Formulation And Evaluation of Bilayer Tablet of Glyburide And Metfomin

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Abstract- *The purpose of this study was to develop a bilayer antidiabetic tablet of Metformin as sustained release and Glyburide as immediate release. In sustained release formulation there was two polymers were used such as HPMC K4M and HPMCK200M and in immediate release formulation there was also two super disintegrants are used such as Croscarmellose and Sodium Starch Glycolate were used. The bilayer formulation was prepared by direct compression method.Type and concentration of super disintegrant among [Sodium Starch Glycolate (SSG)/Croscarmellose] was optimized to enhance the dissolution rate (DR) of Glyburide from the IR layer of BT. Type and concentration of SR polymer among (HPMC K4M / HPMC K200M) was optimized to extend the release of Metformin HCl up to 12 h profile from the SR layer of BT. It was concluded that the optimization of the ratio of Glyburide: Metformin HCl SR polymer (HPMC K200M), had significant effect on extending the release profiles of Metformin HCl. The ratio of Metformin HCl: HPMC K200M at forms a better matrix for the extending the release of Metformin HCl up to 12 h from the SR layer of BT. The optimized formulation: BT6 [IR6 (15% w/w Sodium Starch Glycolate as super disintegrant and SR6 (HPMC K200M as SR polymer)] releases 97.62% of Glyburide from the IR layer within 40 min and extends the release of Metformin HCl up to 12 h with a better release profile. It passes the accelerated stability studies as per ICH guidelines. A combination of these two classes [(Biguanides)(Metformin HCl) and (Sulfonyl urea) (Glyburide)] of glucose-lowering agents and formulating them as a BT is more effective in the treatment and maintenance of type 2 diabetes mellitus.*

Keywords- Metformin HCl, Glyburide, HPMC K200M, HPMC K4M.

I. INTRODUCTION

The main objective of combination therapy is to encourage the utilization of lower doses of drugs to treat patients and also to minimize dose dependent side effect and adverse reactions[1,2].Type 2 diabetes is the most common form of diabetes, accounting for 90 - 95% of cases. Metformin is the first drug doctors usually recommend for people with type 2 diabetes who need to take medication.However, limitations of multiple dosing and risk of triggering gastrointestinal symptoms make its dose optimization difficult. Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose [3].The advantages of sustained release dosage forms over conventional forms include the less fluctuation in drug blood levels, frequency reduction in dosing, enhanced convenience and compliance, reduction in adverse side effects and reduction in overall health care costs [4].Type 2 diabetes mellitus is a progressive disease with multiple underlying patho-physiologic defects. Monotherapy alone cannot maintain glycaemic control and leads to treatment failure. Ideally, a combination of glucose-lowering agents should have complementary mechanisms of action that address multiple patho-physiologic pathways, can be used at all stages of the disease, and be generally well tolerated with no increased risk of hypoglycaemia, cardiovascular events, or weight gain.Bi-layered tablets can be a primary option to avoid chemical incompatibilities between different drugs by physical separation, and to enable the development of different drug release profiles [immediate release (IR) with Sustained release (SR)]. Applications of bi-layered tablets are mainly used in the combination therapy; to deliver the loading dose and sustained dose of the same or different drugs and are used to deliver the two different drugs having different release profiles[5]. Glyburide is used as immediate release layer in the formulation.

II. MATERIALS AND METHODS

Materials

Metformin HCl by Aarti Chem Mumbai, Glyburide from Yarrow chem, HPMC K4M, HPMC K200M, Croscarmellose, Sodium starch glycolate, microcrystalline cellulose,starch maize, magnesium stearate, talc and ferric oxide is received from Research lab Fine chem. Industries, Mumbai.

Methods

Calibration curve of Metformin HCl and Glyburide in 0.1N HCl and Metformin HCl in pH 6.8 Phosphate buffer[6]

100 mg of pure drug was dissolved in 100 mL of 0.1N HCl/ pH 6.8 Phosphate buffer (stock solution; 1000 µg/mL) and then placed in a Sonicator for 10 min, from this 10 mL of solution was taken and the volume was adjusted to 100 mL with 0.1N HCl/ pH 6.8 Phosphate buffer (stock solution-II; 100 µg/mL). The stock solution-II; was suitably diluted with 0.1N HCl/ pH 6.8 Phosphate buffer to obtain the series of working dilutions: 5, 10, 15, 20, 25 and 30 µg/mL of drug solution. The median concentration was scanned for λmax and at the respective λmax working dilutions were analysed by using a double beam UV-Vis spectrophotometer (Shimadzu, Japan UV-1800 double beam Spectrophotometer). The λmax of pure drug in 0.1N HCl and 6.8 phosphate buffer shown in **Fig.1,3,5**The standard calibration curve was plotted by taking concentration on X-axis and absorbance on Y-axis was shown in **Fig.2,4,6.**

Drug-excipient compatibility studies by FT-IR[7]

FT-IR spectra of pure drug(s) and drug: polymer (1:1) physical mixtures were recorded out, in the region of 400-4000 cm-1 at spectral resolution of 2 cm-1, by the potassium bromide pellet method using (Shimadzu-1800, Japan) . The interpretation results of FT-IR of pure drug in Fig. 7 & 10 and drug excipient spectra were shown in **Fig.8,9,11, &12** respectively

Drug- Excipients interaction study using DSC[8]

The compatibility of the excipients with metformin hydrochloride, Glyburide and Metformin HCl were studied by subjecting the blend of different excipients with Metformin hydrochloride and Glyburide to accelerated thermal stability at 40ºC /75% pH for 4 weeks and at 60ºC for 4 weeks. Drug-Excipients interaction study was done by using DSC. 1-2 mg of sample was heated in the aluminium disc over the range of 50-300°C at the rate of 20°C per minute and DSC spectra was recorded using TA 60W software. The obtained spectra of pure drug in **fig 13,14** were then studied for the interaction between drug and the excipients shown in **Fig.15,16,17 &18.**

Preparation of immediate release layer[9]

Super disintegrants SSG, and Croscarmellose and MCC, Maize Starch, and were weighed and cosifted through sieve No. #40 (ASTM), blended in a poly bag for 10 min and lubricated with sieve No. # 60 (ASTM) passed magnesium stearate by mixing in the same poly bag, for additional 2-3 min, which is used as upper IR layer which Shown inTable 1.

