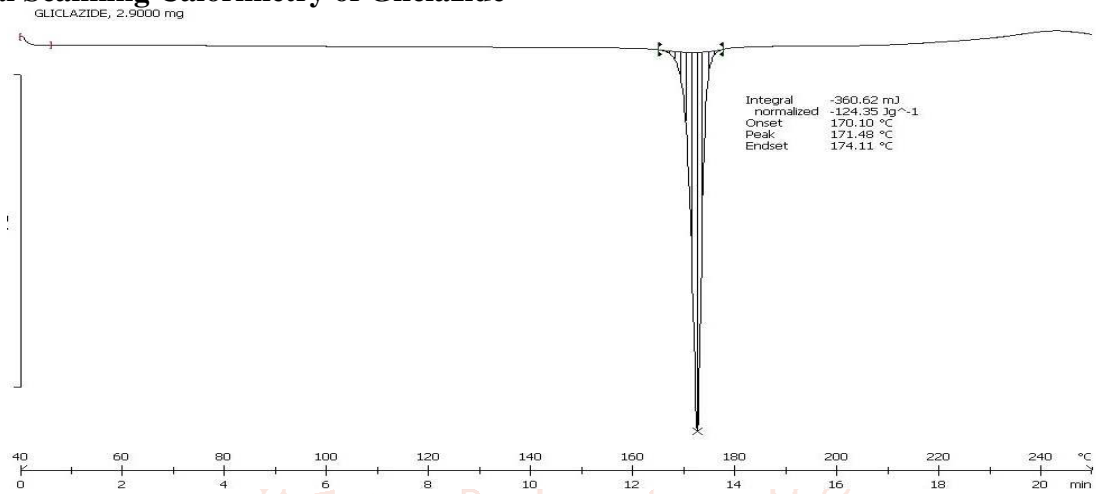


Fig.13: DSC of Gliclazide

Figure shows the DSC curve of pure Gliclazide, which has a distinctive abrupt endothermic peak at 173.34 ^{0}C, showing the drug's melting point. According to the findings of the drug authentication research, the sample of Gliclazide is pure and meets Indian pharmacopeial requirements.

Physical Mixture Gliclazide + CCS

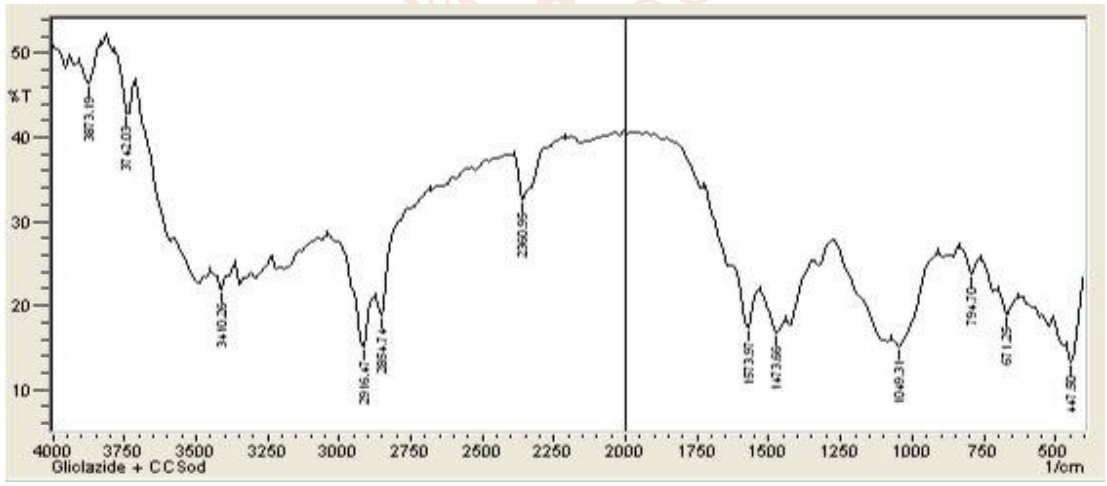


Figure.14: FTIR Spectrum of Physical Mixture of Gliclazide + CCS

Table.14. IR frequencies Physical Mixture of Gliclazide + CCS

Functional group	Characteristic wavenumber or frequency cm^{-1}	Gliclazide + CCS mixtures wave number cm^{-1}
NH bending	1500-1700	1573.97
OH bending	1200-1350	1251.80
C_6H_5 stretching	700-650	671.25

The IR spectra did not show any significant difference from those obtained for their physical mixture. The obtained results indicate that there was no positive evidence for interaction between Gliclazide and CCS. These results clearly indicate that the above excipient can be used without any interaction for preparation of Bilayer tablet.

