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Formulation, Development and Process Optimization of Immediate Release Tablets of Glimepiride

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Abstract

The objective of this study was to design Glimepiride Immediate Release tablets. It is mainly used for the treatment of type 2 diabetics, sulphonylureas plays important role as therapeutic as well as maintenance therapy. Glimepiride is Anti diabetic drug. It is used for type 2 diabetic disorders, very low solubility in aqueous media & oral bioavailability is 100%.its half life is 5-8 hrs & very low clearance 48 ml/min. Tablets were prepared by wet granulation technique using different polymers such as Lactose Monohydrate, Starch, Magnesium Stearate, Povidone K 30 as release rate retardant , Colloidal silicon dioxide, Sodium starch glycolate, Cross carmelose sodium, Crossprovidone, Povidone k-90, Avicel PH 102, as release rate retardant and tablets were evaluated for hardness, friability, weight variation, thickness and drug content uniformity. In vitro release studies were performed using USP type II apparatus (Basket method). In vitro release studies revealed that the release rate decreased with increase of polymer loading. The Drug release was analyzed using zero-order, first order and Higuchi and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the Immediate Release tablets. Mathematical analysis of the release kinetics indicated that release from the immediate tablets followed diffusion. So the Immediate tablets could be a potential dosage form for delivering Glimepiride .

Keywords: Glimepiride, Immediate Release tablets, Hydrophilic polymers, Wet granulation.

Contents

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1. Introduction

The Product development usually begins when the active chemical entity has been shown to process the necessary attributes for a commercial product. Generally product development activities can be sub divided into formulation development and process development[1].

Formulation development

Formulation development provides the basic information on the active chemical, the formula and the impact of raw materials or excipients on the product. A typical supportive data generated during these activities may include:

1. Preformulation profile, which includes all the basic physical or chemical information about the chemical entity.
2. Effect of formulation variable on the bioavailability of the product.
3. Specific test methods.
4. Key product attributes and specification
5. Optimum formulation

Formulation development should not be considered complete until all those factors which could significantly alter the formulation have been studied. Subsequent minor changes to the formulation, however, may be acceptable, provide they are thoroughly tested and as shown to have no adverse effect on product characteristics. In case of drug development process, compound tested is only one. A variety of studies must be performed for this single drug, each designed to characterize its efficacy, safety, selectivity or purity. Much of the data generation is driven by strict and extensive regulatory control and in this most of the studies are interdependent.

Process development can be divided into several stages[2]:

1. **Design**
2. **Ranging**
3. **Characterization**
4. **Verification**

1. Design

This is the initial planning stage of process development. During this stage, technical operation in both the manufacturing and quality-control departments should be consulted. The practically and the reality of the manufacturing operation should be kept in perspective.

Key documents for the technical definition of the process are the flow diagram, the cause and effect diagram and the influence matrix.

The flow diagram provides a convenient basic on which to develop a detailed list of variables and responses. Preliminary working documents are critical, but they should never be “cast in stone”, since new experimental data may drastically alter them. The final version will eventually be an essential part of the process characterization and technical transfer documents.

Ranging

Process-ranging studies will test whether identified parameter are critical to the product and process being developed. These studies determined the:

a. Feasibility of the design process
b. Criticality of the parameter
c. Failure limits for each of the critical variable
d. Validity of the test methods

This is usually a transition stage between the laboratory and the projected final process.

Characterization

Process characterization provides a systematic examination of critical variables found during process ranging.

Advantages

i. The transfer of technology from R & D (sending unit) to manufacturing (Receiving unit) is the first key steps to getting a high quality product to the market place.
ii. It also useful to make a timeframe of the process for that particular product.
iii. Hold time studies is useful for the planning of the product with other batches.

Objectives

The objective of the technology transfer guide in two-fold.

1. To describe the appropriate information set that needs to be complied to support the transfer of the information and provide regulatory filing documents.
2. To provide guidance on effective approaches for ensuring this information is available at “print of use” where guidance on specific topic already exists this will be referred.

Process optimization: In the environment of increasing international competition where counters with lower production cost luckily catch up technologically, new thinking is required in order to meeting the competition is to focus on maximizing the utilization of exiting technology. This means much more than just investing in new

equipment. The ability to optimize or improve a process is dependent upon the ability to control the process. The ability to control the process is dependent upon the access to reliable and valid management.

Optimization technology: There are two type optimization problems. They are:

Constrained optimization: Constrains are those restricted placed on the system due to physical limitation.

Unconstrained optimization: In unconstrained optimization problems there are no restriction (such as tablet hardness and disintegration).

An additional complication in pharmacy is that formulations are not usually simple system. They often contain many ingredients and variables, which may interact with one another to produce unexpected.

The most commonly used member of biguanides is Metformin. Biguanides [Metformin] is an Antihyperglycemic and not Hypoglycemic agent. It does not stimulate pancreas to secrete insulin and does not cause hypoglycemia (as a side effect) even in large doses. Also it has no effect on secretion of Glucagon or Somatostatin

Objectives:

The objective of the study was to develop a formulation for Glimepiride tablets by using lactose monohydrate & starch as diluent, binder such as povidone K-30, and disintegrants such as sodium starch glycolate, croscarmellose sodium; and then evaluating Glimepiride tablets. Preformulation testing is the first step in rational development of dosage form of drug substance. In this study, characterization of API is most important study. Hygroscopicity, solubility study, bulk density, tapped density, compressibility& particle size analysis by Malvern analyzer of API done for characterization of API[3]. For development of Glimepiride formulation know about the details of innovator product so done the characterization of innovator product. For selection of excipients, drug compatibility study was required. The storage condition used to examine compatibility can vary widely in terms of temperature and humidity.

