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Development and Evaluation of Pelletized Delivery System for Effective Treatment of Type Ii Diabetes by Using Extrusion and Spheronization Technique

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Abstract: *Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia resulting from a defect in insulin secretion, insulin action, or both. Type 2 diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity. In these patients, sulphonyl ureas (glimepiride) and biguanide (metformin) are the most commonly prescribed oral treatment options. Because of their complementary mechanism of action, combination therapy with a sulphonyl urea and biguanide rational is this combination lead to benefits in terms of improved glycaemic control and improved tolerability at lower doses of the individual agents. In this study, Metformin hydrochloride sustained release multiparticulate drug delivery system in combination with Glimepiride and Pioglitazone Immediate release multiparticulate drug delivery system were formulated. It was found that Metformin pellets which provide superior release profile than marketed formulations over a period of 12 hours. In case of Glimepiride pellets provides more than 85% drug release which shows superior drug release profile than marketed formulations. Key Words Metformin Hydrochloride, Glimeperide, Diabetes mellitus, sustained release, pellets.*

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I. Introduction

The prevalence of diabetes mellitus has increased sharply over the past 25 years from 3.3/1000 persons in 1980 to 7.4/1000 persons in 2005. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset) results from the body's ineffective use of insulin. Type 2 diabetes comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity. Type 2 diabetes is associated with a loss of life of five to ten years [1]. Diabetes is currently the fourth leading cause of death by disease in the United States. Type 2 diabetes represents about 98% of all diabetes cases among persons older than 45 years of age [2]approximately 18% of persons 65 to 75 years of age and 40% of those older than 80 years of age [3]. In these patients, sulphonyl ureas (glimepiride) and the biguanide metformin are the two most commonly prescribed oral treatment options. However, these agents have different mechanisms of action; the sulphonyl ureas reduce hyperglycaemia by enhancing insulin secretion [4], whereas metformin acts to improve.

Insulin sensitivity and suppress hepatic glucose output [5]. As Type 2 diabetic patients tend to be obese and insulin-resistant, and at increased risk of atherosclerosis [6-8], metformin is now regarded as first-line treatment [9-12]. Because of their complementary mechanism of action, combination therapy with a sulphonyl urea, biguanide and pioglitazone would be rational and may lead to benefits in terms of improved glycaemic control and improved tolerability at lower doses of the individual agents [13]. However, evidence from prospective randomized studies supportive of this strategy is limited. Glimepiride is a sulphonyl urea which is effective and well-tolerated in Type 2 diabetic patients. Studies have shown that most patients are adequately controlled by 1- 2 mg daily [14- 17].

Gastrointestinal absorption of metformin is incomplete with an absolute bioavailability of 40-60% in combination with rapid elimination and 20-30% of an oral dose is recovered in faeces. Biological half-life of metformin is 1.5–1.6 h and the main site of its absorption is proximal small intestines. Studies found that administration of a fixed combination of glimepiride, metformin and pioglitazone was effective and safe as separate administration of glimepiride, metformin and pioglitazone in patients with type 2 diabetes mellitus. A combination tablet of glimepiride 1-2 mg pioglitazone 15 mg with metformin 500-1000 mg sustained release was recently developed.

Multiple-unit sustained-release dosage forms, such as pellets, are believed to have many therapeutic advantages in comparison with the single unit dosage forms. They can distribute in the gastrointestinal tract homogeneously thus maximizing drug absorption and reducing peak plasma fluctuations, minimizing the risk of

local GI tract irritation and dose dumping, decreased dosing frequency and increasing patient compliance, improving the safety and efficacy of the active ingredient. Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm for pharmaceutical applications. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously, since their multiparticulate nature offers some important pharmacological as well as technological advantages over conventional single-unit solid dosage forms. Pellets offer the possibility of combining several active components, incompatible drugs or drugs with different release profiles in the same dosage unit [18]. In this study, it was proposed to formulate metformin hydrochloride sustained release multiparticulate drug delivery system in combination with Glimepiride Immediate release multiparticulate drug delivery system.

Carbopol 971P NF is used as a release modifier in formulating metformin sustained release pellets. Lactose is used as a diluent and solubalizer in formulating Glimepiride immediate release pellets. Finally metformin and Glimepiride pellets filled in hard gelatin capsule of suitable size. This may be used for the treatment of type II diabetes more effectively than marketed single unit dosage thearapy.The final formulation studied and compared with marketed single unit tablet dosage based on drug release profiles.

II. Material and Methods

1] Materials

Metformin Hydrochloride IP gifted from Wanbury Laboratories, India Glimepiride IP gift sample received from Sun Pharma Ltd, India, Carbopol 971P obtained from Noveon, Inc. Germany,. Isopropyl alcohol IP obtained from Lee chang yung chemical. Lactose monohydrate IP obtained from DMV international Inc. Sodium Starch glycolate obtained from DMV Fonterra. Microcrystalline cellulose obtained from FMC Biopolymer.