Preparation of sustained release layer[10]

Metformin HCl, SR polymer HPMC K4M and HPMC K200M,and MCC were weighed were cosifted through sieve No. # 40 (ASTM), blended in a poly bag for 10 min and lubricated with sieve No. #60 (ASTM) passed magnesium stearate and talc by mixing in the same poly bag, for additional 2-3 min, which is used as lower SR layer. Composition of layer and Metformin HCl (SR) layer of bilayered tablets is given in Table 1.

PRE-COMPRESSION STUDIES

Directly compressible tablet blends of Glyburide -IR layer and Metformin HCl-SR layer were evaluated for [angle of repose (θ), bulk density (BD), tapped density (TD), Carr's Index (CI) & Hausner's Ratio (HR)]. The consolidated results of pre-compression studies of IR and SR layers were tabulated in Table 2 &3.

Bulk Density[11]:

Bulk density is the ratio of the mass by the volume of an untapped powder sample. The bulk density is measured in g/ml. The bulk density depends on both the density of the powder particles and the arrangement of the powder particles. The bulk density influences preparation, storage of the sample. The mathematical re-presentation is given below.

Bulk density = weight of the drug / Bulk volume

Tapped Density[12]:

In tapped density, the bulk powder is mechanically tapped in a graduated cylinder until the volume change is observed. Here the tapped density is calculated as mass divided by the final volume of the powder.

Tapped density = weight of the granules / tapped volume

Angle of Repose[13]:

It gives an idea of the flowability of granules or a bulk solid. There is some factor which responsible for the flowability of powders such as particle size, shape, surface area, etc. The flowability of the powder depends on the different environments and can be changed easily. The angle of repose was calculated by the following formula.

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

Where = θ = angle of repose, h = height of the formed cone, r = radius of the circular base

Carr's Index:

It is one of the most important parameters to characterize the nature of granules.

Carr's index (%) = (Tapped density - Bulk density/ Tapped density) × 100

Hausner's ratio

It is an important character to determine the flow property of granules in the presence of different compositions of polymers. The following formula can calculate this.

Hausner's ratio = Tapped density / Bulk density

Values less than 1.25 indicate good flow, and greater than 1.25 indicate poor flow.

Direct compression method

Bilayer tablets were prepared by direct compression method, initially the SR layer was compressed and later the upper punch was lifted, and the blend of layer was poured in the die and compressed using (Rimek mini press India) fitted with an8mm standard capsule punches with an average weight of 850 mg and average hardness of 6.5 kg/cm^2.

POST-COMPRESSION STUDIES OF BI-LAYERED TABLETS

Average weight of tablets 20 tablets (n=20) was randomly selected from each batch and their weight was determined by an electronic balance (Shimadzu, Japan) the results shown in**Table 4.**

Thickness

6 tablets (n=6) were randomly selected from each batch and their thickness was measured using a vernier callipers (Mitutoyo Corporation, Japan.),

Hardness

6 tablets (n=6) were randomly selected from each batch and their hardness was measured using a Monsanto hardness tester (Pfizer mLabs-SE-276).

Friability

The friability of the 20 tablets (n=1) from each batch was tested by a Friabilator (Roche Friabilator, Germany) at a speed of 25 RPM for 4 min. The tablets were then de-dusted, re-weighed, and percentage weight loss was calculated by the equation below,

% Friability = (Initial Wt.− Wt. After friability) / Initial Wt. × 100

Assay

6 tablets from each batch (n=6), were randomly selected from each batch IR and SR layers were separated by scrapping and crushed in a mortar with pestle separately; the quantity of blends equivalent to 100mg of drugs (Glyburide/Metformin HCl) was suspended in 100 mL of 0.1N HCl in a volumetric flask and sonicated for 2 min. The dispersion was filtered through 0.45µm membrane filter, suitably diluted with 0.1N HCl and analysed by a double beam UV-Vis spectrophotometer (Shimadzu-1800, Japan) by measuring absorbance at obtained λmax of the drug (Glyburide/Metformin). The consolidated results of post compression studies of bi-layered tablets are tabulated in **Table 4.**

In vitro dissolution studies of Sustained ReleaseLayer

Bi-layered tablets containing optimized varying SR layers in vitro dissolution studies were carried out by randomly selecting 6 tablets (n=6) from each batch using USP dissolution apparatus type II/ paddle (Electro lab, Mumbai (Model TDT-08L) in 900 mL of 0.1N HCl for first 2 h and in 900 mL of pH 6.8 Phosphate buffer up to 12 h. Speed of paddle was maintained at 50 RPM, the temperature was kept constant at 37°C ± 0.5°C. Samples were collected at time points 1,2,4,6,8,10,12hr, 5 mL of dissolution media was withdrawn, filtered through 0.45µm membrane filter, suitably diluted and analysed at respective λmax of Metformin HCl other time points using a double beam UVis spectrophotometer (Shimadzu-1800, Japan). Each sample withdrawn was replaced with an equal amount of fresh 0.1N HCl, to keep the volume constant. In vitro dissolution profiles of SR bi-layered tablets were shown in**Table.5** and**Fig. 19.**