2. Materials and Methods

Wet granulation:

Wet granules are formed by binding the powder together with the adhesion, instead of by compaction. This process employs a slurry containing a binder , which is usually added to mixture of powder but binder is added to powder mix & liquid is added itself. Liquid will form bridges are developed between particles. During addition of liquid uniform mixing is done. During wet granulation chopper is kept on for kneading so that the lumps of the granules that form will break soon[4]. After this it will keep for drying in dryer and loss on drying is checked .LOD is kept in certain limits. This process is required in all wet granulation procedures to remove the solvent that was required in forming the agglomerate & to reduce the moisture content to an optimum level.

Manufacturing steps[5]:

Dispensing: Dispense and check the weight along with the analytical report nos. of all the ingredients as per the material requisition note.

Sifting: Geometrically mix calculated quantity of Glimepiride USP* and approximately 5 Kg of Lactose IP * from calculated qty in polybag and sift through 60# using vibratory sifter and collect in a suitable container. Sift remaining quantity of Lactose IP through 60# using vibratory sifter. Mix the above materials and resift through 60# and collect in a suitable container. Sift 7.560 Kg of Starch IP through 60# using vibratory sifter and collect in a suitable container. Sift separately 1.050 Kg of Sodium starch glycollate IP through 40# on a vibratory sifter and collect in a suitable container.

Dry Mixing: Load the materials into a clean dry Rapid Mixer Granulator and Mix for 5 minutes with Impeller speed slow & chopper off. Record the time of mixing in the BMR & send the sample to QC for Analysis.

Binder Solution Preparation: Add 1.050 Kg of Povidone K-30 Ph.Eur. in to 2.625 Kg of Purified water USP/Ph.Eur/BP/IP/IH under constant stirring to get a clear solution.

Granulation:

Add binder solution to the powder mix in Rapid mixer granulator within 2 to 3 minutes with impeller at slow speed and chopper off. Knead it for 2-3 minute with impeller and chopper at fast speed. Add extra quantity of Purified water if required. Record the ampere load, additional quantity of Purified Water USP/Ph. Eur/ BP/IP/IH and time of mixing in the BMR.

Unload wet mass into the bowl of FBD through co mill fitted with 0.8 mm SS Screen.

Drying: Dry the wet mass in Fluidized Bed dryer at inlet temperature 65 °C ± 5 °C till to get LOD between 1.5 to 3.0 % w/w at 105 °C.

Sizing: Pass the dried granules through oscillating granulator fitted with 0.8 mm perforated SS screen and collect it in clean dry Conta blender.

Weigh and record the weight of the granules in BMR.

Blending & Lubrication [6]:

Blend the granules with sifted material for 7 minutes in Conta blender. Record the time of blending in the BMR. Add the sifted materials in to the blended material and lubricate for 3 minutes. Record the time of lubrication in the

BMR. Send the sample of lubricated granules along with sample test request slip to QC for analysis. Weigh & record the weight of lubricated granules in the BMR.

Compression[7]: After getting QC/QA approval, compress the lubricated granules into tablets on Rotary Tablet Compression Machine using 8/32" (6.35mm) round shape standard concave punches with plain upper punches, plain lower punches and suitable dies. Check Description, weight of 20 tablets, Average weight, Uniformity of weight, Hardness, Thickness, disintegration time & Friability and record in the BMR. Send the sample of compressed tablet along with Sample test request slip to QC. Weigh and record the weight of compressed tablets in BMR.

Stability Studies [8]:

From the prepared formulation and development of glimepride which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. The prepared formulation were placed in borosilicate screw capped glass containers and stored at three different temperature (27±2°C, 65% RH), Oven temperature (40±2°C, 65% RH) and in freezing temperature (5 – 8°C, 65% RH) in stability chamber for a period of 90 days. The samples were evaluated for cumulative percentage drug release at regular intervals of two week.

Table 1. Composition of Glimepiride tablet

Sr. No	Ingredients	Qty / tablet (mg)	% In tablet (w/w)
1	Glimepiride	4.00	4.44
2	DCP	61.00	67.24
3	Starch	20.00	22.22
4	Sodium Starch Glycolate	3.00	3.33
5	Magnesium stearate	1.00	1.11
6	Colloidal silicon dioxide	1.00	1.11
Total Weight in mg		90.0	99.98

Table 2. Comparative physical parameters

Punch Used	Weight Variation		Disintegration time	Hardness (N)	Friability	Thickness
	Lower	Higher				
8/32"round	12.0	9.0	10 – 20 seconds	40-60 N	1.25%	2.9 – 3.1

Table 3. Characterization of blend

Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
0.498	0.682	26.97	1.369	36.57°

Table 4. Comparative dissolution profiles

Glimepiride Tablet	Dissolution profile in 500 ml 0.2 % SLS In pH 3.0 buffer. @ 40 rpm					
	5 min	10 min	15 min	30 min	45 min	60min
Batch No: 001	91.3	95.6	101.0	101.2	100.8	100.4

Table 5. Composition of Glimepiride tablet

S. No	Ingredients	Qty / tablet (Mg)	% In tablet (W/w)
1	Glimepiride	4.00	4.44
2	Mannitol	61.00	67.24
3	Starch	20.00	22.22
4	Sodium Starch Glycolate	3.00	3.33
5	Magnesium stearate	1.00	1.11
6	Colloidal silicon dioxide	1.00	1.11
Total Weight in mg		90.0	99.98

Table 6. Characterization of blend

Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
0.468	0.652	28	1.39	39.26°

Table 7. Comparative physical parameters

Punch Used	Weight Variation		Disintegration time	Hardness (N)	Friability	Thickness
	Lower	Higher				
8/32" round	2.0	3.0	30- 50 seconds	40-60 N	0.65%	2.9 – 3.1

Table 8. Comparative dissolution profiles

Glimepiride Tablet	Dissolution profile in 500 ml 0.2 % SLS In pH 3.0 buffer. @ 40 rpm					
	5 min	10 min	15 min	30 min	45 min	60min
Batch No: 002	81.3	91.6	95.2	98.2	100.2	101.4

Selection of dissolution medium:

The primary product development of Glimepiride Tablets 4 mg has been initiated in bench scale to match the dissolution profile with the innovator product in the following medias [9]. The two media that are selected for the comparison based on the solubility and pharmacokinetics of the drug are:

a) PH3.0 Buffer with 0.2% SLS
b) Water + 0.5 % SLS

Dissolution testing has emerged in the pharmaceutical field as a very important tool to characterize drug product performance. Dissolution of drug depends upon solubility of the drug in the medium. Solubility is the one of the key determinants for oral bioavailability of drug. Development of dissolution medium for poorly water soluble drug is a critical issue. Glimepiride is a anti-diabetic drug having poor water solubility.