2] Palletisation

The preliminary trials of palletisation by extrusion/Spherenoization using water and isopropyl alcohol in 25:75 ration as wet massing liquid were successful. With water alone, Carbopol 971P could not be extruded/spheronised because the materials turned tacky mass, owing to their solubility in water. In order to avoid the tackiness, water: IPA ration i.e. 25:75 was optimized and therefore did not cause tackiness. Secondly, IPA is widely accepted in pharmaceutical formulations Optimization of granulating system (Water and IPA) for preparation of Metformin hydrochloride pellets was done by selecting different ratios of Water: IPA, like 15:85, 20:80, 25:75 and 30:70, and granulated (Drug(5 parts): Carbopol 971P(1.5 parts) the wet mass was passed through extruder. It was found that with ration of water: IPA (15:85), the extrudates were brittle and could not be spheronized. At the ration of water: IPA (25:75 and 30:70ml), the mass became elastic and could not be passed through extruder. When the ration ofwater: IPA was 25 ml, the wet mass had ideal extrudable properties and good extrudates were formed for Metformin hydrochloride pellets. Optimization of granulating system for Glimepiride was done by adding different quantities of water, like 5, 8ml and 11 ml, to 25 g Drug and excipient mix and the wet mass was passed through extruder. It was found that with low quantity of water (5 ml), the extrudates were brittle and could not be spheronized. At very high quantities of water (11), the mass became elastic and could not be passed through extruder. When the quantity of water was 8 ml, the wet mass had ideal extrudable properties and good extrudates were formed for Glimepiride. For optimization of spheronization speed, spheronization was done at different speeds as shown in Table-8. In this study, it was found that at low speeds, more number of rod shaped and dumb-bell shaped particles were obtained. According to a predicted mechanism of pellet formation, during spheronization, the ends of rods are forced to gather forming a dumb-bell shape and the ends of this dumb-bell shaped particles are compressed inward till the ends merges to form and ellipsoid, which will be rounded further to form a pellets. Dhanorkar et al. / IJDFR volume 3 Issue 1, Jan- Feb. 2012 56 Dhanorkar et al. / IJDFR volume 3 Issue 1, Jan- Feb. 2012 At lower speeds, it was observed that the dumb-bell shaped particles did not get compressed and merge to form ellipsoid, and hence the spheronized mass consisted of a major portion of rods and dumb-bell shaped particles. Only 1200 speed was considered as ideal. During optimization of residence time for Metformin Hydrochloride sustained release pellets , it was found that at lower residence times (less than 30 min) major portion of the granulating mass was not converted into pellets and at longer residence times (above 45 min), due to evaporation of water, the particles became dried and again size reduction was observed. Only at 1200 rpm and 35 min time, pellets with narrow size range were obtained for Metformin hydrochloride sustained release pellets. Hence, these variables were selected to be ideal for the proper formation of pellets. During optimization of residence time for Glimepiride pellets , it was found that at lower residence times (less than 30 min) major portion of the granulating mass was not converted into pellets and at longer residence times (above 45 min), due to evaporation of water, the particles became dried and again size reduction was observed. Only at 900 rpm and 35 min time, pellets with narrow size range were obtained for Glimepiride pellets. Hence, these variables were selected to be ideal for the proper formation of pellets.

3] Preparation of Metformin HCl sustained release pellets.
Process of formulating metformin pellets with the formula components of extended release pellets.
A] Sieving metformin hydrochloride Carbopol 971P through # 40 ASTM and mix in rapid mixer granulator (RMG) for 10 min at slow speed using impellers and keeping chopper off.

B] Adding liquid phase (purified water: Isopropyl alcohol) to the dry mix in the ratio of 25:75.

C] Carry out the granulation for total 5 min including binder addition time 2.0 min at slow speed with main impeller on and chopper off, and kneeding time 3 min at Impeller high speed and chopper slow speed intermittent.

D] The dough mass is passed through the extruder to form extrudates. Extrusion mixtures are formulated to produce a cohesive plastic mass with inherent fluidity permitting flow through during extrusion, self-lubricating properties as it passes through the die and rigidity so that shape imposed by the die is retained.

E] The extrudates formed are rolled in to pellets in the spheronizer. The diameter of extruder screen opening directly controls the diameter of pellets

F] Spheronization involves:
1] Breaking of extrudates in to rods by the interaction of the rotating plates and stationary walls.
2] Agglomeration of small fragments formed during breaking stage.
3] Smoothening of the particles to pellets by rotational motion of granules about its axis in constantly changing planes.

G] Prepared pellets were dried at 50-60 °C for 1 hour.

H] Dried pellets were passed through suitable mesh to obtained uniform pellets and fines should be removed.

4] Preparation of Glimepiride pellets.
A] Sieving: sieve lactose monohydrate (Pharmatose 200 M), sodium starch glycolate, and microcrystalline cellulose, through # 40 ASTM and mix in rapid mixer granulator (RMG) for 10 min at slow speed using impellers and keeping chopper off.

B] Dissolve weighed quantity of tween 80 in warm purified water under starring using over head stirrer, once solution is clear add weighed quantity of glimepiride under continuous starring to form uniform dispersion and use this dispersion for granulation.

C] Carry out the granulation for total 5 min including binder addition time 2.0 min at slow speed with main impeller on and chopper off, and kneeding time 3 min at Impeller high speed and chopper slow speed intermittent using step B] granulating system. [Till desired mass achieved]

D] The dough mass is passed through the extruder to form extrudates. Extrusion mixtures are formulated to produce a cohesive plastic mass with inherent fluidity permitting flow through during extrusion, self-lubricating properties as it passes through the die and rigidity so that shape imposed by the die is retained.

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G] Prepared pellets were dried at 50-60 °C for 1 hour.

H] Dried pellets were passed through suitable mesh to obtained uniform pellets and fines should be removed.

