

Formulation & Evaluation of Gastro-retentive tablets of Glimiperide by melt granulation technique

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Abstract:

Present study aimed to formulate an extended release (gastro-retentive/floating) matrix tablet of Glimiperide by direct compression and melt granulation method. Seven batches of extended release tablets of Glimiperide were prepared using Sodium alginate, Poloxamer 188 and Sodium bicarbonate by direct compression method. (G1 – G7). Seven batches of extended release tablets of Glimiperide were prepared using Bees wax, Cetyl alcohol, ethyl cellulose and Sodium bicarbonate by melt granulation method. (G8 – G14). The tablets were evaluated for parameters like thickness, hardness, friability, Swelling Ability, In vitro Buoyancy Studies, Adhesion Retention Period and In-vitro release study. Based on the results, formulation containing 15% (45mg) poloxamer 188 (D-6) was identified as good and better formulation among all formulations developed for floating tablets of Glimiperide prepared by direct compression method; and formulations prepared using 50mg Bees wax & Cetyl alcohol in combination (G-13) was identified as best formulation among all formulations developed for floating tablets of Glimiperide by melt granulation method. Optimized formulations G13 showed very good stability profile.

Keywords: *Glimiperide*, Gastro-retentive, floating, direct compression, melt granulation.

I. Introduction:

Gastroretentive dosage forms (GRDFs) are a drug delivery formulation that are designed to be retained in the stomach for a prolonged time and release their active materials and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome.^{1,2}

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced³⁻⁷. Diabetes is one of the major causes of death and disability in the world. World Health Organization estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. Non-insulin dependent (Type 2) diabetes mellitus is a heterogeneous disorder characterized by an underlying insufficiency of insulin. This insufficiency results from defective insulin utilization and can be corrected by administration of one or more of the currently available oral hypoglycemic agents⁸.

Glimiperide is an orally administered sulfonyl urea agent and highly selective agonist for the sulfonyl urea receptor (SUR) is found in pancreas, which are target sites of insulin secretion. Activation of the SUR receptors activates the secretion of insulin involved in the control of glucose and lipid metabolism. Glimiperide has an oral bioavailability of 85% and peak plasma concentrations of glimepiride are achieved in 3–3.5 hours. Elimination half of glimepiride is 4 to 7 hrs.^{9,10}

II. Materials & Methods:

2.1. Materials:

Glimiperide (API), was obtained as a gift sample from IPCA Laboratories Limited, Mumbai, India and other excipients HPMC K15M, Sodium alginate, Poloxamer 188, Sodium bicarbonate, Talc, Magnesium stearate, Microcrystalline cellulose, Bees wax, Cetyl alcohol, Ethyl cellulose were procured from R.S. Enterprises, Jaipur, India manufactured by Central Drug House (P) Ltd – CDH, New Delhi, India. All chemicals used were of analytical grade.

2.2 Methods:

2.2.1 Preformulation Studies:

The drug Glimepiride, selected for present study was identified using different methods reported in the literature viz. melting point determination, partition coefficient determination, determination of absorption maxima (λ_{max}), and drug excipient interaction studies.

2.2.2 Drug Polymer Interaction Studies

The drug was white in color and when blended with polymer, the appearance of the physical mixture remains the same. In case of storage at accelerated condition ($40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH), there was no significant change in the physical characteristics of the drug in the presence of the polymer in closed container.

2.2.3 Design of Glimepiride Floating Matrix Tablets by Direct compression Technique:

Tablets containing 1mg of Glimepiride were made by direct compression technique. The active

ingredient Glimepiride, release-retarding polymer(s) (HPMC K15M and sodium alginate/poloxamer 188), a gas-forming agent, NaHCO_3 , were passed through sieve no. 20, individually. Different powder blends were prepared and mixed in a mortar and pestle for 10 minutes. Microcrystalline cellulose and magnesium stearate were then added to the mixed powders. Mixing was continued for another minute and the mixed blend was studied for pre-compression parameters. After evaluation of granules, Powdered blends, each weighing 300mg, were then directly compressed using a single punch tablet machine equipped with convex shaped punches with a die diameter of 10 mm. Machine settings were adjusted to get the desired hardness value, which gives an intact tablet. Composition of the batches prepared is shown in Table 1.

