FORMULATION AND EVALUATION OF GLIMEPRIDE SUSTAINED RELEASE PELLETS

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ABSTRACT

Glimepride is an oral hypoglycemic drug effectively used in treatment of diabetes mellitus type 1&2. The main objective of this work is formulation of glimepride sustain release pellets. The half-life of drug has 5hours, sparingly soluble in water and it shows 100% bioavailability.Glimepride practically freely soluble in methanol and ethanol,sparingly soluble in aceticacid. Solubility of drug plays a major role in absorption and ultimately affects bioavailability.Glimepride lacks to maintain its concentration at site of action and side effects are more in conventional dosage form. Hence to minimize these effects we found it as an excellent candidate for sustained released oral drug delivery system. Drug release from glimepride sustained release pellets in capsules is 94%from the present study,it is concluded that sustained release pellets prepared with cellulose N-22 grade was shows betterdrug release studies using 8% solution for sustained release of glimepride and there is no interaction observed in infrared spectroscopy.

Key words: Glimepride, sustained release pellets, bioavailability,*invitro* drugrelease.

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INTRODUCTION

Pellets[1]: Pellets can be defined as small, free flowing,spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral Administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and Excipients using appropriate processing equipment. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used to day.glimepride is an antidiabetic drug used in treatment of diabetes mellitus type 1&2.the biological halflife of Glimepride is 5hours. It requires multiple dosing to maintain therapeutic drug sugar blood level so it is best candidate to formulate as modified release dosage form. The present study was to develop a pharmaceutically equivalent stable and quality improved formulation. The active pharmaceutical active Glimepride was subjected to pre formulation study.which encompasses the "Accelerated drug excipients compatability study" and the results obtained with selected excipients showed good compatability with Glimepride. The manufacturing procedure was standardized and found to be reproducible.

MATERIALS AND METHODS

Glimepride,Ethylcellulose,Isopropylalcohol, Starch,MicrocrystallineCellulose,Copovidone,HydroxyPropyl Methyl Cellulose.

Melting Point

Melting point of the sample was determined by capillary method.Solubility data of Glimepridewas determined by saturated solubility method.Different solvents were prepared according to the procedure given in I.P.drug was added in excess to 3ml of each solvent in separate test tubes.The test tubes were kept in an ultrasonicator for 15min and on mechanical shaker for 6 hours for equilibration.After, 6hours contents of each test tube were filtered,suitable diluted and analyzed for the drug content using UV spectroscopy.

Calibration curve of Glimepride in pH 7.8 phosphate buffer

The standard solutions of Glimepride was subsequentiy diluted withpH7.8 phosphate buffer containing 1% methanol to obtain series of dilutions containing 2,4,6,8,10 and 12µg/ml of Glimepride in solution.The absorbance of the above solutions was measured in UV spectrophotometer andabsorbance values were plotted against concentration of drug.

PreformulationStudy[2]

Physical Characteristics:

Determination of Bulk Density and Tap Density:

An accurately weighted quantity of the powder (W) was carefully poured into the granulated cylinder and volume (V_o) was measured. Then the graduated cylinder was closed with lid and set into the density determination apparatus (bulk density apparatus)the density apparatus was set for 500 taps,750 taps , and 1250 taps.

After that the volume(V_f) was measured and continued the operation till the two consecutive reading were equal. The bulk density and the tapped density were calculated using the formulas.

Bulk Density – W/V_o

Tapped Density- W/V_f

Where W- Weight of the powder.

V_o- Initial volume.

V_f- Final volume.

Bulk density of Glimepride was found to be 0.41g/ml.

Tap density of Glimepride powder was

found to be 0.65g/ml.

Hausner ratio:–
It indicates the flow properties of the powder and measured by the ratio ofTapped density to bulk density.
Hauser ratio- Tapped density /Bulk density
Table No.1: Range of Hausner Ratio and Its Properties

GlimeprideHausner Ratio was found to be 0.63g/ml.

Sieve Analysis:

The main aim of sieve analysis was to determine the different size of drugParticles present. series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number)occupy top position followed by sieve of decreasing pore size (large sieve number) towards the bottom.

Procedure:

A series of sieves were arranged in the order of their decreasing pore diameter(increasing sieve number) i.e. sieve no. ASTM 40, 60, 80, 100 with 40grams of drug were weighed accurately and transferred to sieve 40 which were kept on top. The sieves were shaken for about 5-10 minutes .Then the drug retained on each sieves were taken, Weighted separately and expressed in terms of percentage.69.4% Glimepride powder pass through sieve 100 (NLT 65% should pass through 100 mesh).