5] Capsule filling

Weigh accurate quantity of metformin pellets equivalent to 500 mg of metformin hydrochloride and weigh accurate quantity of Glimepiride pellets equivalent to 1 mg of Glimepiride and mixed for 10 min at slow speed using bin blender. Finally mixed pellets were filled manually in hard gelatin capsules equivalent to metformin hydrochloride 500 mg, and glimepiride 1 mg.

D] Characterization and Evaluation of formulated pellets:

1] Yield of pellets:

For the determination of yield of the pellets, the obtained pellets were passed through suitable seive to separate only the spherical pellets and the weight of the spherical particles was noted. The percentage yield of spherical pellets was calculated with respect to total weight of the pellets taken for sieving

2] Size distribution analysis by sieve analysis:

The size distribution of pellets should be as narrow as possible due to following reasons.

A) The size distribution affects the release rate of drug. A narrow size distribution will ensure a uniform performance of pellets within the batch.

B) Uniform size distribution decreases chances of segregation which is common occurrence in capsule filling that leads to variations in content uniformity. Size distributions of pellets are determined by different methods. The most common and widely used method is sieve analysis. British standard Seive 10,16,22,44 and 60 were taken and arranged in the order coarser sieve (No 10) is on top and fine sieve (No 60) was at the bottom. Accurately weigh 100 gm of pellets were placed on the stack of sieves and sieves were shaken for 10 min using mechanical sieve shaker and pellets retained on each sieve were collected separately and weighed and mean paricle size of pellets calculated.

3] Morphological characteristics:

One of the important objects of palletisation is to produce spherical and smooth particles. Different methods have been proposed for measuring the shape and surface roughness of the pellets. The commonly used method is the analysis of microscopic or non microscopic pictures of pellets. Electron microscopy (SEM) is the technique of choice for measuring the shape and surface smoothness of the pellets to support the other qualitative and quantitative results.

4] Porosity:

The porosity of pellets influences the rate of release of drug from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured qualitatively by scanning electron microscopy(SEM) and quantitatively by mercury porosimetry. The porosity of pellets also can be determined quantitatively

using optical microscopy and scanning electron microscopy together with image analysis. For determination of shape and surface roughness of the sheroids, and also for qualitative determination of porosity of pellets, SEM was used.

5] Bulk density:

The density of pellets can be affected by changes in the formulation and/or process, which may affect other processes or facter, such as capsule filling, coating and mixing. Variation of densities from batch to batch affect the potency of finished capsule causes problem in batch size determination during coating and produces segregation during mixing.The bulk density of the pellets can be measured by an automated tapper. (Density apparatus).It is indicative of the packing properties of pellets and, therefore, is greatly influenced by the diameter and the size distribution of the pellets. Both untapped and tapped densities were calculated for all the batches of pellets using the formula given below. Bulk density = Weight of sample (g) / Final Volume (cc).

6] Flow Property:

The flow behavior of all the batches of pellets was determined by measurement of angle of repose.

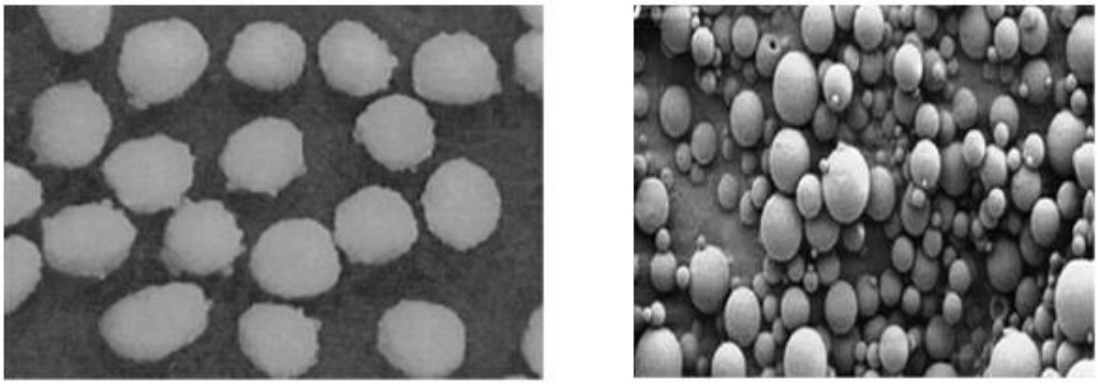
7] In vitro Dissolution Profile:

Dissolutions studies were carried out in USP (XXIII) dissolution apparatus following basket method. Freshly prepared media 0.1 N HCL /900 ml/100 RPM was placed in the dissolution bowl and allowed to maintain a temperature of 37 ± 0.5 °C. The capsules were placed in the basket (USP-I apparatus) and rotated at 100 RPM for 12 hours.5 ml sample were withdrawn, the medium was replaced by equal amount of fresh 0.1 N HCL. The samples were analyzed at 233 nm by using dissolution medium as a blank on suitable UV-Visible Spectrophotometer.

8] Stability Studies

Stability studies were carried out on final optimized batches of pellets according to ICH guide lines.
At 25°C ± 5°C and 60% Relative humidity for 6 months.
At 30°C ± 5°C and 65% Relative humidity for 6 months.
At 40°C ± 5°C/75 % Relative humidity for 3 months.
Samples were withdrawn at 0, 30, 60, 90, and 180 days and were evaluated for the physical observation, drug content and dissolutions.

The logarithms of percent drug remaining were calculated and plotted against time in days. The slopes of the straight line were determined and the degradation rate constant was calculated with equation slope = K/2.303, where K is a degradation rate constant.



