International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Technology Transfer and Process Validation of Metformin Hydrochloride Immediate Release Tablet

Sanket Kumar[1], Annie Gupta[2], Saurabh Kumar[3]

[1]Student, Lloyd Institute of Management & Technology, Noida
[2]Associate Professor, Lloyd Institute of Management & Technology, Noida
[3]QA Manager, Grampus Laboratories, HP

ABSTRACT

Metformin Hydrochloride, inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK, enhancing insulin sensitivity (via effects on fat metabolism) and lowering cAMP, thus reducing the expression of gluconeogenic enzymes. Metformin improves blood sugar levels by lowering the amount of glucose (sugar) that we absorb from our diet. It also helps stop the production of new glucose and improves insulin sensitivity. Metformin Hydrochloride is videly used in the form of sustained release formulation of Tablets. The study aimed to formulate and validate novel process for the Metformin Hydrochloride in immediate release pharmaceutical solid dosage forms. The wet granulation method used for formulation of Metformin Hydrochloride Immediate Release Tablets. Metformin Hydrochloride 500 mg, 850 mg, 1000 mg film coated tablets was prepared using FBE granulation technology on lab scale size. This study was carried out through a systematic plan; critical parameters were optimized to engender a stable & robust manufacturing process. The result of all three batches & its critical steps clearly shows consistency & reproducibility of parameters and all results. Hence the manufacturing method of Metformin Hydrochloride 500 mg, 850 mg, 1000 mg Film Coated tablets are validated at above parameters & equipments. Three validation batches of commercial scale batch size were taken successfully and monitored the in-process critical parameters for commercial batches. Metformin Hydrochloride tablets were manufactured within specified Limits for meeting all quality attributes and loaded for stability study. The overall successful three consecutive validation batches of Metformin Hydrochloride film coated tablets (500, 850 & 1000 mg) verifies the international technology transfer success.

Keywords: Immediate Release, Process Validation, Robustness, Solid dosage form, Metformin Hydrochloride, Technology Transfer.

INTRODUCTION

The following section deals with brief introduction to tablets dosage form, technology transfer, stability study & finally process validation sequentially.

"A dosage form is the physical form of a dose of a pharmaceutical compound used as a drug or medicine intended for administration or consumption."

Common dosage form includes tablets, pills, capsules, syrup, aerosol, inhaler, liquid injection, Dry Injection, Ointment, Lotion, Suspension. Dosage Form decides the route of administration of drug.
Various dosage forms may exist for a single particular drug as above mentioned, but among them solid dosage form (Tablets & Capsules) covers 80% of drugs formulations (Bankar & Anderson, 1986a).
Even other dosage formulations options are available "Tablets holds premier position among all dosage forms," Major advantages of tablets are simplicity, low cost & speed of production. (Mehta, 2002a) The later section introduces tablets dosage form.

1.1 TABLETS

"Tablets may be defined as unit solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either direct compression or moulding methods."
A Tablet has numerous advantages over other dosage form, among which are patient convenience & stability of a drug substance in a drug dosage form. This is the unit dosage form having greatest capabilities among all the oral dosage form for the dose precision and least content variability (Bankar & Anderson, 1986b).
There are various types of tablets are available in market amongst them commonly used types of tablets classified as per their drug release profile are as follows (Mehta, 2002b).

1.1.01 Types of tablets:

- Sugar-coated tablets
- Film-coated tablets
- Enteric-coated tablets
- Layered tablets
- Controlled release tablets
- Immediate Release Tablets
- Buccal or sublingual tablets
- Fast dissolving / disintegrating tablets. *(Mehta, 2002c).*

The product under transfer is a film coated tablets; the following section gives brief idea of film coated tablets.

1.1.02 Film Coated Tablets:

In pharmaceutical industries final appearance of product (tablets) is important for marketing point of view. There are some other reasons of film coating as to protect tablets from physicochemical damage during handling, to mask smell or taste etc. The initial film coating composition employed one or more polymers, which is usually includes a plasticizers for the polymers and possibly a surfactant to facilitate spreading. *(U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Guidance for Industry, 2015).*

The non functional film coating process is an attractive tablet coating method when aqueous-based coating process applied. Drug like as Metformin having daily high dosing quantity requirements & satisfactory plasma half life, which is the basis for selection of Immediate Release tablets. The coating basic formula of film coating is obtained from past experience or from various literatures *(Patel, et al., 2009a).*

The Film coated tablets are generally manufactured by unit operations as given in following flow diagram & each operation describe below.

1.1.03 Tablets manufacturing method: *(Rane & Parmar, 2009a).*

Diagrammatic presentation of film coated tablet manufacturing process is described as.

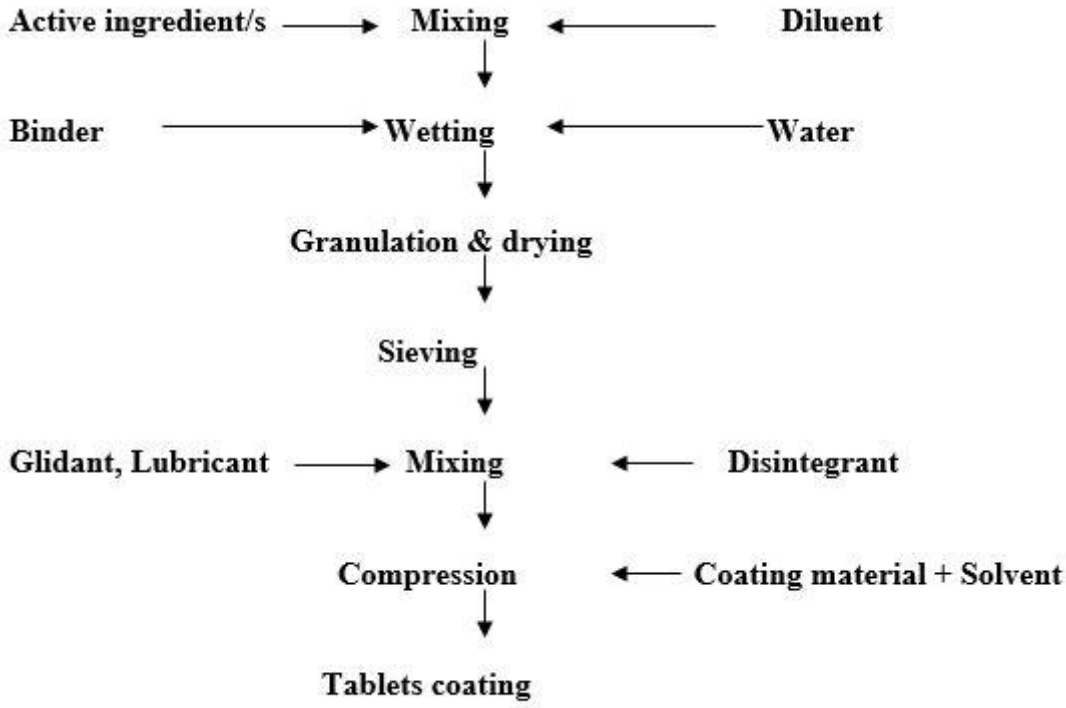


Fig. No. 1.01: TABLETS MANUFACTURING FLOW CHART.

1.1.04 Mixing & blending:

The mixing step is most critical process when active drug contents of dosage form are very less in quantity, while if the active contents are more then mixing operation is not too critical for uniform content distribution. The diffusive mechanism of octagonal blender is commonly employed in pharmaceutical industries for powder mixing. *(Rane & Parmar, 2009b)..*

1.1.05 Conversion in Granular form:

Granulation may be defined as a size enlargement process, which converts small particles into physically stronger & larger agglomerates. Powder granulation mainly done by three processes as solvent granulation, granulation without solvent and direct compression method. The method of granulation is selected on the basis of properties of the drug, behaviour of the powder during mixing processing & the properties required for tablets. The three granulation methods described as follows in briefly. *(Rohokale, et. al. 2010).*

a) Dry granulation:

In this technique there is no use of liquids (Water, Isopropyl Alcohol etc.). The process involves the formation of large granules without using solvent. Then the large granules are shifted or milled to produce fine granules. The granules formed are then compressed to form tablets.

- Slugging machine
- Roller compactor *(Srinivasan, 2015).*

b) Direct compression:

The term direct compression is used to define the process by which tablets are compressed directly from powder blends of active ingredients and suitable excipients (including fillers, disintegrants and lubricants), which will flow uniformly in the die cavity of compression machine. This method generally employed for products with good compressibility properties. *(Mehta, 2002d).*

c) Wet granulation:

Wet granulation is the process in which liquid is added to powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules are then compressed to form tablets *(Shiromani, 2006a).*

Wet granulation is the best option when active content of tablets above 70% and when the tablet size is larger it gives better compressibility properties. The wet granulation is mainly done by using various equipments having different mechanism.

- Shear granulator
- High speed granulator
- Fluidized bed granulator

Various methods are used for wet granulation. But the Fluidised Bed Granulation is commonly used when active drug contents are more & when desired flow properties expected after granulation. For highly water soluble drugs mass mixer granulation is commonly used instead of high shear granulation to avoid lumps formation during granulation process. In the current product under transfer Fluidised Bed Granulation process is used. *(Pamglatt, 2009).*

Fluid beds spray granulation:

The granules prepared by using mass mixer are very homogeneous. The different type of granules (size, density, porosity) can be influenced over a wide range by the adjustment of various parameters. The granulation of fine powder can be performed in mass mixer by spraying the solvent or a solvent/binder solution on to a fluidised powder bed (top spray) or by concurrently spraying the solvent or solvent/binder in to a segregated dilute phase powder stream. The mass mixer top spray granulation was mostly used for preparation of homogeneous granules with desired flow properties *(Parikh & Mogavero, 2005).*

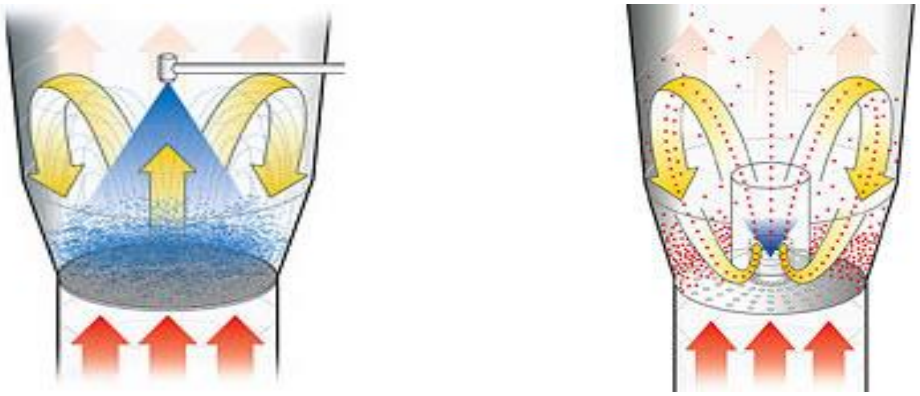


Fig. No. 1.02: A) TOP SPRAY PATTERN B) BOTTOM SPRAY

As the granules formed next step is sifting of granules through selected sieve number. After sifting, granules were blended & lubricated using proper lubricant to promote flow properties. The compression is the next step of lubrication.

1.1.06 Compression:

Tablets compression is the disc formation of granules agglomerate by mechanical force in to compact moulding device. As various shapes of tablets like capsule, round, oval are available in market depends on the punches dimensions.

The final lubricated granules fill volume (Filling depth) determines tablets weight & ultimately other compressed tablets properties. All of the three tablets compression steps are critical: Flow, Compress and Eject (Berry, 2007a).

With few diluents, rotary tablet compression machine operate the same basic way. Many machines having very advanced features that may provide better compression, tablet morphology and weight control at high speed. Having consistent flow of a granules provides the needed avenues to control tablet average weights. Tablet hardness is depending on thickness and weight of tablet (Shiromani, 2006b).

A given volume of granules compressed to a specific thickness will result in a given hardness. Though excipients play a large role in the dissolution rate of tablets, so does tablet hardness. When setting up the tablet compression, adjust tablet average weight, adjust average thickness, weight variation, Friability and machine speed, to get proper hardness.

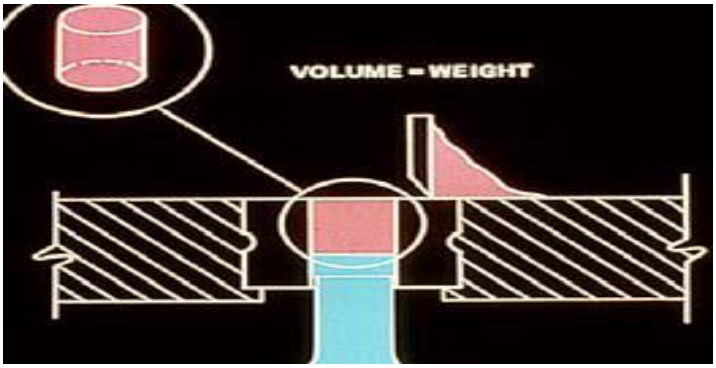


Fig. No.1.03: COMPRESSION MECHANISM.

1.1.07 Tablets coating:

If a tablet meets its physicochemical specifications, it must need to add a coating operation for many purposes as it improves taste, makes the tablet stronger and tougher, Pleasant color, and makes the tablet easy to handle during manufacturing, packing and transportation.

For film coating a water based solution is going to use instead of using a non aqueous solvent to give pleasurable coat. Tablet film coating equipment was evolved to enhance this water percent drying capability. Coating mainly done by using conventional pan system, perforated pan system, but perforated pan system is commonly used. This coating system continuously supplies hot air, at the same time pulling air through small holes in the coating drum. The drum is commonly with small holes called perforated coating pan. (Bankar & Anderson 1986c).

Nowadays latest technology like vertical coating pan systems are emerging & some manufacturers claiming use of mass mixer for coating of small size tablets.

The shape & size of tablets under coating operation influence coating process variables widely. The capsules shapes tablets coating is more difficult than round, circular tablets. (Patel, et al., 2009b).

After successful coating operation tablets are packed in suitable packing system which should not interfere in stability of the tablets during its storage & handling. Tablets are mainly packed in blister, strip, and bottle packing. In current project the product under transfer is packed in blisters pack.

Each of the novel product manufacturing process is considered as technology, which may utilise on commercial scale through technology transfer. Following section gives brief background of technology transfer.

1.2 TECHNOLOGY TRANSFER

"Technology Transfer is a process of transferring technique & responsibility from research and development phase to production group. Whether transfer takes place between two sites, two companies, a company & third party manufacturer, or from R & D to a pilot plant or commercial facility."

In many industries, there is no formal technology transfer procedure & in others, it is poorly managed. This may leads to manufacturing problems difficult & delayed marketing of product. (Ahmed, et. al., 2005).

The feasibility study plays important role at receiving site, because all the related knowledge, information & skill essential for process & equipment selection.

The steps through technology proceeds are represented as follows.

