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# EFFECTIVE TREATMENT OF TYPE II DIABETES BY USING PELLETS MANUFACTURED BY 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, sulphonylureas(glimepiride), biguanide(metformin) and pioglitazones are the most commonly prescribed oral treatment options. Because of their complementary mechanism of action, combination therapy with a sulphonyl urea, biguanide and glitazonerational 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 and Pioglitazone pellets provides more than 85% drug release which shows superior drug release profile than marketed formulations.

**KEYWORDS**: Metformin Hydrochloride, Glimepiride, Diabetes mellitus, sustained release, pellets.

## 1. INTRODUCTION
The prevalence of diabetes mellitus has increased sharply over the past 25 years from 3.3/1000 persons in 1980to 7.4/1000 persons in 2005. Type 2 diabetes resultsfrom the body's ineffective use of insulin. Type 2 diabetes is associated witha loss of life of five to ten years.[1] Type 2 diabetes represents about 98% of all diabetes cases among persons older than 45 years ofage[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, sulphonylureas (Glimepiride) and the biguanide Metformin are the two most commonlyprescribed oral treatment options. The sulphonylureas 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 andinsulin-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 sulphonylurea, 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] Glimepiride 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% incombination with rapid elimination and 20-30% of an oral dose is recovered in faeces. Studies found thatadministration of a fixed combination of Glimepiride, Metformin and Pioglitazone was effective and safe than the individualadministration. Pellets can distribute in the gastrointestinal tract homogeneouslythus maximizing drug absorption and reducing peak plasma fluctuations, minimizing the risk of local GI tractirritation and dose dumping, decreased dosing frequency and increasing patient compliance, improving thesafety and efficacy of the active ingredient. 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 and Poiglitazone Immediate release multiparticulate drug delivery system.

Carbopol 971P NF is used as a release modifier in formulating Metformin sustained release pellets. Lactose isused as a diluent and solubalizer in formulating Glimepiride. Pioglitazone immediate release pellets. Finally Metformin and Glimepiride, Poiglitazone pellets filled in hard gelatin capsule of suitable size.

## 2. MATERIALS AND METHODS

### 2.1Materials required

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 changyung chemical. Lactose monohydrate IP obtained from DMV international Inc. Sodium Starch glycolate obtained from DMV fonterra. Microcrystalline cellulose obtained from FMC Biopolymer.

### 2.2 Methodology

#### 2.2.1 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, Carbopol971P 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 of water: 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 wereselected to be ideal for the proper formation of pellets.

#### 2.2.2 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 speedusing 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 kneading 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 plasticmass with inherent fluidity permitting flow through during extrusion, self-lubricating properties as it passes through the die and rigidityso 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.

**2.2.3 Preparation of Glimepiride and pioglitazone pellets**

A]Sieving: sieve Pioglitazone, 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 kneading 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 rigidityso 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 changingplanes.

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.

**2.2.4Capsule filling**

Weigh accurate quantity of metformin pellets equivalent to 500 mg of metformin hydrochloride and weighaccurate quantity of Glimepiride and Pioglitazone pellets equivalent to 1 mg of Glimepiride and 15 mg of pioglitazone 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, pioglitazone 15 mg and glimepiride 1 mg.

**Characterization and Evaluation of formulated pellets**

**2.2.5 Yield of pellets**

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

**2.2.6 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 uniformperformance of pellets within the batch.

B) Uniform size distribution decreases chances of segregation which is common occurrence in capsule fillingthat 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 Sieve 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 particle size of pellets calculated.

**2.2.7 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 thepellets to support the other qualitative and quantitative results.

**2.2.8 Porosity**

The porosity of pellets influences the rate of release of drug from the pellets by affecting the capillary action ofthe 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 spheroids and also for qualitative determination of porosity of pellets, SEM was used.

**2.2.9 Bulk density**

The density of pellets can be affected by changes in the formulation and/or process, which may affect other processes or factor, such as capsule filling, coating and mixing. Variation of densities from batch to batch affectthe 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. (Densityapparatus).It is indicative of the packing properties of pellets and, therefore, is greatly influenced by thediameter 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).

**2.2.10 Flow Property**

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

**2.2.11 *In vitro* Dissolution Profile**

Dissolutions studies were carried out in USP (XXIII) dissolution apparatus following basket method. Freshlyprepared media 0.1 N HCL /900 ml/100 RPM was placed in the dissolution bowl and allowed to maintain atemperature of 37 ± 0.5 °C. The capsules were placed in the basket (USP-I apparatus) and rotated at 100 RPMfor 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-VisibleSpectrophotometer.

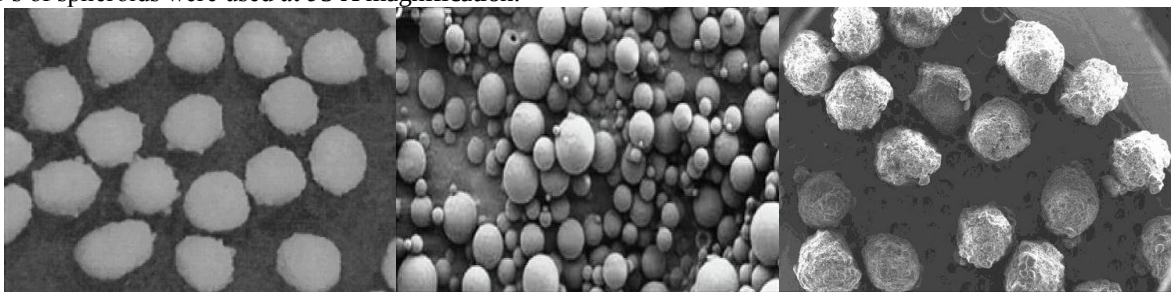
**2.2.12 Stability Studies**

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, drugcontent and dissolutions.