In vitro dissolution studies of IR layer

For to optimize the composition of IR layer, 6 tablets (n=6) with only compressed IR layer, were randomly selected from each batch and undergone dissolution in the USP-II (paddle) dissolution apparatus (Electro lab, Mumbai (Model TDT-08L)), each flask was filled with 900 mL of 0.1N HCl; speed of paddle was maintained at 50 rpm, the temperature was kept constant at 37°C ± 0.5°C. At time points 0, 5, 10,15,20,25,30, 35, 40 min, 5 mL of dissolution media was withdrawn, filtered through 0.45µm membrane filter, suitably diluted and analysed at respective λmax of Glyburide using a

double beam UV-V is spectrophotometer (Shimadzu-1800, Japan). Each sample withdrawn was replaced with an equal amount of fresh 0.1 N HCl, to keep the volume constant. In vitro dissolution profiles of Glyburide-IR tablets were shown in**Table 6**and**Fig 20**.

Accelerated stability studies on optimized formulation[14,15]

Optimized formulation (BT6 or IR6/SR6), of 20 tablets in 10 CC HDPE pack up to 2 months were carried according to International Conference on Harmonization (ICH) guidelines by placing in a humidity chamber (NSW-175, Narang Scientific work, India) maintained at 45°C ± 2°C and 75% ± 5% RH. At the end of every month up to 2 months, the samples were withdrawn and evaluated for post compression studies. The consolidated results of accelerated stability studies were tabulated in Table 7.The chemical stability of drug in the 2M-accelerated stability sample of optimized formulation (BT6); which will influence the in vitro and in vivo dissolution characteristics was investigated using UV Spectroscopy studies. The UV spectra were recorded at 233 nm to 229.