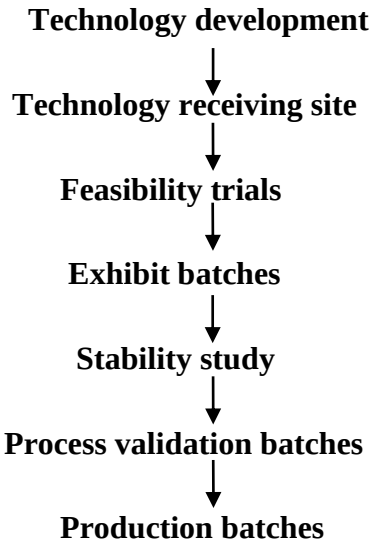


Fig. No.1.04: FLOW CHART OF TECHNOLOGY TRANSFER

In case of Technology transfer the technology developer gives rights of product manufacturing to technology receiver. The dossier data supplied by technology developer is the only source information of previous study. The technology receiver compiles the data satisfactorily and takes feasibility trial for the technology feasibility assessment *(Berry, 2007b).*

After successful feasibility trials the exhibit batches are going to plan. The exhibit batches samples then loaded in stability as per ICH guidelines. If it passes stability study satisfactory, three validation batches was planed. The technology transfer completes with the successful validation of three consecutive batches.

Technology transfer involves mainly stability study of product & process validation study, which is described as in following section.

1.3 STABILITY STUDY

Food and Drug Administration and International Conference for Harmonization specifies and described, the guidelines for stability study of drug, as a technical requirement for the registration of pharmaceutical products. The stability study describes evidence for how the quality of a drug deviates with time under the influence of a variety environmental factors such as temperature, humidity & light.

The ICH guidelines have established the real time stability testing should be done at 25°C/60% RH up to shelf life of dosage form. Accelerated stability testing should be done at 40°C/75% RH for 6 months. Stability testing at intermediate storage condition should do at 30°C/65% RH. Table No.1.01 different storage conditions and duraion of stability testing. *(ICH Guidelines Q1 a (R2) August 2003).*

Table No.1.01: ICH PARAMETERS FOR STABILITY STUDY

STUDY	STORAGE CONDITION	DURATION
Long Term	25°C ± 2°C, RH 60% ± 5%	60 months (up to Expiry)
Intermediate	30°C ± 2°C, RH 65% ± 5%	12 months
Accelerated (ACC)	40°C ± 2°C, RH 75% ± 5%	6 months

1.4 PROCESS VALIDATION

Process validation for solid oral dosage forms in the pharmaceutical industry is required by the Current Good Manufacturing Practices (cGMP) for finished pharmaceutical products. According to the FDA's guideline, process validation is defined as follows:

"Process validation is documented evidence which assures that a specific process will produce a quality product meeting its specifications and quality characteristics."

European commission definition for Validation as follows:

"Process validation is a documented evidence which assures that the process operates within specification can perform efficiently reproducible to produce a quality drug product meeting its quality parameters.''

Depending on the complexity of the manufacturing process, several equipment, unit operations, and product parameters are optimized at a smaller scale compared to the production size batch. Once the formulation composition and manufacturing process are optimized at the smaller scale, the next stage involves optimizing the process at a larger scale, usually using production equipment by technology transfer group. Increases in batch size or scale-up are accomplished by using larger, high speed equipment that may require adjustments to the process parameters established using small scale equipment (U. S. FDA Guidelines 1987; 2008).

1.4.01 Benefits of process validation:

- Compliance with government regulation
- Harmonization of global GMP's
- Acceptable quality is attained
- Reduction in risk of process variables
- Built in quality & hence the small size production batches
- Batch failure, loss during work , rejection & wastage
- Increasing operational safety

- Rationalization of facility (Agalloco & Carleton, 2008).

1.4.02 Types of process validation:

(a) Prospective validation (Premarket validation)

(b) Retrospective validation

(c) Revalidation

(d) Concurrent Validation

Prospective process validation is done during technology transfer. Hence the product under transfer undergoes prospective validation.

a) Prospective process validation:

Prospective process validation is done before product distributed in market. This type of validation is applicable for new drug products and their manufacturing processes. Most validation efforts require some experimentation to generate validation support data. This type of process validation is carried out with the introduction of new drug products and their manufacturing processes on three consecutive successful production size batches. (Vadnere, et. al., 2006).

The objective of prospective validation is to prove that the process will work in accordance with a validation master plan or protocol prepared for pilot-product (100 × sizes) trials. In practice, usually two or three pilot-production (100 ×size) batches are prepared for validation purposes.

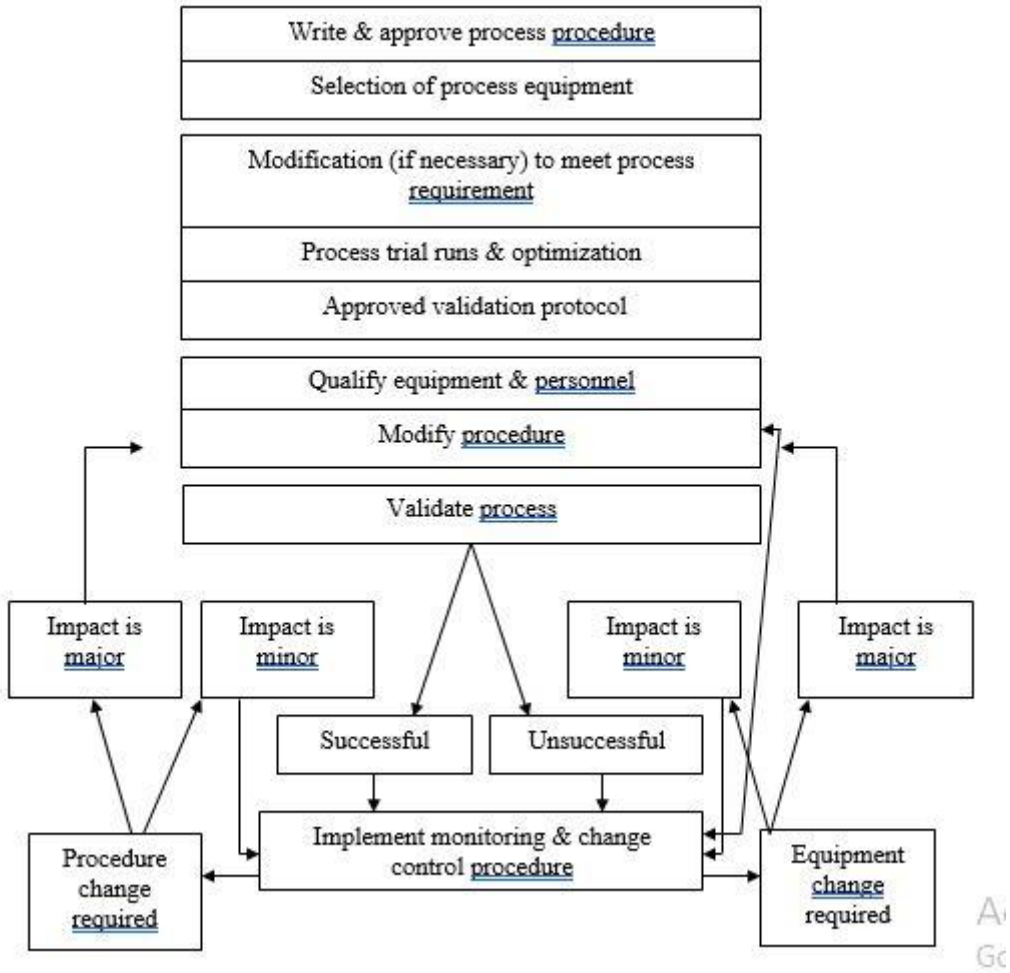
During technology transfer feasibility, optimization and validation batches are the responsibility of technology transfer department.

The plan selected for process validation should be simple and unidirectional. The following factors are considered during prospective process validation:

1. The use of different baches of components should be included, i.e., Active Pharmaceutical Ingredients and excipients.
2. Manufacturing Process should be run in succession and on different days and shifts.
3. Target Batches must be manufactured in equipment and facilities designed for eventual commercial production.
4. Critical process parameters must be set within their operating ranges and should not above than their upper and lower limits during process Unit operation. Output responses should be well within finish product specifications.
5. If critical variables are fails to meet the specification of the validation protocol with respect to process inputs and output limits then process should be subjected to re-validation following a thorough analysis of manufacturing process data and Formal review by the CMC coordination committee (Chao, et. al., 2003a).

The prospective process validation diagrammatically represented in following

Fig. No.1.05 : PROSPECTIVE PROCESS VALIDATION:



b) Retrospective process validation:

The retrospective process validation is chosen for established products whose manufacturing processes are stable and when on the basis of economic considerations alone and resource limitations, prospective validation programs cannot be justified.

Retrospective process validation produces evidence that a system does what it is supposed to based on a review and analysis of past information. It is normally conducted on a product already being distributed in market and is based on combined production, testing and control data. (Chao & Forebes, 2003b).

c) Revalidation:

This type of validation is going to conducted in following conditions as.

- Change in a critical component
- Change in a critical piece of modular equipment
- Change in a facility and/or plant (location or site)
- Paramount increase or decrease in Batch size that fail to meet the specification.

d) Concurrent validation:

Concurrent validation is carried out during normal production. This process validation method is effective only if the development stage has resulted in a proper understanding of the parameters of the

process. The first three engenderment- batches must be monitored as comprehensively as possible. The nature and specifications of in-process and final tests are based on the evaluation of the results of monitoring.

1.4.03 Process validation protocol & report:

As US FDA defines validation protocol is a written stating how validation will be conducted, including test parameters, product characteristics, production equipments & decision points on what constitutes the acceptable test results.

The validation batches results are documented in a process validation report (PVR). The validation report should include, a description of the process, and detailed summery of the results obtained form in process and final testing. The current project involves technology transfer of tablets manufacturing process**.**

CHAPTER-2
LITERATURE REVIEW

Literature suggests that a great deal of studies has been performed by the scientists on Metformin Hydrochloride Tablets.

Patel, et. al., (2013a): Described the types of Process Validation:

TYPES OF VALIDATION

Prospective Validation:

The established documented evidence that a system does what it purports to do based on a pre-planned protocol is called Prospective Validation. This validation is carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive production-sizes. (Consecutive batches) [45].

Concurrent Validation:

It is similar to prospective validation, except the fact that operating firm will see the product during the qualification, to the public at its market place, and also it is similar to retrospective validation. This validation comes in process monitoring of critical processing steps and product testing. This helps to generate and document evidence to show that the production process is in a state of control [45].

Retrospective Validation:

The established documented evidence that a system does what it purports to do on review and analysis of historical information is called retrospective validation. This is concluded by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process is done for a product already in distribution [45].

Panchal, et. al., (2012): NEEDS OF IMMEDIATE RELEASE

A. For Bolus administration of drug.
B. For good absorption of drug.
C. For good bioavailability of drug.
D. For immediate effect. [41]

The following section gives brief discussions of formulation design, process & excipients selection then critical process variables for given formulation.

Manthan, (2008): Pharmaceutical technology generally originates in developed country, because of mainly economic constrain. In other hands developing countries having very poor financial, equipment or human capital, so developing countries like India generally interested to exploit technology through technology transfer (in licensing). In current project technology transfer is from outside country to India [33].

Cheng, et al, (2004): The drug under transfer is solid immediate release Metformin Film coated tablets. Solid & liquid dosage form of Metformin shows same dissolution but both are permeability limited for absorption because Metformin Hydrochloride comes under BCS class 3 Drug, (High Solubility & low permeability). Hence no solubilizers are added in to the given formulation [14].

Wong, et al., (2005a): The bioavailability of Metformin is between 40-60% decreasing with increasing dose due to saturation mechanism. The Metformin Hydrochloride is mainly absorbed in upper part of gastro intestinal track as it provides larger surface with microvilli in upper portion of GI track. The transcellular & Para cellular both systems involves in Metformin absorption through epithelial cell membrane. The mechanism involves in drug transport is passive diffusion & carrier mediated transport. The residence time of Metformin in upper GI track is about 4 to 6 hrs & it having poor colonic absorption so it needs low disintegration time of tablets for fast drug content release. As the drug absorbs in body through a period of four to six hrs & having poor colonic absorption Immediate Release dosage form is best option for dosage design [69].

Shiva, et al., (2009): Metformin Hydrochloride now present in extended release dosage form for long time drug release. But Metformin Hydrochloride is very highly soluble in water, it is not easy to control dose bursting the release in order to obtain a sustained release formulation [57].

Kumar V., (2000a): Metformin Hydrochloride is considered as high dose drug as its formulations contains a substantial part of the total compressed tablet weight.

This high dose drug have poor physical characteristics for compression, hence not use the direct compression method of tablets manufacturing [29].

Pfeffer, et al., (2006): Metformin Hydrochloride is hygroscopic, presents stability problems, and is not inherently compressible. Consequently there is need to provide a free flowing & cohesive Metformin Hydrochloride composition capable of being compressed in to strong & large tablets with an acceptable in vitro dissolution profile. This properties limits selection of proper excipients in formulation as Excipients uses [48].

Rowe, et. al., (2003): Diluents added in to formulation to increase the bulk weight of the blend but in given formulation it provides good compression properties. Other most commonly used excipients in wet granulated product are binder. Binder imparts cohesive qualities to the powdered material but they affect tablets hardness. Hence disintegrant are often included to insure that the tablet has an acceptable

rate of disintegration time. Lubricants are typically added to prevent the tableting material from sticking to punches, minimize friction during tablets compression, & allow for removal of the large size compressed tablet from the die. The Metformin tablets film coated as it provides resistance to physicochemical damage & some individuals reported nausea with characteristics smell of the Metformin [52].

Wong, et al., (2005b): The non functional film coating of Metformin was done by using HPMC as a polymer with diluents for achieving desired weight build up. The film coating also includes coloring matter with smoothening agent for uniform coating.

Choice of all excipients will depends on the chemical & physical properties of drug, behavior of the mixture during processing & the properties of the final tablets.

Preformulation studies were done to determine the chemical & physical compatibility of the active component with proposed excipients [70].

Kumar V., (2000b): Metformin is not directly compressed because it is not having inherent compressibility properties. Wet granulation is often preferred over direct compression, because wet granulation has a greater chance of overcoming any problems associated with the physical characteristics of various ingredients in the formulation. The wet granulation method is used to convert a powder mixture into granules having suitable flow & cohesive properties for tableting. The size & shape of particles comprising the granulate to be compressed are optimized through the wet granulation process. The active content in formulation is more than 70% with hygroscopic nature it forms lumpy mass in RMG process. These properties restrict it for FB Granulation to get desired granules porosity, granules size, particles distribution & their flow properties[30].