Solubility- Slightly soluble in methanol, freely soluble in acetonitrile.

Melting Point-205^{o}C

Description- White Crystalline Form
Preparation of Drug Pellets:

Inert pellets (1.0-18 mm) were first prepared by extrusion – spheronizationmethod using Standard formula; lactose: Avicel: water (1:1:0:9) and were used for drug pellets.

Formulation Development[3,4]

No.	Hausner ratio	Properties
1	0-1.2	Free flowing
2	1.2-1.6	Cohesive powder

Drug Loading(stage-1):
The raw materials were collected. Suffiecient quantity of isopropyl alcohol was weighed and to this 5gm of glimepride ,pvp-k-305gms and non pariel seeds 90gms was and pass all owderded material through 100mesh size sieve before adding to get uniform particle size.

Drying(Stage - 2):

Dry the Stage I pellets in SS Tray Drier at 45^{0}C for 8 hours.Check moisture content. It should be below 1%. Pass the dried Pellets through sifter to remove fines.

Sub Coating(Stage-3):

In clean and dry SS vessel, Charge Purified Water and Hydroxy Propyl Methyl Cellulose 5 cps and stir till dissolution to form clear colloidal subcoating solution. In clean, dry Fluid Bed Coater, charge dried Pellets. Spray above coating solution through Nozzle on Pellets along with continuous flow of warm air in to dry the coat as soon as it forms for uniform coating.

Continue coating till minimum weight gain of coated Pellets is achieved.

Sustain release Coating(stage-4):preparation of coating solution

HPMC E15- 4%,8%
ECN-14 - 4%,8%
ECN-50 -4%,8%
IPA+MDC-Q.S

The above solutions are mixed together and stirred for 15 min.

The Stage-3 pellets were loaded into fluidized bed coater and the sustain release coating solution was sprayed.Drying and sifting for sustain release coated pellets. The pellets were dried under maintained temperature of 48^{o}c-50^{o}c for 30min and sifted using 18-20# mesh.The pellets retained on #20 mesh were collected. 30 mg equivalent of glimepride pellets were filled in capsules according to the bulk density data obtained.These capsules were used for drug content analysis and the invitro dissolution studies. The whole process preparation of solution,Coating and capsule filling performed under mercury lamp to avoid photo degradation of the drug.

Evaluation of pellets[5]

Bulk density:

Apparent bulk density was determined by pouring the blendinto graduated cylinder and calculated bulk density of the pellets.

Friability test:-

The essential requirement of pellets is to have an acceptable friability to with stand further processing.Friability less than 0.08% is generally accepted for tablets,but for pellets this value could be higher due to the higher surface /unit and subsequent involvement of frictional force.45g of pellets were placed in friabilator which was then operated for 100 revolutions at 25rpm.

Angle of repose:-

The angle of repose of glimepride pellets was determined by the funnel method.

Hard ness:

Hardness of pellets in the range of 9 -17 N determined by Dr.Schieunigerhardness tester.

Hardness of pellets of different formulation:

Formulation	F1	F2	F3	F4	F5
Hardness (N)	9 N	10 N	14 N	17 N	17 N

Evaluation of sustain release capsules

Drug content analysis:-

Standard preparation:-

Accurately 100mg of glimepride was weighed and transferred into 100ml volumetric flask.50 ml of methanol was added to dissolve and made up to volume with water. From the above solution 2ml was transferred into another 100ml volumetric flask and made up to volume with methanol.

Sample preparation:-

Accurately weighed pellets equivalent to 100mg of glimepride was transferred into 100ml volumetric flask and 50 ml of methanol was added to dissolve and made up to volume with water. From the above solution 2ml was transferred into another 100ml volumetric flask and made up to volume with methanol.

DissolutionProcedure[6,7,8]

In vitro release studies were carried out in the dissolution test apparatus (USP Type II). The tests were carried out in 900 ml of Phosphate buffer P^{H}-7.8 for 6hrs at 75 rpm at 37±0.5^{o}C. 10 ml of the aliquot were

withdrawn at different predetermined time intervals (1, 2, 3, 4, 5, 6hr) and filtered. The required dilutions were made with 0.1N HCl and the solution was analyzed for the drug content by UV spectrophotometer detecting at λ max 228 nm, Phosphate buffer 7.8pH was replaced in the vessel after each withdrawal to maintain sink condition. From this percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release.The apparatus was allowed to run for 6 hours during the release studiesa 5ml of medium was taken out in amber colored glass vials and filtered and drug analysis by UV Spectrophotometer.