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

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



**A] SEM-Metformin Pellets. B] SEM-Glimepiride Pellets. C] SEM-Pioglitazone Pellets.**

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

**Fig-1: SEM's of Metformin hydrochloride, Glimepiride and Pioglitazone pellets.**

**Table No1: Physical characterization of Metformin.**

| Batch Code | Yield (%) | Average Particle size ¥ (mm | | | Mean n=3 | Untapped bulkdensity(g/cc) | | | Mean n=3 | Tapped bulkdensity(g/cc) | | | Mean n=3 | Angle of repose £ (degrees) | | | Mean n=3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A1 | 91.25 | 0.256 | 0.257 | 0.255 | 0.256 | 0.693 | 0.694 | 0.693 | 0.693 | 0.78 | 0.79 | 0.77 | 0.78 | 41.5 | 41.6 | 41.8 | 41.6 |
| A2 | 93.5 | 0.223 | 0.224 | 0.226 | 0.224 | 0.682 | 0.681 | 0.68 | 0.681 | 0.79 | 0.79 | 0.78 | 0.78 | 42.5 | 42.6 | 42.4 | 41.6 |
| A3 | 90.6 | 0.302 | 0.301 | 0.302 | 0.301 | 0.702 | 0.701 | 0.703 | 0.702 | 0.8 | 0.81 | 0.82 | 0.81 | 39.8 | 39.9 | 39.7 | 41.6 |
| A4 | 93.8 | 0.232 | 0.231 | 0.233 | 0.232 | 0.71 | 0.7 | 0.72 | 0.71 | 0.8 | 0.81 | 0.82 | 0.81 | 40.5 | 41 | 39.5 | 41.6 |
| A5 | 96.2 | 0.255 | 0.257 | 0.253 | 0.255 | 0.68 | 0.69 | 0.67 | 0.68 | 0.77 | 0.78 | 0.79 | 0.78 | 44.5 | 43.5 | 45.5 | 41.6 |

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.

**Table No2: Physical characterization of Glimepiride and Determination of surface roughness, shape and qualitative determination of porosity-Glimepiride and pioglitazone combination pellets.**

| Batch Code | Yield (%) | Average Particle size ¥ (mm | | | Mean n=3 | Untapped bulkdensity(g/cc) | | | Mean n=3 | Tapped bulkdensity(g/cc) | | | Mean n=3 | Angle of repose £ (degrees) | | | Mean n=3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B1 | 89.9 | 0.290 | 0.271 | 0.278 | 0.280 | 0.701 | 0.71 | 0.7 | 0.70 | 0.80 | 0.82 | 0.83 | 0.82 | 42.6 | 42.7 | 42.6 | 42.6 |
| B2 | 91.2 | 0.301 | 0.303 | 0.302 | 0.302 | 0.69 | 0.67 | 0.68 | 0.68 | 0.79 | 0.82 | 0.81 | 0.80 | 44 | 42.7 | 41.7 | 42.8 |
| B3 | 94.2 | 0.287 | 0.291 | 0.290 | 0.289 | 0.67 | 0.65 | 0.68 | 0.66 | 0.78 | 0.79 | 0.80 | 0.79 | 42.6 | 43.5 | 41 | 42.3 |
| B4 | 93.6 | 0.259 | 0.257 | 0.259 | 0.258 | 0.71 | 0.69 | 0.73 | 0.71 | 0.80 | 0.82 | 0.83 | 0.82 | 45.6 | 44.6 | 45.2 | 45.1 |
| B5 | 92.5 | 0.310 | 0.280 | 0.287 | 0.292 | 0.72 | 0.72 | 0.69 | 0.71 | 0.81 | 0.83 | 0.85 | 0.83 | 43.2 | 40.5 | 41.3 | 41.6 |

Pioglitazone 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.

**2.2.13 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 *invitro* dissolution profile and suitable product characteristics.

Different compositions enlisted below in Table No 4 and Comparative dissolution enlisted in below Table No 5along with graphical representation.

During development of Glimepiride and Pioglitazone combination 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, whereas microcrystalline cellulose help in bursting pelletswhen comes in contact with media, so improves disintegration and ultimately dissolution and microcrystallinecellulose is spheronization enhancer.

Different trials executed to achieve desired invitro dissolution profile and suitable product characteristics. Different compositions enlisted below Table No 6 and Comparative dissolution enlisted in below Table No 7along with graphical representation.

In vitro drug release was determined for Metformin, Glimepiride and pioglitazone pellets filled in capsules using a USP Type I dissolution testingapparatus. In this the 0.1N HCl, 900ml dissolution medium was kept at 37± 0.5°C and the speed was 100rpm.

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

| 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 4: Comparative dissolution profile for Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.**

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 |

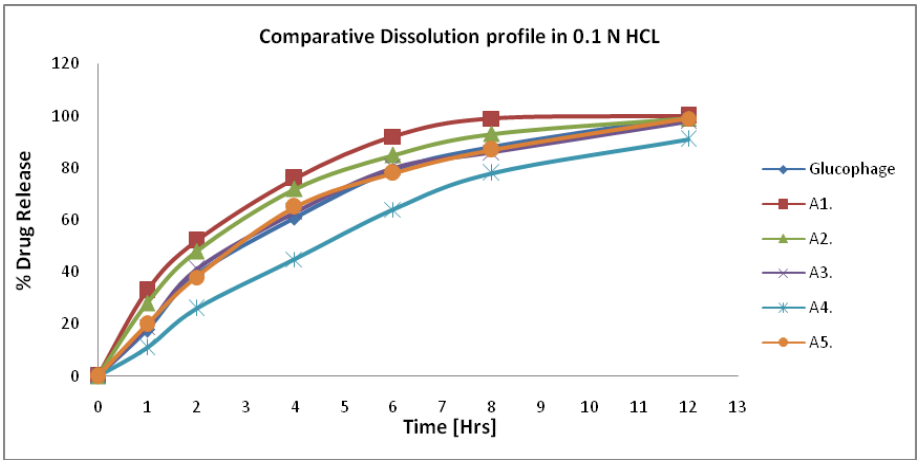



**Fig. 2: Graphical representation of comparative % drug release from different pellet formulation in comparison with Innovator formulation (Glucophage ER Tablet 500 mg).**