Table 1: Formulation of Glimepiride tablet by direct compression method

Batch no.	G1	G2	G3	G4	G5	G6	G7
Glimepiride	1	1	1	1	1	1	1
HPMC K15M	90	90	90	90	90	90	135
Sodium alginate	15	30	45				-
Poloxamer 188				15	30	45	-
Sodium bicarbonate	50	50	50	50	50	50	50
Talc	4	4	4	4	4	4	4
Magnesium stearate	5	5	5	5	5	5	5
Microcrystalline cellulose (Avicel PH101)	qs	qs	qs	qs	qs	qs	qs
Total tablet weight	300mg						

2.2.3 Design of Glimepiride Floating Matrix Tablets by melt granulation technique:

Floating tablets, each containing 1mg Glimepiride were formulated by a conventional melt technique. The composition of various formulations of the tablets with their codes is listed in table 2. The composition with respect to polymer combination was selected on the basis of trial preparation of tablets. The amount of bees wax was increased gradually. As per each formulation batch code required quantity of bees wax and cetyl alcohol were weighed and melted separately in a large china dish over a water bath. The drug was added to molten wax and mixed well. Previously weighed

quantities of ethyl cellulose, HPMC, Micro crystalline cellulose and sodium carbonate were added to the drug wax mixture and mixed well. After through mixing china dish was removed from water bath and cooled. The coherent mass was then scrapped from the china dish and was passed through sieve no 30. The amount of ingredients that are added for each tablet is given in following table 2. After evaluation of granules were then compressed in to the tablet by direct compression technique using single punch tablet machine equipped with convex shaped punches with a die diameter of 10 mm.

Table 2: Formulation of Glimepiride tablet by melt granulation method

Batch no.	G8	G9	G10	G11	G12	G13	G14
Glimepiride	1	1	1	1	1	1	1
Bees wax	10	20	30	10	20	30	50

Cetyl alcohol	10	10	10	20	20	20	-
HPMC K15M	70	70	70	70	70	70	70
Ethyl cellulose	30	30	30	30	30	30	30
Sodium bicarbonate	50	50	50	50	50	50	50
Talc	4	4	4	4	4	4	4
Magnesium stearate	5	5	5	5	5	5	5
Microcrystalline cellulose (Avicel PH102)	qs	qs	qs	qs	qs	qs	qs
Total tablet weight (mg)	300						

III. Evaluation of Compressed Tablets:^[11,12]

4.1 Tablet Thickness:

The Thickness of the tablets was determined by using Digital vernier calliper. Five tablets were used, and average values were calculated. The data is shown in Table3.

4.2 Hardness:

The hardness of five tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². The data is shown in Table3.

4.3 Weight Variation^[13]:

All the batches of gastro-retentive/floating tablets were subjected to weight variation test, as per IP-2018. Twenty tablets were taken and weighted

individually; their average weight was calculated and compared with the individual tablet weight to notice the variation in tablet weights. The data is shown in Table3.

4.4 Friability^[14]:

Friability of tablets was determined using Roche friabilator. Sample of 20 pre-weighed gastro-retentive/floating tablets were placed in a friabilator and revolve at a speed of 25 rpm for 4 min. Now dust removed from the tablets, weighed again, and percentage weight loss (friability) was calculated.

$$\% \text{ Friability} = \left\{ 1 - \frac{W_o}{W} \right\} \times 100 \quad \text{.....Eq.1}$$

Where, W₀ is initial weight of the tablets before the test and W is the weight of the tablets after test. Results are presented in Table3.

5.5.6 Swelling Ability¹⁵

The swelling behaviour of the tablets was determined, in triplicate, according to the method described by Dorozynski et al. Briefly, a tablet was weighed (W₁) and placed in the petridish with 20 ml of HCl (0.1 N), maintained at 37 ± 0.5 °C. After 8 hours the tablets were removed from the petridish and the swollen tablet was then reweighed (W₂). The swelling index (SI) was calculated using following formula.

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1} \quad \text{.....Eq.2}$$

Where, W₂ is the weight of the swollen tablets, and W₁ is the initial weight of the tablets. Size of tablets, before and after swelling, was also measured.

5.5.7 In vitro Buoyancy Studies¹⁶

The floating behavior of the tablets was visually determined, in triplicate, according to the floating lag time method described by Rosa et al. Briefly, a tablet was placed in a glass beaker, containing 200

ml of 0.1 N HCl, maintained in a water bath at 37 ± 0.5°C. The floating lag time, “the time between tablet was placed in a glass beaker with HCl and its buoyancy” and total floating duration, “the time during which tablet remains buoyant”, were recorded.

5.5.8 Adhesion Retention Period¹⁷

The adhesion retention period of the tablets was evaluated, in triplicate, by an in vitro method reported by Nakamura et al. Briefly, an agar plate (2%, w/w) was prepared in 0.1 N HCl (pH 1.2). A side of the tablet was wetted with 0.1 N HCl and attached to the centre of agar plate by applying a light force with a fingertip. Five minutes later, the agar plate was attached to a USP disintegration test apparatus and moved up and down in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. The tablet adhered on the plate was immersed into the solution at the lowest point and got out of the solution at the highest point. The retention period of the tablet on the plate was noted visually.