Dissolution Parameters:

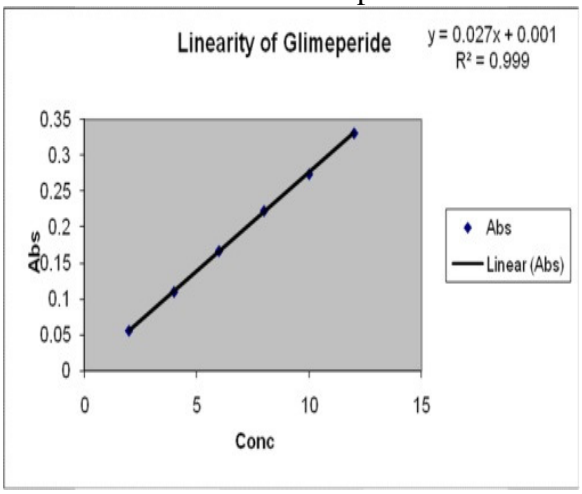
Apparatus: Dissolution apparatus Type I of USP (basket)
Medium:900ml,7.8 pH phosphate buffer
Speed:75rpm
Time: 6hrs.

RESULTS AND DISCUSSION

Table1. Dissolution of Glimepride

Time (hrs)	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8
1	94.3	87.74	20.95	18.33	22.26	18.99	18.33	15.6
2	98.23	94.3	35.36	28.16	38.63	30.77	36.42	31.86
3			53.04	47.8	60.24	45.18	57.23	50.72
4			73.34	68.1	75.96	62.86	66.98	68.28
5			88.4	74.65	85.78	75.3	81.3	84.54
6			89.71	91.02	88.4	90.36	88.44	94.3[i]

Standard Curve of Glimepride



Compatibility study data at 25ºC/60%RH and 40ºC/75%RH for one month revealed that there were no physical and chemical change and discoloration observed between drug and different excipients. All formulation trials were met their specifications like bulk density, friability, and angle of repose test. The hardness of the pellet was found to be in the range of 9N to 17N.

All parameters were found within the limit. In the present study, an attempt has been made to formulate and evaluate sustained release pellets of Glimepride by solution spray technique method; employing release retard polymers like ethyl cellulose with 8%.

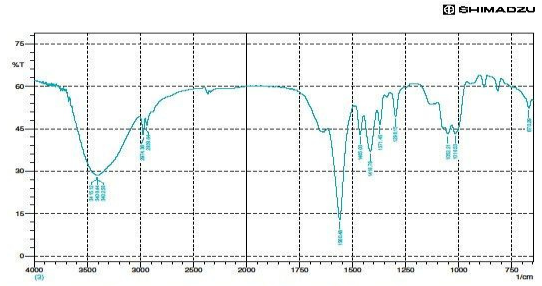
In vitro dissolution study:

In vitro dissolution studies were performed in pH 7.8 phosphate buffers on the above promising formulation, namely, formulation 8 .From the above data it is evident that the promising formulation 8

released 94 drug in 6hours (pH 7.8 phosphate buffer).

FT-IR STUDIES:

Infrared Spectroscopy of Glimepride



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	670.29	52.299	3.827	735.87	656.79	19.629	0.605
2	1016.53	43.22	6.617	1032.93	961.56	21.684	2.257
3	1052.21	43.112	2.713	1066.68	1032.93	11.882	0.461
4	1298.15	49.277	9.184	1324.19	1259.57	16.43	1.445
5	1371.45	46.46	7.275	1384.95	1351.19	9.899	0.921
6	1416.78	36.972	13.657	1448.6	1385.91	22.793	4.257
7	1465	42.891	8.209	1487.18	1448.6	12.493	1.26
8	1560.48	12.886	35.924	1615.42	1495.86	59.195	21.811
9	2939.64	46.335	2.896	2956.04	2892.36	19.8	0.531
10	2974.36	42.8	6.043	3009.08	2956.04	17.567	1.11
11	3402.58	28.586	0.114	3404.51	3010.05	170.395	3.594
12	3406.44	28.598	0.015	3410.29	3405.47	2.621	0.001
13	3415.12	28.613	0.009	3416.08	3411.26	2.62	0

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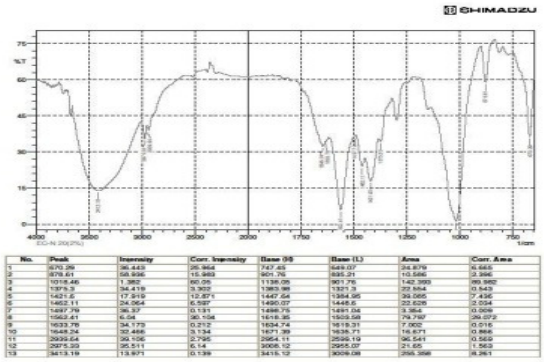
Drug with Ethyl Cellulose