Lawrence X. Y., (2008) Blending step is less critical when drug itself acquires larger portion of tablets weight. The large tablets size produces a lot of problems during compression. High compression force required for compression of larger size tablets and it also arise weight problems.
The large size tablets produce many problems during film coating. The caplet shape large size tablets commonly produces problems like edges loss, breakage, sticking & capping during coating. To avoid edged loss pan speed kept at lower side at initial time of coating. To understand more about process variables, following section gives idea about critical process variables [31].

Glodek, et al., (2006a): “Critical process parameters are the inputs of process, when varied beyond a limit range, has a direct & significant influence on a critical quality parameters”

Typical sources of variability may include process, equipments, its capabilities, calibration limits, testing method variability & raw material (like. API & Excipients variability in lots or vendors, human factors, sampling variability, environmental factors of plant) [22].

Among all of them some of critical variables related with process of each unit operation is discussed as follows:

Milling:

Critical variables during milling operation listed below

- Loading rate
- Powder size required
- Blades direction

Glodek, et al., (2006b): **FBG parameters:**

The mixing of active pharmaceutical ingredients depends on the time of mixing & air flow of FBG, which provides the uniform distribution of drug during mixing.

Amount of granulating solution added, inlet temperature, product temperature, atomization pressure, air flow & spray rate are critical variables. This variable affects granules strength (fines), bulk density of granules, flow characteristics of granules.

Drying of wet granules directly affect LOD, as LOD is more in granules it will lead to poor flow & poor hardness. If LOD is less it will leads to capping, high friability and chipping. During drying the desirable LOD will be maintained in the granules [23].

Glodek, et al., (2006c): **Powder mixing:**

This step involves mixing of granules with other blending material. The purpose of blending is to get a uniform distribution of active content (Metformin hydrochloride)

This is flowed by mixing of the blend with lubricant to get good flow & anti-adhesion property of blend. Mixing speed & time is critical parameters as less blending results in non uniform distribution of drug & poor flow, whereas more blending will result in de-mixing ultimately non uniform distribution & increase in disintegration time [24].

- Blender speed
- Blending time
- Blender occupancy

Lionberger R. A., (2008): Tablet compression:

This step converts blended granular material in to tablets as per parameters. Speed of machine & hopper occupancy is major variables. Speed of machine influence compression cycle thus impacts on physicochemical properties of tablets. Hopper occupancy can influence blend flow rate & physical uniformity of blend, thus impacts physical properties of tablets. The tablets under transfer having larger size hence machine speed kept lower to get proper compression force [32].

- Machine rotation speed (RPM)
- Feeder flow rate
- Tablets weight
- Pre compression force
- Main compression
- Upper punch penetration
- Ejection force
- Cam used
- Room temperature & humidity

- Fill volume

Ispcorp.com, (2009a): Film coating:
The coating step involves the covering of tablets surface with polymer film. The RPM of coating pan should be within the specified limit for even distribution of the coating solution on tablet. The high speed at starting of coating leads to edges loss. The spray rate is most important for neat, proper & uniform surface coating, air pressure imbalance results in peeling or rough surface of tablets [60].

Ispcorp.com, (2009b): If the temperature of coating pan is not within limit specified then the drying will be insufficient, which results twining & sticking of tablets or rough surface & cracking of the film. Gun to bed distance affects tablets surface smoothness [61].

- Coating solution mixing time & speed
- Coating powder addition rate
- Coating solution spray rate
- Pan load
- Pan rotation speed
- Atomization pressure
- Pre heating time
- Inlet air temperature
- Bed temperature
- Exhaust temperature

Packaging:
Sealing & forming temperature with the speed of machine are important variables.
Adequate cavity/pocket forming temperature essential for proper formation while sealing temperature is needed for sealing of the formed blisters.

Bolton S., (1997): Quality control of drug product:
Adequate specifications are applied for the drug product for both release and shelf-life, including a specification for uniformity of dosage units (Ph. Eur. 2.9.40; acceptance value NMT 15) and an adequate specification on Impurity A (1-cyanoguanidine; NMT 0.02%). Also the other Ph. Eur. impurities (B-F) are adequately limited (NMT 0.1%). In view of high maximum daily dosage (3 g, is > 2 g) the specification of any individual unknown impurity NMT 0.10% is correct [11].

Michel Levin, (2006): All other specifications are in accordance with or more tight (microbiological purity) than specifications or are otherwise not unreasonable. All quantitative analytical methods have been adequately validated [39].

Hinak T., (2000): Breakability:
The 1000 mg tablets contain a score-line. The MAH performed the test on breakability on two pilot-scale batches of Metformin 1000 mg tablets, and it showed that the tablets were very difficult to break by hand, similarly as is the case with the NL originator product Glucophage 1000 mg tablets. Because of this difficulty, it is mentioned in the SPC that although the 1000 mg tablets have a score-line, the score

at issue is not a functional score, and that the tablets are not breakable. ("The tablets have a non-functional groove and therefore cannot be broken.") [25].

Porter, et. al., (1980): Stability tests on the finished product:
During stability testing, no significant changes have been observed for one of the test parameters. At six months the microbial purity testing was meeting the requirements during normal and accelerated testing. All results on individual and total impurities are below 0.1%. Up to 36 months there is no change or very slight decrease of assay, and no increase of (total) impurities. Herewith the claimed shelf life of 4 years without specific storage condition can be accepted [49].

CHAPTER-3
OBJECTIVE AND PLAN OF WORK

AIM: TECHNOLOGY TRANSFER AND PROCESS VALIDATION OF METFORMIN HYDROCHLORIDE IMMEDIATE RELEASE TABLETS.

3.01: OBJECTIVES OF THE STUDY

"To Transfer the technology & optimize the manufacturing process of Metformin Hydrochloride IR tablets for commercial production with successful process validation."

The objective of present study is to develop a stable and robust manufacturing process for Metformin Hydrochloride immediate release tablets (500, 850 & 1000 mg). A number of lab scale batches (trial batches) have to take for understanding product behaviour extensively. The critical variables were optimised. The present study is aimed to produce Metformin Hydrochloride tablets meeting their predetermined specification. Prospective process validation was completed with three consecutive batches.

The source of information provided by technology developer is only dossier, in which the data and results of previous study was given. This is converted in to desired format & language at receiving site. In the present study the tablets have to prepare using fluidised bed equipment technique for (500, 850 & 1000 mg) strengths.

The future work is to enable the process on commercial use for production of tablet meeting its predetermined specification and quality parameters after this technology transfer.

3.02: PLAN OF STUDY

The plan of work designed based on master manufacturing formula

- Literature review
- Process flow chart
- Feasibility assessment
- Laboratory trials
- Identification of critical process parameters
- Challenging the identified variables
- Validation protocol
- Execution of validation batches
- Stability study
- Results & discussion

CHAPTER-4
DRUG PROFILE

The following section gives brief idea about chemical, physicochemical & pharmacological properties of Metformine Hydrochloride.

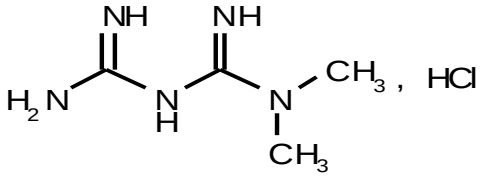
4.1 CHEMICAL PROPERTIES: [8] [10] [19] [20][27].

Name of drug : Metformin Hydrochloride

- **Category:**

Metformin Hydrochloride is biguainide hypoglycaemic agent.

- **Chemical structure:**
- **IUPAC name:**



N, N-dimethyllimidodicarbonimic diamide hydrochloride
1, 1-dimethylbiguanide hydrochloride
N, N-dimethylbiguanide hydrochloride
N'-dimethylguanylguanidine hydrochloride

- **Empirical formula:**

Metformin : $C_4H_{11}N_5$
Metformin Hydrochloride: $C_4H_{12}ClN_5$

- **CAS registry:**

Metformin free base**:** 657-24-9
Metformin Hydrochloride**:** 1115-70-4

- **Appearance:**

White or almost white hygroscopic crystalline powder, It is an odorless & bitter taste powder.

4.2 PHYSICOCHEMICAL PROPERTIES [59]

- **Molecular weight:** 165.6

- **Solubility:** Metformin Hydrochloride is freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone & methylene chloride.

Solubility behavior of drug & its salt form is most important parameter in dosage form design as it affects in vivo & in vitro drug release profile. The BSC classification also depends on drug solubity parameter.

- **Melting point:** Metformin Hydrochloride having melting point is 222 ºC to 226 ºC. This physicochemical property of drug substance is mainly used in identifying drug & to access effect of temperature variation on drug stability during various operations of dosage form manufacturing.

- **Loss on drying:** Not more than 0.5 % of Metformin Hydrochloride.

These physicochemical properties mainly considered during wet granulation, tablets compression because it directly affects powders flow behaviors, compression, tablets coating & dissolution of tablets

- **Sulphated ash:** Not more than 0.1 % in Metformin Hydrochloride.
- **Specified impurities:** Cynoguanidine
- **Other detectable impurities:**
  (4, 6-diamino-1, 3, 5-triazin-2-yl) guanidine

N, N-dimethyl-1, 3, 5-triazine-2,4,6-triamine
1, 3, 5,-triazine-2, 4, 6-triamine (melamine)
1-methylbiguanide
N-methylmethanamine
The impurities consideration is most important during stabilization of formulation and selection of excipients.

4.3 PHARMACOLOGY

4.3.01 History:

The synthesis of Metformin was first reported in the 1920's as a biguanides series member. In 1929, slotta & Tschesche also synthesized Metformin as part of a series of biguanides, which were examined for hypoglycaemic activity. Metformin dose not suffer from the lactic acidosis & less toxic than Phenformin so it is widely prescribed. Three salts forms of Metformin available (hydrochloride, embonate/pamoate & chlorophenoxy acetate salt,) but hydrochloride is by far the most commonly used salt form [9]. Our growing secondary habits & changing lifestyle has made us susceptible to Type 2 diabetes [68].

4.3.02 Mechanism of action [15]:

Metformin does not cause insulin release from the pancreas and generally does not cause hypoglycaemia, even in large doses. Metformin reduces glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat.

At a molecular level, these actions are mediated at least in part by activation of the cellular kinase AMP-activated protein kinase (AMP kinase). Metformin also may decrease plasma glucose by reducing the absorption of glucose from the intestine, but this action has not been shown to have clinical relevance.

4.3.03 Pharmacokinetics [16]:

Onset of action: Within Day, maximum effect up to 2 weeks

It's Volume of distribution is 654 ± 358 Lit, protein binding is negligible & not metabolised in liver. The bioavailability of Metformin at fasting stage is 50-60% & elimination half life is 4-9 hrs. Metformin peak time in serum for immediate release is 2-3 hrs & for extended release is 4-8 hrs.It is excreted in urine 90% as unchanged drug.

4.3.04 Precautions and adverse effects [62]:

Patients with renal impairment should not receive Metformin. Other contraindications include hepatic disease, a past history of lactic acidosis (of any cause), cardiac failure requiring pharmacological therapy, or chronic hypoxic lung disease. The reported incidence of lactic acidosis during Metformin treatment is less than 0.1 cases per 1000 patient-years, and the mortality risk is even lower.

Acute side effects of Metformin, which occur in up to 20% of patients, include diarrhoea, abdominal discomfort, nausea, metallic taste, and anorexia. These usually can be minimized by increasing the dosage of the drug slowly and taking it with meals.

4.3.05 Contraindications [18]:

GLUCOPHAGE and GLUCOPHAGE XR are contraindicated in patients with:

- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal clearance of creatinine which may also result from conditions such as cardiological collapse and septicemia
- Known hypersensitivity to Metformin hydrochloride.
- Acute & chronic metabolic acidosis , Diabetic ketoacidosis.

4.3.06 Dosing [18]:

Immediate release Tablet is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every two weeks, up to a total of 2000 mg per day, given in divided doses.

The usual starting dose of Metformin hydrochloride Extended-Release Tablets is 500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal.

4.3.07 Uses:

Used in non insulin dependent diabetes mellitus.

4.3.08 Laboratory tests [54]:

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated haemoglobin levels, with a goal of decreasing these levels toward the normal range.

HAPTER-5
MATERIALS AND METHODS

The following section briefly explains materials (formula), equipments & standard manufacturing process used for three strengths of Metfomin Hydrochloride film coated tablets production.

The manufacturing formula consists of various excipients each specific in their function used for smoothing the process.

Without excipients most drug & pharmaceutical ingredients cannot be compressed in to tablets. This is primarily due to the poor flow & cohesive properties of most drugs. They may include various diluents, binders, disintegrants, lubricants, glidants & colorants. By taking all consideration of formulation, technology developer selected a formula for Metformin Hydrochloride Immediate release tablets three strengths as follows as

5.1 STANDARD MANUFACTURING FORMULAE

Table No.5.01: FORMULAE FOR METFORMIN HYDROCHLORIDE FILMCOATED TABLETS

Ingredients	Unit formula in percentage (%)		
	500 mg Strength	850 mg Strength	1000 mg Strength
GRANULATION			
Metformin Hydrochloride	74.00	74.50	75.05
Diluent part A	5.606	5.10	5.339
Disintegrant part A	2.50	1.21	1.33
Binder	4.00	4.00	4.21
BLENDING & LUBRICATION			
Diluent part B	5.394	5.89	5.74
Disintegrant part	2.50	3.50	3.08
Glidant	1.00	1.00	1.06
Lubricant	1.00	1.00	0.53
FILM COATING			
Coating material	4.00	4.00	3.75
Purified water	qs	qs	qs
Total quantity	**100.00**	**100.00**	**100.00**

qs= Quantity sufficient

The given formula in above table is unit formula in percent for three Metformin Hydrochloride strengths. The F&D lab scale batch size was 1.5 kg while validation batch size was calculated for 3 batches from same formula.

All the above used material should meet the specifications of Indian Pharmacopoeia (IP). The Metformin hydrochloride API was supplied by Aarti drugs limited. The diluents & disintegrant was divided in two parts one is intragranular, while another part is extra granular. The product under transfer is non functional aqueous film coated tablets. The formulations like Metformin contain 70 to 80 % of only API, and then selection of each excipient becomes difficult to avoid bigger tablets size.

These equipments are used of different capacities for different batch sizes but working on same principle. The equipments used during tablets manufacturing of metformin hydrochloride with manufacturer of that instruments are given in following table. All the equipments under use are well qualified.

5.2 EQUIPMENT USED

The following equipments were used during tablets manufacturing process in present study.