**Table 5: 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 |

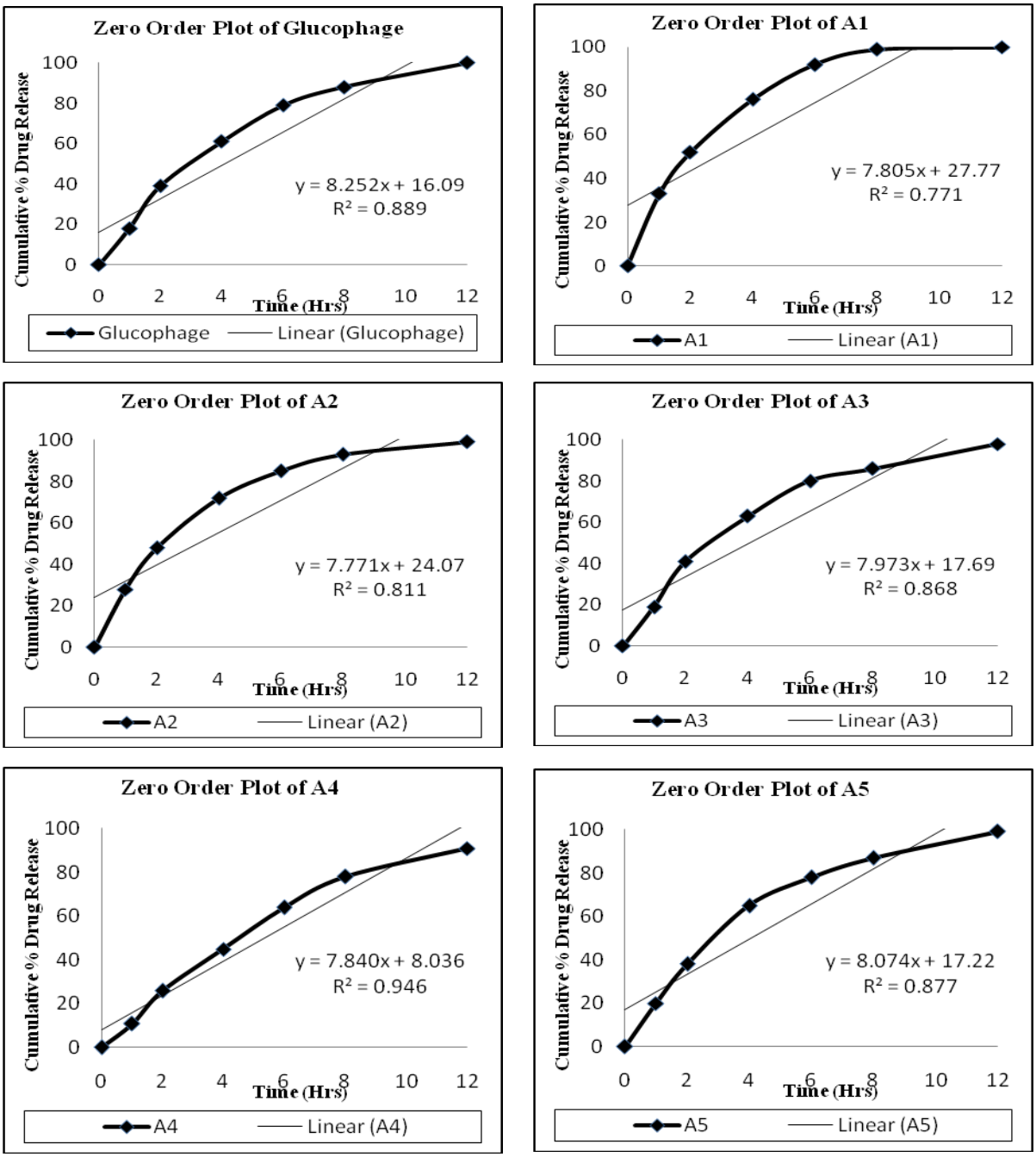



**Fig.3- Zero order Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.**

**Table.-6 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 |

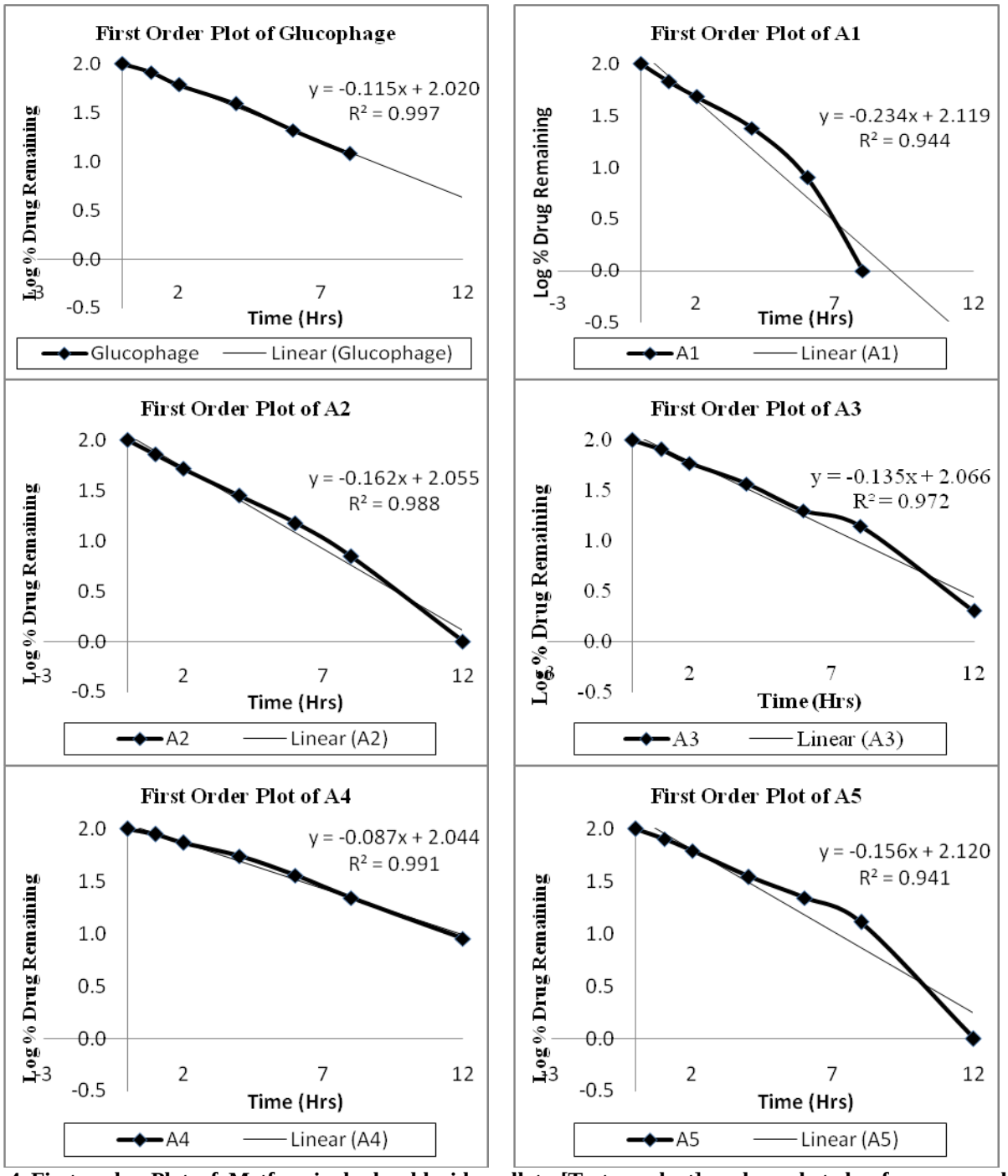



**Fig.-4 First order Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.**

**Table.-7 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 |

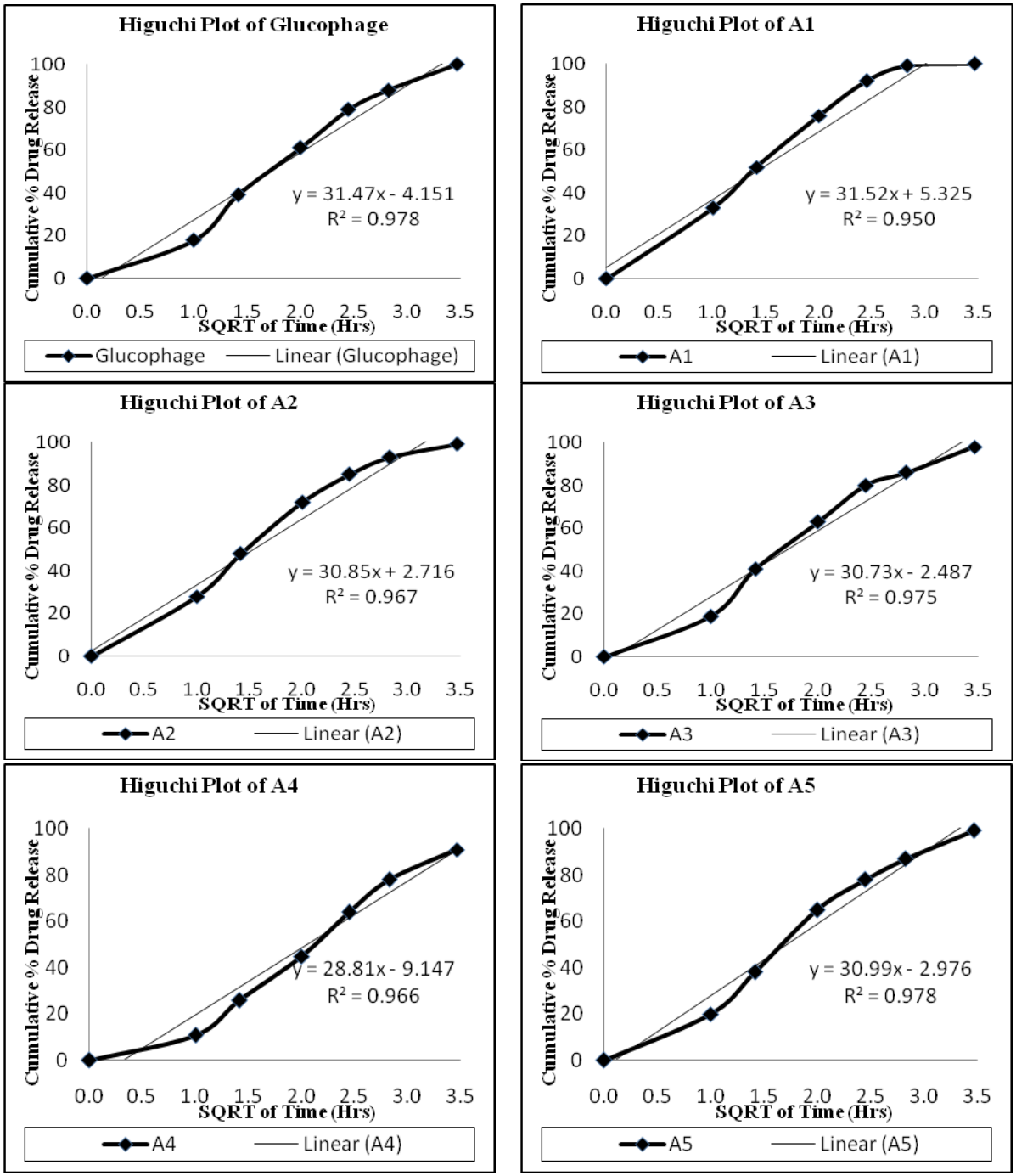



**Fig 5: Higuchi Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.**

**Table.-8 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 |

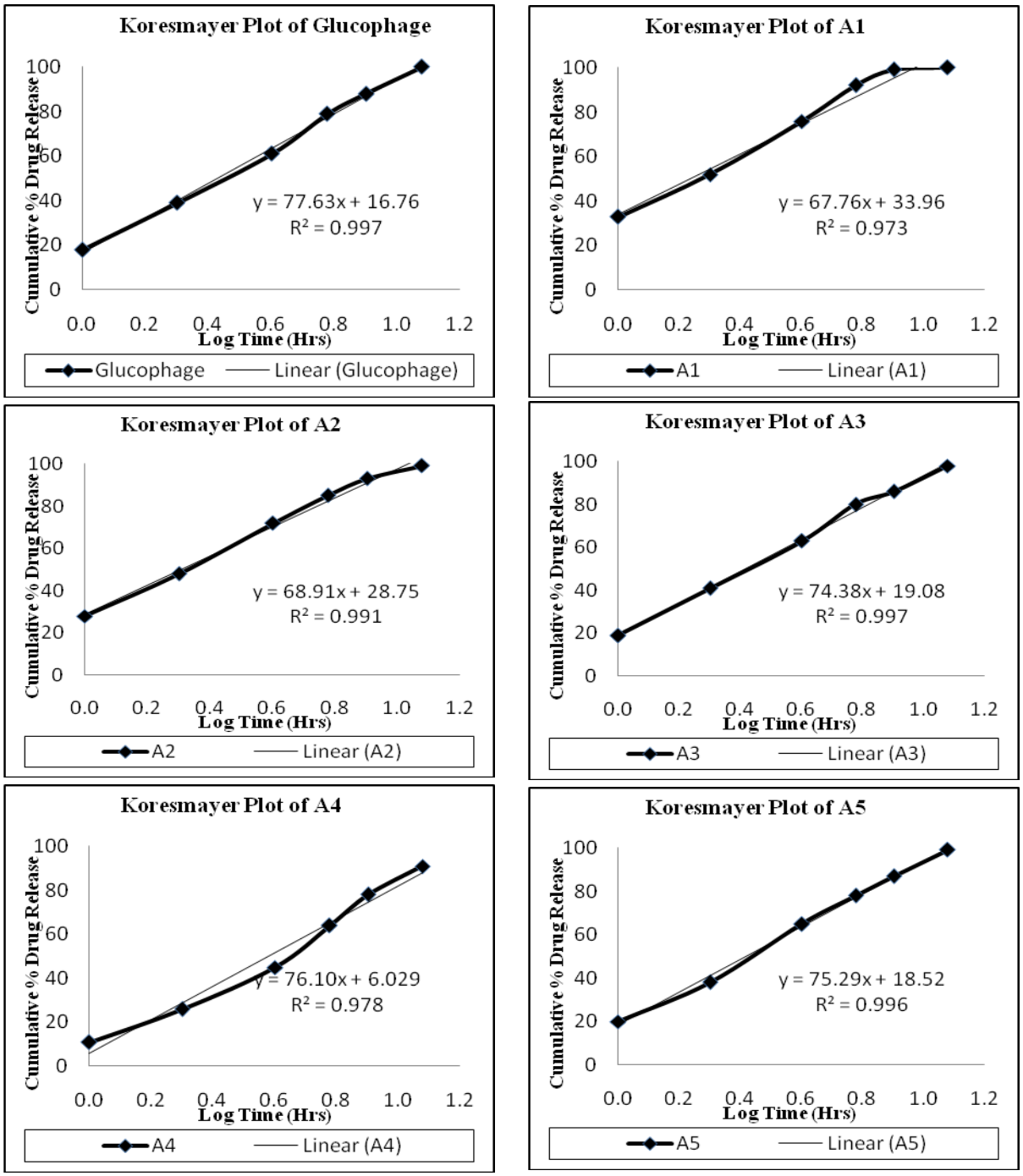