A] SEM-Metformin Pellets.B] SEM-Glimepiride Pellets.
Fig-1: SEM's of Metformin hydrochloride and Glimepiride.

SEM's of spheroids were used at 55 X magnification.

Determination of surface roughness, shape and qualitative determination of porosity-Metformin Pellets

Batch Code	Yield (%)	Average particle size ¥ (mm)	Untapped bulk density(g/cc)	Tapped bulk density(g/cc)	Angle of repose £ (degrees)
A1	91.25	0.256	0.693	0.78	41.50
A2	93.50	0.223	0.682	0.79	42.50
A3	90.60	0.302	0.702	0.80	39.80
A4	93.80	0.232	0.710	0.80	40.50
A5	96.20	0.255	0.680	0.77	44.50

Table No 1: Physical characterization of Metformin Values in parentheses are SCM; n=3

¥ The average particle size was determined using sieve analysis
£ The angle of repose was determined using funnel method.

Determination of surface roughness, shape and qualitative determination of porosity-Glimepiride pellets.

Batch Code	Yield (%)	Average particle size ¥ (mm)	Untapped bulk density(g/cc)	Tapped bulk density(g/cc)	Angle of repose £ (degrees)
B1	89.90	0.280	0.710	0.820	42.50
B2	91.20	0.302	0.680	0.792	43.50
B3	94.20	0.290	0.660	0.775	42.00
B4	93.60	0.258	0.720	0.812	45.00
B5	92.50	0.290	0.710	0.833	42.00

Table No 2: Physical characterization of Glimepiride values in parentheses are SCM; n=3
¥ The average particle size was determined using sieve analysis
£ The angle of repose was determined using funnel method.

D] In-vitro Dissolution and Composition

During development of Metformin pellets it was found that when the total concentration of Metformin and Carbopol 971P increase above 1: 0.75, the granulating mass became elastic and extrudes were

not formed similarly when granulating solvent ratio Isopropyl alcohol and water 75: 25 is optimized and suitable for granulation.

Different trials executed to achieve desired *in-vitro* dissolution profile and suitable product characteristics.

Different compositions enlisted below in Table No 4 and Comparative dissolution enlisted in below Table No 5

along with graphical representation.

During development of Glimepiride pellets it was found that lactose monohydrate (Pharmatose 200M) and microcrystalline cellulose are having duel role as lactose is highly soluble acts as a solubilizer and also its suitable material for spheronization, where as microcrystalline cellulose help in bursting pellets when comes in contact with media, so improves disintegration and ultimately dissolution and microcrystalline cellulose is spheronization enhancer.

Different trials executed to achieve desired in-vitro dissolution profile and suitable product characteristics. Different compositions enlisted below Table No 6 and Comparative dissolution enlisted in below Table No 7 along with graphical representation. In vitro drug release was determined for Metformin and Glimepiride pellets filled in capsules using a USP Type I dissolution testing apparatus. In this the 0.1N HCl, 900ml dissolution medium was kept at 37± 0.5°C and the speed was 100rpm.

Ingredients	**A1**	**A2**	**A3**	**A4**	**A5**
Metformin Hydrochloride	500	500	500	500	500
Carbopol 971P	62.5	125	250	375	250
Sodium citrate	0.75	0.75	0.75	0.75	0.75
Citric Acid	0.75	0.75	0.75	0.75	0.75
Microcrystalline Cellulose powder grade	436.0	373.5	248.5	123.5	248.5
Isopropyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight (mg)	1000.0	1000.0	1000.0	1000.0	1000.0

Table No 3: Composition of different trials for Metformin hydrochloride pellets

Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.

Time[Hrs]	**Glucophage**	**A1**	**A2**	**A3**	**A4**	**A5**
0	0	0	0	0	0	0
1	18	33	28	19	11	20
2	39	52	48	41	26	38
4	61	76	72	63	45	65
6	79	92	85	80	64	78
8	88	99	93	86	78	87
12	100	100	99	98	91	99

Table No 4: Comparative dissolution profile for Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.

Comparative % drug release from different pellet formulation in comparison with Innovator formulation (Glucophage ER Tablet 500 mg)

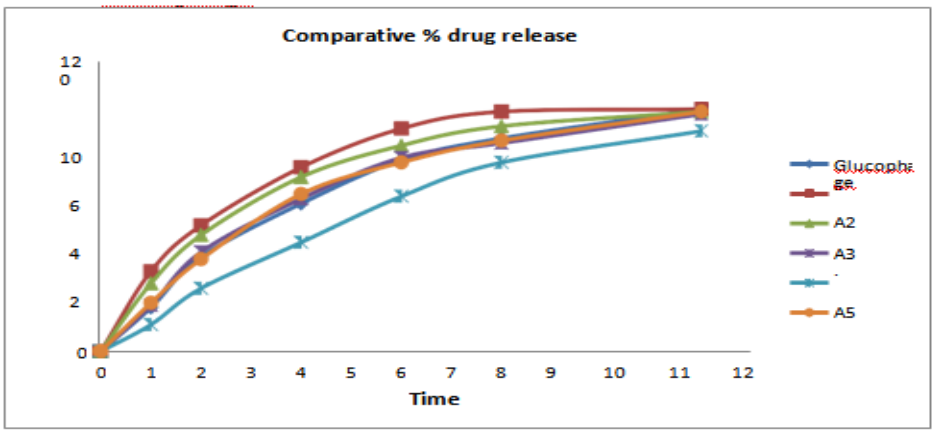


Fig-2: Graphical representation of % Drug release Test product VS Reference product-Metformin Hydrochloride

Graphs

E. Zero order Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.

Time[Hrs]	Cumulative % Drug Release					
	Glucophage	A1	A2	A3	A4	A5
0	0	0	0	0	0	0
1	18	33	28	19	11	20
2	39	52	48	41	26	38
4	61	76	72	63	45	65
6	79	92	85	80	64	78
8	88	99	93	86	78	87
12	100	100	99	98	91	99

Table :5 Comparative dissolution profile for Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.