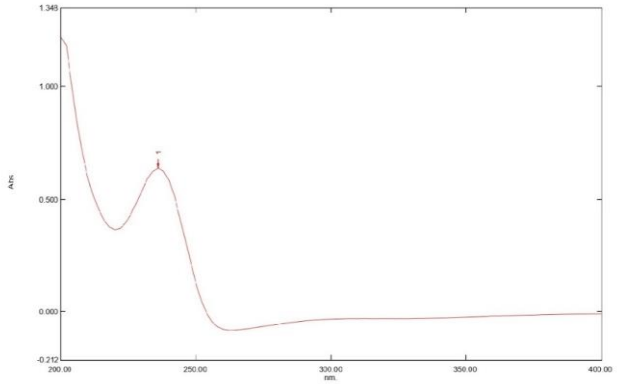

Fig.1 UVSpectrum of Metformin HCl in 0.1 N HCl at 232 nm

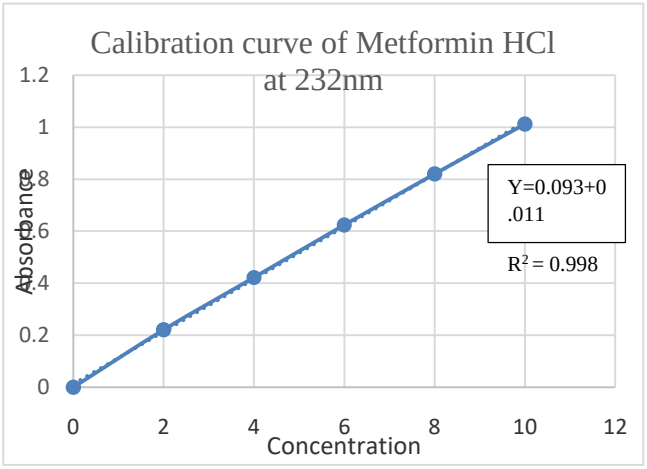

Fig.2Calibration curve of Metformin HCl in 0.1 N HCl

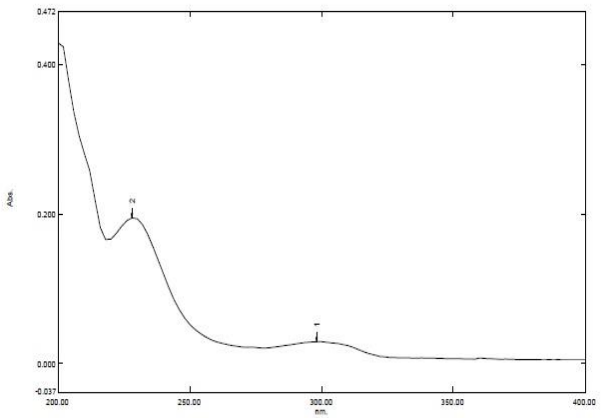

Fig.3 UV Spectroscopy of Glyburide in 0.1 N HClat 229 nm

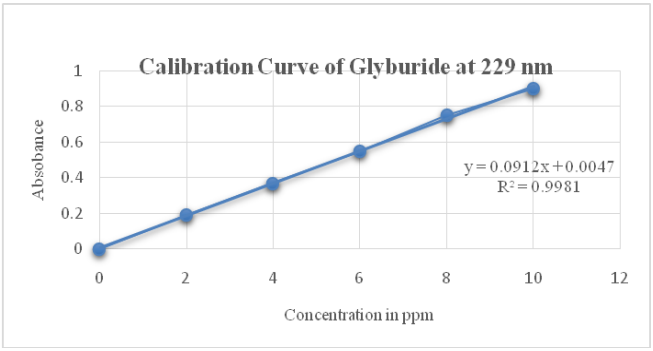

Figure4 Standard Graph of Glyburide in 0.1 N HCl at 229nm

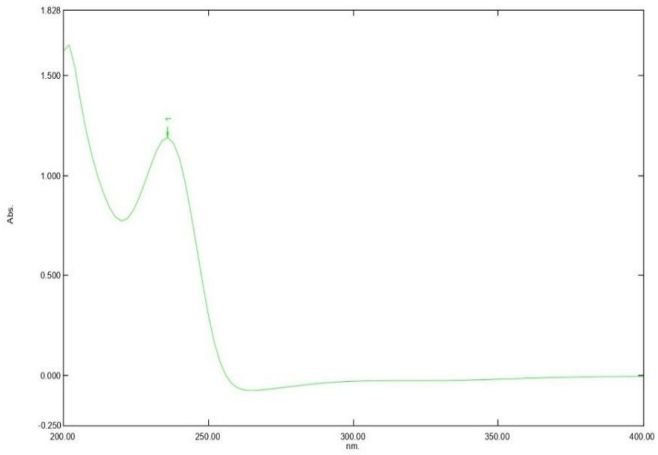

Fig.5UV Spectrum of Metformin HCl in 6.8 Phosphate Buffer at 234nm

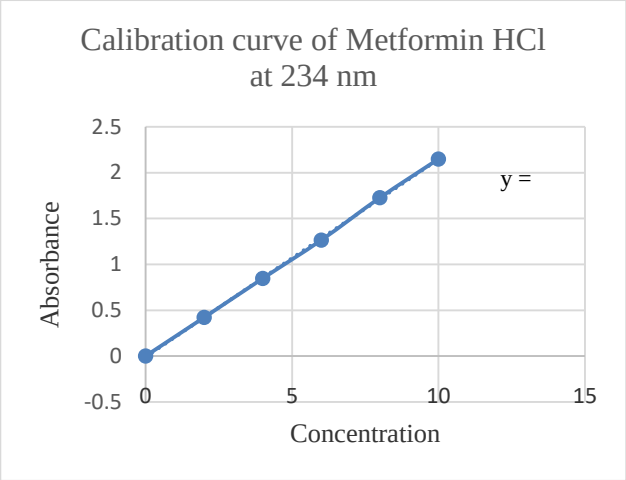

Fig.6 Calibration curve of Metformin HClin 6.8 Phosphate Buffer

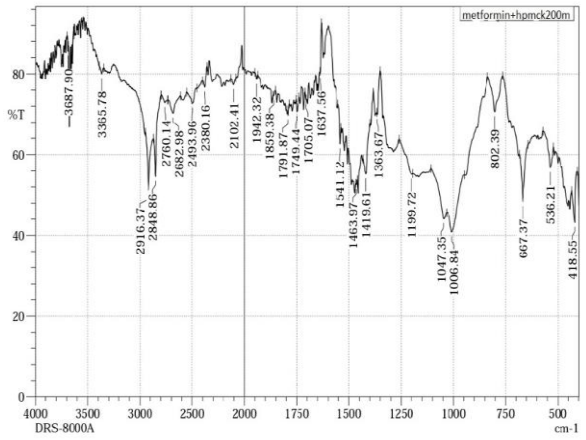

Fig9IR spectra of Metformin HCl + HPMC K200M

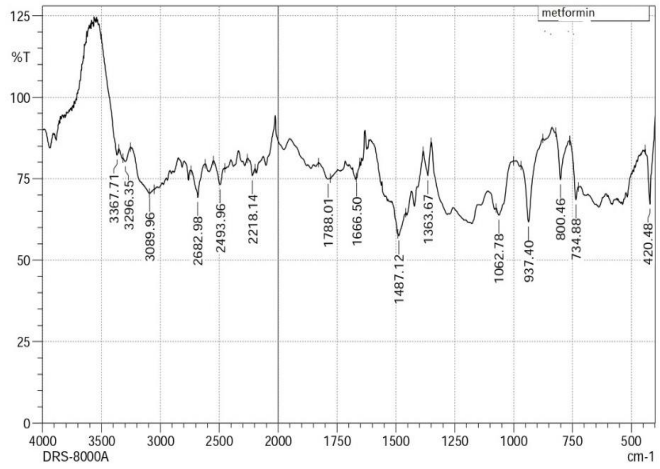

Figure.7IR Spectra of Metformin HCl

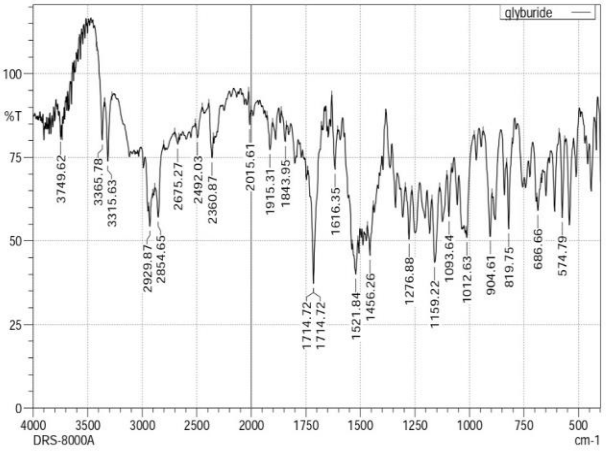

Fig.10IR spectra of Glyburide

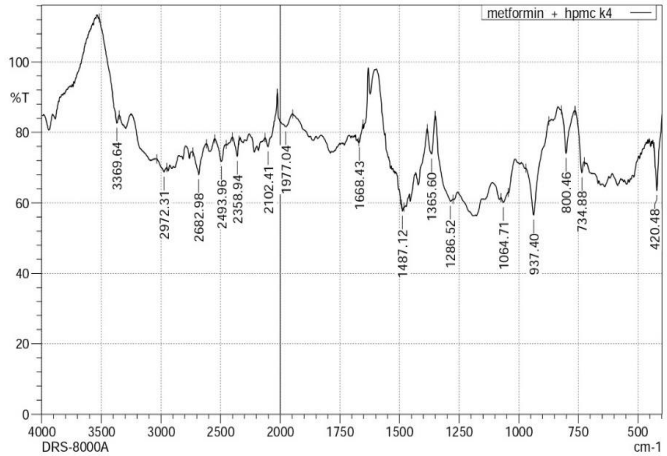

Fig.8IR Spectra of Metformin HCl + HPMC K4M

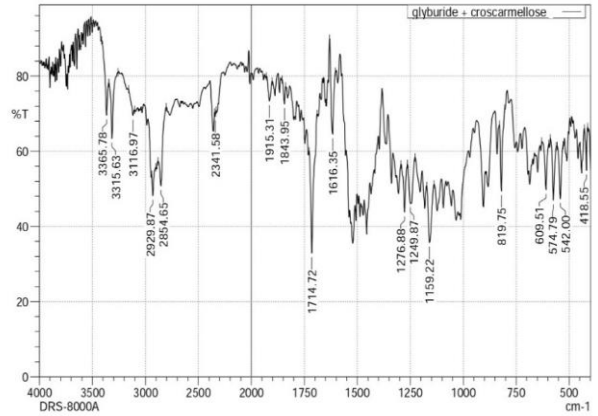

Fig.11IR spectra of Physical Mixture Glyburide + Croscarmellose

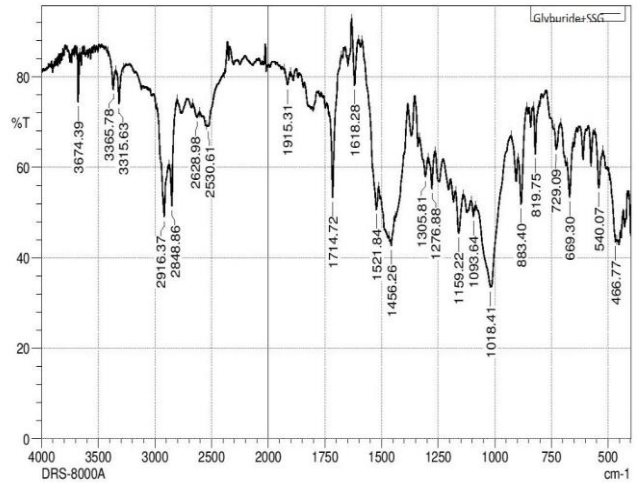

Fig.12IR spectra of Physical Mixture Glyburide + SSG

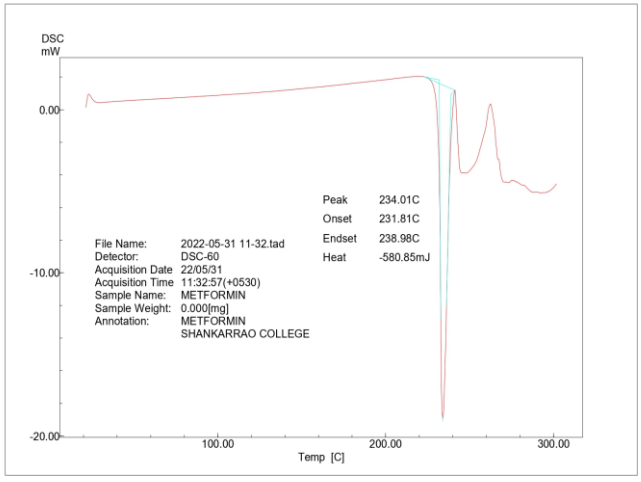

Figure 13 DSC Thermogram of Metformin HCl