PRE-COMPRESSION EVALUATION OF SUSTAINED RELEASE FORMULATION

The sustained release tablet blends are evaluated for pre-compression parameters and results are as follows.

Formulation Code	Bulk Density gm/ml	Tapped Density gm/ml	Compressibility Index (%)	Hausner's Ratio	Angle of Repose θ˚
SR1	0.591±0.06	0.681±0.02	13.21±0.43	1.15±0.43	24±0.24
SR2	0.530±0.03	0.614±0.03	13.11±0.12	1.16±0.52	24.50.16
SR3	0.510±0.02	0.590±0.01	13.55±0.21	1.16±0.11	25±0.13
SR4	0.505±0.05	0.575±0.04	12.17±0.33	1.14±0.21	22.5±0.11

Table 16. - Pre-Compression Evaluation of powder of Sustained Release Formulation

*Results are mean of three determinations

In Vitro Drug Release Study for Sustained Released Tablet of Metformin

Table 17. In Vitro Drug Release Profile of Formulations of Sustained Released tablet

TIME IN Hr	SR1	SR2	SR3	SR4
1	7.15±0.30	6.55±0.65	6.15±0.30	**5.75±0.65**
2	14.62±0.46	13.20±0.36	13.12±0.46	**12.86±0.35**
3	20.15±0.52	19.78±0.74	19.15±0.52	**16.99±0.48**
4	33.52±0.46	32.45±0.58	29.52±0.46	**27.38±0.39**
5	48.10±0.69	46.65±0.30	44.10±0.69	**38.85±0.47**
6	62.43±0.26	59.29±0.56	58.43±0.26	**51.95±0.58**
7	78.13±0.51	69.54±0.60	67.13±0.51	**63.35±0.61**
8	86.42±0.63	85.29±0.53	83.42±0.63	**74.70±0.30**
9	98.62±0.78	97.15±0.66	94.46±0.25	**81.26±0.42**
10			98.12±0.71	**86.60±0.28**
11				**92.22±0.43**
12				**98.60±0.68**