**Fig. 6 Koresmayer Plot of Metformin hydrochloride pellets [Test product] and marketed reference product Glucophage.**

**2.2.12 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.

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

| 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 |

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.

**Table No 10: Composition of different trials for Glimepiride and Pioglitazone pellets filled in capsules.**

| Ingredients | BG-1 | BG-2 | BG-3 | BG-4 | BG-5 |
|---|---|---|---|---|---|
| Glimepiride | 1 | 1 | 1 | 1 | 1 |
| Pioglitazone | 15 | 15 | 15 | 15 | 15 |
| Lactose Monohydrate (Pharmatose 200 M) | 66.5 | 65.5 | 63.5 | 63 | 63 |
| Microcrystalline cellulose | 15 | 15 | 15 | 15 | 15 |
| Sodium starch glycolate (Primogel) | 2 | 3 | 5 | 5 | 5 |
| Tween 80 | 0.5 | 0.5 | 0.5 | 1 | 1 |
| Purified water | q.s | q.s | q.s | q.s | q.s |
| Total Weight [mg] | 100 | 100 | 100 | 100 | 100 |

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

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 |

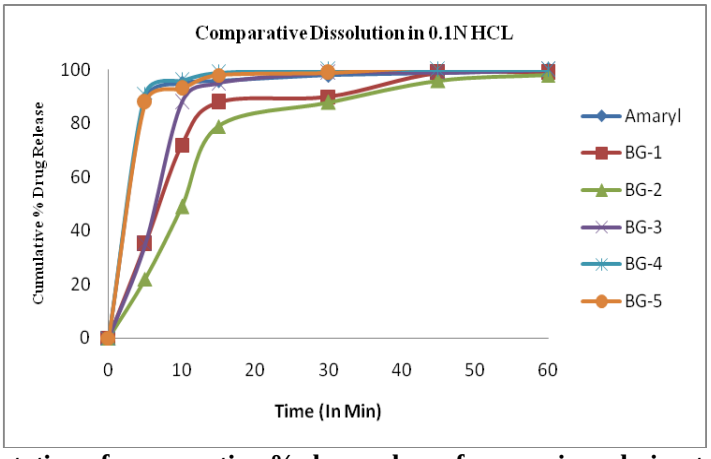



**Fig. 7 Graphical representation of comparative % drug release from various design trails of glimepiride pellet formulation in comparison with Innovator formulation (Amaryl IR Tablet 1 mg).**

**Table- 12: Zero order Plot of Glimepiride alone from Test product and Amaryl as marketed reference product. Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.**

| Time[Hrs] | Cumulative % Drug Release | | | | | |
|---|---|---|---|---|---|---|
| | 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 |

