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Design & Characterization of Glimepiride Fast Dissolving Tablets

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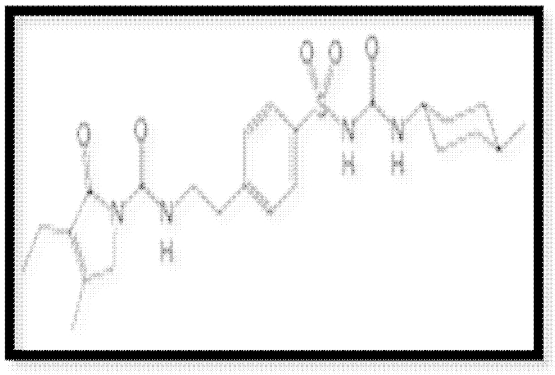
Abstract: The aim of the present study was to formulate, Evaluate and optimize fast dissolving tablets of Glimepiride. Glimepiride is a Third generation sulphonylureas used for the treatment of type-2 diabetes and belongs to BCS class II drugs (Low Solubility and High Permeability). Glimepiride was the drug of choice because of its low dose. Glimepiride fast dissolving tablets (F1- F18) were prepared using superdisintegrants like sodium starch Glycolate, Crosscarmelose sodium, Crosspovidone by employing direct compression technique. Prepared tablets were evaluated for angle of repose, weight variation, Hardness, % friability, wetting time, drug content, disintegration and invitro dissolution studies.The results of stability studies revealed no change in physical appearance, drug content and in-vitro dissolution profile, thus indicating that formulations was stable. FTIR studies revealed that there was no significant interaction between drug and polymer in the formulations. Among all the formulations (F1-F18), F-15 was found to be optimized as compared to other formulations.
Keywords: Glimepiride; fast dissolving tablets; Superdisintegrants and direct compression.

Introduction:

Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route. Fast Dissolving Tablets are one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self administration without water or chewing. This delivery system offers convenience for treatment-resistant population who has difficulty in swallowing unit oral dosage form, namely tablets and capsules[1-3]. The demand for these formulations is particularly beneficial to pediatric and geriatric patients. It is estimated that 50 % of the population is affected by dysphagia which results in high incidence of on compliance and ineffective therapy. To overcome this problem it is necessary to design a formulation which rapidly disperse / dissolve in the oral cavity without the need of water for swallowing. Such dosage form should disintegrate when placed in the mouth and can be swallowed in the liquid form[4-5]. Fast dissolving drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation.

Glimepiride is approved by the Food and Drug Administration (FDA) for “once-daily use as monotherapy or in combination with insulin to lower blood glucose in diabetes mellitus by binding to β-cell ATP dependent potassium channel. It has a long duration of effect with a half-life of about 5 hours, allowing once daily dosing and therapy improving compliance[6-7].



Structure of Glimepiride

Materials and Methods:

Glimepiride procured from Dr. Reddy's Laboratories, Hyderabad, Crospovidone, Sodium starch Glycolate, Microcrystalline cellulose & Mannitol, from FMC Bio polymer, Mumbai, Crosscarmelose sodium from ISP, Hyderabad, Sodium lauryl sulphate & Saccharin sodium from Signet chemical corporation, Magnesium Stearate from Ferro, Mumbai, Electronic weighing balance (BBA422-3SM Scale Tec, Mumbai)

Methods:

Glimepiride Fast dissolving tablet was prepared by using direct compression technique. Glimepiride and the other excipients were passed through sieve no 40 and blended for 10 minutes. Add magnesium stearate to the above mixture and blended for 5 minutes. Compressed the blend in to tablets by using 6 mm round flat punches on a 16 stationary rotary punching tablet machine.

Evaluation of Pre-Compression Parameters:

The angle of repose of the blend was determined by fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using formula[8]

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

Where, θ is angle of repose, h is height of pile and r is the radius of the base pile.

Bulk densities[9] of the blend were determined by pouring gently some amount of sample through a glass funnel into a graduated cylinder. The volumes occupied by the sample were recorded. Bulk density was calculated

$$\text{Bulk density (g/ml)} = \frac{\text{weight of sample in gms}}{\text{volume occupied by the smaple}}$$

Tapped densities[5] of the blend were determined by pouring gently some amount of sample through a glass funnel into a graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained (300 taps). Volume occupied by the sample after tapping were recorded and tapped density was calculated.

$$\text{Tapped density (g/ml)} = \frac{\text{weight of sample in gms}}{\text{volume occupied by the smaple}}$$

% compressibility was determined by the Carr's compressibility index[10].