*Results are mean of three determinations

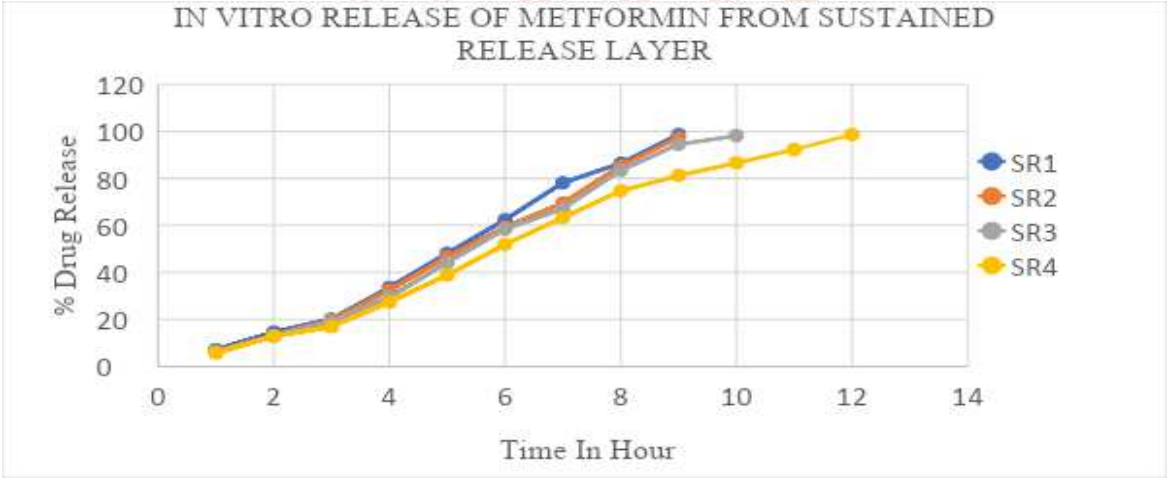


Fig.16. In-vitro Drug Released Study of Metformin Sustained Released tablet

Sustained release tablets of Metformin were prepared by using HPMC K100M polymer. The release profiles of Metformin sustained Released tablet were plotted as in fig.10.16 The release rate of Metformin mainly controlled by polymer. The effect of polymer concentration on drug release could be clearly seen from the variation of dissolution profiles. It was found that drug release from SR4 composed of HPMC K100M in high concentration was 12 hr and also shows significant drug release rate than other formulations. Formulation SR4 containing 110 mg of HPMC K100M controlled drug released for relatively 12 hr and shows 98.60% Cumulative drug release which comparatively effective than other formulation batches so SR4 was selected for further formulation of bilayer tablet of Metformin.

PRE-COMPRESSION EVALUATION OF IMMEDIATE RELEASE FORMULATION

The Immediate release tablet blends were evaluated for pre-compression parameters and results are as follows.

Table 18: Pre-compression Evaluation of Immediate Release Tablet Blend

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hauser's Ratio (HR)	Compressibility Index (%)	Angle of Repose (0˚)
IR1	0.65±0.072	0.79±0.082	1.21	17.6	22.6 ±0.28
IR2	0.54±0.012	0.69±0.032	1.28	22	21.7±0.5
IR3	0.57±0.019	0.71±0.015	1.24	19.6	19.7±0.28
IR4	0.52±0.062	0.68±0.082	1.23	22.4	19.3±1.96

*Results are mean of three determinations

In Vitro Drug Release Study for Gliclazide Immediate Released Tablet

Table 19. In Vitro Drug Release Profile of Different Formulations of Immediate Released Tablet

TIME IN Min	IR1	IR2	IR3	IR4
5	5.22±0.28	6.22±0.35	6.56±0.63	**8.52±0.52**
10	12.55±0.26	13.56±0.66	15.50±0.65	**19.18±0.56**
15	25.65±0.42	28.36±0.52	36.89±0.57	**39.89±0.28**
20	43.75±0.49	44.59±0.23	47.35±0.29	**51.36±0.75**
25	55.63±0.53	56.35±0.51	58.36±0.36	**62.45±0.53**
30	61.76±0.36	65.40±0.40	67.33±0.44	**75.36±0.34**
35	74.48±0.43	76.25±0.36	79.59±0.53	**85.03±0.43**
40	91.25±0.33	93.43±0.25	95.36±0.48	**98.34±0.68**

*Results are mean of three determination.