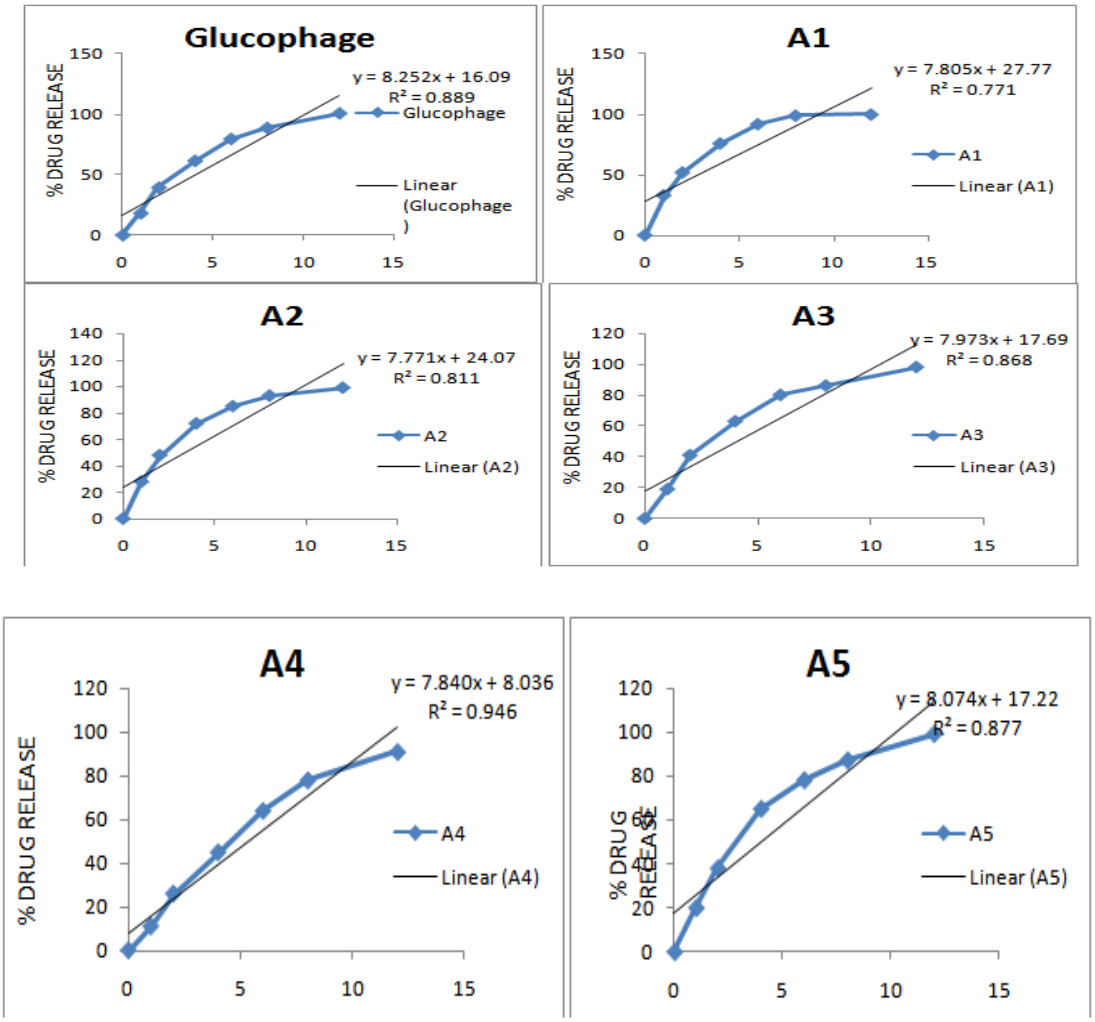


Fig-3: Zero order Plot of Metformin hydrochloride pellets [Test product] and marketedreference product Glucophage.

F. First order Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.

Time[Hrs]	LOG % Drug Remaining					
	Glucophage	**A1**	**A2**	**A3**	**A4**	**A5**
0	2	2	2	2	2	2
1	1.9138	1.8261	1.8573	1.9085	1.9494	1.9031
2	1.7853	1.6812	1.7160	1.7709	1.8692	1.7924
4	1.5911	1.3802	1.4472	1.5682	1.7404	1.5441
6	1.3222	0.9031	1.1761	1.3010	1.5563	1.3424
8	1.0792	0.0000	0.8451	1.1461	1.3424	1.1139
12	NA	NA	0.0000	0.3010	0.9542	0.0000