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Evaluation of Post-Compression Parameters:

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution and results reported in Table no 5 & 6.

Thickness:

Thickness and Diameter of the tablet was measured by using Vernier calipers in mm.

Weight Variation Test:

Weight variation[11] was evaluated on 20 tablets using an electronic balance and test was performed according to official method.

Friability Test:

Friability[12] was determined by taking 10 tablets in a Roche Friabilator for 4min at 25 rpm. % Friability was calculated by using the formula:

% Friability = (Loss in weight/Initial weight) x 100

Hardness Test:

Tablet hardness[12] was determined for 6 tablets using a Monsanto hardness tester.

In-Vitro Disintegration Time:

The disintegration test was performed using an USP disintegration apparatus, with 900ml distilled water at 37^0C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported.

Fourier Transforms Infrared Spectroscopy (Ftir):

FTIR spectral studies were carried out for the pure drug and the excipients to check the compatibility using SHIMANDZU FTIR-8400 S. The spectrum was recorded in the range of 4000- 400 cm^{-1}. Interaction between the components, if any, was indicated by either producing additional peaks or absence of characteristic peak corresponding to drug and carrier.

In-Vitro Dissolution Studies:-

Dissolution[13] rate studies were performed in phosphate buffer (pH 7.8) at 37 ± 0.5^oC using USP II rotating paddle apparatus (ELECTROLAB Dissolution tester TDT-08L) at 75 RPM. All the Formulations were subjected to dissolution. 10ml of the samples were withdrawn at time intervals of 2, 4, 6, 8, 10, 12, 14 and 16 minutes. The sample was filtered through Whatman paper (0.45 µ size). The volume of the dissolution fluid was adjusted by replacing 10ml of dissolution medium after each sampling. The absorbance of the solution was measured at 228 nm using dissolution medium as reference standard. The concentration of Glimepiride was calculated by using standard curve equation.

Results and Discussion

The Ultraviolet Spectro-photometric method was used to analyze glimepiride at a wavelength of 228nm in 7.8 pH phosphate buffer.

The batches F1 – F18 are formulated using different concentrations of super disintegrant are tabulated in the Table no 1, 2 & 3. Formulations were formulated using direct compression technique.

The blends of different formulations were evaluated for bulk density and tapped density. The percentage compressibility of powder was determined using Carr's compressibility index. Compressibility index lies within the acceptable range of 10.9 to 26.21 for all the batches between F1 – F18. Of all the batches

F7 showed excellent compression properties. All formulations showed good compressibility. Angle of repose for all the formulations were found to be in the range of 29.2 to 35.5. Hausner's ratio values were found to be in the range of 1.12-1.32. The results were shown in Table no-4.

Table No-01: Formulation containing Crosspovidone (F1-F6)

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Glimepiride	2	2	2	2	2	2
Avicel PH 101	55	55	55	55	55	55
Mannitol	56.7	55.4	54.1	52.8	51.5	50.2
Cross povidone	1.3	2.6	3.9	5.2	6.5	7.8
Sodium saccharin	5	5	5	5	5	5
SLS	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total	130	130	130	130	130	130

Table No-02: Formulation containing Sodium starch Glycolate (F7-F12)

Ingredients (mg)	F7	F8	F9	F10	F11	F12
Glimepiride	2	2	2	2	2	2
Avicel PH 101	55	55	55	55	55	55
Mannitol	56.7	55.4	54.1	52.8	51.5	50.2
Sodium Starch Glycolate	1.3	2.6	3.9	5.2	6.5	7.8
Sodium saccharin	5	5	5	5	5	5
SLS	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total	**130**	**130**	**130**	**130**	**130**	**130**

Table No-03: Formulation containing Cross carmellose sodium (F13-F18)

Ingredients (mg)	F13	F14	F15	F16	F17	F18
Glimepiride	2	2	2	2	2	2
Avicel PH 101	55	55	55	55	55	55
Mannitol	56.7	55.4	54.1	52.8	51.5	50.2
Cross Carmellose Sodium	1.3	2.6	3.9	5.2	6.5	7.8
Sodium saccharin	5	5	5	5	5	5
SLS	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total	**130**	**130**	**130**	**130**	**130**	**130**