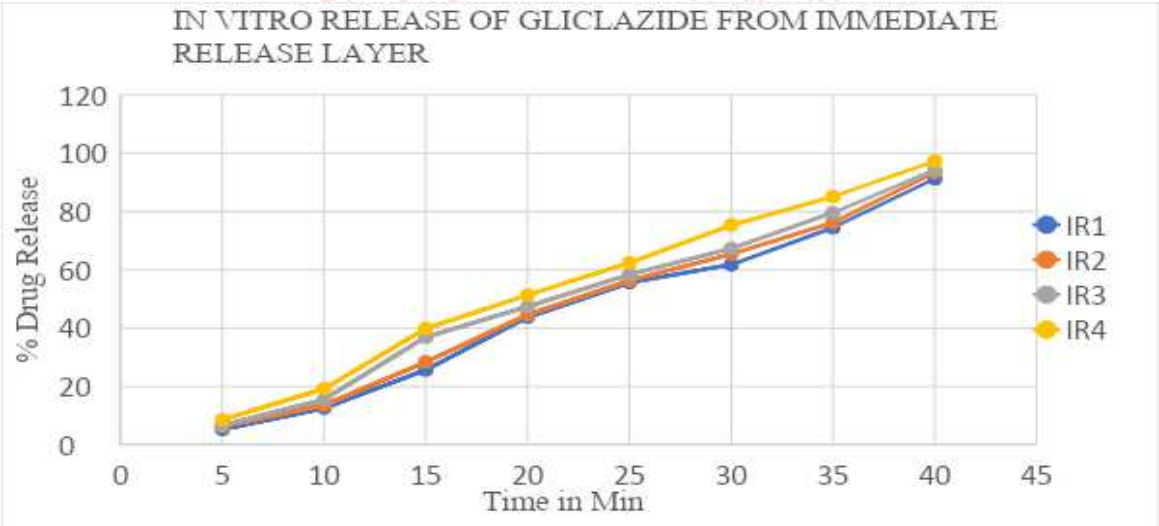


Fig.17: In Vitro Drug Release Study for Gliclazide Immediate Released Tablet

EVALUATION OF OPTIMIZED BILAYER TABLET OF METFORMIN AND GLICLAZIDE

The optimized bilayer tablets of sustained released batch SR4 and immediate released batch IR4 was combined to get final bilayer tablet of Metformin and Gliclazide which was evaluated and results are shown as follows.

Table 20. Evaluation Parameters of Optimized Bilayer Tablet

Sr. No	Parameter	Result
1	Color	Off yellow(IR), Off White (SR)
2	Weight Variation (mg)	900.5 ±0.25 (Complies)
3	Thickness (mm)	7.3 ± 0.3
4	Hardness (kg/cm^2)	7.9 ± 0.6
5	Friability (% wt. loss)	0.81±0.08
6	Drug Content (%)	98.60±0.7%

The appearance of bilayer tablet was observed by visual observation, and other parameters like weight variation, hardness, thickness and friability were evaluated and found to be within the acceptable limit. The high concentration of polymer HPMC K100M shows good property and shows good rate of in vitro drug release for longer period of time.

Table 21. Disintegration Time of Bilayer Tablet

Batch Code	Disintegrating Time (min)
IR1	2.26 ± 0.35
IR2	1.67 ± 0.35
IR3	1.55 ± 0.43

In Vitro Drug Release Study for Optimized formulation of bilayer tablet

Table 22. In Vitro Drug Release Profile of bilayer tablet

Time in min/hr	% Drug Release from Bilayer Tablet	
	Immediate Release	Sustain Release
0 min	**0**	
5 min	**8.52±0.52**	
10 min	**19.18±0.56**	
15 min	**39.89±0.28**	
20 min	**51.36±0.75**	
25 min	**62.45±0.53**	
30 min	**75.36±0.34**	
35 min	**85.03±0.43**	
40 min	**98.34±0.68**	
1 hr		5.75±0.65
2		12.86±0.35
3		16.99±0.48
4		27.38±0.39
5		38.85±0.47
6		51.95±0.58
7		63.35±0.61
8		74.70±0.30
9		81.26±0.42
10		86.60±0.28
11		92.22±0.43
12 hr		98.60±0.68