Table: 6 First order Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

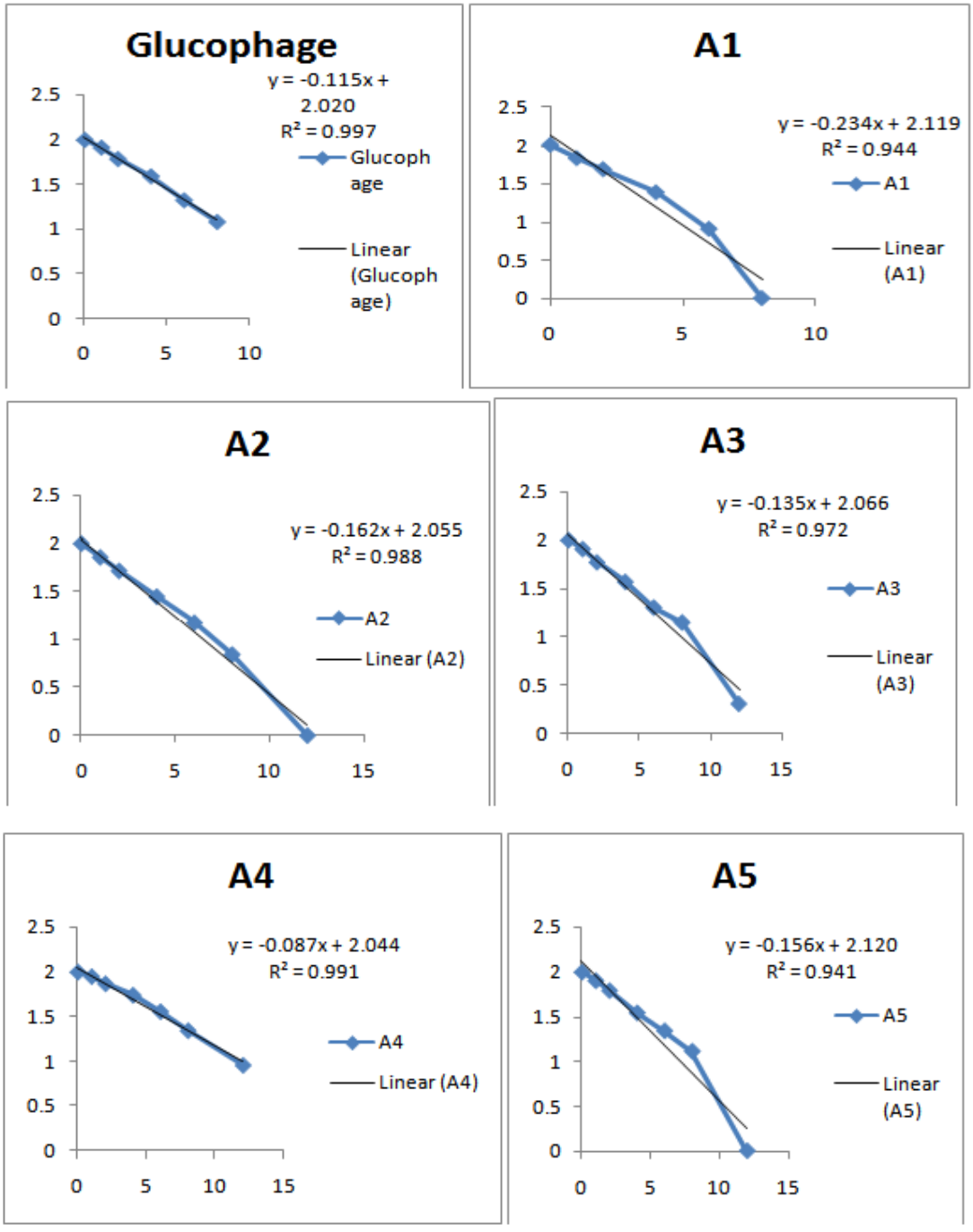


Fig-4: First order Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

G. Higuchi Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.

Square root of Time	Cumulative % Drug Release					
	Glucophage	A1	A2	A3	A4	A5
0.000	0	0	0	0	0	0
1.000	18	33	28	19	11	20
1.414	39	52	48	41	26	38
2.000	61	76	72	63	45	65
2.449	79	92	85	80	64	78
2.828	88	99	93	86	78	87
3.464	100	100	99	98	91	99