Table No.5.02: LIST OF EQUIPMENTS USED DURING PROCESSING

NAME OF THE EQUIPMENT	MANUFACTURER
Electronic balance	Metter toledo
Density apparatus	Electro lab
Vibro sifter	Ganson
Sieve No. 18	Pharma spares
Fluid Bed Granulator	Pam glatt(500Lt), Umang 1.5 kg
IR moisture sensitive Balance	Metter toledo
Propeller type pneumatic stirrer	Silversion
Octagonal blender	Ganson
Coating Pan(51 Inches)	Sejong
Sieve shaker	Ganson
Tablets Compression Machine (16, 37 Station)	Sejong , Cadmach
Hardness tester	Schleunger
Digital vernier caliper	Mitutoyo
Friability tester	Electro lab
Disintegration apparatus	Electro lab
Dissolution apparatus	Electro lab
HPLC apparatus	Perkin elmer

5.3 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS (FOR METFORMIN HYDROCHLORDE 500 / 850 / 1000 mg)

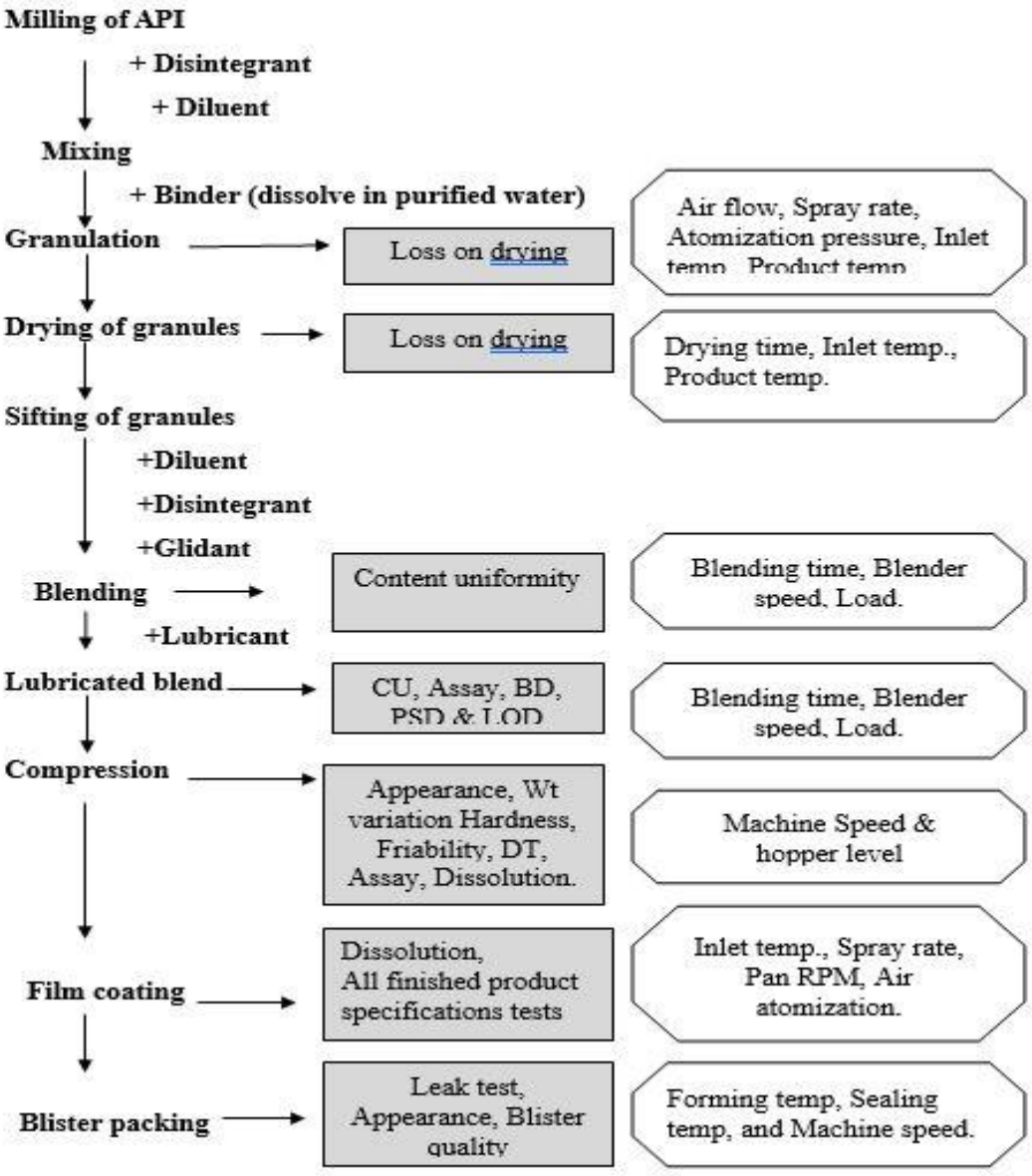


Fig. No.: 5.01 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS:

After understanding formula & equipments used for tablets manufacturing the following section explains standard manufacturing process of Metfomin Hydrochloride film coated tablets. The specifications and parameters were given stepwise for each unit operations are as per dossier specifications of technology developer. The same specifications & standard manufacturing process was used for trial batches as well as validation batches.

5.4 STANDARD MANUFACTURING PROCESS

5.4.01 Dispensing & sifting:

All the ingredients dispensed as per the manufacturing formula given in Table No.5.01 Metformin API was milled using multi mill with 1.5 mm screen & then sifted through #30 mesh.

The diluents & disintegrant were divided in two parts Intra-granular (Part A) and

Extra granular (Part B).

Then Sift Intra-granular portion of diluents & disintegrant through #18 mesh separately.

5.4.02 Granulation by FBG top spray:

Binder solution was prepared by dissolving appropriate amount of binder in sufficient amount of water & stirred it until clear solution was obtained.

The mixture of Metformin, diluents and disintegrant were loaded in FBG. Binder solution spraying was started once product temperature has reached to 30-35° C. The granulation parameters were maintained within limit as shown in Table No.5.04. When granules were formed, it was dried at 30-40° C to get LOD in between 1-4 % w/w.

Then the dried granules were sifted through #16 meshes**.** Remaining (Extra granular) part B of diluent, disintegrant & glidant was sifted through # 18 mesh

sieves separately. The following Table No. 5.03 gives all parameters limits during granulation of all three strengths.

Table No. 5.03: OPTIMIZED GRANULATION AND DRYING PARAMETERS

Parameters	**Optimized granulation parameters for different strengths of tablets**		
	500 mg	**850 mg**	**1000 mg**
Air flow (CFM)	600-1300	600-1300	600-1300
Spray rate (g/min)	300-550	300-550	300-550
Atomization pressure (kg/cm^2)	3.0-5.0	3.0-5.0	3.0-5.0
Inlet temperature (˚C)	40-60	40-60	40-60
Bed temperature (˚C)	30-45	30-45	30-45
FBG % occupancy	48	48	48

Optimized parameters during drying of granules			
Drying time (min.)	10	10	10
Inlet temperature (˚C)	30-50	30-50	30-50
Product temperature (˚C)	30-40	30-40	30-40
% LOD w/w	01-04	01-04	1.5-3.0

5.4.03 Blending & lubrication:

Above sifted material were loaded in Octagonal blender & blended it for 15 min at 10 RPM speed. After blending sampling was done as per sampling protocol & samples were sent to QC for testing LOD & Assay.

Table No. 5.04: PARAMETERS FOR LUBRICATION & BLENDING STEPS.

Process parameters	Metformin 500 mg	Metformin 850 mg	Metformin 1000 mg
Blender occupancy %	65	65	65
Blender speed (RPM)	10	10	10
Blending time (min.)	15	15	15
Lubrication Time (min.)	05	05	05

Then lubricant was sifted through #60 mesh and this sifted lubricant were added in octagonal blender & blend it for 5 min at 10 RPM speed. After completion of blending, samples were taken as per sampling protocol & send for following tests.

Micromere tics test with acceptance criteria for all three strengths of Metformin Hydrochloride lubricated blend tabulated below.

Table No. 5.05: EVALUATION PARAMETERS OF LUBRICATED BLEND.

Test performed	Technology developers requirements for strength		
	500 mg	**850 mg**	**1000 mg**
Loss on drying	01 to 04 %	01 to 04 %	1.5to 3.0 %
Uniformity of content & % RSD	100 ± 10% (Avg. 100 ± 5%) % RSD NMT 5.0%	100 ± 10% (Avg. 100 ± 5%) % RSD NMT 5.0%	100 ± 10% (Avg.100 ± 5%) % RSD NMT 5.0%
Assay	As per I.P. 2014	As per I.P. 2014	As per I.P. 2014
Bulk density & tapped density			
Bulk density	0.4-0.6	0.4-0.6	0.4-0.6
Tapped density	0.3-0.7	0.3-0.7	0.400-0.60
Comp. Index	15-25	15-25	15-25
Hausner ratio	01-03	01-03	01-03
Particle size distribution test			
% Retained on #18	01-05	01-05	01-05
% Retained on #35	10-30	10-30	10-30
% Retained on #60	30-60	30-60	30-60
% Retained on#120	10-30	10-30	10-30
% Retained on#230	01-10	01-10	01-10
% At bottom	01-05	01-05	01-05

5.4.04 Compression:

Test Performed	Specifications for strength		
	500 mg	**850 mg**	**1000 mg**
Description	White, oblong biconvex tablet.	White, oblong biconvex tablet	White, oblong biconvex tablet
Group weight variation(20 Tablets)	12.824 g ± 5%	21.80 g ± 5%	25.647 g ± 5%
Individual weight variation	641.20 mg ± 5% (609.2 mg – 673.2 mg)	1090.0mg ± 5% (1035.5 mg – 1144.5 mg)	1282.36 mg ± 5% (1218.24mg-1346.48 mg)
Hardness	NLT 4.0 Kg/cm^2	NLT 4.0 Kg/cm^2	NLT 4.0 Kg/cm^2
Thickness	5.9 ± 0.4 mm (5.5 to 6.3 mm)	7.5 ± 0.2 mm (7.3 to 7.7mm)	7.5 ± 0.4 mm (7.1 to 7.9 mm)
Disintegration time	NMT 15 minutes	NMT 15 minutes	NMT 15 minutes
Friability	NMT 1.0 % w/w	NMT 1.0 % w/w	NMT 1.0 % w/w
Specifications for assay and dissolution			
Assay	As per I.P. 2014	As per I.P. 2014	As per I.P. 2014
Dissolution	Dissolution Profile comparison with innovator sample	Dissolution Profile comparison with innovator sample	Dissolution Profile comparison with innovator sample

The lubricated blend was compressed as per dossier specifications for each strength as given in Table No. 5.06.Tablets were compressed using 37 station double rotary Cad mach machine with D tooling. In process check was done continuously during compression. The samples were collected at different location as per sampling protocol & tested.

Table No. 5.06: IN PROCESS SPECIFICATIONS DURING TABLETS COMPRESSION

5.4.05 Film coating of tablets:

The coating solution was prepared by dissolving calculated amount of colouring agent (from Table No. 5.01) in sufficient amount of water with continuous stirring.

After inspection of the tablets were weighed & loaded in coating pan with respect to coating pan capacity & occupancy. The coating parameters were maintained during coating as given in Table No. 5.07.

Table No. 5.07: TABLETS FILM COATING PARAMETERS

Parameters	Set parameters during film coating for		
	500 mg	850 mg	1000 mg
Inlet temperature (°C)	**60-70**	**60-70**	**60-70**
Exhaust temperature (°C)	**40-50**	**40-50**	**40-50**
Bed temperature (°C)	**40-50**	**40-50**	**40-50**
Pan speed (RPM)	**03-08**	**03-08**	**03-08**
Atomization pressure (Kg/cm²)	**3.0 – 6.0**	**3.0-6.0**	**3.0-6.0**
Spray rate (g/min/gun)	**10-60**	**10-60**	**10-60**
Gun to bed distance (cm)	**20-30**	**20-30**	**20-30**

These film coating parameters were optimized, based on trial batches results.

5.4.06 Blister packing:

The coated tablets were packed in PVC/PVDC Alu foil. Parameters maintained during packing were tabulated in Table No. 5.08. In process test was performed on packed blisters as given in Fig. No. 5.01.

Table No.5.08: PARAMETERS DURING BLISTER PACKING

Parameters	**500 mg**	**850 mg**	**1000 mg**
Sealing temperature (°C)	170±20	170±20	170±20
Forming temperature (°C)	150±20	150±20	150±20
Machine speed	70-100	70-100	70-100

This standard manufacturing method was applied in next section for trial as well as validation batches.

CHAPTER-6
EXPERIMENTAK WORK

The following section deals with trial batches and later on validation batches, which includes sampling plan, stability study.

6.1 PROCESS FEASIBILITY AND OPTIMIZATION TRIALS

Feasibility trial for Metformin Hydrochloride 850 mg tablets was done on lab scale batch size. The trial was performed as per standard manufacturing process (Table No. 5.04). The equipments and process parameters were selected from dossier data.

The observations & results obtained during processing compared with dossier data. Following section shows comparative success of trial batches against dossier data.

Table No. 6.01: COMPARISON OF TRIAL BATCHES WITH DOSSIER DATA.

Sr.No.	**Critical steps consider**	**Technology developers data**	**Trial batches results**
01	**Granulation**	Top spray granulation	Top spray granulation
		Process parameters	Complies

		(As per Table No. 5.03)	
02	**Drying**	Top spray granulation	Top spray granulation
		Process parameters (As per Table No. 5.03)	Complies
03	**Blending & lubrication**	Octagonal blender (Diffusive)	Octagonal blender (Diffusive)
		Process parameters (As per Table No. 5.04)	Complies
		Micromere tics results (As per Table No. 5.05)	Complies
04	**Compression**	Not specified	Cad mach
		In process tests (As per Table No. 5.06)	Complies
05	**Film coating**	Suitable Perforated pan system	Gansons
		In process tests (As per Table No.5.07)	Complies
		Finished product specifications	Complies

The same trials were conducted for Metformin 500 mg & 1000 mg Film coated tablets. During trial batches, process was understood thoroughly. The all process parameters were optimized & product behaviours understood on available equipments.

After taking all trial batches successfully, validation batches were planned as per following planning.

6.2 PROCESS VALIDATION

Prospective process validation was performed on consecutive three batches after successful trial batches. A validation protocol was prepared & approved prior to validation batches .Three consecutive batches were taken process validation at batch size 150 kg for each of Metformin strength.

The three validation batches were labelled as (X1, X2, X3), (Y1, Y2, Y3) & (Z1, Z2, Z3) for Metformin Hydrochloride 500 mg, 850 mg, & 1000 mg strengths respectively . The protocol has the sampling plan & acceptance criteria at different process variables as given below. During the manufacturing, samples were collected as per the sampling plan & send for analysis.

The all three strengths were carried out as per standard manufacturing process (Table No. 5.04).

6.3 SAMPLING PLAN FOR VALIDATION BATCHES

Samples were collected as per sampling plan. The sampling procedure and sample size at each sampling location was carried out as per the protocol.

6.3.01 Sampling procedure during processing:

a) Blending:

The blending was performed in Octagonal Blender. The sample form each location was collected using a sampling rod. Samples were drawn form 10 position of the octagonal blender as

shown in Fig. No.6. Triplicate samples were collected form each location at both Pre lubricated and lubricated stages and tested for content uniformity. One set of sample was subjected to analysis and the other two sets were kept as reserve samples. The sample quantity was between 1x-3x (x- total quantity of ingredients used for one unit).