Table 9. Comparative dissolution profiles of Amaryl 4 mg tablets in different media

Amaryl Tablet 4 mg B.No. 303154	% drug dissolved						
	5 min	10 min	15min	20 min	30 min	45 min	60 min
5 % IPA in water	50.0	62.9	65.2	64.2	67.1	69.8	69.8
0.2 % SLS in pH 3.0	43.4	64.7	72.3	77.8	81.5	84.6	87.4
0.5 % twin in water	24.0	32.4	35.7	35.9	37.5	37.7	39.4
0.1% SLS in pH 3.0	42.9	47.1	49.8	50.3	52.8	55.2	56.7
0.2 twin 80 in 6.8 pH	29.3	38.5	40.2	42.6	44.7	41.3	44.5
0.3 % SLS in pH 3.0	68.1	81.1	85.8	90.4	92.1	95.0	96.1
0.1 % twin 80in pH 7.4	68.4	72.0	90.3	92.6	95.4	95.5	96.5
0.1% twin 80 in pH 6.8	23.5	28.0	30.8	32.9	32.7	34.3	34.0
0.05% SLS in water	36.8	41.5	42.3	40.8	44.8	48.2	50.2
1% SLS in water	46.2	50.9	56.2	57.7	57.9	60.4	61.1
0.5 % SLS in water	85.4	99.0	99.9	100.5	100.6	101.6	101.9
0.1% SLS in pH 4.5	39.3	47.3	51.5	52.6	53.7	56.4	58.5

The composition of the medium was determined on the basis of solubility data of the drug in different Medias. Saturation solubility of drug was found to be more in pH 3. The effects of surfactant (Sodium lauryl sulphate and Tween 80) in the different concentrations were studied of solubility of drug in pH 3. The study reveled that pH 3 with 0.2% SLS showed higher solubility, hence, was considered to be a suitable dissolution medium. Dissolution can be used as a test to reflect the bioavailability of the product in humans. Dissolution testing has emerged in the pharmaceutical field as a important tool to characterize drug product performance. The composition of the medium was determined on the basis of solubility data and dissolution profile of drug in different medias [10]. In 0.2 % SLS in pH 3.0 buffer at 50 RPM the drug is completely released at 45 minutes. Besides, since this is an immediate release formulation, this media is bio-relevant media because drug shall be completely released and will be available for absorption in-vivo at this pH. Hence this media was selected for routine and QC analysis.

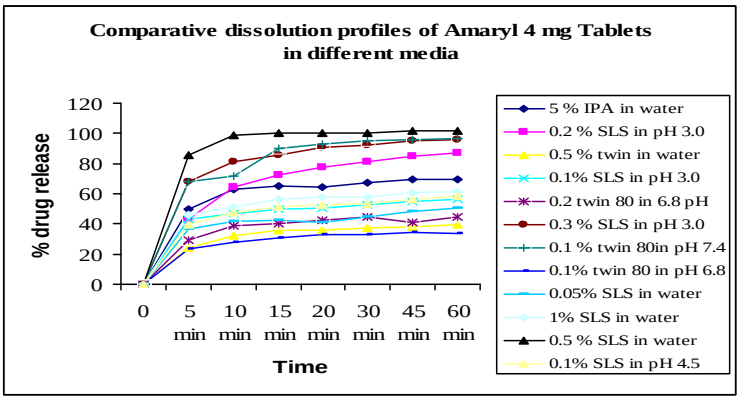

Figure 1. Comparative dissolution profiles of Amaryl 4 mg tablets in different media

Table 10. Composition of Glimepiride tablet

Sr.No	Raw material	Qty/tablet in mg		
		B.No:003	B.No:004	B.No:005
1.0	Glimepiride	4	4	4
2.0	Lactose	58.00	56.50	55.00
3.0	Starch	20.00	20.00	20.00
4.0	PVP K 30	**3.0 (3.35%)**	**4.5 (5.0%)**	**6.0 (6.65%)**
5.0	Sod. Starch glycolate	3.00	3.00	3.00
6.0	Mg. Stearate	1.00	1.00	1.00
7.0	Aerosil 200	1.00	1.00	1.00
8.0	Purified Water	q.s	q.s	q.s
Tablet Weight		**90.00**	**90.00**	**90.00**

Table 11. Comparative physical parameters

B. No.	Thickness (mm)	Hardness (N)	D.T.
003	2.82-2.98	60 – 80	2.45
004	3.85-3.10	70 – 100	8.30
005	3.82-3.10	75 - 110	9.10

Table 12. Comparative dissolution profiles

Product	B.No.	% of Binder	Dissolution profile in 500ml pH 3.0 with 0.2 % SLS @ 40rpm (Type II)				
			5 min	10 min	15 min	30 min	45 min
Glimepiride 4 Mg Tabs	003	3.35	54.0	81.5	89.8	93.7	94.0
	004	5.0	30.9	55.5	78.2	98.9	98.8
	005	6.65	28.1	49.6	66.4	85.3	86.9