4.9 In vitro Release study^[18,19]:

The *in vitro* release studies of all the formulations were carried out using USP type II dissolution test apparatus. For Glimepiride, tablets were placed in dissolution bowls containing 900 ml of phosphate Buffer (pH 7.2); containing 1% SLS maintained at 37°C ± 0.5 and stirred at 75 rpm. Sample (5 ml) was collected by after 45 minutes.

$$\text{Amount released (mg)} = \frac{\text{Concentration} \times \text{Bath volume} \times \text{Dilution factor}}{1000} \dots\dots\dots \text{Eq.3}$$

$$\text{Percent drug release (PDR)} = \frac{\text{Amount released}}{\text{Drug content}} \times 100 \dots\dots\dots \text{Eq.4}$$

IV. Result & Discussion:

5.1 Pre-compression Evaluation:

Flow properties – Angle of repose, loose bulk density, tapped density and % Carr’s compressibility was determined for all the formulations which showed good flow property.

5.2 Post-compression Evaluation:

Average tablet thickness was found to be consistent throughout the batch. Hardness was maintained to be within 5.5 kg/cm² to 6.5 kg/cm², as these tablets

The absorbance was determined spectrophotometrically at 228 nm. Comparison of dissolution profiles were constructed as shown in fig. 1. Cumulative drug release was calculated on the basis of mean amount of drug present in the respective tablet by the formula:

are sustained release gastro-retentive type. Average tablet thickness (Table No. 3) was found to be consistent throughout the batch. Tablet thickness ranges between 3.50mm to 3.55mm. Friability of different batches was found between 0.17%-0.37%. The percent drug content of the tablets was found between 97.04%-99.82% of Glimepiride. Drug content of all the formulations was found to be within the limits as specified in IP.

Table 3: Post compression evaluation

Formulation	Average weight/tablet (mg)	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Drug Content Uniformity (n = 10) (%)
G1	340	3.51	6.1	0.26	97.56 ± 0.25
G2	350	3.50	5.4	0.32	99.71 ± 0.12
G3	345	3.52	5.7	0.35	97.04 ± 0.23
G4	355	3.53	5.5	0.35	98.85 ± 0.56
G5	347	3.55	6.3	0.37	98.29 ± 0.78
G6	350	3.54	6.4	0.32	99.62 ± 0.28
G7	345	3.52	5.7	0.22	98.47 ± 0.45
G8	349	3.53	6.1	0.17	97.33 ± 0.12
G9	351	3.50	6.2	0.30	99.24 ± 0.45
G10	349	3.52	6.3	0.18	97.67 ± 0.67
G11	348	3.53	5.5	0.25	99.82 ± 0.78
G12	355	3.55	6.2	0.33	97.15 ± 0.13
G13	353	3.54	6.2	0.19	98.96 ± 0.34
G14	345	3.52	5.6	0.23	98.4 ± 0.89

All the formulations had floating lag time less than 31 seconds and floating time, more than 10hrs except G7 & G14 may be due to the reason that formulation G7 do not contain Sodium alginate & Poloxamer 188 and formulation G14 do not contain Cetyl alcohol. The swelling indices of all the preliminary batches were found to be in range of 1.734 to 3.864, as shown in table 4. Formulation G6, with Poloxamer 188 & sodium bicarbonate

exhibited highest swelling index in the formulations prepared by direct compression method, it was also observed that Formulation G13, with bees wax & cetyl alcohol exhibited highest swelling index in the formulations prepared by melt granulation method. The formulations gave the tablet retention between the ranges of 18 to 94 minutes, as shown in table no 4.

Table 4: Results of *in vitro* Buoyancy Studies, Swelling Ability, and Tablet Adhesion Retention Period

Formulation code	Buoyancy lag time in sec*	Total floating time in hrs	Swelling Index (ratio)	Tablet adhesion retention period* (min.)
G1	20.24 ± 1.10	>10	1.52	21.12 ± 2.15
G2	18.45 ± 2.10	>10	1.74	32.23 ± 1.35
G3	17.15 ± 1.50	>10	2.25	45.34 ± 2.20
G4	15.24 ± 1.20	>10	2.64	57.43 ± 2.45
G5	12.54 ± 1.40	>10	3.16	69.32 ± 2.20
G6	11.61 ± 2.10	>10	3.52	80.21 ± 1.25
G7	28.50 ± 3.17	>8	1.14	40.12 ± 2.15
G8	15.24 ± 1.10	>10	1.80	25.23 ± 1.35
G9	13.45 ± 2.10	>10	2.24	37.34 ± 2.20
G10	12.15 ± 1.50	>10	2.76	49.43 ± 2.45
G11	12.24 ± 1.20	>10	2.98	64.32 ± 2.20
G12	11.54 ± 1.40	>10	3.42	78.32 ± 2.20
G13	10.61 ± 2.10	>10	3.94	90.42 ± 1.45
G14	29.40 ± 3.17	>8	2.34	80.12 ± 2.15