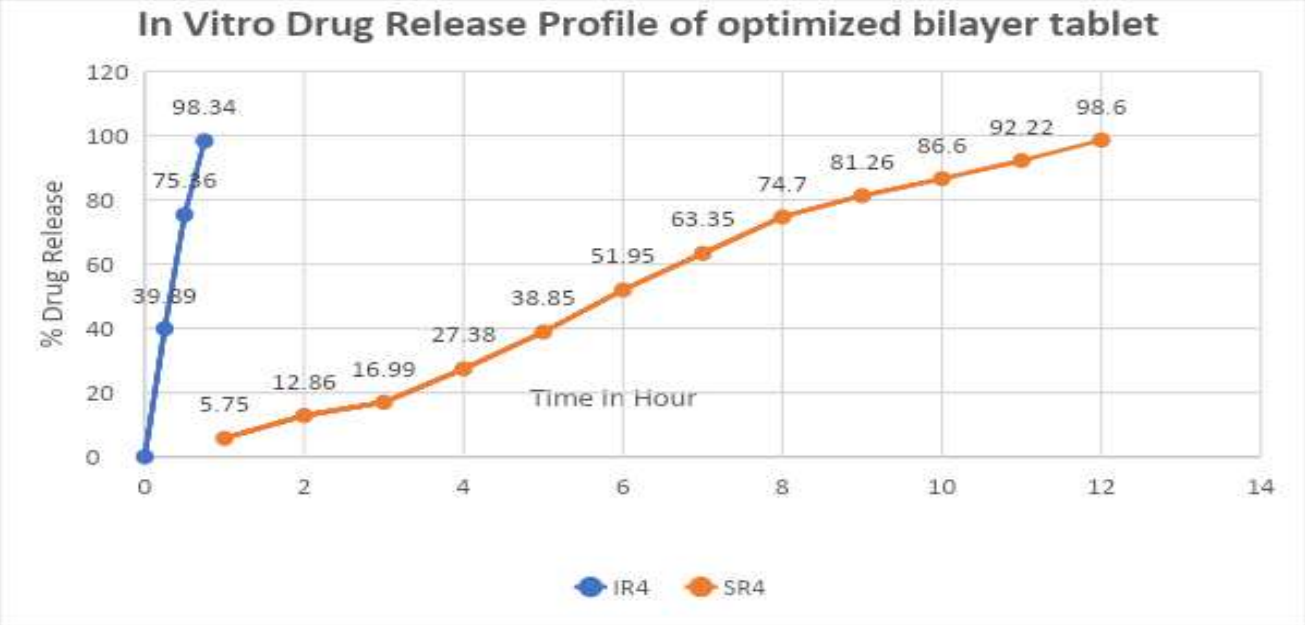


Fig 18. In Vitro Drug Release Study for Optimized formulation of bilayer tablet

The formulation F4 as a optimized formulation because of the these batches showed satisfactory result of the tablets parameter. Result of in vitro % drug release profile a indicated that formulation (F4) was the most promising formulations as the drug release from this formulation and assay was high as compared to other formulations. So, F4 was found to be optimized formulation and was selected for further % assay, stability study.

ASSAY:

Assay of the tablet formulation:

Observation: % Assay of Selected Formulation Batch F4 for Metformin HCl is **100.1 %** and for Gliclazide is **100.4%**

Stability study:

Stability study for the developed formulation F4 were carried out as per ICH guideline by storing at 40°C/75% RH up to three months. The formulation F4 was selected on the basis of their high cumulative percentage drug release.

Table .23 Stability Study of Optimized Batch F4

Sr. No.	Parameter	Initial	After three months
01	Hardness (kg/cm$^{2)}$	7.9	7.9
02	Friability (% wt. loss)	0.81	0.83
03	Disintegration Time (IR layer) (min)	120 Sec.	116 Sec.
04	% Drug Release	98.34±0.68(IR4)& 98.60±0.68(SR4)	98.14±0.24(IR4)& 98.280±0.18(SR4)
05	% Assay	100.2.±12 (IR4)& 100.4±0.38 (SR4)	100.1.±22 (IR4)& 100.3±0.24 (SR4)

The stability study showed that the formulation F4 was physically stable when stored at 40±20°C and 75±5% RH for three months and there was no significant difference in dissolution parameters of optimized formulation.

CONCLUSION

The goal of this study was to formulate, evaluate, and test the stability of a bilayer tablet with different polymers for anti-diabetic purpose. Two active components and polymers were chosen for the development of a tablet to treat diabetics based on a assessment of the literature. All raw materials were subjected to pre-formulation tests such as bulk density, tap density, compressibility index, and Houser's ratio. In IR spectra, there was no physical contact between the medication and the polymer combination. The best batches for tablet formulation were chosen from the pre-formulation experiments. Physiochemical characteristics were used to assess the prepared tablet. The physiochemical analysis of the tablet reveals a pale yellow colour, a oval form, and a smooth look. The formulation IR4 & SR4 selected as a optimized formulation because of the these batches showed satisfactory result of the tablets parameter.

Result of in vitro % drug release profile a indicated that formulation (IR4 & SR4) was the most promising formulations as the drug release from this formulation and assay was high as compared to other formulations. So, this was found to be optimized formulation and was selected for further % assay, stability study.

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