Table 13. Composition of Glimepiride tablet

Sr. No	Raw material	Qty/tablet in mg		
		B.No:006	B.No:007	B.No:008
1.0	Glimepiride	4	4	4
2.0	Lactose	61.60	58.90	58.90
3.0	Starch	20.00	20.00	20.00
4.0	PVPK 30	3.00	3.00	3.00
5.0	Sod. Starch glycolate	-	**2.7(3. 0%)**	-
6.0	Croscarmellose Sodium	-	-	**2.7(3. 0%)**
7.0	Mg. Stearate	1.00	1.00	1.00
8.0	Aerosil 200	1.00	1.00	1.00
9.0	Purified Water	q.s	q.s	q.s
Total Weight		**90.00**	**90.00**	**90.00**

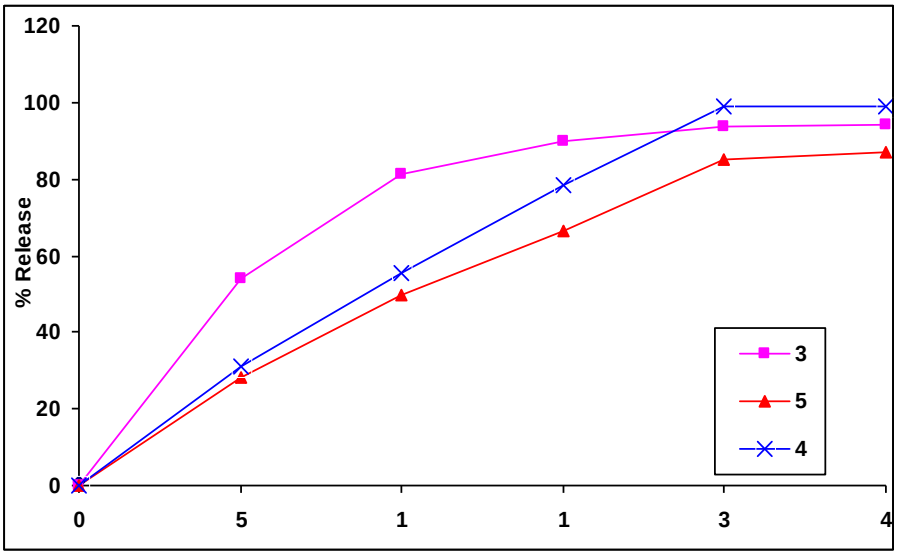

Figure 2. Comparative dissolution profiles

Table 14. Comparative physical parameters

B. No.	Thickness (mm)	Hardness (N)	D.T.(mins)
006	2.85-2.97	45 – 58	6.45
007	3.89-3.10	55 – 90	3.14
008	3.80-3.10	60 – 85	3.58

Table 15. Comparative dissolution profiles

Product	B.No.	Dissolution profile in 500ml pH 3.0 with 0.2 % SLS @ 40rpm (Type II)				
		5 min	10 min	15 min	30 min	45 min
Glimepiride 4 Mg Tabs	006	28.4	42.5	67.0	83.90	90.70
	007	48.9	75.5	83.10	88.90	89.60
	008	45.1	69.6	75.60	82.60	84.10

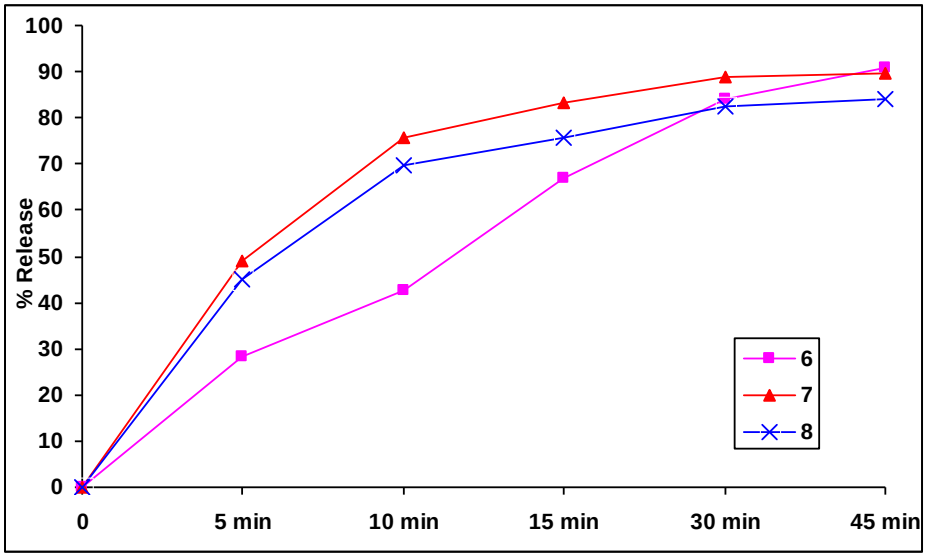

Figure 3. Comparative dissolution profiles

Table 16. Composition of Glimepiride tablet

Sr.No	Raw material	Qty/tablet in mg					
		B.No:009	**B.No:010**	**B.No:011**	**B.No:012**	**B.No:013**	**B.No:014**
1.0	Glimepiride	4	4	4	4	4	4
2.0	Lactose	61.00	57.40	56.50	55.60	54.70	53.80
3.0	Starch	20.00	20.00	20.00	20.00	20.00	20.00
4.0	PVP K 30	3.00	3.00	3.00	3.00	3.00	3.00
5.0	Sod. Starch glycolate	--	**3.6(4.0%)**	**4.5(5.0%)**	**5.4(6.0%)**	**6.3(7.0%)**	**7.2(8.0%)**
6.0	Mg. Stearate	1.00	1.00	1.00	1.00	1.00	1.00
7.0	Aerosil 200	1.00	1.00	1.00	1.00	1.00	1.00
8.0	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s

