AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

PROSPECTIVE PROCESS VALIDATION OF GLICLAZIDE TABLET

Onkar J. Deshmukh[1]*, Swaroop R. Lahoti[2], Vivek B. Rajendra[3], Bhushan S. Gulecha[1], Pavan Kumar Rawat[1], Snehal A. kulkarni[3]

1. Sherya Life Sciences, B9/2, MIDC Wlauj, Aurangabad-431136
2. Y.B.Chavan College of Pharmacy, Dr.Rafiq Zakaria Campus, Rauza Bagh, Aurangabad-01.
3. JSPM's Jayawantrao Sawant College of Pharamcy and Research, Hadapsar, Pune-28.

ABSTRACT

The objective of designing a dosage form is to achieve predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. In order to ensure quality of product various features are required, like chemical and physical stability, preservation against microbial contamination, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labeling, and validation. The present research work focused on prospective process validation for the gliclazide 40mg tablet. Tablet was manufactured by wet granulation method. Formulation of tablet using Maize Starch, Avicel Ph 102, PVP-K30, sodium starch glycolate, Purified Talc, Aerosil 200 and Magnesium stearate. Uniformity of dry mixing is excellent in 10min because % RSD found to be 0.4267-0.9021%. Granulating agent was prepared of desired consistency. Drying time 30 min is sufficient to achieve LOD 2-3%. Evaluation parameter of sizing shows effective LOD, % fine, BD & CI. Lubrication stage uniformity was achieved with 10min because % RSD found 0.8320-1.032% and flow properties was satisfactory. Compression machines optimum speed (20RPM) was satisfactory for effective compression. Based on results at each of the stages for the specified parameters it is concluded that gliclazide tablets can be effectively prepared with the desired specification & reproducible quality standards.

Keywords: Prospective Validation**,** Gliclazide, Tablet.

*Corresponding Author Email: vivekrajendra@gmail.com

Received 22 September 2011, Accepted 5 October 2011

Please cite this article in press as: Deshmukh OJ *et al.*, Prospective Process Validation Of Gliclazide Tablet American Journal of PharmTech Research 2011.

INTRODUCTION

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. To ensure product quality, numerous features are required, like chemical and physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labeling, and validation.[1]

Process development is actual transfer of the manufacturing process from R & D to production along with necessary knowledge & skill to be able to make the product, is referred to as technology transfer. The ultimate objective for successful technology transfer is to have documented proof that the process is robust and effective in producing product meeting with registered specification & cGMP requirements .[2, 3]

USFDA Defines validation as: "Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

WHO guidelines Defines validation as: "Validation is documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results." Validation act of proving, in accordance of GMPs that any process actually leads to expected results. Documented evidence that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

European commission: Validation is defined as "action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results."

Why Validation [5]

- If would not be feasible to use equipment not knowing if it will produce the product we want, not to employ the people with no assurance that they can do or fail to implement process checks or examination to assure that product meet specifications.
- The pharmaceutical industry uses expensive material sophisticated facilities and equipments and highly qualified personals.

- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failure, rejects, reworks, recalls, complaints are the sufficient part of total production cost.
- Detailed study and controlled of the manufacturing process batch validation is necessary if failure cost is to be reduced and productivity is improved. There are three reasons by pharmaceutical industry are concerned that their processes perform consistently expected that is, that are validated.
- Assurance of quality, cost reduction.

Process Validation [6]

"Process Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

Objectives of process validation [7]

1) The manufacturing process, in addition to the individual equipment, must be validated.

2) The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.

3) A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.

4) Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.

5) In the end, process validation will ensure a robust product that is highly reproducible over time.

Advantages of Process Validation [7]

1) Expanded real time monitoring and adjustment of process.

2) Enhanced ability to statistically evaluate process performance and product variables. e.g., individuals; mean; range; control limits

3) Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.

4) Improved ability to set target parameters and control limits for routine production, correlating with validation results.

5) Enhanced reporting capability.