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	670.29	36.443	25.964	747.45	649.07	34.879	6.665
2	878.41	58.936	15.993	901.76	835.21	10.586	2.396
3	1018.46	1.382	60.05	1136.05	901.76	142.393	69.382
4	1375.3	34.419	3.302	1383.96	1321.3	22.664	0.543
5	1421.6	17.919	12.871	1447.64	1384.95	39.065	7.436
6	1462.11	24.064	6.597	1490.07	1448.6	22.629	2.554
7	1497.79	36.37	0.131	1498.75	1491.04	3.364	0.009
8	1562.41	6.04	36.106	1618.35	1503.58	79.797	26.072
9	1633.78	34.173	0.212	1634.74	1618.31	7.902	0.016
10	1648.24	32.466	3.134	1671.39	1636.71	16.671	0.866
11	2939.64	39.106	2.795	2954.11	2896.19	96.541	0.569
12	2975.33	35.511	6.14	3008.12	2955.07	21.65	1.563
13	3413.19	13.971	0.139	3415.12	3009.08	256.398	8.261

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EC-N 20(2%)

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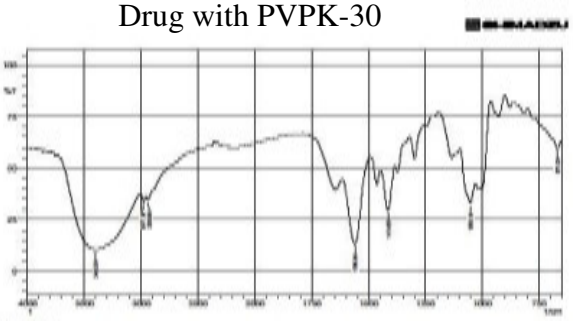
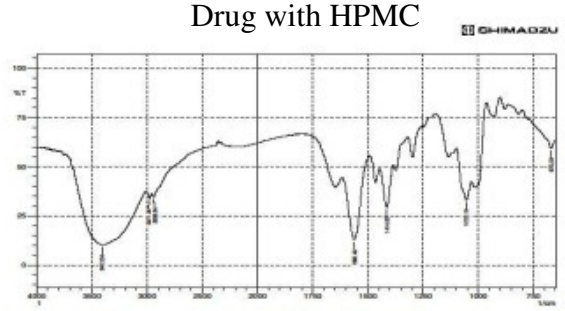
Drug with PVPK-30



Drug + Ipmc

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	670.29	59.456	5.105	763.63	653.9	20.408	1.091
2	1053.18	51.051	13.954	1098.51	1031	26.197	5.011
3	1414.65	29.488	20.545	1446.67	1384.95	25.208	6.621
4	1560.48	13.051	36.592	1615.46	1490.97	64.238	37.166
5	2939.64	34.623	2.536	2957	2406.19	182.813	19.183
6	2977.26	33.807	3.09	3036.12	2957	22.964	0.861
7	3403.54	10.369	0.429	3665.87	3400.65	186.814	14.871

Drug with HPMC



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	670.29	59.456	5.105	763.63	653.9	20.408	1.091
2	1053.18	51.051	13.954	1098.51	1031	26.197	5.011
3	1414.65	29.488	20.545	1446.67	1384.95	25.208	6.621
4	1560.48	13.051	36.592	1615.46	1490.97	64.238	37.166
5	2939.64	34.623	2.536	2957	2406.19	182.813	19.183
6	2977.26	33.807	3.09	3036.12	2957	22.964	0.861
7	3403.54	10.369	0.429	3665.87	3400.65	186.814	14.871

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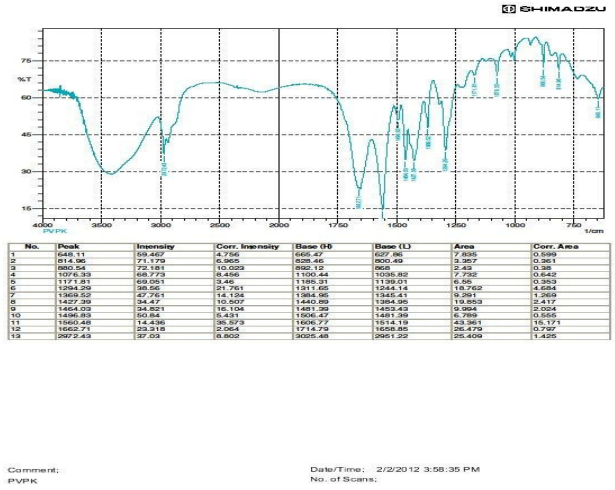
Formulation FG2