In vitro release of optimized formulation of Glimepiride extended release tablets of G6 was found to be 95.45% drug release in 12hrs; of G13, 78.5% drug release in 12hrs & 100% release within 18hrs and *in-vitro* floating time larger than 10hrs. Though formulation G6 & G13 good and sustained

release (>75% in 12hrs) but it was found that tablets prepared with melt granulation method using bees-wax and cetyl alcohol in combination with sodium bicarbonate (G13) showed extended and complete release.

Table 5: Percentage release of Glimepiride in 0.1 N HCl buffer from tablets prepared by direct compression technique

Time(hrs)	G1	G2	G3	G4	G5	G6	G7
1	4.75	5.60	4.07	5.85	4.75	4.60	5.07
2	8.25	9.12	9.42	9.52	8.25	8.12	11.62
3	25.65	24.25	18.15	26.15	28.65	12.25	27.15
4	52.26	50.41	29.98	53.45	55.26	23.41	59.98
5	76.98	72.45	48.29	75.65	72.98	35.45	78.29
6	99.35	96.24	61.23	99.12	97.35	48.24	99.23
8	96.25	100.15	72.51	96.11	99.25	62.15	98.51
10	93.25	95.84	83.12	93.88	95.25	77.84	98.12
12	89.64	91.45	93.28	90.12	93.64	95.45	97.28

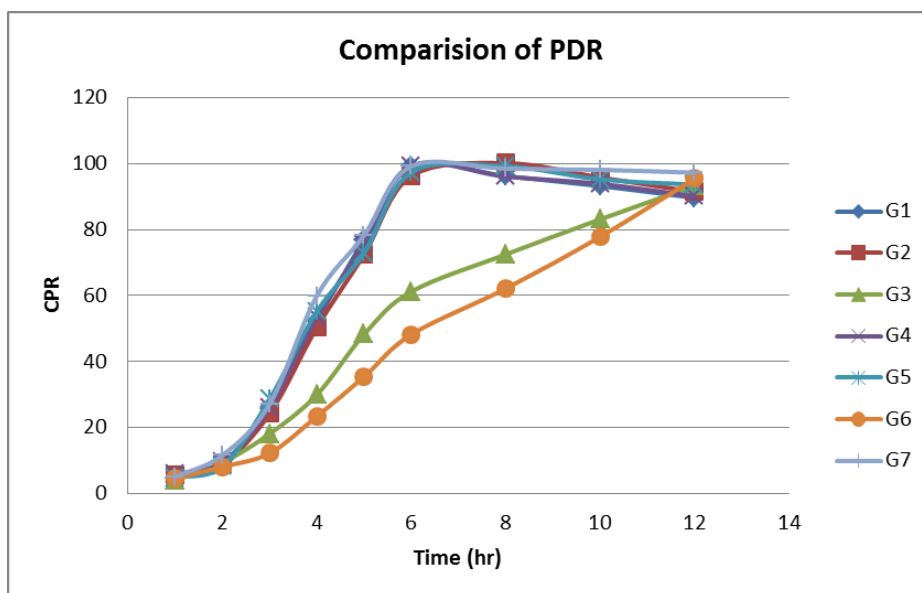


Fig. 1: Comparison of percent release of Glimepiride from SR tablets prepared by direct compression technique

Table 6 & fig. 2 showed percentage release of Glimepiride in 0.1 N HCl buffer from tablets prepared by melt granulation technique.