Table 17. Comparative physical parameters

B. No.	% of Disintegrant	Thickness (mm)	Hardness (N)	Friability (%)	D.T.
009	**0**	2.81-3.07	50 - 58	0.14	6 min 58 sec
010	**4**	2.79-3.00	76-86	0.24	2 min 37 sec
011	**5**	2.90-3.19	39-53	0.23	2 min 25 sec
012	**6**	3.15-3.27	32– 43	0.32	1 min 20sec
013	**7**	3.92-3.11	40-52	0.35	1 min 15 sec
014	**8**	3.82-3.14	45-64	0.30	65 seconds

Table 18. Comparative dissolution profiles

Product	B.No.	Dissolution profile in 500ml pH 3.0 with 0.2 % SLS @ 40rpm (Type II)				
		5 min	**10 min**	**15 min**	**30 min**	**45 min**
Glimepiride4 Mg Tabs	**009**	28.4	42.5	67.0	83.90	90.70
	010	49.7	76.5	83.60	91.0	91.80
	011	52.6	82.5	84.30	88.20	88.20
	012	79.4	83.5	89.10	93.90	97.30
	013	71.5	78.9	79.40	85.50	86.50
	014	64.8	76.4	80.80	86.70	87.10

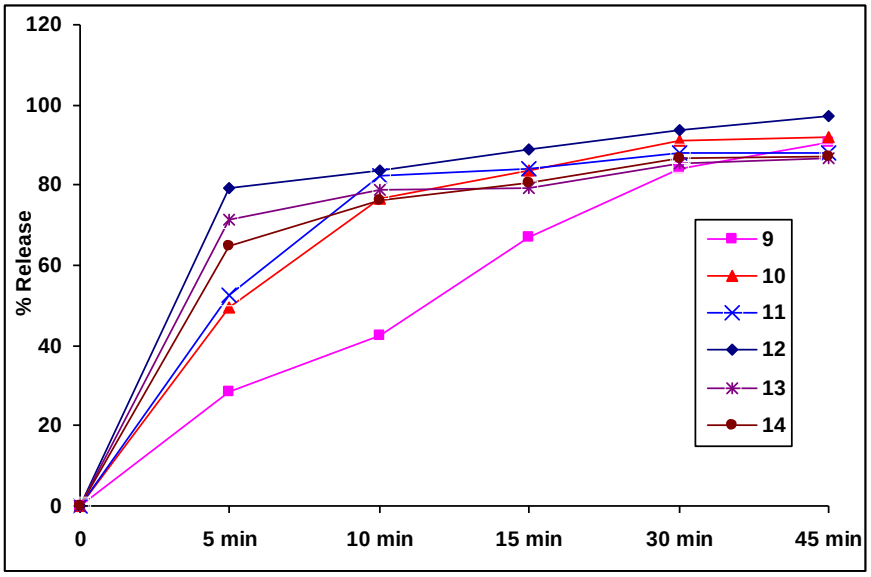

Figure 4. Comparative dissolution profiles

Table 19. Composition of Glimepiride tablet

Sr.No.	Ingredients	Qty per tablet in mg			
		015	016	017	018**
1.	Glimepiride	4	4	4	4
2.	Lactose	59.00	58.50	58.00	57.00
3.	Starch	**10.00**	**20.00**	**30.00**	**30.00**
4.	PVPK 30	3.00	3.00	3.00	3.00
5.	Sod. Starch glycolate	3.00	3.00	3.00	3.00
7.	Purified water	-			
10.	Silica, Colloidal Anhydrous	1.00	1.00	1.00	1.00
11.	Magnesium Stearate	1.00	1.00	1.00	1.00
Tablet Weight		230.00	230.00	230.00	230.00

018** in this batch 15 mg intragranular & 15 mg extragranular of starch.

Table 20. Comparative physical parameters

B. No.	Thickness (mm)	Hardness (N)	D.T.(mins)	Angle of repose
015	2.88 – 3.05	34 – 97	3.41	23.25
016	2.81 – 3.10	50 – 82	2.58	25.48
017	2.80 – 3.20	54 – 84	1.42	28.24
018**	2.90 – 3.10	56 – 89	2.18	29.45

Table 21. Comparative dissolution profiles

Product	B.No.	Dissolution profile in 500ml pH 3.0 with 0.2 % SLS @ 40rpm (Type II)				
		5 min	10 min	15 min	30 min	45 min
Glimepiride4mg tablets	**015**	38.9	78.4	84.9	89.5	97.4
	016	42.9	74.8	85.9	92.8	98.4
	017	45.9	72.9	87.4	93.4	102.5
	018**	39.8	70.4	82.6	90.7	101.7