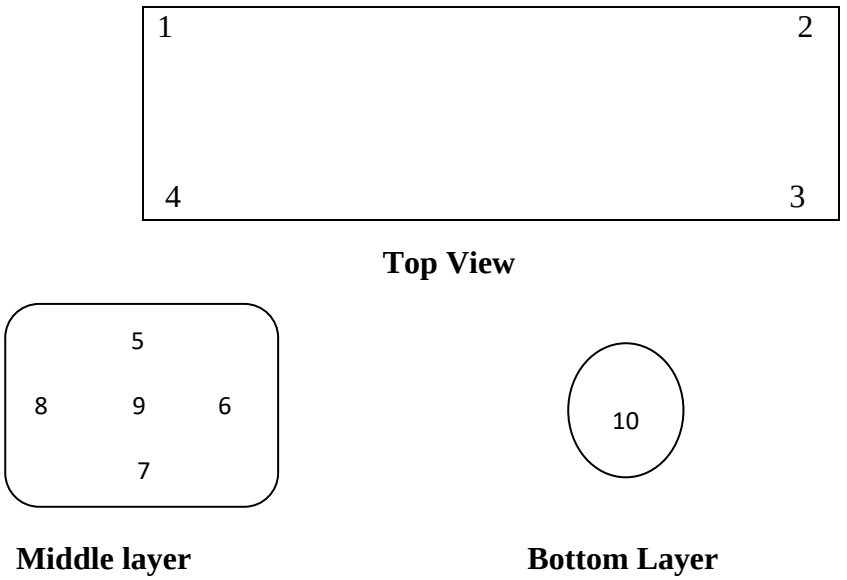


Fig. No.6.01: OCTAGONAL BLENDER SAMPLING LOCATIONS

b) Compression:

Tablets were compressed using 37 station double rotary compression machine with punches of given dimension to get tablets of required specifications. (one side snap tab score notch other side score notch and embossed M 500, one side snap tab score notch other side score notch and embossed M 850, one side snap tab score notch other side score notch and embossed M 1000 for Metformin 500, 850 & 1000 mg respectively.)

I) Machine speed study:

The machine was run at three different speed high low and target compression speed in rpm of the turret and checked for the in process parameters. At each speed pooled samples were collected at each speed and tested for uniformity of weight and dissolution. (Speed for Metformin 500 mg 15, 20 & 25, for 850 and 1000 mg speed is 10, 15 & 20 RPM slow, target & high respectively.)

II) Hopper study:

The effect of vibration during compression on blend uniformity was evaluated with hopped study the hopper was filled completely and the compression machine was run at target speed for compression. The tablets were collected when the powder level in the hopper was full, approximately middle of the hopper and when it was nearing end of the hopper the tablets were evaluated for uniformity of weight.

III) Dissolution study:

For Metformin 850 & 1000 mg check the dissolution profile of 12 tablets each at 15, 30, 45 & 60, min from the pooled sample after the completion of film-coating. While for Metformin 500mg film

coated tablets samples collect and tested at 05, 15, 30, 45 and 60 min. time interval dissolution test perform as per specified procedure of technology developer.

c) Film coating:

During coating operation monitoring various in process test was performed continuously like build up achieved, spray rate validation, CFM measurement.
Tablets from 5 different locations of pan collect. The tablets collected should be about 10-15 tablets from each location.

d) Blister packaging:

The blisters are collected during packing for in process test like leak test & some sample (approx 5 blister) were collected for final testing.

The samples were collected as per sampling plan & tested by QC department as per standard procedures provided by technology developer. The following table gives clear idea of sampling plan & critical process parameters which are considered during validation study.

6.3.02 Sampling plan & acceptance criteria:

Table No.6.02: IN PROCESS SAMPLING PLAN AND ACCEPTANCE CRITERIA.

<table>
<tr><th>Stage</th><th>Selected critical process variables for study</th><th>Approximate sample size</th><th>Test needed</th></tr>
<tr><td>Granulation & drying</td><td>Product temp, Spray rate, Inlet temp, powder load, LOD, Air CFM, Atomization</td><td>5 gm from 5 different locations</td><td>LOD</td></tr>
<tr><td rowspan="5">Blending</td><td>Blending time (15min), Blender load , Blending speed</td><td>3X, 10 sample each of strength</td><td>Content uniformity (CU)</td></tr>
<tr><td rowspan="4">Lubrication time (5min)</td><td>3X, 10 sample each of strength</td><td>Content uniformity</td></tr>
<tr><td rowspan="3">Pooled Samples</td><td>Appearance</td></tr>
<tr><td>Assay</td></tr>
<tr><td>BD & PSD</td></tr>
<tr><td rowspan="8">Compression speed</td><td>Low speed</td><td rowspan="8">2×37 tablets for each test</td><td>Description</td></tr>
<tr><td rowspan="3">High speed</td><td>Wt. variation</td></tr>
<tr><td>Thickness</td></tr>
<tr><td>Hardness</td></tr>
<tr><td rowspan="3">Target speed</td><td>Disintegration time</td></tr>
<tr><td>% friability</td></tr>
<tr><td>Dissolution</td></tr>
</table>

Initial	Initial of Hooper (1/3rd)	25 tablets	Uniformity of weight & content
	Hopper (2/3rd)	25 tablets	
Middle	Middle of run	50 tablets	
End	End of run	50 tablets	
Film coating	Spray rate, Inlet temp., outlet temp. & bed temp., sample loaded etc.	Aprrox. 25 tablets for each test	All finished product specifications
			Dissolution
Blister packing	Machine speed, Forming temp. Sealing temp.	Leak test, Blister quality, Appearance	As per current SOP for GMP compliance.
		Impurities	As per current finished product specification

The critical process variables selected for validation batches are given below with sample size & test required to control these variables.

As the film coated tablets were manufactured as per standard manufacturing process then following tests perform on finished product for their regulatory release in market.

Table No.6.03: FINISH PRODUCT RELEASE SPECIFICATIONS

Test performed	**Specifications for strength**		
	500 mg	**850 mg**	**1000 mg**
Description	White, biconvex, oblong film-coated tablet.	White, biconvex, oblong film-coated tablet.	White, biconvex, oblong film-coated tablet.
Individual weight variation	671.2 mg ± 5%	1130.0 mg ± 5%	1332.4 mg ± 5%
Hardness	NLT 4.0 kg/cm^2	NLT 4.0 kg/cm^2	NLT 4.0 kg/cm^2
Thickness	5.60 mm to 6.40 mm	7.3 mm to 7.7 mm	7.10 mm to 7.90 mm
Disintegration time	All six tablets should disintegrate completely within 30 minutes	All six tablets should disintegrate completely within 30 minutes	All six tablets should disintegrate completely within 30 minutes
Assay	As per I.P. 2014	As per I.P. 2014	As per I.P. 2014
Dissolution	Dissolution profile comparison with innovator sample	Dissolution profile comparison with innovator sample	Dissolution profile comparison with innovator sample

Uniformity of mass	As per I.P. 2014	As per I.P. 2014	As per I.P. 2014
Microbial limit test	As per I.P. 2014	As per I.P. 2014	As per I.P. 2014

All the three strengths of Metformin Hydrochloride tablets were compressed as per standard manufacturing process & tested as per sampling plan. The results of all three batches for each strength were discussed in later section.

The finished product tested for finish product release specifications and some specified samples of each batch were loaded in stability as per stability protocol. The conditions used during stability study of product under study are discussed below.

6.4 STABILITY STUDY

The samples were charged for stability, long term stability was conducted at (25°C & 75% RH), and Accelerated stability studies were conducted at (40°C & 75 % RH). Intermediate term stability was conducted at (40°C & 75% RH). The sample were analyzed at initial, 1, 3, 6 months intervals as:
The following table gives brief description of stability study.

Table No.6.04: STABILITY STUDY CONDITIONS

Study	Condition	Duration (Months)
ACC	40°C & 75 % RH	1, 3, 6
Long Term	25°C & 65%RH	3, 6
Intermediate Term	30°C & 65% RH	3, 6

The results of stability study & validation batches were recorded in later section.

CHAPTER-7
RESULTS AND DISCUSSION

The following section briefly discuses the results & parameters found during three validation batches of all three strengths.

7.1 VALIDATION STUDY OF METFORMIN HYDROCHLORIDE 500 mg FILM COATED TABLETS

The all three batches of Metformin Hydrochloride tablets were manufactured using standard manufacturing process for 7 kg batch size. The samples were collected & tested as per sampling protocol. The observations made during each critical step were discussed as below.

7.1.01 Granulation & drying:

After milling & sifting the material as per standard manufacturing process (Table No. 5.04) next step is granulation.

FIXED VARIABLES DURING GRANULATION
FBG Load: (48.2% occupancy)

The observations made during FBG top spray granulation for following process variables are discussed below

Table No. 7.01: GRANULATION PARAMETERS DURING METFORMIN 500 mg FBG TOP SPRAY GRANULATION & DRYING

Granulation variables	**Specified values**	**Batch X1**	**Batch X2**	**Batch X3**
Spray rate (g/min)	300-550	340-450	345-440	340-450
Inlet temp.(˚C)	40-60	45-55	46-53	47-53
Outlet temp. (˚C)	30-50	34-36	35-38	34-37
Bed temp. (˚C)	30-40	32-37	40-35	32-37
Atomization(kg/cm^2)	03-05	3.5-05	04	04
Air CFM	600-1300	600-1200	600-1250	600-1300
Drying Parameters				
Product temp.	30-40	32	34	32
Inlet temp	30-50	42	44	41
Total time	07	07	07	07
LOD (NMT 4%)	01-04	1.54	1.67	1.40

Discussion:

As per the above results all critical parameters during granulation of three batches were found to be consistent & reproducible.

The granulation & drying step was validated at the all above set parameters as it shows consistent & reproducible results within predetermined specifications.

7.1.02 Blending & lubrication:

The blending of granules & extragranuler part was done in OGB at 10 RPM speed.
FIXED VARIABLES DURING BLENDING & LUBRICATION STEPS
Blender speed: 10 RPM
Blending time: 15 min.
Lubrication time: 05 min.
Samples were collected after blending & lubrication as per sampling plan and sent to QC for testing. The obtained flow kinetics & mixing efficiency results of lubricated blend are given as follows:
Table No. 7.02: RESULTS OF LUBRICATED BLEND.

Test performed		**Flow properties results of validation batches**		
	Specification	**Batch X1**	**Batch X2**	**Batch X3**
Loss on drying	01-04	1.54	1.67	1.40
Assay (%)	As per I.P. 2014	Complies	Complies	Complies

Bulk density (g/min)	0.40-0.60	0.496	0.505	0.505
Tapped density (g/min)	0.55-0.65	0.588	0.603	0.602
Comp. Index (%)	15-20	18.42	16.16	16.16
Hausner ratio	1.15-1.25	1.19	1.18	1.20
% Retained on #18	01-05	0.01	0.03	0.02

Discussion:

The flow properties result of lubricated blend of all three batches was found to be reproducible & satisfactory within dossier limits.

7.1.03 Mixing efficiency of the blender (OGB):

The assessment of active content distribution in blend was done by content uniformity test of both blended & lubricated material. The results of mixing efficiency testing were tabulated for blending & lubrication step as follows:

Table No.7.03: ANALYSIS RESULTS OF BLENDING (15 MIN.) & LUBRICATION (05 MIN.) STEP

Sample No.	**Content uniformity not less than 90 % & not more than 110% of label amount of Metformin Hydrochloride (% RSD NMT 5.0%)**					
	X1 blending	**X1** lubrication	**X2** Blending	**X2** lubrication	**X3** blending	**X3** lubrication
01	97	99	99	100	102	100
02	95	102	94	98	97	97
03	100	96	99	94	99	96
04	96	98	95	97	98	103
05	99	95	98	99	95	99
06	95	100	97	95	96	95
07	96	96	95	97	97	97
08	102	98	98	98	100	99
09	94	97	103	99	99	98
10	99	98	99	96	98	99
Mean	**97.3**	**97.9**	**97.7**	**97.7**	**98.1**	**98.3**
SD	**2.58**	**2.07**	**2.62**	**1.88**	**2.02**	**2.26**
Mini.	**94**	**95**	**94**	**94**	**95**	**95**
Max .	**102**	**102**	**103**	**100**	**102**	**103**

Discussion:

The above results of all tests were found to be reproducible and satisfactory within limits for both blending & lubrication step.

The all results of different tests were found consistent & reproducible on 15 min. blending & 05 min. lubrication. So the blending & lubrication steps are validated at specified parameters.

7.1.04 Compression:

The tablets were compressed at critical process variables as three different hopper level & three different machine speeds. Samples were collected at these critical variables as per sampling plan. These collected samples were evaluated for various tests (in process check, uniformity of mass, dissolution & equal breakability test.)

The results of the in process parameters were found at three different speeds tabulated as follows:

Table No. 7.04: IN PROCESS COMPRESSION DATA OF METFORMIN 500 mg TABLETS.

In process parameters (Specifications)	**Batch No.**	**Compression machine speed**		
		Low speed (15 RPM)	**High speed (25 RPM)**	**Target speed (20RPM)**
Description White, oblong biconvex tablet.	X1	Complies	Complies	Complies
	X2	Complies	Complies	Complies
	X3	Complies	Complies	Complies
Wt. of 10 tablets	X1	12.75-12.96	12.74-13.0	12.77-13.1
	X2	12.74-12.95	12.76-12.98	12.80-13.1
	X3	12.69-12.98	12.72-12.99	12.75-12.89
Wt. variation (609.2 to 673.2 mg)	X1	634-660	637-664	639-659
	X2	637-664	630-664	638-660
	X3	639-659	629-665	625-658
Thickness (5.5 to 6.3 mm)	X1	5.8-6.1	5.9-6.01	5.99-6.06
	X2	5.87-6.1	5.9-6.13	6.0-6.1
	X3	5.9-6.1	5.8-6.1	5.9-6.16
Hardness NLT 4.0 Kg/cm^2	X1	Complies	Complies	Complies
	X2	Complies	Complies	Complies
	X3	Complies	Complies	Complies
% Friability NMT 1.0 % w/w	X1	0.1	0.14	0.09
	X2	0.12	0.1	0.11
	X3	0.089	0.13	0.14
DT NMT 15 minutes	X1	5.41	5.12	5.10
	X2	4.54	5.06	4.56
	X3	5.10	5.40	5.14

Discussion:

All results of above three batches after compression was found to be satisfactory & within limits at three given speeds.