Table: 7 Higuchi Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

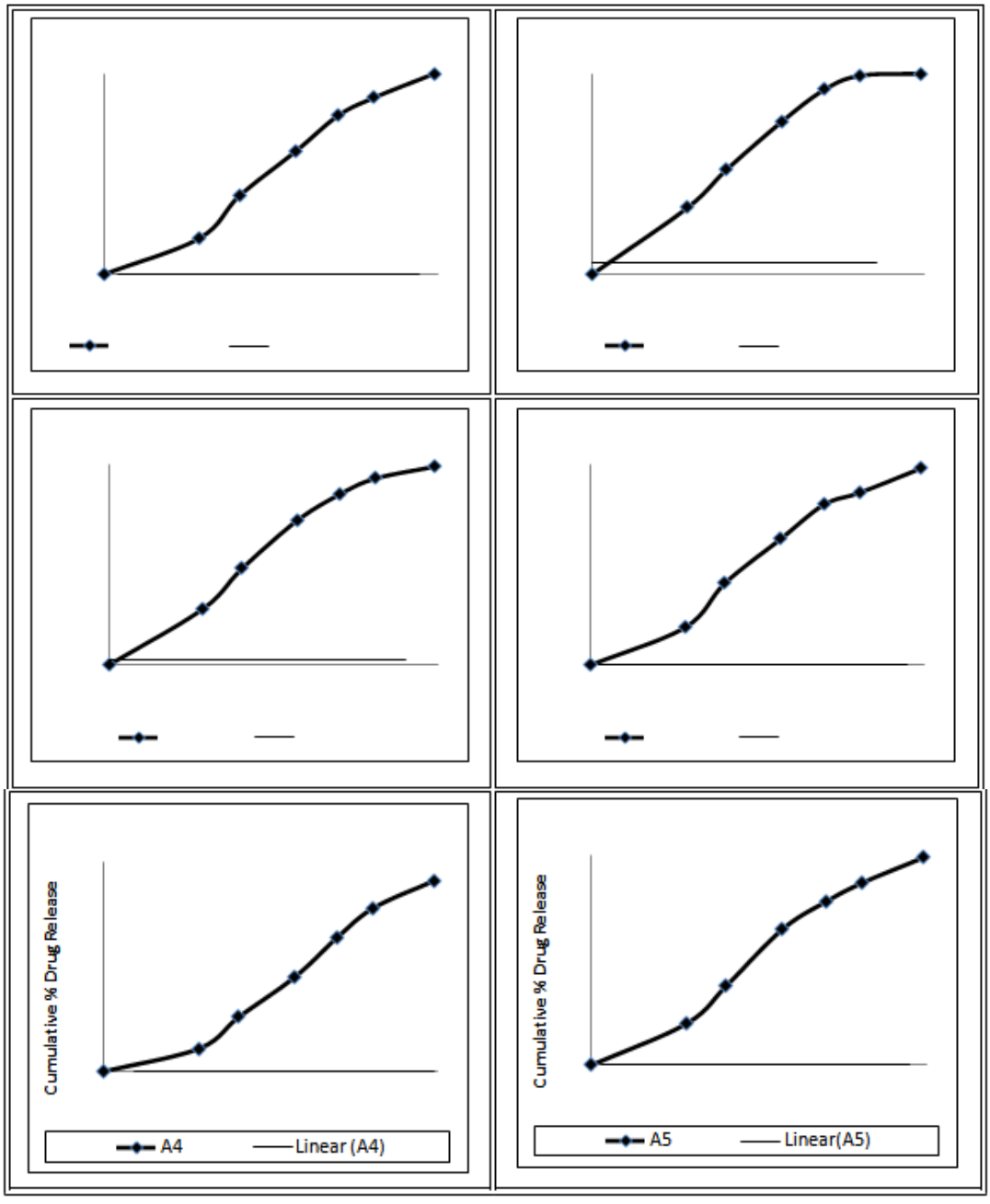


Fig-5: Higuchi Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.

H. Koresmayer Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.

Log Time(Hr.)	Cumulative % Drug Release					
	Glucophage	A1	A2	A3	A4	A5
0.000	18	33	28	19	11	20
0.301	39	52	48	41	26	38
0.602	61	76	72	63	45	65
0.778	79	92	85	80	64	78
0.903	88	99	93	86	78	87
1.079	100	100	99	98	91	99