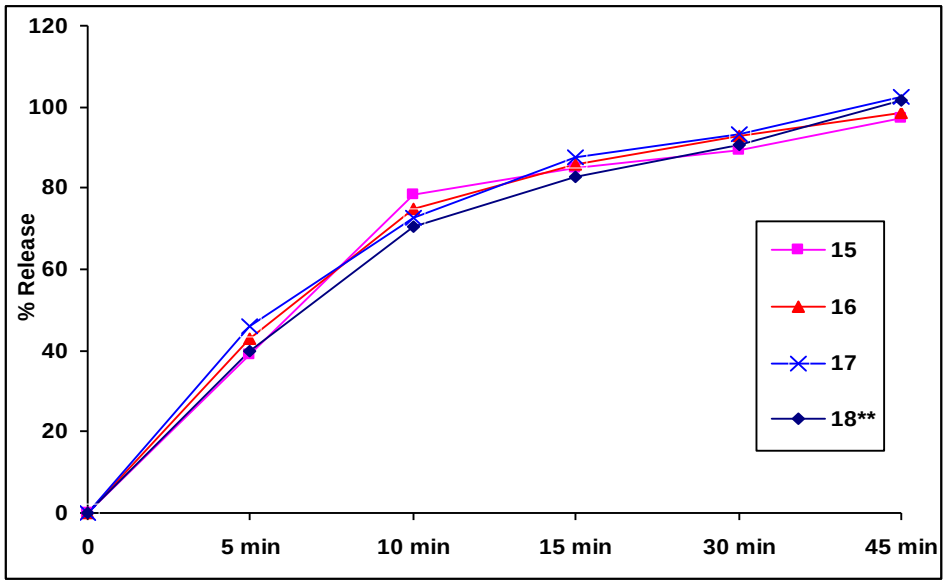

Figure 5. Comparative dissolution profiles

Table 22. Composition of Glimepiride tablet

Sr.No.	Ingredients	Qty per tablet in mg			
		019	**020**	**021**	**022**
		0%	**0.55%**	**1.10%**	**2.20%**
1.	Glimepiride	4	4	4	4
2.	Lactose	59.00	58.50	58.00	57.00
3.	Starch	20.00	20.00	20.00	20.00
4.	PVP K 30	3.00	3.00	3.00	3.00
5.	Sod. Starch Glycolate	3.00	3.00	3.00	3.00
6.	Purified water	-----			
7.	Silica, Colloidal Anhydrous	**0**	**0.50**	**1.00**	**2.00**
8.	Magnesium Stearate	1.00	1.00	1.00	1.00
Tablet Weight		230.00	230.00	230.00	230.00

Table 23. Effect of glidant on physical parameters

Batch No.	% of Glidant	Hardness (N)	Friability (%)	Angle of Repose	D.T.
019	**0**	47 - 64	0.16	23.05^{o}	2 min 30 sec
020	**0.55**	65-81	0.14	22.32^{o}	2 min 20 sec
021	**1.10**	74 - 93	0.18	20.20^{o}	2 min 20 sec
022	**2.20**	68-89	0.24	20.67^{o}	2 min

Table 24. Composition of Glimepiride tablet

Sr. No.	Raw material	Qty/tablet in mg		
		B.No:023	**B.No:024**	**B.No:025**
1.0	Glimepiride	4	4	4
2.0	Lactose	61.60	58.90	58.90
3.0	Starch	20.00	20.00	20.00
4.0	PVP K 30	3.00	3.00	3.00
5.0	Sod. Starch glycolate	3.00	3.00	3.00
7.0	Mg. Stearate	**1.00(1.11%)**	**2.00(2.20%)**	**3.00(3.30%)**
8.0	Aerosil 200	1.00	1.00	1.00
9.0	Purified Water	q.s	q.s	q.s
Tablet Weight		**90.00**	**90.00**	**90.00**

Table 25. Comparative physical parameters

Batch No.	% of Lubricant	Thickness (mm)	Hardness (N)	Friability (%)	D.T.
023	**1.11**	2.85 – 3.26	33 - 76	0.22	2 min 36 sec
024	**2.20**	2.89 – 3.27	46 - 73	0.18	2 min 50 sec
025	**3.30**	3.10 – 3.30	33 - 60	0.17	3 min 20 sec

Table 26 Effect of different concentrations of lubricant on dissolution

Product	B.No.	Dissolution profile in 500ml pH 3.0 with 0.2 % SLS @ 40rpm (Type II)				
		5 min	**10 min**	**15 min**	**30 min**	**45 min**
Glimepiride 4 Mg Tabs	**023**	58.9	78.4	89.10	93.90	97.30
	024	32.9	54.8	69.80	78.70	85.20
	025	35.9	52.9	75.20	83.30	86.60

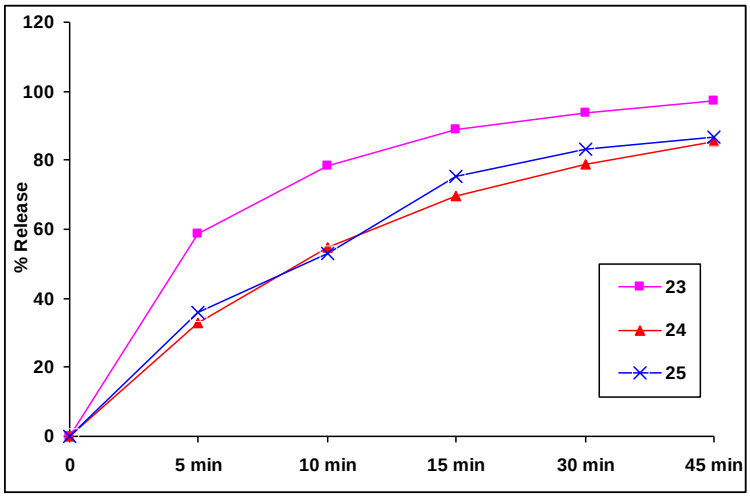

Figure 6. Comparative dissolution profiles

3. Results and Discussion

Flow properties of the powder can be judged from the angle of repose. The powder flow depends on 3 general areas: 1) The physical properties of the particle (E.g: shape, size, compressibility) 2)the bulks powder properties (e.g. size, distribution compaction): and 3)the processing environment (e.g. storage, humidity) The angle of response of batch no 1&2 >35° so, very poor flow of the powder blend so, during compression weight variation observed11. Poor CI (%) & poor HR so, hardness was not achieved of higher side & friability was 1.25%. DT of tablets was 10-20 sec. In 5 min 91.3% of drug release was observed. These in process parameters & dissolution were not match with the innovator product. In batch no.2 replace the DCP by the Mannitol. Mannitol has direct compressible property. But the flow property of the powder blend was very poor. During compression sticking was observed. In 5 min 81.3% of drug released. So, to formulate the tablets of Glimperide using wet granulation. The tablet formulation were prepared by compression method using punch size 8/32" round shaped, upper lower side flat using Cadmach 16-station compression machine. A rapid mixer granulator was used for wet granulation in the study. Suitable selection of binder concentration was done[12].