The samples collected at different machine speed were tested for mass uniformity test. The results of mass uniformity test at three different speed was found as:

Table No.7.05: RESULTS OF COMPRESSED TABLETS AT DIFFERENT MACHINE SPEED

Compression speed	**Batch X1**	**Batch X2**	**Batch X3**
Uniformity of mass (NMT 2 of 20 individual units deviates by more than 05% of average mass of label claim of Metformin Hydrochloride)			
Low speed (15 RPM)	634	633	634
High speed (25 RPM)	646	647	647
Target speed (20 RPM)	642	642	642

The tablets compressed at target speed (20 RPM) & samples were collected. The collected samples were analyzed for uniformity of mass & equal breakability tests. The results of tests were tabulated as:

Table No. 7.06: RESULTS OF COMPRESSED TABLETS AT DIFFERENT HOPPER LEVEL

Batch No.	**Different hopper level**			
Uniformity of mass (NMT 2 of 20 individual units deviates by more than 05% of average mass of label claim of Metformin Hydrochloride)				
	Initial 1/3rd	**(1/3-2/3rd)**	**Middle of run**	**End of run**
Batch X1	640-644	640-644	639-643	637-640
Batch X2	643-46.2	640-645	638-644	636-642
Batch X3	640-46.2	640-645	639-645	638-643
Breakability test (Weight of each half should be equivalent to average wt. of 20 tablets ±17%)				
Batch X1	Complies	Complies	Complies	Complies
Batch X2	Complies	Complies	Complies	Complies
Batch X3	Complies	Complies	Complies	Complies

Discussion:

All three batches result clearly shows that the tablet mass were found to be within specifications even at different machine speed & hopper level.

The all in process parameters are well within specifications giving consistent & reproducible results at given three different speed & hopper level.

7.1.05 Tablets film coating & packaging:

The compressed tablets were subjected for film coating in two lots of same size. The following variables considered during film coating. The parameters set during coating for three batches are as follows.

Table No. 7.07: TABLETS FILM COATING PARAMETERS

Critical parameters	Specified limit	Batch X1	Batch X2	Batch X3
No. of guns	02	02	02	02
Inlet temperature. (˚C)	60-70	64.7-66.2	63.8-65.9	64.6-66.5
Bed temperature. (˚C)	42-46	42.9-45.2	43.0-45.6	42.9-45.8
Spray rate (g/min)	10-60	25-35	30-45	34-45
Gun to bed distance (cm)	20-30	25	25	25
Pan RPM	030-8	03-05	03-07	03-06
Pan load (Kg)	74.5	74.03	73.9	74.3
Air pressure (kg/cm^2)	03-06	04-05	04	04

The three different variables considered during blister packing are sealing temperature, forming temperature & machine speed. The observations made during three batches are as follows.

Table No. 7.08: BLISTER PACKAGING PARAMETERS

Critical parameters	Specified limit	Batch X1	Batch X2	Batch X3
Sealing temperature	170±20 (˚C)	170	170	170
Forming temperature	150±20 (˚C)	150	150	150
Machine speed	70-100	90	90	90
Test & results				
Leak test	As per I.P. 2014	Passes	Passes	Passes
Blister appearance & quality	Inhouse Specification	Complies	Complies	Complies

Discussion:

Thus, all the results clearly shows that the parameters during coating & blister packaging of three batches were found to be satisfactory and within the limits.

7.1.06 Dissolution study of Metformin Hydrochloride 500 mg film coated tablets.

Pooled samples were collected from all the containers & dissolution studies were carried out. The dissolution profile data for Metformin hydrochloride X1, X2, X3 & Innovator batches were given below.

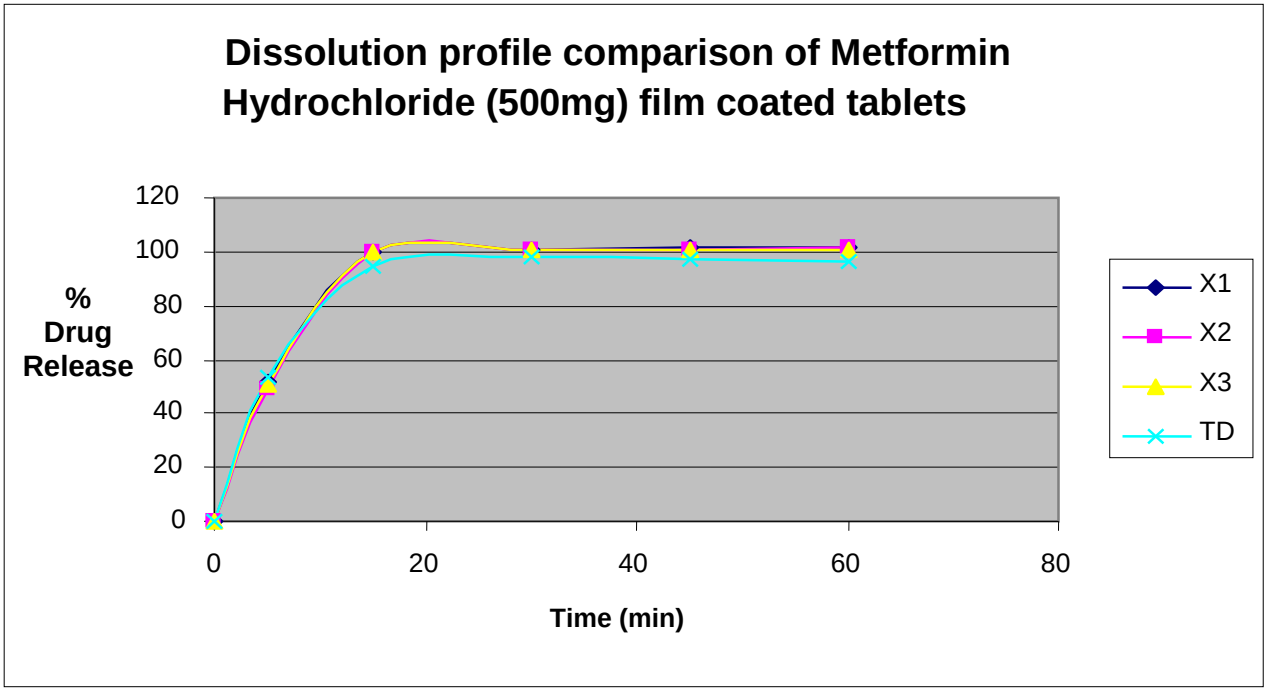
Table No.7.09: DISSOLUTION PROFILE RESULTS OF METFORMIN 500 mg FILM COATED TABLETS.

	% of Metformin dissolve									
	Batch X1					Batch X2				
Time (min.)	05	15	30	45	60	05	15	30	45	60
Sr.No.										

01	50	100	101	102	102	47	99	100	100	101
02	54	99	100	101	101	48	101	101	102	101
03	52	100	101	102	102	45	100	101	101	102
04	51	100	102	102	101	52	100	102	101	101
05	49	99	101	101	101	51	99	100	101	101
06	55	100	102	102	101	50	100	101	101	102
Mini.	49	99	100	101	101	45	99	100	100	101
Max.	55	100	102	102	102	52	101	102	102	102
Avg	52	100	101	102	101	49	100	101	101	101
% RSD	4.46	0.52	0.74	0.51	0.51	5.40	0.75	0.75	0.62	0.51

	% Dissolution of Metformin dissolve									
	Innovator					**Batch X3**				
Time (min.)	05	15	30	45	60	05	15	30	45	60
Sr.No.										
01	48	91	99	96	96	50	99	100	101	101
02	53	94	96	95	95	47	101	101	100	101
03	57	96	100	100	99	51	100	101	101	102
04	53	95	97	97	93	54	99	101	101	101
05	60	98	98	99	99	49	100	102	102	101
06	52	93	98	97	96	52	101	101	101	101
Mini.	48	91	96	95	93	47	99	100	100	101
Max.	60	98	100	100	99	54	101	102	102	102
Avg.	53.8	94.5	98	97.3	96.3	50.5	100	101	101	101
% RSD	7.74	2.57	1.02	1.92	2.41	4.81	0.89	0.62	0.63	0.47

The comparative evaluation of validation batches dissolution data with innovators dissolution data was graphically represented as



Graph No. 7.01: DISSOLUTION PROFILE COMPARISON OF METFORMIN 500 MG FILM COATED TABLETS

Discussion:

The dissolution profile of validation batches were complying with that of innovator dissolution data satisfactorily.

The desired weight buildup & dissolution profile get at all above set critical coating parameters for three batches. The blisters are found to be complying with specified tests of blister packing.

The all above results clearly shows consistency & reproducibility of all critical parameters for film coating & blister packing operations.

7.1.07 Finished product release specification:

The following test was performed on finished product (Metformin Hydrochloride 500 mg film coated tablets). The results of three packed batches was found as per Table No. 7.10.

Table No. 7.10: FINISHED PRODUCT RELEASE SPECIFICATIONS

Test	**Specifications**	**Batch X1**	**Batch X2**	**Batch X3**
Description	**White, biconvex, oblong film-coated tablet.**	Complies	Complies	Complies
Individual weight variation	**671.2 mg ± 5% (Bet. 637.64-704.76 mg)**	654-684	650-694	655-695

Hardness	**NLT 4.0 Kg/Cm^2**	Complies	Complies	Complies
Thickness	**Between 5.60 mm and 6.40 mm**	6.18 Mini: 6.10 Max: 6.21	6.20 Mini: 6.18 Max: 6.22	6.19 Mini: 6.12 Max: 6.21
Disintegration time	**All six tablets should disintegrate completely within 30 minutes**	Complies	Complies	Complies
Assay	**As per current I.P. 2014**	Complies	Complies	Complies
Dissolution	**Dissolution profile comparison with innovator sample**	Complies	Complies	Complies
Uniformity of mass	**When 20 tablets are weighed not more than two of the individual weights deviate from the average weight by more than ± 5.0 % w/w and no tablet deviates by more than ± 10.0 % w/w than ± 10.0 % w/w**	Complies	Complies	Complies

Discussion:

Thus, all the above results show that, the test required for finish product release of Metformin 500 mg film coated tablets was found to be within specification.

7.1.08 Summary:

The validation study of Metformin 500 mg tablets were carried out by considering critical parameters at each unit operation. The following critical steps were considered during three validation batches.

a) Granulation & drying:

The granulation & successive drying step of granules were found to be stable, consistent & reproducible for three consecutive batches at following parameters. This is evident from comparison of powder data of technology developer with obtained results of three batches given in Table No. 7.01
The validated critical process parameters of granulation & drying steps are as follows

- **Spray rate:** 300-550 g/min
- **Air CFM:** 600-1300
- **Inlet temp:** 40-60˚C
- **Bed temp:** 28-32˚C
- **Atomization pressure:** 03-05 kg/cm
- **Drying time:** 07 min.

- **LOD:** 01-04% W/W

b) Blending & lubrication:

The blending & lubrication step was found to be satisfactory, stable, consistent & reproducible at following parameters. This is evident from content uniformity test results of consecutive three batches as given in Table No. 7.03.

The validated parameters for blending & lubrication steps are as follows:

- **Pre lubrication time**: 15 min.
- **Lubrication time:** 05 min.
- **Blender speed:** 10 RPM

c) Compression:

The Metformin 500mg tablets compression data was found stable, consistent& reproducible at following parameters. This is evident from in process testing & content uniformity data of three consecutive batches as per Table No. 7.04, 7.05 & 7.06.

The following table compares different parameters obtained during three validation batches even at different machine speed & hopper level.

Table No. 7.11: VALIDATION BATCHES COMPRESSION RESULTS

Compression parameters	**Specification**	**Observed value**	
		Mini.	**Max.**
WT variation	**(609.2 to 673.2 mg)**	629	665
Thickness	**(5.5 to 6.3 mm)**	5.80	6.16
Hardness	**NLT 4.0 Kg/Cm^2**	Complies	Complies
DT	**NMT 15 min.**	4.54	5.41

d) Film coating:

The following coating parameters were found stable, consistent & reproducible during three validation batches, which is evident from finished product release specification data & dissolution data comparison as per Table No. 7.07.

The coating parameters found during three validation batches were compared with the given specifications in following table.

Table No. 7.12: VALIDATION BATCHES COATING RESULTS

Coating parameters	**Specification**	**Observed value**	
		Mini.	**Max.**
Spray rate	**10-60 g/min**	25	45
Atomization	**04-06 kg/cm^2**	04	05
Bed temp.	**40 ± 5˚C**	42.9	45.8
Pan RPM	**02-05**	02	05

e) Blister packing:

The following parameters were found to be consistence & reproducible during three validation batches for blister packing.

- **Sealing temperature (ºC):** 170±20
- **Forming temperature (ºC):** 150±20
- **Machine speed:** 70-110

This result of all three batches & its critical steps clearly shows consistency & reproducibility of parameters and all results. Hence the manufacturing method of Metformin Hydrochloride 500 mg Film Coated tablets say validated at above parameters & equipments.

7.2 VALIDATION STUDY OF METFORMIN HYDROCHLORIDE 850 mg FILM COATED TABLETS

The all three batches of Metformin Hydrochloride tablets were manufactured using standard manufacturing process for 11 kg batch size. The observations made during each critical step was discussed below.

7.2.01 Granulation & drying:

After milling & sifting the material as per standard manufacturing process (Table No. 5.04) next step is granulation.

Fixed Variables During Granulation

FBG Load: (48 % occupancy)

The observations made during FBG top spray granulation for following process variables are discussed below:

Table No.7.13: GRANULATION PARAMETERS DURING METFORMIN 850 mg FBG TOP SPRAY GRANULATION & DRYING

Granulation parameters	**Specified values**	**Batch Y1**	**Batch Y2**	**Batch Y3**
Spray rate (g/min)	300-550	340-460	335-440	340-500
Inlet temp.(˚C)	40-60	42-53	46-53	45-52
Outlet temp. (˚C)	30-55	34-37	35-38	33-38
Bed temp. (˚C)	30-45	32-39	34-39	33-38
Atomization(kg/cm^2)	03-05	04-05	04	04
Air CFM	750-1300	780-1100	940-1152	945-1154
Drying parameters				
Product temp.	30-40	34	34	34
Inlet temp.	30-50	47	46	46
Total time.	07	07	07	07
LOD (NMT 4%)	01-04%	1.6	1.59	1.78

Discussion:

As per the above results all critical parameters during granulation of three batches were found to be consistent & reproducible.

The granulation & drying step was validated at the all above set parameters as it shows consistent & reproducible results within predetermined specifications.

7.2.02 Blending & lubrication:

The blending of granules & extragranuler part was done in OGB at 10 RPM speed.

Fixed variables during blending & lubrication steps:

Blender speed: 10 RPM

Blending time: 15 min.

Lubrication time: 05 min.

Samples were collected after blending & lubrication as per sampling plan and sent to QC for testing. The obtained flow kinetics & mixing efficiency results of lubricated blend are given as follows:

Table No.7.14 RESULTS OF LUBRICATED BLEND.