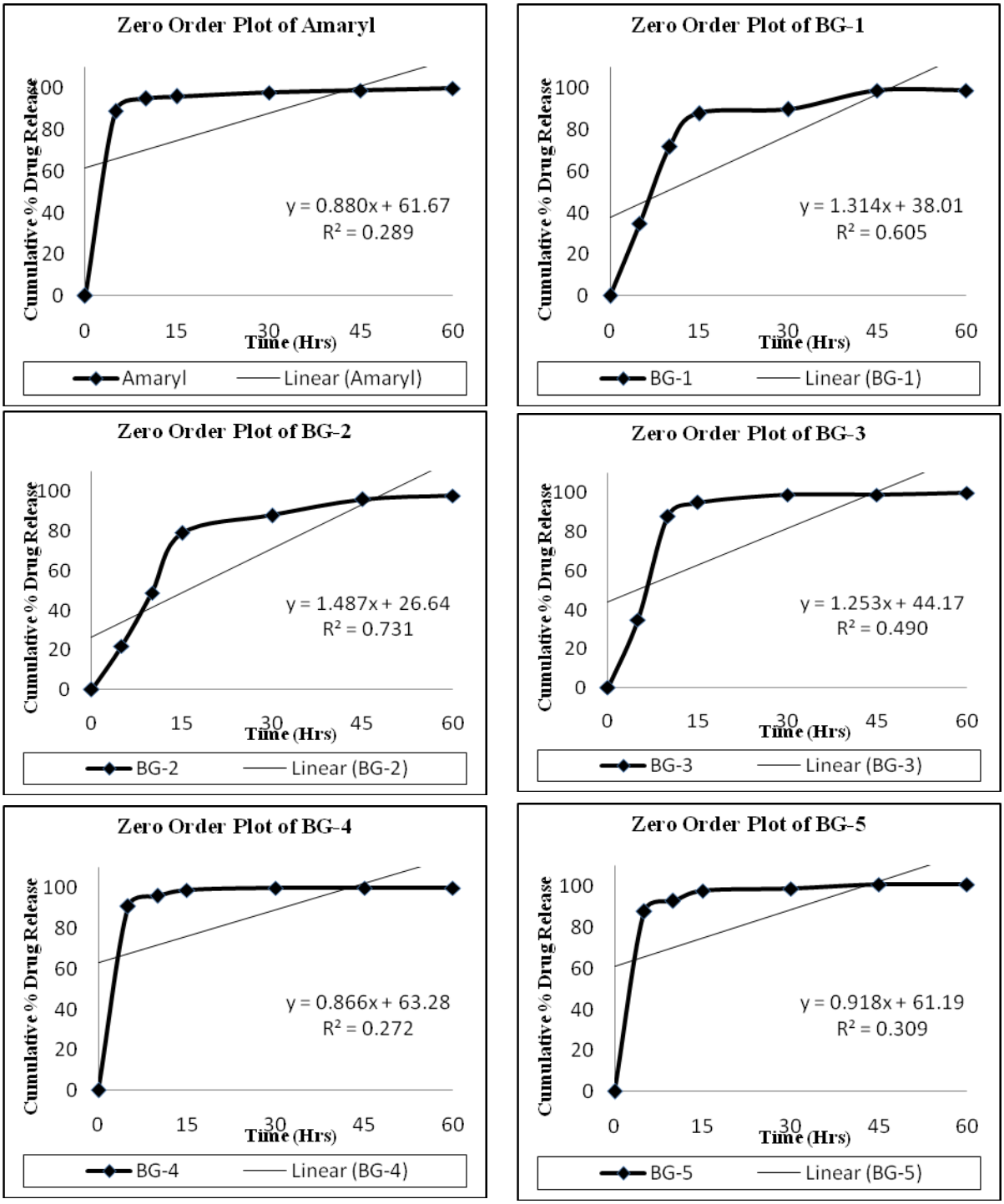



**Fig.8- Zero order Plot of Glimepiride alone from Test product and Amaryl as marketed reference product.**

**Table.13: First order Plot of Glimepiride alone from Test product and Amaryl as marketed reference product. Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.**

| Time[mins] | LOG % Drug Remaining | | | | | |
|---|---|---|---|---|---|---|
| | **Amaryl** | BG-1 | BG-2 | BG-3 | BG-4 | BG-5 |
| 0 | 2.000 | 2.000 | 2.000 | 2.000 | 2.000 | 2.000 |
| 5 | 1.041 | 1.813 | 1.892 | 1.813 | 0.954 | 1.079 |
| 10 | 0.699 | 1.447 | 1.708 | 1.079 | 0.602 | 0.845 |
| 15 | 0.602 | 1.079 | 1.322 | 0.699 | 0.000 | 0.301 |
| 30 | 0.301 | 1.000 | 1.079 | 0.000 | #NUM! | 0.000 |
| 45 | 0.000 | 0.000 | 0.602 | 0.000 | #NUM! | #NUM! |
| 60 | #NUM! | 0.000 | 0.301 | #NUM! | #NUM! | #NUM! |

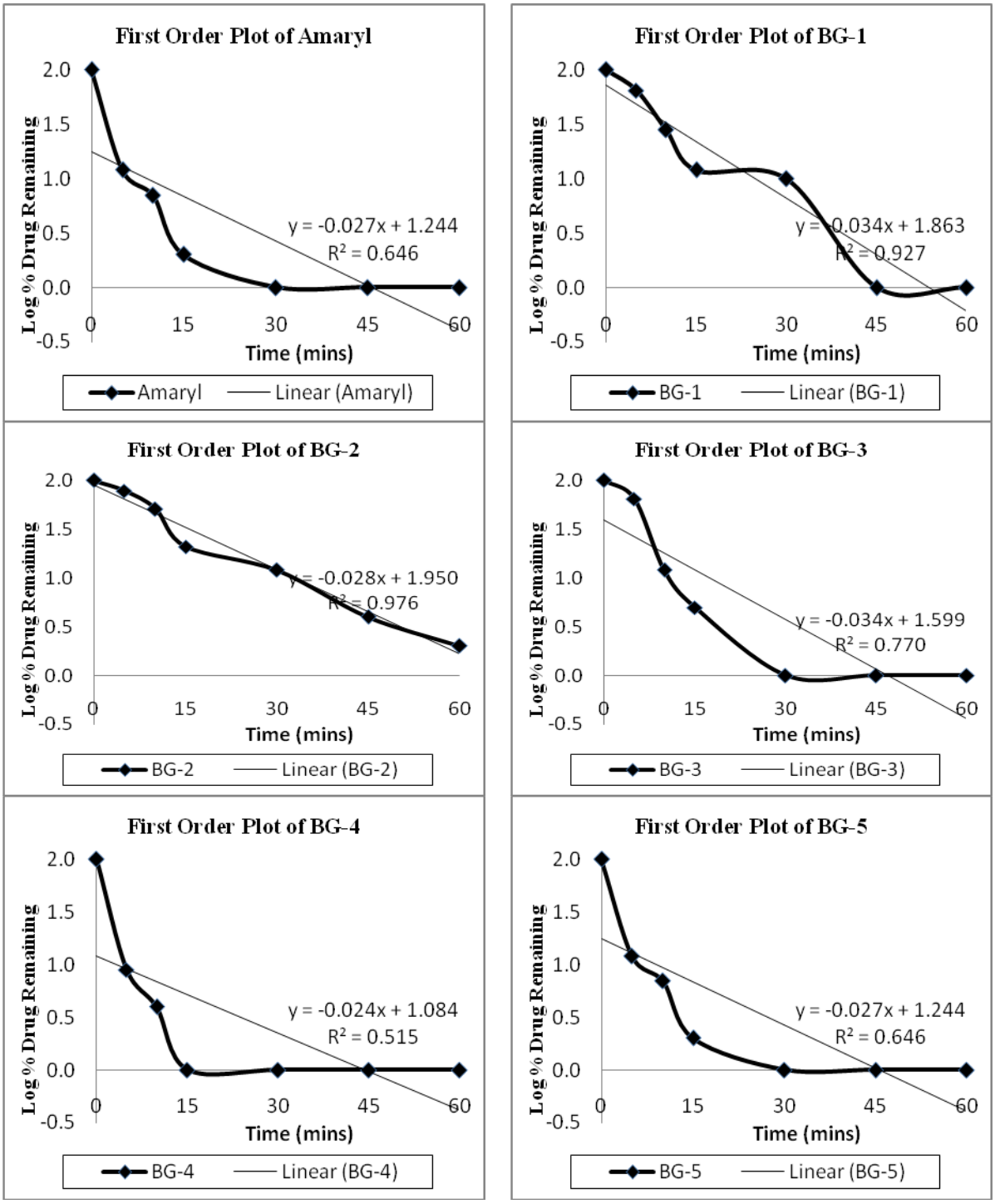



**Fig.9: First order Plot of Glimepiride alone from Test product and Amaryl as marketed reference product.**

**2.2.14 Drug release kinetic**

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.