Manufacturing Process:

Table 27. Product Composition

Sr.No	Ingredient	Specification#	Function	Qty / Tab. (In mg)		Qty./ batch (In Kg)
				Theoretical	Actual	
01	Glimepiride	USP	Active	3.000	3.000	1.050
02	Lactose *	IP	Diluent	59.000	59.000	20.650
03	Starch**	IP	Diluent	20.000	21.600	7.560
04	Povidone (K-30)	Ph.Eur	Binder	3.000	3.000	1.050
05	PurifiedWater @	USP /Ph. Eur/ BP/IP/IH	Vehicle	q.s.	q.s.	2.625
06	Sodium starch glycollate	IP	Disintegrant	3.000	3.000	1.050
07	Magnesium Stearate	IP	Lubricant	1.000	1.000	0.350
08	Colloidal Silicon dioxide(Aerosil)	IP	Glidant	1.000	1.000	0.350
Total weight				90.00	90.00	31.500

*Potency of Glimepiride USP should be adjusted to 100 % and simultaneously quantity of Lactose IP should be adjusted as per calculation .

**8 % extra starch added to compensate moisture loss on drying.

Formula Calculation:

Calculation for Glimepiride USP:

(Depending on how the assay of Glimepiride USP is reported, use the appropriate factor) Assay on anhydrous or such basis Basis Qty of Glimepiride USP

$$\text{Required per batch of} = \frac{1.050 \times 100 \times 100}{\text{350,000 Tablets Q (Kg)}} \text{ or } \frac{1.050 \times 100}{\frac{B}{A \times (100 - W)}}$$

Where A = Assay of Glimepiride USP on anhydrous basis in % w/w
B= Assay of Glimepiride USP on as such basis in % w/w
W= Water content in % w/w

Facility required during manufacturing process

Table 28. Facility required

Area	Temperature	Relative Humidity
Sifting	NMT 27 °C	NMT 60 %
Granulation & Drying	NMT 27 °C	NMT 60 %
Blending	NMT 27 °C	NMT 60 %
Compression	NMT 27 °C	NMT 60 %

Table 29. In process test parameters

STAGE	TEST	ACCEPTANCE CRITERIA
Dry mixing	Blend Uniformity Analysis	NLT 90.0 % and NMT 110.0% (RSD: NMT 5.0 %).
Drying	Loss on Drying at 105°C	1.5 % to 3.0%w/w.
Lubrication	Description	White c olored free flowing granular powder.
	Assay	NLT 95.0% and NMT 105.0% of labeled amount.
	Blend Uniformity Analysis	NLT 9NLT 90.0% and NMT 110.0% of Labeled amount and RSD is not more than 5.0 %.
Compression	Description	White coloured round shaped biconvex uncoated tablets plain on both sides.
	Theoretical weight of individual tablets	90.0 mg
	Average weight	90.0 mg ± 5 % (85.5 mg to 94.5 mg)
	Weight of 20 Tablets	1.80 g ± 3 % (1.746 mg to 1.854 mg)
	Uniformity of weight	Average weight ± 7.5 % (83.25 mg to 96.75 mg)
	Hardness	40 to 100 N (4 to 10 Kg/cm^2)
	Thickness	2.6 ±0.3 mm
	Disintegration time	NMT 15 min.
	Friability	NMT 1.0 % w/w
	Uniformity of content	Out of 10 units, not more than one of the individual values should be outside the limits of 85.0 to 115.0% of the average value and none is outside the limits of 75.0 to 125.0% of the average value.

Sampling protocol:

Table 30. Details of operating parameter of horizontal oscillating granulator(Sizing)

Sr.No	Time taken	Parameter	Operating condition
1	10 min	Screen	0.8 mm

Table 31. Details of the physical characteristics of blend after sizing

Sr.No	Parameter	Result
1	Description	White colored free flowing granules

Table 32. Sampling to be done at various stages

Stage	Parameter to be monitored	Sampling Interval	Sample container	Sample Quantity
Dry mixing	Blend Uniformity Analysis	After mixing	Glass vials, rubber closures & aluminum seals	10 samples in triplicate (Each approximately 82.0 to 246.0 mg)
Lubrication	Blend Uniformity Analysis	After Lubrication	Glass vials, rubber closures & aluminum seals	10 samples in triplicate (Each approximately 90.0 to 270.0 mg)
	Description, Bulk Density, Tapped Density, Sieve Analysis, LOD (For reference only)		LDPE Bag	Approximately 200 mg (Composite)
	Assay			
Compression	Content uniformity	Initial, Middle & End	LDPE Bag	Approximately 100 Tablets
	Dissolution.	At low, Optimum & High Hardness	LDPE Bag	Approximately 100 Tablets

Table 33. Process steps

Process Stage	Process Control Step	Expected response	Observed Response	Remarks
Granulation:	1.Binder Addition Time 2.Kneading Time	2-3 minutes 2-3 minutes	3 minutes 2 minutes	100 gm extra water was used
Drying	LOD@105°C	1.5-3.0%w/w	2.85 % w/w	------
Lubrication	BUA	90.0 %to 110.0% and RSD not more than 5.0%.	S1:96.9 S2:94.5 S3:97.0 S4:97.4 S5:95.8 S6:96.8 S7:97.5 S8:95.5 S9:94.4 S10:97.0 Mean: 96.3, RSD: 1.2	------
Compression	Average weight Uniformity of weight Hardness Friability Thickness DT	90.0 mg ± 5 %Av. Av.weight ± 7.5% 50 to 100 N NMT 1% 2.60 mm ± 0.2 mm NMT 30 min.	Passes Passes 43-69 N(opt.) 0.25% 2.67-2.73mm 1 min 30 sec	Hardness limit to be changed

Table 34. Details of the monitoring and results of uniformity blend

	Dry mix	Blending Time:5 min	Blending Time:7 min	RFC
		S1:96.8	S1:97.4	S1:96.9
		S2:96.5	S2:93.2	S2:94.5
		S3:94.0	S3:91.9	S3:97.0
		S4:96.2	S4:96.0	S4:97.4
	S1:96.2	S5:97.3	S5:97.3	S5:95.8
	S2:96.1	S6:91.8	S6:95.2	S6:96.8
	S3:95.5	S7:96.5	S7:97.9	S7:97.5
	S4:95.7	S8:93.0	S8:98.0	S8:95.5
	S5:96.8	S9:93.0	S9:94.1	S9:94.4
	S6:96.8	S10:96.1	S10:98.1	S10:97.0
Mean	**96.2**	**95.1**	**95.9**	**96.3**
RSD	**0.58**	**2.06**	**2.31**	**1.2**