Types of Process Validation [8]

Prospective Process Validation. Prospective validation is defined as the establishment of documented evidence that a system does what it purports to do based on a pre planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally under taken when ever new formula, process or facility must be validated before routine pharmaceutical formulation commences. In fact validation of process by this approach often leads to transfer of the manufacturing process from the development function to product. The objective of prospective validation is to prove or demonstrate that the process will work in accordance with a validation master plan or protocol prepared for pilot product trails.

Concurrent Process Validation. It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

Retrospective Process Validation. Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past.

***Revalidation*:** It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes.

The Regulatory Basis for Process Validation [6, 9, 10, 11]

The concept of process validation from its beginnings in the early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to various analytical, quality assurance, pilot plant, production, and sterile product and solid dosage forms considerations. In the early 1990s, the concept of preapproval inspection (PAI) was born and had as one of its basic tenets the assurance that approved validation protocols and schedules were being generated and that comprehensive development, scale-up, and bio-batch and commercial batch validation data were required in order to achieve a successful regulatory PAI audit. There are several important reasons for validating a product and/or process. First, manufacturers are required by law to conform to cGMP regulations.

Second, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches. Third, validation helps to ensure product uniformity, reproducibility, and quality. Although the original focus of validation was directed towards prescription drugs, the FDA Modernization Act of 1997 expanded the agency's authority to inspect establishments manufacturing over-the-counter (OTC) drugs to ensure compliance with cGMP. Once the concept of being able to predict process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The ultimate legal authority is Section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or were not operated or administrated in conformity with cGMP. The cGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)).

Strategy for Industrial Process Validation of Solid Dosage Forms. [6 - 9]

The strategy selected for process validation should be simple and straightforward.

The following five points gives strategy for process validation:

1. The use of different lots of raw materials should be included. i.e. active drug substance and major excipients.

2. Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).

3. Batches should be manufactured in the equipment and facilities designated for eventual commercial production.

4. Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.

5. Failure to meet the requirements of the Validation protocol with respect to process input and output control should be subjected to process requalification and subsequent revalidation following a thorough analysis of process data and formal discussion by the validation team.

MATERIAL AND METHODS

Gliclazide (Dishman Pharmaceutical), Maize Starch (universal starch), Avicel Ph 102 (Brahmar cellulose products private limited), PVP-K30 (ISP technology), sodium starch glycolate (DMV International), Purified Talc (Analyst India), Aerosil 200 (Degussa) Magnesium stearate (Nikita chemical), purified Water (INH) was used for this Formulation. All raw material used of BP grade and chemicals used in the analysis in the study were of analytical grade.

Machineries:

Machineries and equipments used was as sifter, multi mill (Ganson Ltd), rapid mixing granulator [RMG] (250L, Sainath), steam kettle (Anchor mark), fluid bed drier [FBD] (250L,Pam Glatt), octagonal blender (250L, Sams Techno Mehch), compression machine 27 station single rotary (CIP), UV visible spectrophotometer (Shimadzu 1800), six stage dissolution rate test apparatus IP/BP/USP (Tab machine), Monsanto hardness tester (Rolex), disintegration and friability test apparatus (Electo lab), Mitutoyo thickness tester.

Manufacturing process [10-11]

Tablet was manufactured by wet granulation method using ingredients as per Table 1. During manufacturing temperature NMT (Not more than) 25^0c & RH NMT 50% were maintained. After dispensing of material they were sifted through sifter. Gliclazide, Avicel Ph 102 was dry mixed in RMG at slow speed for time intervals 5min, 10min & 15min.

Table 1: Composition of various process validation batches.