Test performed	**flow properties results of Validation batches**			
	Specification	**Batch Y1**	**Batch Y2**	**Batch Y3**
LOD %w/w	01-04	1.6	1.59	1.78
Assay%	As per I.P. 2014	Complies	Complies	Complies
Bulk density (g/min)	0.40-0.60	0.456	0.442	0.454
Tapped density(g/min)	0.55-0.65	0.558	0.576	0.557
Comp. index (%)	15-25	19.42	20.6	20.1
Hausner ratio	1.15-1.25	1.16	1.19	1.22
% Retained on #18	01-05	3.03	4.82	4.3

Discussion:

The flow properties result of lubricated blend of all three batches was found to be reproducible & satisfactory within dossier limits.

7.2.03 Mixing efficiency of the blender (OGB):

The assessment of active content distribution in blend was done by content uniformity test of both blending & lubricated material. The results of mixing efficiency testing were tabulated for blending & lubrication step as follows.

Table No.7.15: ANALYSIS RESULTS OF BLENDING (15 MIN.) & LUBRICATION (05 MIN.) STEP

Sam-Ple No.	**Content uniformity not less than 90 % & not more than 110% of label amount of Metformin Hydrochloride (% RSD NMT 5.0%)**					
	Y1 blending	**Y1 lubrication**	**Y2 blending**	**Y2 lubrication**	**Y3 blending**	**Y3 lubrication**
01	99	100	99	100	100	100
02	99	101	98	98	100	99

03	98	99	100	99	99	100
04	100	98	101	99	98	101
05	99	100	99	100	99	101
06	101	101	100	101	100	99
07	99	100	98	99	101	100
08	98	99	101	100	100	99
09	100	98	99	101	99	98
10	101	100	99	102	98	99
Mean	**99.4**	**99.6**	**99.4**	**99.9**	**99.4**	**99.6**
SD	**1.08**	**1.07**	**1.07**	**1.19**	**0.96**	**0.96**
Mini.	**98**	**98**	**98**	**98**	**98**	**98**
Max.	**101**	**101**	**101**	**102**	**101**	**101**

Discussion:

The above results of all tests were found to be reproducible and satisfactory within limits for both blending & lubrication step.

The all results of different tests were found consistent & reproducible on 15 min. blending & 05 min. lubrication. So the blending & lubrication steps are validated at specified parameters.

7.2.04 Compression:

The tablets were compressed at critical process variables as three different hopper level & three different machine speeds. Samples were collected at these critical variables as per sampling plan. These collected samples were evaluated for various tests (in process check, uniformity of mass, dissolution & equal breakability test.)

The results of the in process parameters were found at three different speeds tabulated as follows:

Table No. 7.16: IN PROCESS COMPRESSION DATA OF METFORMIN 850 mg TABLETS.

In process parameters (Specifications)	**Batch No.**	**Compression machine speed**		
		Low 10 RPM	**High 20 RPM**	**Target 15 RPM**
Description White, oblong biconvex tablet.	**Y**	Complies	Complies	Complies
	Y1	Complies	Complies	Complies
	Y2	Complies	Complies	Complies
Wt. of 10 tablets (21.146 g to 22.454 g)	**Y**	21.64-21.98	21.60-22.08	21.65-22.02
	Y1	21.64-21.99	21.65-21.90	21.64-21.89
	Y2	21.66-21.89	21.66-21.91	21.64-21.90
Wt. variation (1035.5 - 1144.5 mg)	**Y**	1070-1112.3	1075-1106	1075-1108
	Y1	1070-1109	1072-1108	1076-1110.4
	Y2	1076-1107	1069-1109	1075-1110
Thickness (7.3 to 7.7 mm)	**Y**	7.4-7.51	7.46-7.54	7.43-7.53
	Y1	7.51-7.59	7.52-7.61	7.50-7.60

	Y2	7.51-7.57	7.52-7.59	7.50-7.66
Hardness NLT 4.0 Kg/cm^2	**Y**	Complies	Complies	Complies
	Y1	Complies	Complies	Complies
	Y2	Complies	Complies	Complies
% Friability NMT 1.0 % w/w	**Y**	0.12	0.10	0.09
	Y1	0.14	0.10	0.16
	Y2	0.08	0.15	0.11
DT NMT 15 minutes	**Y**	6.40	6.31	6.55
	Y1	6.54	6.34	7.12
	Y2	6.45	7.24	6.54

Discussion:

All results of above three batches after compression was found to be satisfactory & within limits at three given speeds.

The samples collected at different machine speed were tested for mass uniformity test. The results of mass uniformity test at three different speed was found as

Table No.7.17: RESULTS OF COMPRESSED TABLETS AT DIFFERENT MACHINE SPEED

Compression speed	**Y1**	**Y2**	**Y3**
Uniformity of mass (NMT 2 of 20 individual units deviates by more than 05% of average mass of label claim of Metformin Hydrochloride)			
Low (10 RPM)	1070-1112.3	1070-1109	1076-1107
High (20 RPM)	1075-1106	1072-1108	21.66-21.91
Target (15 RPM)	1075-1108	1076-1110.4	1075-1110

The tablets compressed at target speed (15 RPM) & samples were collected. The collected samples were analyzed for uniformity of mass & equal breakability tests. The results of tests were tabulated as:

Table No.7.18: RESULTS OF COMPRESSION CRITICAL PARAMETERS.

Batch No.	**Hopper level**			
Uniformity of mass (NMT 2 of 20 individual units deviates by more than 05% of average mass of label claim of Metformin Hydrochloride)				
	Initial 1/3rd	**(1/3-2/3rd)**	**Middle of run**	**End of run**
Y1	1075-1121	1076-1119	1075-1110	1070-1109
Y2	1075-1123	1078-1120	1075-1119	1071-1108
Y3	1073-1119	1077-1124	1077-1121	1070-1110
BREAKABILITY TEST				

(Weight of each half should be equivalent to average wt. of 20 tablets ±17%)				
Y1	Complies	Complies	Complies	Complies
Y2	Complies	Complies	Complies	Complies
Y3	Complies	Complies	Complies	Complies

Discussion:

All three batches result clearly shows that the tablet mass were found to be within specifications even at different machine speed & hopper level.

The all in process parameters are well within specifications, giving consistent & reproducible results at given three different speed & hopper level.

7.2.05 Tablets film coating & packaging:

The compressed tablets were subjected for film coating in two lots of same size. The following variables considered during film coating. The parameters set during coating for three batches are as follows:

Table No.7.19: TABLETS FILM COATING PARAMETERS

Critical Parameters	Specified Limit	Batch Y1	Batch Y2	Batch Y3
No of guns	02	02	02	02
Inlet temperature.(˚C)	60-70	64.7-67.2	63.6-67.9	64.6-66.9
Bed temperature.(˚C)	42-46	41.9-45.9	42.0-46.6	42.3-46.8
Spray rate(g/min)	10-60	25-49	30-45	30-46
Gun to bed distance (cm)	20-30	25	25	25
Pan RPM	03-08	03-08	03-06	02-07
Pan load (Kg)	74.5	73.22	73.34	74.02
Air pressure(kg/cm^2)	03-06	04	04	04

The three different variables considered during blister packing are sealing temperature, forming temperature & machine speed. The observations made during three batches are as follows:

TABLE No.7.20: BLISTER PACKAGING PARAMETERS

Critical Parameters	Specified Limit	Batch Y1	Batch Y2	Batch Y3
Sealing temperature	170±20.(˚C)	160	160	160
Forming temperature	150±20.(˚C)	150	150	150
Machine speed	70-100	90	90	90
Test & Results				
Leak test	As Per I.P. 2014	Passes	Passes	Passes
Blister appearance & quality	In-house Specificatio	Complies	Complies	Complies

	n			

Discussion:

All the results clearly shows that the parameters during coating & blister packaging of three batches were found to be satisfactory and within the limits.

7.2.06 Dissolution study of Metformin Hydrochloride 850 mg film coated tablets

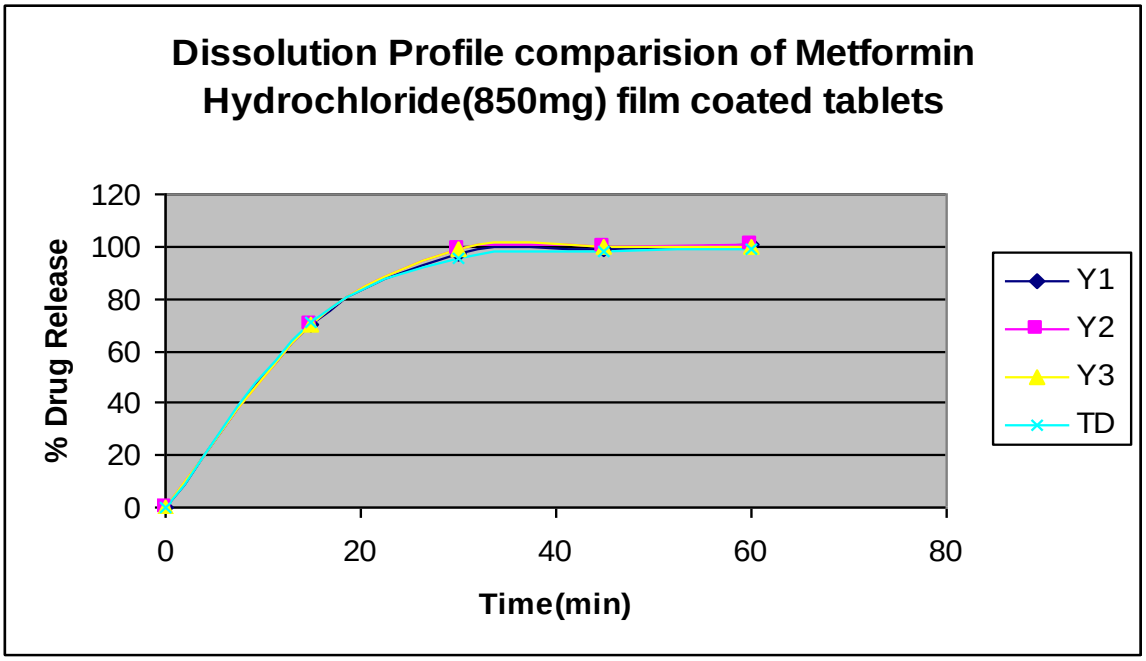
Pooled samples were collected from all the containers & dissolution studies were carried out. The dissolution profile data for Metformin hydrochloride Y1, Y2, Y3 & innovator batches were given below:

Table No.7.21: DISSOLUTION PROFILE RESULTS OF METFORMIN 850mg FILM COATED TABLETS

Time (min.)	**% Dissolution of Metformin**							
	Batch Y1					**Batch Y2**		
	15	**30**	**45**	**60**	**15**	**30**	**45**	**60**
Sr. No.								
01	71	97	98	100	68	100	100	100
02	70	97	99	101	71	99	100	100
03	70	96	99	100	70	98	99	101
04	69	98	100	102	69	99	100	100
05	71	97	99	100	68	99	100	101
06	70	97	98	101	72	100	101	102
Avg.	70	97	99	100	70	99	100	101
% RSD	1.07	0.65	0.76	0.81	2.34	0.75	0.63	0.81

Time (min.)	**% Dissolution of Metformin**							
	Batch Y3				**Innovator**			
	15	**30**	**45**	**60**	**15**	**30**	**45**	**60**
Sr. No.								
01	70	98	99	100	70	93	96	98
02	68	99	100	100	74	96	98	100
03	71	97	99	101	71	96	97	99
04	69	100	100	100	70	95	97	97
05	72	98	99	100	72	97	96	98
06	69	100	100	100	69	97	98	99
Avg.	70	99	99	100	71	95	98	99
% RSD	2.10	1.22	0.55	0.41	2.51	1.53	0.91	1.19

The comparative evaluation of validation batches dissolution data with innovators dissolution data was graphically represented as



Graph No.7.02: DISSOLUTION PROFILE COMPARISON OF METFORMIN 850 MG FILM COATED TABLETS

Discussion:

The dissolution profile of validation batches were complying with that of Innovator dissolution data satisfactorily.

The desired weight buildup & dissolution profile get at all above set critical coating parameters for three batches. The blisters are found to be complying with specified tests of blister packing.

The all above results clearly shows consistency & reproducibility of all critical parameters for film coating & blister packing operations.

7.2.07 Finished product release specification:

The following test was performed on finished product (Metformin Hydrochloride 850mg film coated tablets). The results of three packed batches was found as:

Table No.7.22: FINISHED PRODUCT RELEASE SPECIFICATIONS

Test	**Specifications**	**Batch Y1**	**Batch Y2**	**Batch Y3**
Description	**White, biconvex, oblong film-coated tablet.**	Complies	Complies	Complies
Individual Weight Variation	**(Between 1074 mg to 1145 mg)**	1098	1106	1102
Hardness	**NLT 4.0 Kg/cm^2**	Complies	Complies	Complies

Thickness	**Between 7.30 mm - 7.70 mm**	7.56 Mini: 7.45 Max: 7.59	7.54 Mini: 7.42 Max: 7.61	7.55 Mini: 7.50 Max: 7.59
Disintegration time	**All six tablets should disintegrate completely within 30 minutes**	7.40	8.21	7.54
Assay	**As per current I.P. 2014**	Complies	Complies	Complies
Dissolution	**Dissolution Profile comparison with innovator sample**	Complies	Complies	Complies
Uniformity of mass	**When 20 tablets are weighed not more than two of the individual weights deviate from the average weight by more than ± 5.0 % w/w and no tablet deviates by more than ± 10.0 % w/w than ± 10.0 % w/w**	Complies	Complies	Complies

Discussion:

All the above results show that, the test required for finish product release of Metformin 500 mg film coated tablets was found to be within specification.

7.2.08 Summary:

The validation study of Metformin 850 mg tablets were carried out by considering critical parameters at each unit operations. The following critical steps were considered during three validation batches.

a) Granulation & drying:

The granulation & successive drying step of granules were found to be stable, consistent & reproducible for three consecutive batches at following parameters. This is evident from comparison of powder data of technology developer with obtained results of three batches given in Table No. 7.13.
The validated critical process parameters of granulation & drying steps are as follows

- **Spray rate:** 300-500 g/min
- **Air CFM:** 600-1300
- **Inlet temp:** 28-32ºC
- **Bed temp:** 32-39ºC
- **Atomization pressure:** 03-05 kg/cm^2
- **Drying time:** 07 min
- **LOD:** 01-04% w/w

b) Blending & lubrication:

The blending & lubrication step was found to be satisfactory, stable, consistent & reproducible at following parameters. This is evident from content uniformity test results of consecutive three batches as given in Table No. 7.15

The validated parameters for blending & lubrication steps are as follows:

- **Pre lubrication time**: 15 min.
- **Lubrication time:** 05 min.
- **Blender speed:** 10 RPM

c) Compression:

The Metformin 850mg tablets compression data was found stable, consistent& reproducible at following parameters. This is evident from in process testing & content uniformity data of three consecutive batches as per Table No. 7.16, 7.17 & 7.18.

The following table compares different parameters obtained during three validation batches even at different machine speed & hopper level.