Table No.04: Evaluation of Pre-Compression parameters of powder blend

Formulation	Bulk Density	Tapped Density	Carr's Index	Hausner ratio (%)	Angle of repose(θ)
F1	0.52	0.65	20.02	1.25	34.2
F2	0.55	0.64	26.21	1.16	35.5
F3	0.49	0.57	14.04	1.163	33.2
F4	0.48	0.55	12.72	1.14	32.4
F5	0.5	0.58	13.79	1.16	33
F6	0.53	0.61	13.11	1.15	32.1
F7	0.49	0.55	10.9	1.12	33.5
F8	0.53	0.61	13.11	1.15	32.1
F9	0.53	0.66	19.69	1.24	31.8
F10	0.51	0.65	21.53	1.27	35.4
F11	0.54	0.61	11.47	1.12	32.5
F12	0.52	0.65	20	1.25	33.1
F13	0.51	0.58	12.06	1.13	29.4
F14	0.52	0.65	20	1.25	32.1
F15	0.54	0.61	11.47	1.32	29.2
F16	0.52	0.65	20	1.25	32.5
F17	0.53	0.61	13.11	1.15	32.1
F18	0.48	0.55	12.72	1.14	32.4

Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was shown in Table no-5. The values are almost uniform and were within the specifications. Thus all the formulations passed the test for weight variation. Among all the batches F-10 showed minimum weight variation.

Table no.05: Evaluation Post Compression Parameters of formulations

Formulation	Hardness (Kg / cm^2)	Friability (%)	Thickness (mm)	Average weight of tablet (mg)
F1	3.5	0.41	2.5	132
F2	3.8	0.46	2.4	130
F3	3.6	0.48	2.4	131
F4	4.0	0.42	2.3	132
F5	3.8	0.49	2.5	133
F6	3.5	0.45	2.5	131
F7	3.5	0.44	2.4	130
F8	3.6	0.47	2.5	127
F9	3.8	0.49	2.3	132
F10	3.9	0.48	2.5	130.5
F11	3.5	0.41	2.4	129
F12	3.2	0.42	2.5	128
F13	3.1	0.46	2.4	131
F14	3.4	0.45	2.4	129
F15	3.2	0.41	2.5	126
F16	3.4	0.48	2.5	132
F17	3.2	0.51	2.4	131
F18	3.5	0.52	2.5	130

The thickness of tablets was determined using Vernier caliper and results were shown in Table no-5. Tablet thickness is almost uniform in all the formulations and the values obtained are from 2.3 to 2.5 mm. The standard deviation values indicated that all the formulations were within the range with uniform thickness.

The values of hardness for tablets are ranged from 3.1 to 4.0 kg/cm^2. The lower values of standard deviation indicate that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. The mean values of hardness of tablets were as given in Table no-5.

The friability values of tablets were mentioned in Table no-5. The values ranged from 0.41 to 0.52 %. All the values are below 1% indicating that the tablets of all formulations are having good friability property. Of all the batches F1, F11 and F15 showed least friability.

Table no.06: Evaluation of Post Compression Parameters of formulations

Formulation	Wetting time(sec)	Drug content (%)	Disintegration time (sec)
F1	215	93.1	112
F2	198	98.3	115
F3	184	95.5	121
F4	201	96.5	124
F5	215	95.1	96
F6	214	96.9	124
F7	219	94.3	127
F8	225	92.6	114
F9	183	98.5	131
F10	214	97.2	98
F11	215	93.6	122
F12	214	98.2	124
F13	158	96.4	105
F14	146	97.8	121
F15	144	99.2	116
F16	140	96.4	106
F17	141	95.2	73
F18	134	96.8	80

The disintegration test was performed for formulations batches F1 to F18. The range of disintegration time for batches F1 to F18 ranged from 73 sec to 131 sec. Thus the range of disintegration time was found to be within the pharmacopoeial specifications. Of all the batches F17 showed least disintegration time. The individual disintegration times of batches F1 – F18 were tabulated in Table no 6.

The content uniformity test was performed for all formulations and results were shown in Table no-6. Three replicates from each test were recorded. The mean and standard deviation of all the formulations are calculated. The drug content of glimepiride fast dissolving tablets was found to be between 92.6 to 99.2%.