Table: 8 Koresmayer Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage\

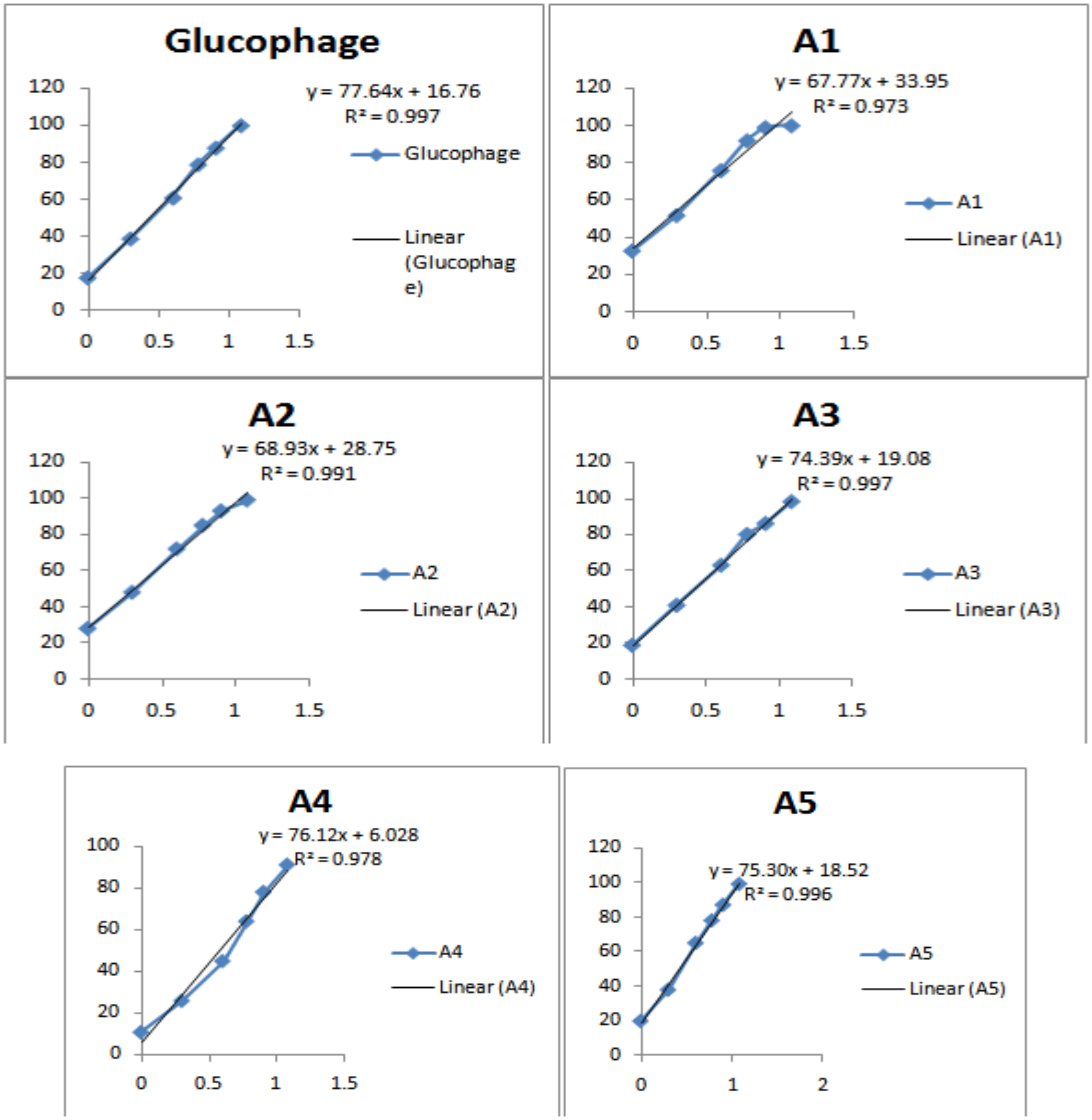


FIG 6- Koresmayer Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage

III. Drug release kinetic

Regression coefficients (R^2) of zero-order, first- order, Higuchi and Koresmayer model of Metformin hydrochloride extended release formulations were plotted in the following table.

Dissolution profiles of test batches were compared with reference dissolution profile of Glucophase by calculating Similarity factor F2 value to find optimized formulation of metformin hydrochloride.

Formulation	Drug release kinetics (R^2) and F2 Value of Metformin hydrochloride				
	Zero-order	**First-order**	**Higuchi**	**Koresmayer**	**F2 Value**
Glucophage	0.8896	0.9970	0.9784	0.9971	NA
A1	0.771	0.9444	0.9507	0.9732	45.5
A2	0.8116	0.9881	0.9675	0.9912	55.4
A3	0.8680	0.9729	0.9753	0.9973	87.5
A4	0.9464	0.9917	0.9661	0.9788	45.8
A5	0.8778	0.9414	0.9782	0.9966	84.5

Table- 9: Drug release kinetic and model for Metformin hydrochloride formulations

IV. Conclusion

From the above regression coefficients it was concluded that Metformin hydrochloride follows first order release kinetic which satisfies Koresmayer drug release model. And from F2 values, formulation A3 shows comparable dissolution profile with the reference Glucophase extended release capsule.

Composition of different trials for Glimepiride pellets :

Ingredients	B1	B2	B3	B4	B5
Glimepiride	1	1	1	1	1
Lactose Monohydrate (Pharmatose 200 M)	63.5	93.5	92.5	96.5	96.5
Microcrystalline cellulose	15	15	15	35	35
Sodium starch glycolate (Primogel)	5	5	5	2	2
Tween 80	0.5	0.5	1.5	0.5	0.5
Purified water	0	0	0	0	0
Total Weight [mg]	85	85	85	135	135

Table No 10: Composition of different trials for Glimepiride pellets filled in capsules

Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.

Time[mins]	**Amaryl**	BG-1	BG-2	BG-3	BG-4	BG-5
0	0	0	0	0	0	0
5	89	35	22	35	91	88
10	95	72	49	88	96	93
15	96	88	79	95	99	98
30	98	90	88	99	100	99
45	99	99	96	99	100	101
60	100	99	98	100	100	101

Table No 11: Comparative dissolution profile for Glimepiride alone from Test product and Amaryl as marketed reference product.

Graphical representation of comparative % drug release from various design trails of glimepiride pellet formulation in comparison with Innovator formulation (Amaryl IR Tablet 1 mg)

N. Drug releasekinetic:

Regression coefficients (R^2) of zero-order and first- order of Glimepiride immediate release formulations were plotted in the following table.

Dissolution profiles of test batches were compared with reference dissolution profile of Amaryl by calculating Similarity factor F2 value to find optimized formulation of Glimepiride..

Formulation	Drug release kinetics (R^2) and F2 Value of Glimepiride		
	Zero-order	**First-order**	**F2 Value**
Amaryl	0.2892	0.6464	NA
BG-1	0.6050	0.9277	No, ≥ 85% in 15 min
BG-2	0.7319	0.9766	No, ≥ 85% in 15 min
BG-3	0.4906	0.7704	No, ≥ 85% in 15 min
BG-4	0.2720	0.5154	No, ≥ 85% in 15 min
BG-5	0.3096	0.6464	No, ≥ 85% in 15 min

Table- 14: Drug release kinetic and model for Glimepiride formulations

From the above regression coefficients it was concluded that Glimepiride follows first order release kinetic. F2 values were not calculated as cumulative % drug release is ≥ 85% in 15 min, but formulation BG-4 shows comparable dissolution profile with the reference Amaryl.

V. Conclusion

From the above Similarity factor (F2) and regression parameters of Metformin hydrochloride, and Glimepiride formulations were optimized and it was concluded that Metformin hydrochloride sustained release multiparticulate drug delivery system in combination with Glimepiride Immediate release multiparticulate drug delivery system were formulated. It was found that Metformin pellets which provide superior release profile than marketed formulations over a period of 12 hours. In case of Glimepiride pellets provides more than 85% drug release which shows superior drug release profile than marketedformulations.

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