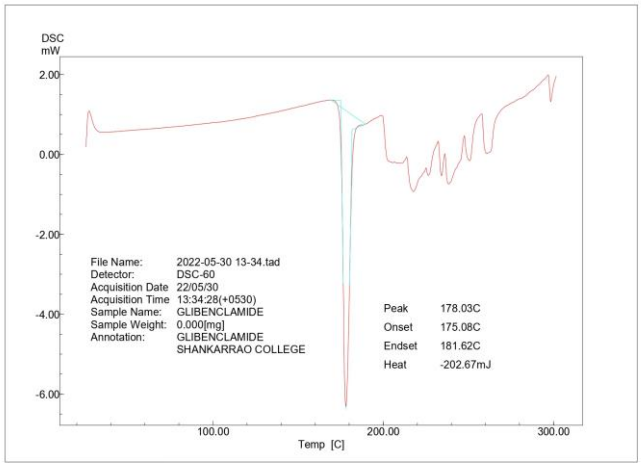

Fig.14 DSC Thermograph of Glyburide

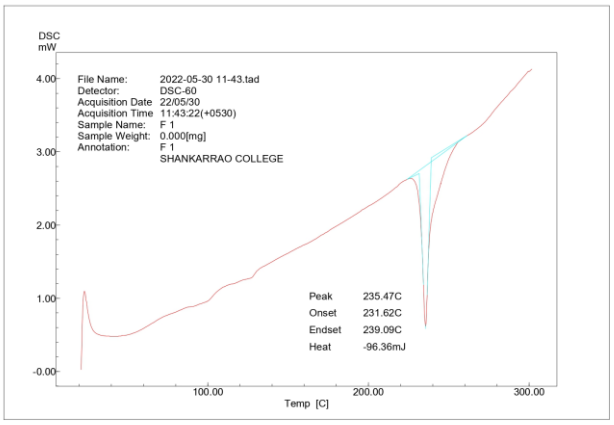

Figure15DSC ThermogramofMetformin+HPMCK4M

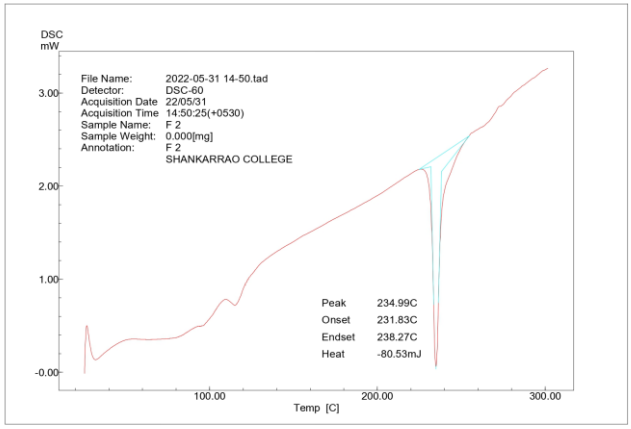

Figure16DSC Thermogramof Metformin+HPMCK200M

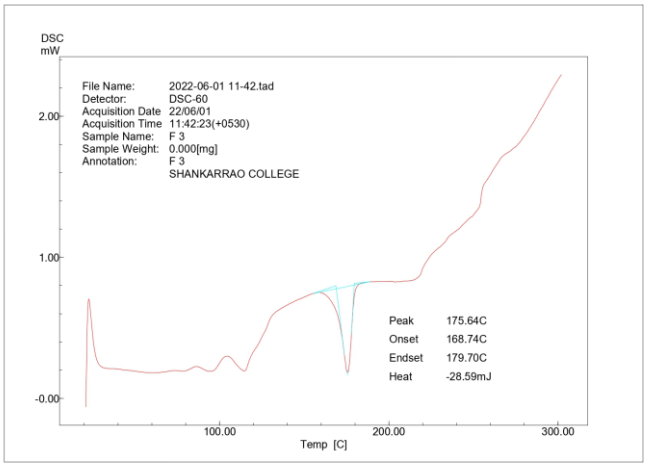

Figure17DSC ThermogramofGlyburide+Croscarmellose

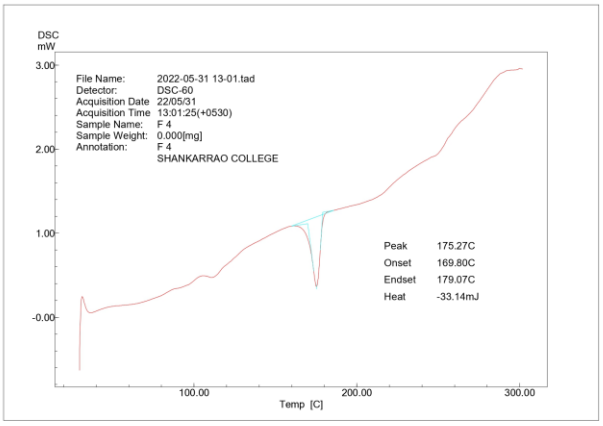

Figure18DSC ThermogramofGlyburide+Sodium Starch Glycolate

Table.1. Formulation Table for Metformin HCl Sustained Release and Glyburide Immediate Release

Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Sustained release layer	**SR 1**	**SR 2**	**SR 3**	**SR 4**	**SR 5**	**SR 6**
Metformin HCl(mg)	500	500	500	500	500	500
HPMC K4M(mg)	160	180	200	---	---	---
HPMC K200M(mg)	---	---	---	160	180	200
Microcrystalline Cellulose(mg)	80	60	40	80	60	40
Magnesium Stearate(mg)	5	5	5	5	5	5
Talc(mg)	5	5	5	5	5	5
Total (mg)	750	750	750	750	750	750
Immediate release layer	**IR 1**	**IR 2**	**IR 3**	**IR 4**	**IR 5**	**IR 6**
Glyburide(mg)	5	5	5	5	5	5
Croscarmellose(mg)	5	10	15	---	---	---
Sodium starch Glycolate(mg)	---	---	---	5	10	15
Microcrystalline cellulose(mg)	45	40	35	45	40	35
Maize starch(mg)	40	40	40	40	40	40
Magnesium stearate(mg)	5	5	5	5	5	5