The *in-vitro* study was carried out by using USP dissolution apparatus II (Paddle type) and results were shown in the table 7 and Graphs (Fig No-1-3). For all the formulation batches F1 – F18, 7.8 pH phosphate buffer was used as a dissolution medium. 10 ml samples were taken from the vessel using syringe capped with a 0.45 µm filter at every 2,4,6,8,10,12,14,16 minutes of the dissolution test. The samples were analyzed by UV – Spectroscopy using an UV Spectrophotometer. The dissolution rates of each formulation batch from F1 – F18 were tabulated in Table no 7.The results were plotted by taking % of drug release on Y-axis and Time in min on X – axis. The results showed that all batches from F1 – F18 released more than 70% of the drug in 16 min. Of all the batches F15 showed better dissolution rates compared to other batches.

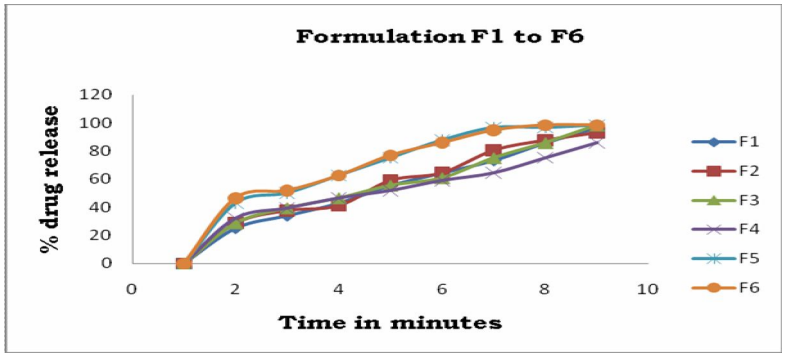


Figure No 1: Dissolution Profile of Formulation F1 to F6

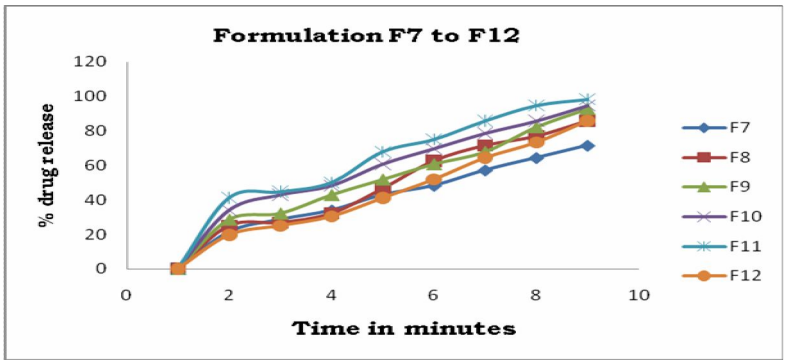


Figure No 2: Dissolution profile of Formulation F7 to F12

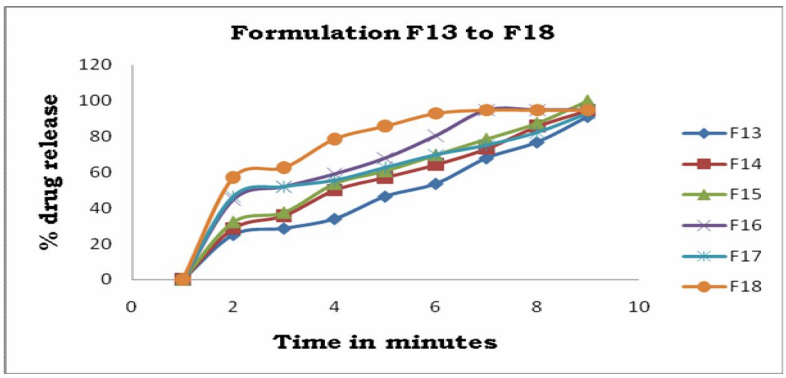


Figure No 3: Dissolution profile of Formulation F13 to F18

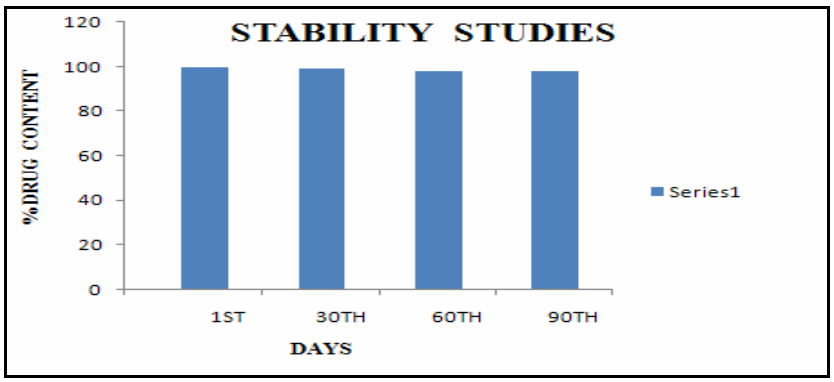


Figure No 4: Graph of stability studies

Table no.7: Percentage drug release of formulations

	Time (min)							
Formulation	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
F1	25.03	33.97	42.91	55.43	64.37	73.31	85.82	96.55
F2	28.6	37.54	41.12	59	64.37	80.46	87.61	92.98
F3	28.6	39.33	46.49	55.43	60.79	75.09	85.82	98.34
F4	32.18	39.33	46.49	51.85	59	64.37	75.09	85.82
F5	42.91	50.06	62.58	75.09	87.61	96.55	96.55	98.34
F6	46.49	51.85	62.58	76.88	85.82	94.76	98.34	98.34
F7	21.45	28.6	33.97	42.91	48.27	57.21	64.37	71.52
F8	25.03	26.82	32.18	46.49	62.58	71.52	76.88	85.82
F9	28.6	32.18	42.91	51.85	60.79	67.94	82.28	92.9
F10	33.97	42.91	48.27	60.79	69.73	78.67	85.82	94.76
F11	41.12	44.7	50.06	67.94	75.09	85.82	94.76	98.34