Table 6: Percentage release of Glimepiride in 0.1 N HCl buffer from tablets prepared by melt granulation technique

Time(hrs)	G8	G9	G10	G11	G12	G13	G14
1	1.75	2.60	2.07	3.85	3.75	3.60	3.07
2	5.25	6.12	6.42	8.52	7.25	6.12	7.62
3	11.65	14.25	16.15	14.15	15.65	12.25	16.15
4	22.26	23.41	26.98	25.45	27.26	18.41	28.98
5	30.98	32.45	36.29	33.65	37.98	23.45	38.29
6	38.35	40.24	46.23	40.12	47.35	35.24	47.23
8	44.25	48.15	52.51	47.11	53.25	48.15	53.51
10	50.25	56.84	60.12	53.88	61.25	62.84	61.12
12	58.64	64.45	68.28	60.12	69.64	78.50	70.28

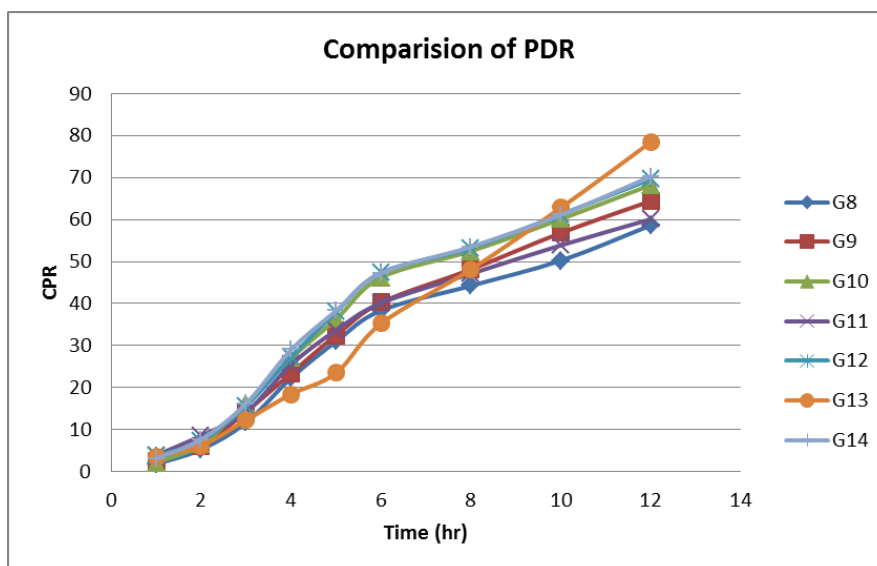


Fig. 2: Comparison of percent release of Glimepiride from SR tablets prepared by melt granulation technique

6. Study of Release Kinetics of optimized batch G6^[20,21]

Study of Release Kinetics of batch

The correlation coefficient values obtained for all five models, Zero order, first order, Korsmeyer Peppas, Hixson Crowell & Higuchi models were fitted on the optimized formulations. Statistical kinetics values of batch G6 is shown in table 7.

Table 7: *In vitro* drug release parameters for Batch G6

Time (hours)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
1	4.60	0.662758	0.072291	1.98	1	0
2	8.12	0.909556	0.129195	1.96	1.414214	0.30103
3	12.25	1.088136	0.197845	1.94	1.732051	0.477121
4	23.41	1.369401	0.394832	1.88	2	0.60206
5	35.45	1.549616	0.630163	1.81	2.236068	0.69897
6	48.24	1.683407	0.914829	1.71	2.44949	0.778151
8	62.15	1.793441	1.284043	1.58	2.828427	0.90309
10	77.84	1.891203	1.832773	1.35	3.162278	1
12	95.45	1.979776	2.984533	0.66	3.464102	1.079181

Table 6.14: Statistical kinetics values of batch G6

Kinetic models	R2	Slope
Zero-order	0.965	11.62
First-order	0.835	-0.097
Higuchi kinetics	0.956	39.02
Hixon-crowell	0.938	0.252
Korsmeyer-peppas	0.979	1.314

Stability Studies^[22]:

There was no significant change in physical and chemical properties of the tablets of formulation G6 after 3 months.

7. Conclusion

Seven batches of extended release tablets of Glimepiride were prepared using Sodium alginate, Poloxamer 188 and Sodium bicarbonate by direct compression method. (G1 – G7). Seven

batches of extended release tablets of Glimepiride were prepared using Bees wax, Cetyl alcohol, ethyl cellulose and Sodium bicarbonate by melt granulation method. (G8 – G14). The tablets were evaluated for parameters like thickness, hardness, friability, Swelling Ability, In vitro Buoyancy Studies, Adhesion Retention Period and In-vitro release study. Based on the results, formulation containing 15% (45mg) poloxamer 188 (D-6) was identified as good and better formulation among all formulations developed for floating tablets of Glimepiride prepared by direct compression method; and formulations prepared using 50mg Bees wax & Cetyl alcohol in combination (G-13) was identified as best formulation among all formulations developed for floating tablets of Glimepiride by melt granulation method. Optimized formulations G13 showed very good stability profile. From this observation it was concluded that the formulated extended release (gastro-retentive/floating) matrix tablet of Glimepiride (G13) prepared by melt granulation method were superior, economic and effective in achieving patient compliance.

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