**Table 14: Drug release kinetic and model for Glimepiride formulations.**

| 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 |

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.

**Table No 15: Comparative dissolution profile for Pioglitazone pellets alone [Test Product] and marketed product [Reference product].**

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

| Time[mins] | Actos | BP-1 | BP-2 | BP-3 | BP-4 | BP-5 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 35 | 12 | 11 | 21 | 39 | 36 |
| 10 | 66 | 25 | 23 | 32 | 69 | 70 |
| 15 | 82 | 45 | 44 | 59 | 84 | 81 |
| 30 | 95 | 79 | 72 | 85 | 96 | 96 |
| 45 | 96 | 94 | 91 | 96 | 99 | 99 |
| 60 | 99 | 98 | 99 | 99 | 100 | 100 |

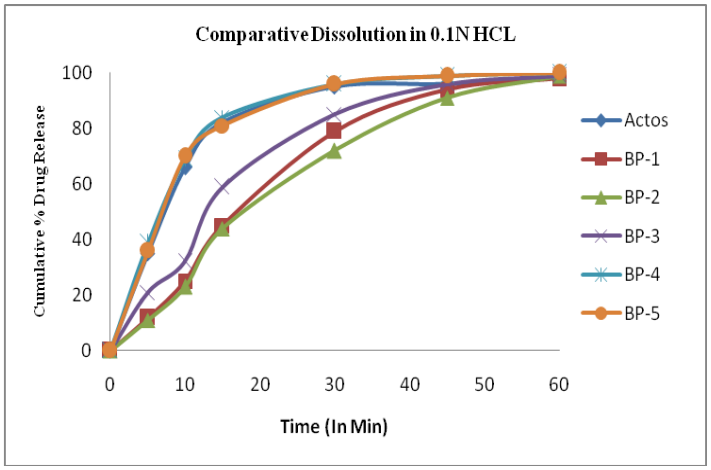



**Fig. 10: Graphical representation of comparative % drug release from various design trails of pioglitazone pellet formulation in comparison with Innovator formulation (Actos).**

**Table 16: Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.**

| Time[Hrs] | Cumulative % Drug Release | | | | | |
|---|---|---|---|---|---|---|
| | Actos | BP-1 | BP-2 | BP-3 | BP-4 | BP-5 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 35 | 12 | 11 | 21 | 39 | 36 |
| 10 | 66 | 25 | 23 | 32 | 69 | 70 |
| 15 | 82 | 45 | 44 | 59 | 84 | 81 |
| 30 | 95 | 79 | 72 | 85 | 96 | 96 |
| 45 | 96 | 94 | 91 | 96 | 99 | 99 |
| 60 | 99 | 98 | 99 | 99 | 100 | 100 |