F12	19.66	25.03	30.39	41.11	51.85	64.37	73.31	85.82
F13	25.03	28.6	33.97	46.49	53.64	67.94	76.88	91.19
F14	28.6	35.76	50.06	57.21	64.37	73.31	85.82	94.76
F15	32.18	37.54	53.64	60.79	69.73	78.67	87.61	100.13
F16	44.7	51.85	59	67.94	80.46	94.76	94.76	94.76
F17	46.49	51.85	55.43	62.58	69.73	75.09	82.25	92.98
F18	57.21	62.58	78.67	85.82	92.98	94.76	94.76	94.76

Table No 8: Stability Data of Formulation F-15 at 40 ± 2^0C / 75 ± 5% RH

S. No.	**Time in days**	**Physical changes**	**Percentage of drug content*±SD**	**Moisture content**	**Percentage of drug release *±SD** (99.5% of release label claim in 10 min).
1.	1st day (initial)	Round flat shaped tablets, using 6.00 mm punch	99.51±0.48	0.82	99.5%
2.	30th day (1 month)	No changes	99.35±0.11	0.78	99.3%
3.	60th day (2 month)	No changes	98.12±0.13	0.80	98.6%
4.	90th day (3 month)	No changes	97.81±0.28	0.78	98.2%

* SD- Standard deviation

Table No-9: FTIR Data of Drug, Drug-Polymer and Optimized Formulation

Group	Functional Range	Observed Ranges in Drug	Observed Ranges in Drug + SSG	Observed Ranges in Drug + CP	Observed Ranges in Drug + CCS	Observed Ranges in Optimized Formulation
CH_3	2850-3000	2974.36	2973.45	2924.21	2924.21	2924.21
CH_2	1350-1470 1630-1680	1465.00	1466.10	1674.28	1674.28	1556.62
CH	1370-1390	1371.45	1370.15	---	--	---
NH	1000-1250 1550-1650	1016.53 1560.48	1024.25	1036.76	1082.11	1210.38
C=O	1400-1450 1500-1560	1414.85	1409.06	1543.12	1543.12	1545.05
C-N	660-900	670.29	687.65	687.65	687.65	704.05
S=O	1030-1060	1053.18	1035.82	1036.78	1036.78	1042.57
S=C	1050-1200 1350±5	1052.21	1347.34	1347.34	1347.34	1347.34
C=C	780-850	786.56	783.13	784.10	784.10	782.12
SH	2550-2600	---	---	---	2567.18	---

FTIR study was carried out for the Drug, Polymers & the optimized formulation (F15). The studies revealed that there was no significant interaction between drug and polymer. FTIR Data was given in Table no-9 & Fig no-5-10.