Ferric oxide(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total(mg)	100	100	100	100	100	100
Overall Total(mg)	**850**	**850**	**850**	**850**	**850**	**850**

Table.2.Evaluation of prepared tablet blends for pre compression study of sustained release layer

Formulations	**Angle of Repose(θ°)**	**Bulk Density (gm/ml)**	**Tapped Density (gm/ml)**	**Hauser's Ratio (HR)**	**Carr's Compressibility Index (%)**
F1	28.39±0.35	0.47±0.54	0.55±0.43	1.1702	14.54
F2	29.05±0.24	0.48±0.38	0.56±0.24	1.1666	14.28
F3	29.39±0.54	0.46±0.26	0.53±0.29	1.1521	13.20
F4	28.16±0.13	0.44±0.37	0.54±0.47	1.2272	18.51
F5	28.65±0.17	0.45±0.26	0.54±0.25	1.2022	16.66
F6	28.78±0.26	0.46±0.53	0.55±0.28	1.1956	16.36

Table.3. Evaluation of prepared tablet blends for pre compression study of immediate release layer

Formulations	**Angle of Repose(θ°)**	**Bulk Density (gm/ml)**	**TappedDensity (gm/ml)**	**Hauser's Ratio (HR)**	**Carr's Index (%)**
F1	27.56±0.23	0.41±0.03	0.50±0.06	1.2195	18.20
F2	26.60±0.38	0.42±0.04	0.49±0.07	1.1545	14.28
F3	28.28±0.23	0.44±0.07	0.52±0.06	1.264	15.38
F4	26.08±0.37	0.43±0.06	0.51±0.01	1.1818	16.68
F5	25.40±0.32	0.42±0.02	0.51±0.05	1.2142	17.64
F6	27.20±0.12	0.43±0.06	0.51±0.03	1.1657	15.68