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	648.11	59.467	4.766	665.47	627.96	7.835	0.599
2	814.96	71.179	6.965	828.46	800.49	3.357	0.361
3	880.54	72.181	10.023	892.12	868	2.43	0.38
4	1076.33	68.773	8.456	1100.44	1035.82	7.732	0.642
5	1171.81	69.051	3.46	1185.31	1139.01	6.56	0.353
6	1294.29	38.56	21.761	1311.65	1244.14	18.762	4.684
7	1369.52	47.761	14.124	1384.95	1345.41	9.261	1.269
8	1427.39	34.47	10.507	1440.89	1384.95	19.853	2.417
9	1464.03	34.821	16.104	1481.39	1453.43	9.994	2.024
10	1496.83	50.64	5.431	1506.47	1481.39	6.769	0.555
11	1540.48	14.436	35.573	1606.77	1514.19	43.361	15.171
12	1662.71	29.318	2.964	1714.79	1658.85	26.479	0.797
13	2972.43	37.03	8.802	3025.48	2951.22	25.409	1.425

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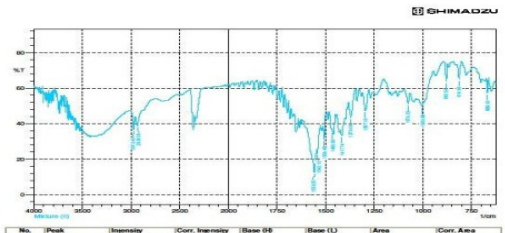
Formulation FG6



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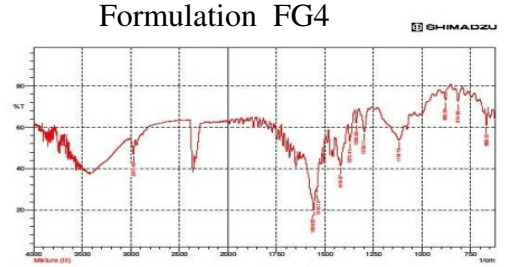

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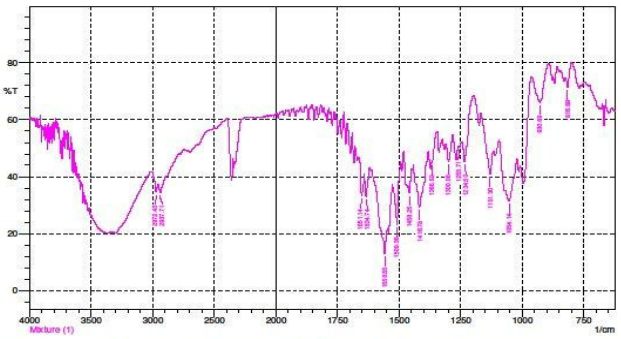
Formulation FG8



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	816.89	71.565	5.034	824.6	801.46	2.875	0.305
2	990.69	66.145	11.21	963.48	893.08	10.14	2.338
3	1054.14	31.583	7.616	1071.5	1022.32	21.622	2.29
4	1131.3	40.817	11.52	1168.91	1117.8	15.454	2.229
5	1234.5	45.325	10.86	1246.07	1197.85	12.074	1.324
6	1255.71	50.27	0.993	1260.54	1246.07	4.227	0.06
7	1300.08	45.204	7.547	1310.69	1282.72	8.6	0.91
8	1366.62	45.025	0.526	1367.59	1346.37	6.204	-0.146
9	1416.78	29.337	8.383	1431.24	1399.42	15.064	1.598
10	1458.25	34.2	4.63	1463.07	1450.53	5.401	0.332
11	1509.36	23.253	16.845	1522.87	1494.9	13.799	2.659
12	1558.55	12.957	6.529	1565.3	1547.94	13.527	1.306
13	1634.74	33.064	8.632	1641.49	1622.2	8.327	1.056
14	1651.14	33.289	6.354	1659.82	1647.26	5.454	0.603
15	2937.71	34.552	3.713	2968.93	2888.53	30.181	1.226
16	2972.43	34.58	4.075	3007.15	2956.93	20.251	0.828

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Mixture (1)

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The above IR graphs the Drug Functional groups are identified with polymers and there is no interaction observed in formulation.

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