Ingredient	Batch 1	Batch 2	Batch 3	Mesh
Gliclazide	4 kg	4 kg	4 kg	40
Avicel Ph 102	5.095 kg	5.095 kg	5.095 kg	40
Maize starch	1.5 kg	1.5 kg	1.5 kg	40
PVP K30	0.1 kg	0.1 kg	0.1 kg	40
Sodium starch glycolate	0.15 kg	0.15 kg	0.15 kg	40
Talc	0.09 kg	0.09 kg	0.09 kg	60
Aerosil - 200	0.015 kg	0.015 kg	0.015 kg	60
Magnesium stearate	0.05 kg	0.05 kg	0.05 kg	60
Water	3.5 Liter	3.5 Liter	3.5 Liter	--

Granulating agent was prepared in steam kettle, maize starch for paste was dispersed in 1/3 quantity of P/W, remaining quantity in steam kettle with boiling to this PVP-K 30 & starch mucilage was added with stirring and cool 45 -50^0c. To dry mix granulating agent was added and mixed on slow and high speed till desired consistency of dough mass was formed. Then this material was wet passed with turbosifter with mesh with impact forward slow speed. Drying in

FBD (Fluidized bed dryer) was done at inlet temp 65^0c till outlet temp. reaches 38- 40^0c & LOD 2-3% w/w for 20min, 25min & 30min. Sizing was done by passing dried mass through 20 mesh sieve & retention generated passed through 1.5mm mesh of multimill knives forward, slow speed. Lubrication was done in octagonal blender after geometric mixing of sifted lubricant with sized granules at 14RPM, slow speed for 5min, 10min & 15min intervals.

Compression of Batches:

Tablets were compressed using 6.35mm, FB round Punch, having break line on Upper punch & lower punches plain. Each 110 mg tablet contains 40 mg Gliclazide. The specification for tablet was average weight 110mg (±5%), hardness NLT 3kg/cm^2, thickness 2.80mm(±0.3mm), friability NMT 1%w/w, DT NMT 15 Min, Assay 100%(± 5%), Dissolution NLT 70% of stated amount released in 45 min.

Process validation stage, control variables and measuring justification [12-16]

In sifting sieve integrity was checked before and after sieving. Dry mixing uniformity, the samples are withdrawn (5, 10 & 15min) and analyzed. Consistency of binder was evaluated in preparation of granulating agent. Wet mixing dough mass consistency was evaluated by studying speed of chopper & beater, time of mixing and ampere reading. Drying stage LOD obtained within predefined interval of drying. Representative samples were selected for evaluation of % fine, LOD, BD & CI. Lubrication stage uniformity of mixing, the samples were withdrawn with predefined time interval (5, 10&15min) and representative samples was studied for %fine, LOD, BD & CI. Compression stage speed challenge study was done by compression of 30% batch at minimum speed (15 RPM), 30% at maximum speed (50 RPM) & remaining at optimum speed (20RPM) & parameter evaluated were appearance, weight variation, thickness, hardness, DT, friability, assay & dissolution.

RESULTS AND DISCUSSION

Integrity of sieve before and after was satisfactory for all Batches. Uniformity of dry mixing was obtained by assay of 30 locations per batch & % RSD (must be NMT 2% for effective mixing) was calculated by mean assay of all location as shown in Table 2.

Table 2: Dry mixing results

Batch no.	% RSD		
	5 min	10 min	**15 min**
1	1.926	0.4267	**1.2021**
2	1.810	0.9021	**1.0951**
3	**1.680**	**0.8295**	**1.2121**

% RSD was calculated by taking mean of assay of all 10 locations [{Top(Four location), middle(Two location) & bottom(Four location)}].

Consistency of granulating agent was found excellent with given proportion. Dough mass consistency was excellent with respect to speed of beater & choppers as per Table 3. Drying stage LOD obtained at different time interval was shown in Table 4. Sizing process evaluation result was as per Table 5. Uniformity of mixing in lubrication stage obtained by assay of 30 locations per batch & % RSD was calculated by mean assay of all locations. The % fine, LOD, BD & CI result are shown in Table 6. Compression stage speed challenge study evident in Table 7.