Table.4.PostCompressionParameterofbi layered tablet

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Dug content (%)		Disintegration time(sec)
					SR	IR	
F1	848±0.53	5.3±0.05	5.7±0.02	0.78±0.06	98.2±0.45	97.6±0.17	77±0.32
F2	850±0.85	5.2±0.04	5.9±0.10	0.73±0.05	98.3±0.14	98.2±0.38	76±0.25
F3	847±0.76	5.4±0.06	6.1±0.05	0.70±0.04	97.9±0.16	98.7±0.68	74±0.31
F4	849±0.38	5.3±0.04	5.8±0.04	0.84±0.04	98.5±0.36	97.9±0.12	79±0.43
F5	849±0.68	5.2 ±0.09	5.8±0.02	0.81±0.08	98.1±0.56	98.3±0.36	75±0.26
F6	851±0.48	5.3±0.05	6.1±0.12	0.71±0.02	98.7±0.13	98.8±0.23	72.±0.34

Table.5InVitroDrugReleaseProfileofFormulationsofSustainedReleasedTablet

Times inHr.	%Cumulativedrugrelease					
	SR1	SR2	SR3	SR4	SR5	SR6
0	0	0	0	0	0	0
1	8.69±0.23	7.98±0.32	7.68±0.23	10.52±0.18	8.98±0.31	7.57±0.32
2	24.09±0.45	18.2±0.23	17.54±0.25	22.3±0.13	18.27±0.25	16.27±0.41
4	38.43±0.52	35.3±0.25	36.43±0.31	42.33±0.29	38.36±0.09	29.46±0.23
6	67.56±0.37	56.4±0.37	60.45±0.28	69.32±0.26	59.35±0.04	48.5±0.08
8	86.54±0.36	72.7±0.13	70.27±0.15	89.26±0.21	74.83±0.43	64.67±0.36
10	97.37±0.21	93.8±0.32	81.38±0.18	98.14±0.32	92.04±0.34	81.31±0.29
12	----	----	93.6±0.24	----	-----	97.83±0.24

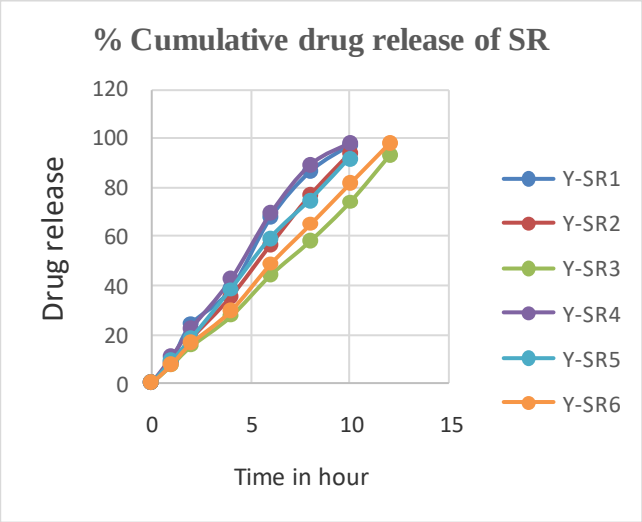

Fig.19% Cumulative drug release of sustained release

Table6InVitroDrugReleaseProfileofImmediateRelease Layer

Time inminute	%Cumulativedrugrelease					
	IR1	IR2	IR3	IR4	IR5	IR6
0	0	0	0	0	0	0
5	11.57±0.32	11.57±0.06	18.25±0.24	12.17±0.32	15.99±0.21	18.99±0.25
10	22.61±0.27	22.61±0.12	28.94±0.07	26.11±0.37	28.29±0.27	32.81±0.12
15	32.71±0.14	35.32±0.19	38.11±0.24	34.53±0.41	36.42±0.31	39.80±0.18
20	42.81±0.21	44.33±0.43	48.76±0.19	45.84±0.13	47.58±0.31	52.88±0.05
25	58.41±0.43	60.19±0.31	62.19±0.42	56.51±0.27	58.71±0.12	64.83±0.05
30	72.27±0.24	77.70±0.24	81.88±0.08	74.13±0.27	77.44±0.17	83.61±0.32
35	83.39±0.25	85.96±0.07	87.78±0.09	81.04±0.15	83.39±0.16	88.17±0.28
40	92.91±0.34	94.39±0.08	96.34±0.02	90.48±0.04	95.61±0.11	97.62±0.16

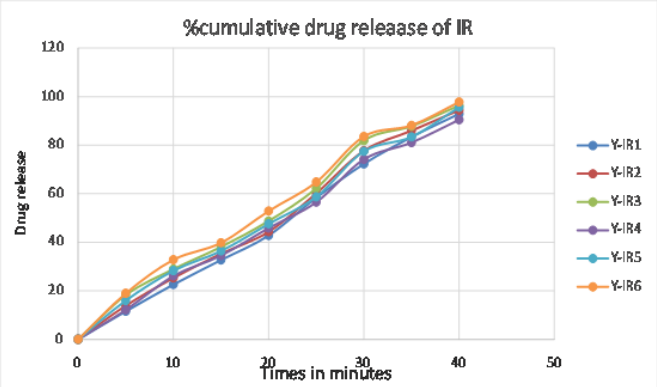

Fig.20 %cumulative drug release of IR

Table. 7 Comparative stability study of Bilayer Tablet

Sr.No.	Parameter	Initial	Aftertwo months
1	Hardness ($Kg/cm^{2)}$	6.1±0.12	6.0±0.24
2	Thickness(mm)	5.3±0.05	5.2±0.05
3	Friability (%)	0.71±0.02	0.70±0.32
4	WeightVariation(mg)	851±0.48	850±0.36
5	Disintegration Time (Sec)	72±0.34	73±0.34
6	Drug content (%)	98.7±0.13(SR) 98.8±0.23(IR)	98.4±0.21(SR) 98.5±0.17(IR)
7	%DrugRelease	97.83±0.24(SR) 97.62±0.16(IR)	95.13±0.54(SR) 94.38±0.32(IR)