Blending without Magnesium stearate: 7 min
Lubrication with Magnesium stearate: 3 min

Blend Uniformity Analysis during different stage:
A) Stage: Dry mixing

Table 35. Blend Uniformity Analysis:

Dry mixing time	Min (%)	Max (%)	Average (%)	RSD
3 min	98.66	101.41	100.22	0.8
4 min	99.08	101.05	100.17	0.66
5 min	99.38	101.43	100.19	0.67

B) Stage: Lubrication
1. Composite assay – 100.95%
2. Blend Uniformity Analysis:

Table.36

Lubrication time	Min (%)	Max (%)	Average (%)	RSD
1 min	99.56	101.58	100.36	0.75
2 min	99.19	102.09	100.73	0.85
3 min	99.09	102.74	100.47	1.08

C) Stage: Precompression
1. Assay- 98.37%
2. Dissolution:

Table.37

Hardness	Min (%)	Max (%)	Average (%)	RSD
Low (4-5 Kg)	89.84	95.59	92.47	2.37
Optimum (6-7 Kg)	91.73	95.03	93.46	1.24
High (9-10 Kg)	89.37	95.12	92.26	2.50

Table 38. Details of the physical characteristics of final blend

Sr.no.	Parameter	Results
1	Description	White colored granular powder
2	Assay	96.3 %
3	Untapped density	0.63 g/cc
4	Tapped density	0.81 g/cc
5	Particle size distribution/Sieve analysis:	% Cumulative
6	Retention over #40	24.93
7	Retention over #60	30.58
8	Retention over #80	32.51
9	Retention over #100	35.80
10	Retention over #200	52.93
11	Pass through # 200	99.98

Compression details:
Details of the monitoring & observations during compression which was operated at optimum speed:

Type of M/C used: 20 station machine.
Type of tooling: B tooling
Punch size: 8/32" round SC punches with plain on the both sides.
No of punches: 4 sets
Weight of 20 tablets: 1.800 gm
Machine Optimum RPM: 25 RPM
Average wt: 88.65 mg
Hardness: 43-69 N
Thickness: 2.67-2.73 mm

DT: 2 min 30 sec
Friability: 0.25 % w/w

Table 39. Content uniformity analysis of tablets:

Sr. No	Initial (%)	Middle (%)	End (%)
1	99.20	97.79	99.75
2	99.06	98.00	97.72
3	98.10	97.24	97.06
4	96.82	97.49	97.43
5	97.98	97.69	97.74
6	98.49	99.95	97.09
7	98.72	98.24	95.94
8	99.16	100.12	97.01
9	99.02	97.08	97.06
10	98.60	97.61	99.00
Min	96.82	97.08	95.94
Max	99.20	100.12	99.75
Avg	**98.52**	**98.12**	**97.58**
RSD	0.74	1.08	1.11

Analytical method:

Analyte : Glimepiride
Bio analytical technique : LC-MS/MS
Instrument : LC-MS/MS (TSQ Quantum Finnigan)
Internal standard : Imipramine hydrochloride
Type of extraction : Solid phase extraction
Number of samples : A series (17x6 ml) of venous blood sample were Collected over a period of 24 hrs in each period.
Sampling time : Predose ,0.5,1.0,1.5,2.0,2.5,3.0,3.5, 4.0,5.0, 6.0,8.0,10.0,12.0,15.0,18.0 & 24.0hrs.
Washout period : 10days

Table 40. Pharmacokinetic parameters.

Parameters	Test formulation		Reference formulation	
	Mean ±SD	CV (%)	Mean ±SD	CV (%)
AUC_{0-t} (ng.h/ml)	2340.419±2474.57	105.73	2343.414±2411.36	102.9
AUC_{0-inf} (ng.h/ml)	3489.873±5722.7	164.84	3223.938±4865.01	150.9
C_{max} (ng/ml)	205.063±124.59	60.76	228.193±136.12	59.65
Residual Area (%)	10.124±14.95	147.70	08.857±12.87	145.36
T_{max} (h)	6.00±5.00	----	6.0 ± 4.5	----
K_{el} h^{-1}	0.149±0.05	35.46	0.155±0.05	32.68
$T_{1/2}$ el (h)	06.310±5.84	92.58	5.662±4.35	76.91
$MRT_{0-t\ (h)}$	9.033±1.98	21.90	8.891±2.27	25.49
$MRT_{0-inf\ (h)}$	12.408±8.45	67.77	11.357±6.48	57.02

Stability study:

Table 41. Stability data of Glimepiride tablet

Condition/ Period	Physical Observation	Assay (%)	D.T.	Dissolution (45 min)
Specification	White colored, round shaped uncoated tablet plain on the both side.	90-110	NMT 15 min	NLT 70
Initial	White colored round shaped tablet	98.6	1-33	95.1
60°C 1 M	Same as initial	98.5	3-04	92.6
40^0C 75%RH 1 M	Same as initial	100.74	3-18	92.2
40^0C 75%RH 2 M	Same as initial	99.62	-	-

4. Conclusion

The present study seems to be routine and of course Glimepiride tablets of various manufacturers are available in the Indian Market. But one view on excipients are highly illustrative, which should not be restricted to the knowledge of use in Glimepiride tablet formulations only. It is study for any a new conventional tablet dosage form in which selection, quantity and combination of excipients play a major role. Hence present effects should be observed as a highly fruitful study and may be helpful for new entrepreneur in establishing tablet as a dosage form.

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