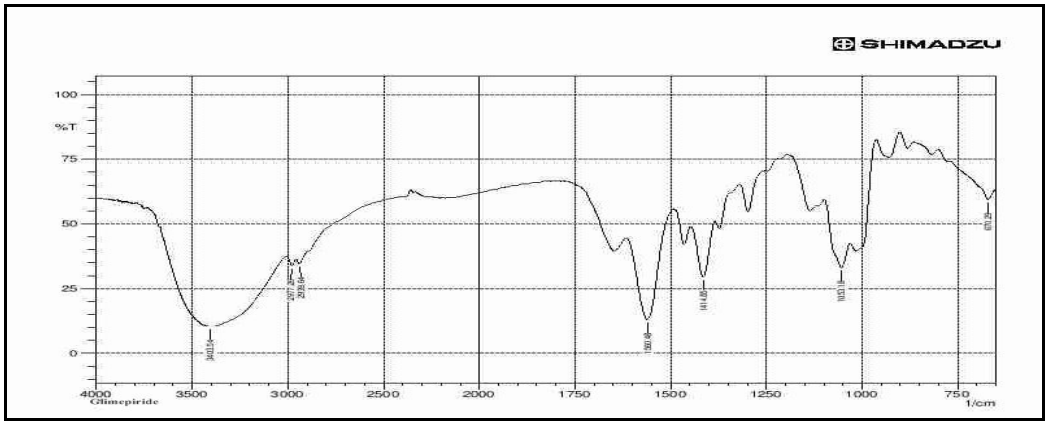


Fig No 5: FTIR Spectroscopy of Glimepiride

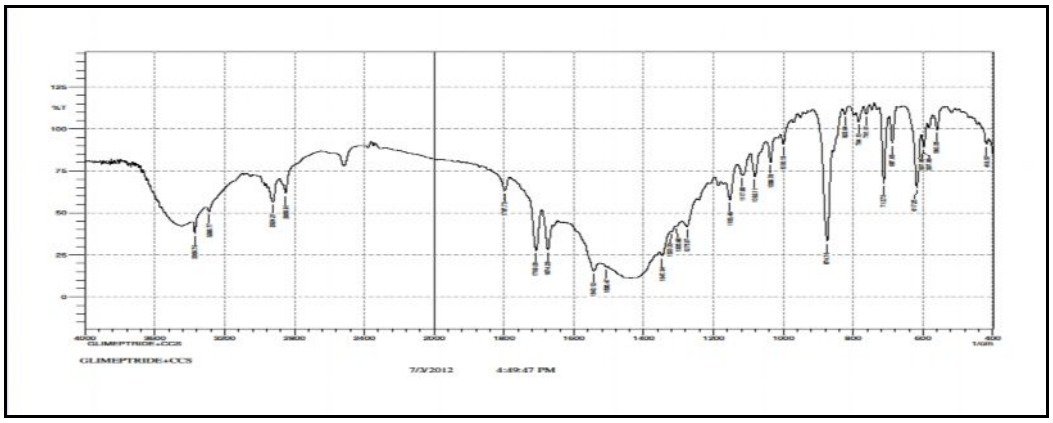


Fig No 6: FTIR Spectroscopy of Crosscarmelose sodium

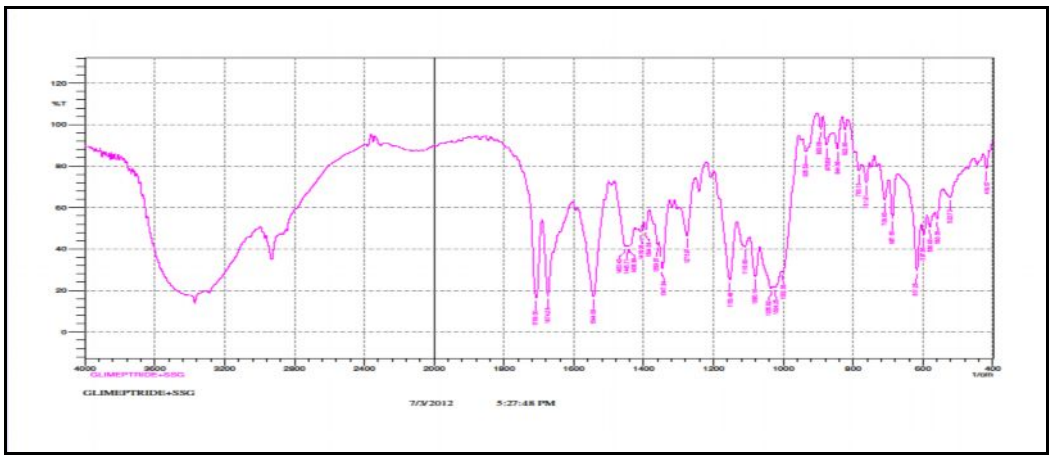


Fig No-7: FTIR Spectroscopy of sodium starch Glycolate

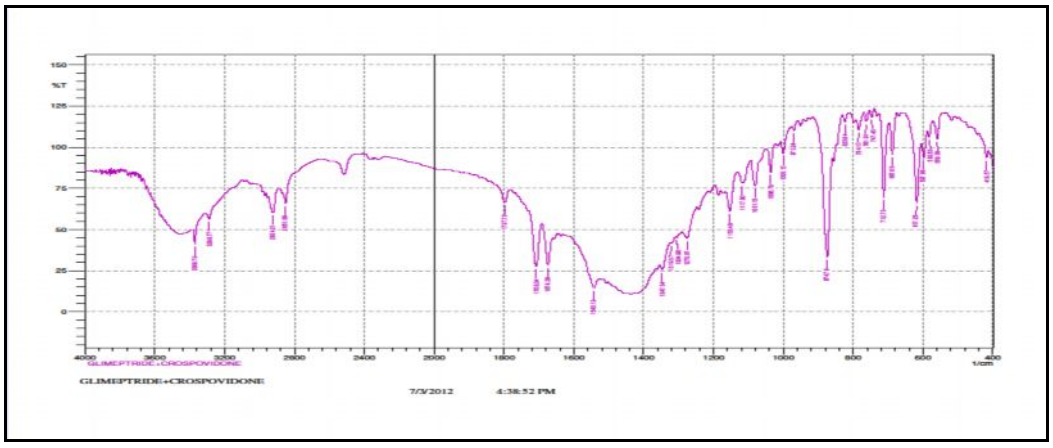


Fig No-8: FTIR Spectroscopy of Crospovidone

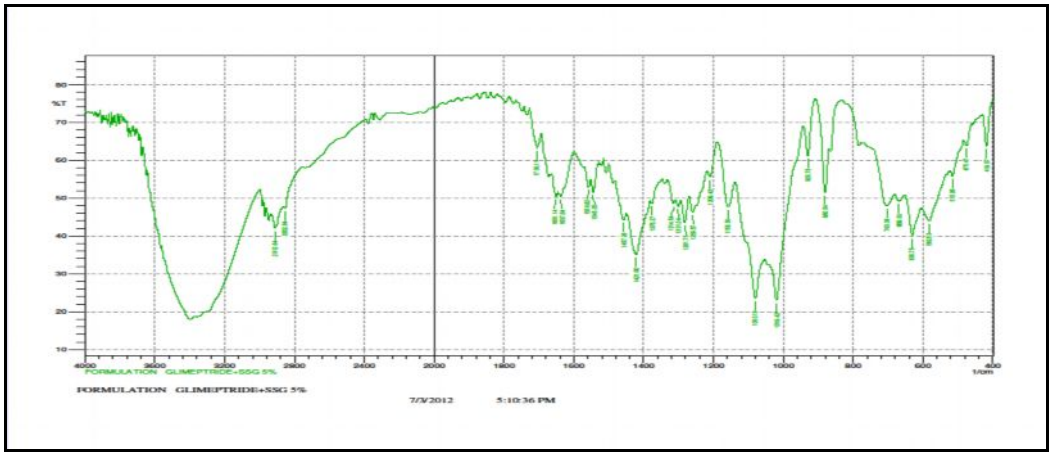


Fig No-10: FTIR Spectroscopy of optimized formulation (F15)

The stability of this optimized formulation was known by performing stability studies for 6 months at accelerated conditions of 40^0C $\pm$ 75 % RH on optimized formulation. The results were shown in table no 8 fig no-4. The formulation was found to be stable, with no change in the hardness, disintegration time, drug content and *in- vitro* drug release pattern.

Conclusion

Glimepiride fast dissolving tablets were prepared by direct compression technique by using fixed quantity of drug and mixed with various quantities of super Disintegrants. Among all the batches, F15 shows better linearity compared to all other batches. It complies with all the physicochemical parameters. It has better flow properties compared to all the other batches. Better In-vitro dissolution rate compared to other batches. It complies with all the standards of the stability tests. Hence Glimepiride fast dissolving tablets is used for the treatment of Type-2 Diabetes mellitus (or) Non-Insulin-Dependent Diabetes Mellitus.

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