Table 3: Wet mixing result

Batch no	Chopper (speed & time)		Chopper (speed & time)		Ampere reading end point	Dough mass Consistency
Speed	Slow	Fast	Slow	Fast		
1	1 min	2 min	3 min	4 min	20	Excellent
2	1 min	2 min	3 min	4 min	22	Excellent
3	1 min	2 min	3 min	4 min	22	Excellent

Table 4: Drying stage results

Batch no	Loss on drying (% w/w)								
Time	20 min			25 min			**30 min**		
Layer	T	M	B	T	M	B	T	M	**B**
1	4.40	5.0	5.25	3.60	3.20	3.20	2.48	2.65	2.50
2	4.20	5.0	5.0	2.70	2.40	2.80	2.50	2.63	2.52
3	4.20	3.78	4.7	2.75	2.55	3.20	2.49	2.75	2.49

T=Top M=Middle B=Bottom

Table 5: Sizing stage results.

Batch no	% Fine	% LOD	BD	CI %
1	34.10	2.50	0.556	11.11
2	38.90	2.52	0.598	10.59
3	36.04	2.49	0.605	11.16

BD= Bulk density (gm/ml), CI= Compressibility index (%)

Table 6: Lubrication stage results

Batch no	% RSD			% Fine	%LOD	BD	CI %	% Yield sizing
Time	5 Min	10 min	15 min					
1	1.973	0.823	1.321	33.20	2.56	0.491	10.23	97.83
2	1.753	0.825	1.231	37.35	2.62	0.526	9.47	98.34
3	1.888	1.032	1.324	35.24	2.59	0.543	10.24	95.76

% RSD was calculated by taking mean of assay of all 10 locations [{Top(Four location), middle(Two location) & bottom(Four location)}].

Table 7: Compression results at different speeds of compression machine

Stage	Test	Batch Number		
Start up		1	2	3
	Uniformity of weight (mg)	Complies	Complies	Complies
	Average weight (mg)	110.00	110.32	111.00
	Friability(% w/w)	0.10	0.12	0.13
	Disintegration time	4 min	4:30 min	5 min
	Hardness(kg / cm^2)	5	5	5
	Thickness (mm)	2.80	2.83	2.80
	Assay %	100.2	99.38	99.21
	Dissolution %	90.50	92.20	90.10
Different speed 20 RPM	Uniformity of weight (mg)	Complies	Complies	Complies
	Average weight (mg)	111.3	110.40	110.45
	Friability (% w/w)	0.11	0.13	0.14
	Disintegration time	4:30 min	4 min	4:20
	Hardness(kg / cm^2)	5	4	4
	Thickness (mm)	2.80	2.85	2.83
	Assay %	99.82	99.32	99.54
	Dissolution %	90.20	90.10	92.10
Different speed 50 RPM	Uniformity of weight (mg)	Complies	Complies	**Complies**
	Average weight (mg)	110.30	110.20	111.10
	Friability (% w/w)	0.12	0.10	0.13
	Disintegration time	4:30 min	4 min	4:40 min
	Hardness(kg / cm^2)	4	4	4
	Thickness (mm)	2.85	2.84	2.84
	Assay %	99.52	99.45	99.23
	Dissolution %	91.20	90.30	92.40

CONCLUSION

The selected sieve was suitable for sifting. Uniformity of dry mixing is excellent in 10min because % RSD found 0.4267-0.9021%. Granulating agent was prepared of desired consistency.

Dough mass was formed satisfactory within 7min wet mixing & ampere reading 09-11 Amp. Drying time 30 min is suitable for achieving LOD 2-3%. Evaluation parameter of sizing shows effective LOD, % fine, BD & CI. Lubrication stage uniformity was achieved with 10min because % RSD found 0.8320-1.032% and flow properties was satisfactory. Compression machines optimum speed (20RPM) was satisfactory for effective compression. Therefore based on results at each of the stages for the specified parameters it is summarized and concluded that with the prospective process validation for the gliclazide 40mg tablet produces the batches with no significant deviation and reported documented evidence, that process can be effectively produce a product which complies with the present specification & reproducible quality standards.

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