III. RESULT AND DISCUSSION

Calibration curve of Glyburide and Metformin HCl

λmax of Metformin HCl in 0.1N HCl; Glyburide in 0.1N HCl and Metformin HCl in pH 6.8 Phosphate buffer are 232 nm, 229 nm and 234 nm respectively. The standard curves are following linearity with a regression coefficient of (r^2=0.999). They are obeying the Beer's law in the conc. range of 0-30 µg/mL. Lower standard deviation (SD) values ensured reproducibility of the method. As the excipients used in the study were not interfering and good % recovery of drug(s) indicates this spectrophotometric method was suitable for the estimation of drug(s) in dissolution studies and % assay of formulations.

Drug-excipient compatibility studies by FT-IR

An interpretation of FT-IR spectrum of Metformin HCl and Glyburide (pure drugs) reveals that the IR bands of pure drug and drug(s) + excipients show no significant shifts or reduction in intensity of the FT-IR bands. Hence there was no incompatibility problem between the drug and excipients used in the study.

DSC

Drug-Excipient Compatibility Studies: DSC thermograms are presented in Fig. 13,14,15, 16,17,18, There are no significant differences in onset melting points and peak melting points of initial and 40°C/75% RH, 4 weeks samples. Corresponding data represented in the above figures Hence, it was concluded that there was no interaction between the drug substances and the chosen excipients. Hence, these excipients were considered for the use in the development of the formulation.

Pre-compression studies

The directly compressible blends of IR layer of Glyburide, reveals that the angle of repose was found between 25.40 θ˚ to 28.28 θ˚, Hausner's Ratio between 1.15 to 1.26. and Carr's index between 14.28 % to 18.20 %.The directly compressible blends of SR layer of Metformin HCl, reveals that the angle of repose was found between 28.16 θ˚ to 29.39 θ˚, Hausner's Ratio between 1.15 to 1.22 and Carr's index between 14.28 % to 18.51 %The micromeritic studies indicate a good flow and compression characteristic of all the IR and SR blends as per USP limits as mentioned in Table 2 and 3. In these IR &SR directly compressible blends MCC is used as diluent, which imparts good flow and compressibility to the blends.

Post-compression studies of bi-layered tablets

Reveals that the average weight of tablets was found to be 847.60 to 851.40 mg. The average thickness of tablets was found to be 5.2 to 5.4 mm. The average hardness of the tablets ranges between 5.7±0.02 kg/cm2 to 6.1±0.12 kg/cm2, indicating satisfactory mechanical strength. The % weight loss in the friability test ranges fromf 0.70 to 0.84 %, which was NMT 1 % as per pharmacopoeia limits indicating a good mechanical resistance of tablets. % Assay of Glyburide-IR layer all the batches are within 97.6% to 98.8% and of Metformin HCl-SR layer all the batches are within 97.9% to 98.7% of the labelled content, indicating the content uniformity of drug(s) in both IR and SR layers.

In vitro dissolution studies of IR layer

For the optimization of the composition of IR layer In vitro dissolution studies of compressed IR layers alone of formulations IR1-IR6 were conducted in 0.1N HCl up to 40 min. Among all the formulations IR6 (15% w/w Sodium Starch Glycolate as super disintegrant) shows the better dissolution efficiency at 40 min. As the concentration of super disintegrant increases, tablet dissolution rate (DR) enhances. Among the used super disintegrant. Hence IR6 is selected as optimized one and in the formulation of all bilayered tablets, its composition is taken as IR layer.

In vitro dissolution studies of Sustained release layer

Sustained release layer of Metformin HCl were prepared by using HPMC K4M and KPMC K200M polymers. The release profiles of Metformin HCl sustained Released Layer were plotted as in fig.19. The release rate of Metformin HCl mainly controlled by the hydration and swelling properties of polymers. 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 SR6 composed of HPMC K200M in high concentration was 12 hr and also shows significantly higher drug release rate than other formulations. Formulation SR6 containing 200 mg of Cumulative drug release which comparatively greater than other formulation batches so SR6 was selected for further formulation of bilayer tablet of Metformin HCl.

Accelerated stability studies of optimized formulation

As there were no significant differences in post compression studies (weight variation, thickness, hardness, friability and in vitro dissolution studies) of initial and accelerated stability samples of optimized formulation BT6 in the final up to 2 months, it passes the test for stability as per ICH guidelines. Comparative FT-IR spectra of optimized BT6-Initial and 40°C/75%RH-2M, reveals there is no significant change in the functional group's peaks of the Glyburide and Metformin HCl due to interaction with polymers and other excipients in the accelerated stability studies.

IV. CONCLUSION

The present research work was carried out to develop antidiabetic bilayer tablet ofMetformin HCl and Glyburide using polymer HPMC K 4M and HPMC K200M at high concentration for Sustained Release layer and super disintegrant Croscarmellose and Sodium Starch Glycolate for Immediate release layer.

All raw materials were subjected to pre-formulation studies such as bulk density, tapped density, compressibility index and Hausner's ratio showed good flow properties. In FTIR spectra there is no physical interaction between drug and all excipients.

The Batch F6 as chosen as optimized formulation which showed satisfactory results.

As high and optimum concertation of polymer and super disintegrant used in the formulation F4 showed 97.83% of drug release at the end of 12 hr. and 97.62% of drug release at the end of 40 minutes for SR and IR respectively which showed good results.

The stability study was performed which showed stable formulation after two months.

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