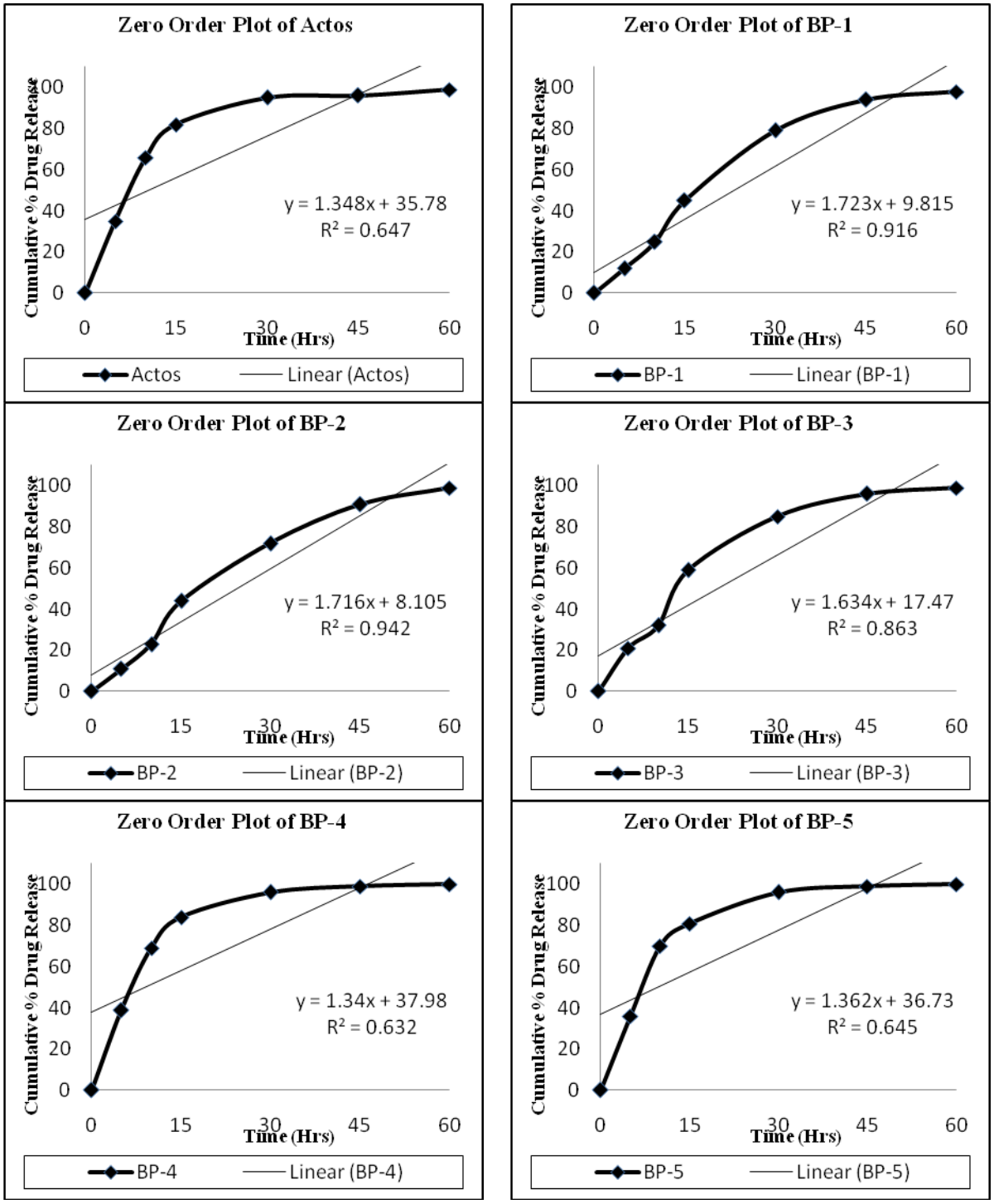



**Fig.11- Zero order Plot of Pioglitazone pellets alone [Test Product] and marketed product [Reference product].**

**Table 17: Condition: 0.1 N HCL 900ml/100 rpm/USP type I Apparatus.**

| Time[mins] | LOG % Drug Remaining | | | | | |
|---|---|---|---|---|---|---|
| | Actos | BP-1 | BP-2 | BP-3 | BP-4 | BP-5 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 35 | 12 | 11 | 21 | 39 | 36 |
| 10 | 66 | 25 | 23 | 32 | 69 | 70 |
| 15 | 82 | 45 | 44 | 59 | 84 | 81 |
| 30 | 95 | 79 | 72 | 85 | 96 | 96 |
| 45 | 96 | 94 | 91 | 96 | 99 | 99 |
| 60 | 99 | 98 | 99 | 99 | 100 | 100 |

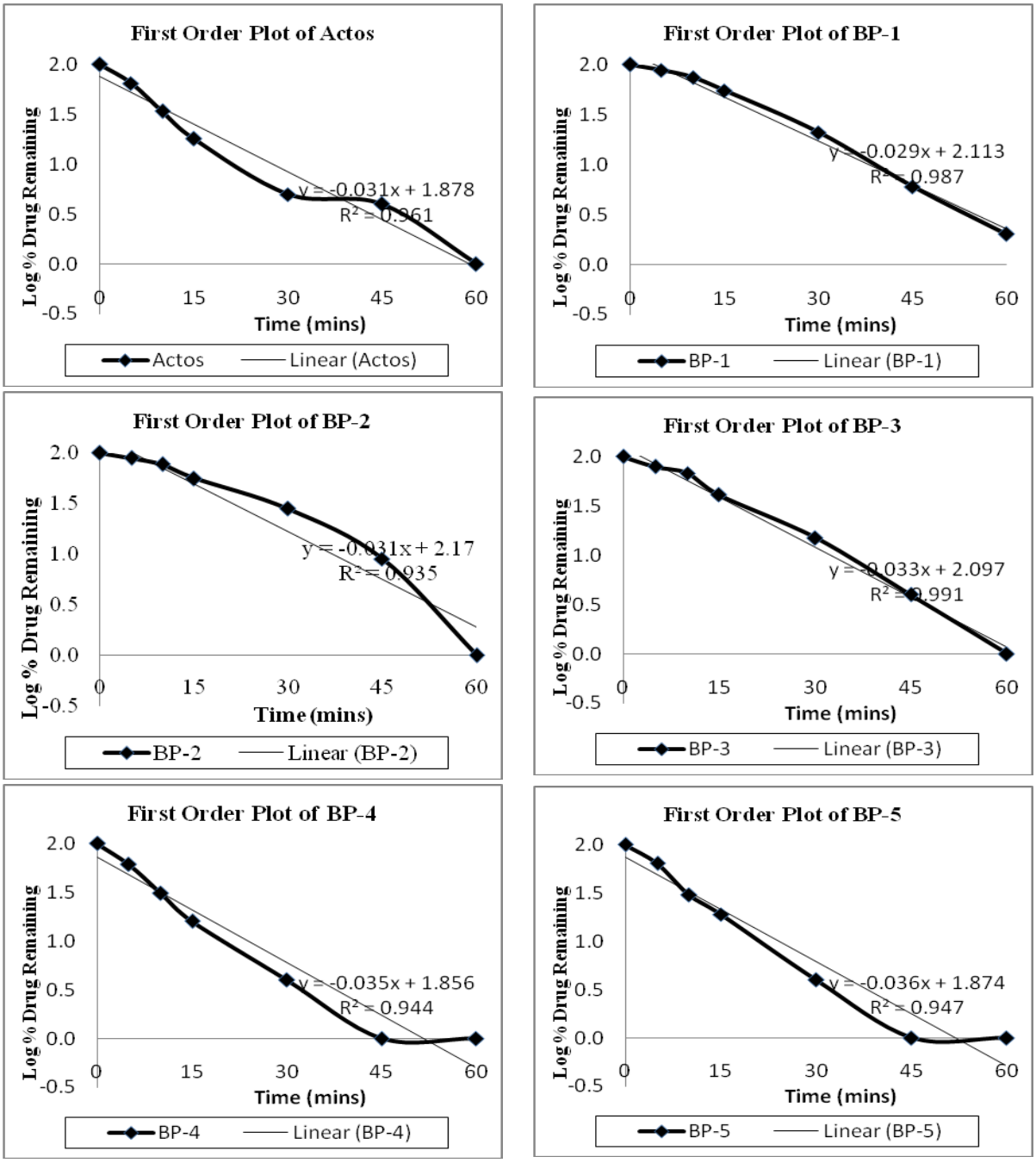



**Fig.12: First order Plot of Pioglitazone pellets alone [Test Product] and marketed product [Reference product].**

**Drug release kinetic**

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

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

**Table 18: Drug release kinetic and model for Pioglitazone formulations.**

| Formulation | Drug release kinetics ($R^2$) and F2 Value of Pioglitazone | | |
|---|---|---|---|
| | Zero-order | First-order | F2 Value |
| Actos | 0.6473 | 0.9614 | NA |
| BP-1 | 0.9162 | 0.9878 | 27.8 |
| BP-2 | 0.9424 | 0.9355 | 26.3 |
| BP-3 | 0.8636 | 0.9911 | 35.0 |
| BP-4 | 0.6326 | 0.9449 | 77.7 |
| BP-5 | 0.6458 | 0.9475 | 82.5 |

From the above regression coefficients it was concluded that Pioglitazone follows first order release kinetic.

And from F2 values, formulation BP-5 shows comparable dissolution profile with the marketed reference Actos immediate release formulation.

## 4. CONCLUSION

From the above Similarity factor (F2) and regression parameters of Metformin hydrochloride, Glimepiride and Pioglitazone formulations were optimized and it was concluded that 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 and Pioglitazone pellets provides more than 85% drug release which shows superior drug release profile than marketed formulations.

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## 6. Conflict of Interest

The authors suggest no conflict of Interest.

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