Table No.7.23: VALIDATION BATCHES COMPRESSION RESULTS

Parameters	**Specification**	**Observed value**	
		Min.	**Max.**
WT variation	**1035.5-1144.5 mg**	1069	1112.3
Thickness	**7.3-7.7 mm**	7.40	7.66
Hardness	**NLT 4.0 Kg/cm^2**	Complies	Complies
DT	**NMT 15 min**	6.31	7.24

d) Film coating:

The following coating parameters were found stable, consistent & reproducible during three validation batches, which is evident form finished product release specification data & dissolution data comparison as per Table No. 7.19.

The coating parameters found during three validation batches were compared with the given specifications in following table:

Table No.7.24: VALIDATION BATCHES COATING RESULTS

Parameters	**Specification**	**Observed value**	
		Mini.	**Max.**
Spray rate	**10-60 g/min**	25	49
Inlet temp	**60-70°C**	63.6	67.9
Bed temp	**40-50°C**	41.9	46.8
Atomization pressure	**04-06 kg/cm^2**	04	04

e) Blister packing:

The following parameters were found to be consistence & reproducible during three validation batches for blister packing.

- **Sealing temperature (ºC):** 170±20
- **Forming temperature (ºC):**150±20
- **Machine speed:** 70-110

This result of all three batches & its critical steps clearly shows consistency & reproducibility of parameters and all results. Hence the manufacturing method of Metformin Hydrochloride 850 mg Film Coated tablets say validated at above parameters & equipments.

7.2 VALIDATION STUDY OF METFORMIN HYDROCHLORIDE 1000MG FILM COATED TABLETS

The all three batches of Metformin Hydrochloride tablets were manufactured using standard manufacturing process (Table No. 5.04) for 14 kg batch size. The observations made during each critical step is discussed below:

7.3.01 Granulation & drying:

After milling & sifting the material as per standard manufacturing process (Table No. 5.04) next step is granulation.

FIXED VARIABLES DURING GRANULATION

FBG Load: (48 % occupancy)

The observations made during FBG top spray granulation for following process variables are discussed below

Table No. 7.25: GRANULATION PARAMETERS DURING METFORMIN 1000 mg FBG TOP SPRAY GRANULATION & DRYING

Granulation parameters	**Specified values**	**Batch Z1**	**Batch Z2**	**Batch Z3**
Spray rate (g/min)	300-550	314-440	300-451	310-450
Inlet temp.(˚C)	40-60	43-52	47-54	48-53
Outlet temp. (˚C)	30-55	33-38	34-39	34-39
Bed temp. (˚C)	30-45	32-40	33-38	33-39
Atomization (kg/cm^2)	03-05	04	04	04
Air CFM	750-1300	820-1100	840-1102	915-1254
Drying Parameters				
Product temp. (˚C)	30-40	33	33	34
Inlet temp.(˚C)	30-50	49	48	48
Total time (min.)	05	05	05	05
LOD (NMT 4%)	1.5-3.0%	1.71	1.69	1.88

Discussion:

As per the above results all critical parameters during granulation of three batches were found to be consistent & reproducible.

The granulation & drying step was validated at the all above set parameters as it shows consistent & reproducible results within predetermined specifications.

7.3.02 Blending & lubrication:

The blending of granules & extragranuler part was done in OGB at 10 RPM speed.

Fixed variables during blending & lubrication steps

Blender speed: 10 RPM

Blending time: 15 min.

Lubrication time: 05 min.

Samples were collected after blending & lubrication as per sampling plan and sent to QC for testing. The obtained flow kinetics & mixing efficiency results of lubricated blend are given as follows:

Table No.7.26: RESULTS OF METFORMIN 1000 mg LUBRICATED BLEND.

Test performed	**Specification**	**Flow properties results of Validation batches**		
		Batch Z1	**Batch Z2**	**Batch Z3**
Loss on drying (%w/w)	**1.5-3.0**	2.12	1.98	2.21
Assay(%)	**As per current I.P. 2014**	Complies	Complies	Complies
Bulk density (g/min.)	**0.40-0.60**	0.496	0.519	0.504
Tapped density (g/min.)	**0.45-0.65**	0.546	0.558	0.557
Comp. index (%)	**15-25**	17.4	18.2	18.7
Hausner ratio	**1.15-1.25**	1.16	1.19	1.18
% Retained on #18	**01-05**	2.02	3.02	2.3

Discussion:

The flow properties result of all three batches lubricated blend was found to be reproducible & satisfactory within dossier limits.

7.3.03 Mixing efficiency of the blender (OGB):

The assessment of active content distribution in blend was done by content uniformity test of both blended & lubricated material. The results of mixing efficiency testing were tabulated for blending & lubrication step as follows:

Table No.7.27: ANALYSIS RESULTS OF BLENDING (15 MIN.) & LUBRICATION (5 MIN.) STEP

Sample No.	**Content uniformity not less than 90 % & not more than 110% of label amount of Metformin Hydrochloride (% RSD NMT 5.0%)**					
	Batch Z1 Blending	**Batch Z1 Lubrication**	**Batch Z2 Blending**	**Batch Z2 Lubrication**	**Batch Z3 Blending**	**Batch Z3 Lubrication**
01	98	100	97	96	99	97

02	95	96	99	100	98	98
03	98	99	95	98	102	95
04	94	97	97	97	97	99
05	99	95	99	98	98	98
06	100	98	103	97	95	101
07	98	99	99	99	99	98
08	102	102	96	101	99	97
09	96	98	98	98	97	98
10	99	97	97	99	96	99
Mean	**97.9**	**98.1**	**98**	**98.3**	**98**	**98**
SD	**1.47**	**2.02**	**2.21**	**1.49**	**1.94**	**1.56**
Mini.	**94**	**95**	**95**	**96**	**95**	**95**
Max.	**102**	**102**	**103**	**101**	**102**	**101**

Discussion:

The above results of all tests were found to be reproducible and satisfactory within limits for both blending & lubrication step.

The all results of different tests were found consistent & reproducible on 15 min. blending & 05 min. lubrication, so the blending & lubrication steps are validated at specified parameters.

7.3.04 Compression:

The tablets were compressed at critical process variables as three different hopper level & three different machine speeds. Samples were collected at these critical variables as per sampling plan. These collected samples were evaluated for various tests.

The results of the in process parameters were found at three different speeds tabulated as follows:

Table No. 7.28: IN PROCESS COMPRESSION DATA OF METFORMIN 1000 mg TABLETS.

In process parameters (Specifications)	**Batch No.**	**Compression Machine Speed**		
		Low speed (10RPM)	**High speed (RPM20)**	**Target speed (RPM15)**
Description	**Z1**	Complies	Complies	Complies
	Z2	Complies	Complies	Complies
	Z3	Complies	Complies	Complies
Wt. of 10 tablets (24.877g to 26.417g)	**Z1**	24.987-25.87	25.54-26.12	25.41-26.25
	Z2	24.98-25.83	24.988-	25.978
	Z3	25.12-25.98	24.98-25.89	25.07-25.97
Wt. Variation (1218.24 - 1346.48 mg)	**Z1**	1269-1324	1274-1321	1267-1309
	Z2	1264-1307	1260-1310	1257-1297
	Z3	1269-1308	1264-1309	1267-1307
Thickness (7.1 to 7.9 mm)	**Z1**	7.64-7.69	7.56-7.70	7.65-7.72
	Z2	7.61-7.73	7.59-7.71	7.63-7.72
	Z3	7.59-7.72	7.51-7.71	7.54-7.74

Hardness NLT 4.0 Kg/cm^2	**Z1**	Complies	Complies	Complies
	Z21	Complies	Complies	Complies
	Z3	Complies	Complies	Complies
Friability NMT 1.0 %	**Z1**	0.1	0.12	0.11
	Z2	0.09	0.10	0.13
	Z3	0.12	0.10	0.089
DT NMT 15 minutes	**Z1**	8.12	7.54	8.24
	Z2	8.01	8.12	8.24
	Z3	7.54	7.16	7.42

Discussion:

All results of above three batches after compression was found to be satisfactory & within limits at three given speeds.

The samples collected at different machine speed were tested for mass uniformity test. The results of mass uniformity test at three different speed was found as:

Table No.7.29: RESULTS OF COMPRESSED TABLETS AT DIFFERENT MACHINE SPEED

Compression speed	**Batch Z1**	**Batch Z2**	**Batch Z3**
Uniformity of mass (NMT 2 of 20 individual units deviates by more than 05% average mass of label claim of Metformin Hydrochloride)			
Low (10RPM)	1269-1324	1264-1307	1269-1308
High (20RPM)	1274-1321	1260-1310	1264-1309
Target (15RPM)	1267-1309	1257-1297	1267-1307

The tablets compressed at target speed (15 RPM) & samples were collected. The collected samples were analyzed for uniformity of mass & equal breakability tests. The results of tests were tabulated as:

Table No.7.30: RESULTS OF COMPRESSED TABLETS AT DIFFERENT HOPPER LEVEL

Batch No.	**Hopper level**			
Uniformity of mass (NMT 2 of 20 individual units deviates by more than 05% average mass of label claim of Metformin Hydrochloride)				
	Initial 1/3rd	**(1/3-2/3rd)**	**Middle of run**	**End of run**
Batch Z1	1274.1-1319	1276-1310	1269-1309	1259-1304
Batch Z2	1275-1325	1272-1312	1265-1312	1264-1306
Batch Z3	1278-1320	1272-1309	1269-1311	1262-1305
BREAKABILITY TEST (Weight of each half should be equivalent to average wt. of 20 tablets ± 17%)				

Batch Z1	Complies	Complies	Complies	Complies
Batch Z2	Complies	Complies	Complies	Complies
Batch Z3	Complies	Complies	Complies	Complies

Discussion:

All three batches result clearly shows that the tablet mass were found to be within specifications even at different machine speed & hopper level.

The all in process parameters are well within specifications, giving consistent & reproducible results at given three different speed & hopper level.

7.3.05 Tablets film coating & packaging:

The compressed tablets were subjected for film coating in two lots of same size. The following variables considered during film coating. The parameters set during coating for three batches are as follows:

Table No.7.31: TABLETS FILM COATING PARAMETERS

Process parameters	**Specified limit**	**Batch Z1**	**Batch Z2**	**Batch Z3**
No. of guns	02	02	02	02
Inlet temperature.(˚C)	60-70	65.4-68.2	64.6-67.8	64.9-67.9
Bed temperature.(˚C)	42-46	41.9-44.1	42.0-43.6	42.3-43.8
Spray rate(g/min)	10-60	25-49	30-45	30-46
Gun to bed distance (cm)	20-30	25	25	25
Pan RPM	02-08	02-04	03-04	02-04
Pan load (Kg)	Constant	74.3	74.2	74.2
Air pressure(kg/cm^2)	03-06	04	04	04

The three different variables considered during blister packing are sealing temperature, forming temperature & machine speed. The observations made during three batches are as follows:

Table No.7.32: BLISTER PACKAGING PARAMETERS

Process parameters	**Specified limit**	**Batch Z1**	**Batch Z2**	**Batch Z3**
Sealing temperature(˚C)	200±20.	200	200	200
Forming temperature(˚C)	180±20.	190	190	190
Machine speed	80-100	90	90	90
Test & results				
Leak test	As Per I.P. 2014	Passes	Passes	Passes
Blister appearance & quality	In house Specification	Complies	Complies	Complies

Discussion:

All the results clearly shows that the parameters during coating & blister packaging of three batches were found to be satisfactory and within the limits.

7.3.06 DISSOLUTION STUDY OF METFORMIN HYDROCHLORIDE 1000 mg FILM COATED TABLETS

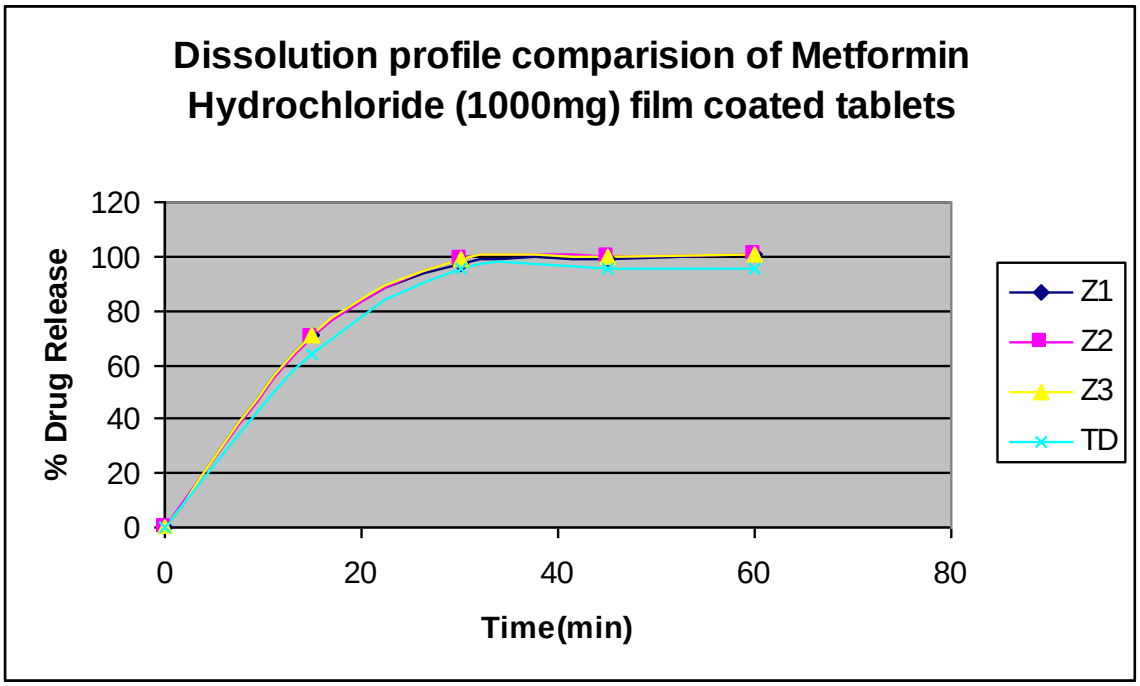
Pooled samples were collected from all the containers & dissolution studies were carried out. The dissolution profile data for Metformin Hydrochloride Z1, Z2, Z3 & innovator batches were given below:

Table No.7.33: DISSOLUTION PROFILE RESULTS OF METFORMIN 1000 mg FILM COATED TABLETS.

Batch No.	**% Dissolution of Metformin**							
	Z1				**Z2**			
Time (min)	**15**	**30**	**45**	**60**	**15**	**30**	**45**	**60**
Sr. No.								
01	72	98	99	100	69	100	100	101
02	74	97	97	101	72	99	100	100
03	69	97	99	100	70	98	99	100
04	71	98	100	101	70	99	101	100
05	71	98	99	100	68	99	100	101
06	70	97	98	100	71	98	100	102
Avg.	71.1	97.5	98.6	100.3	70	98.8	100	100.6
% RSD	2.42	0.56	1.05	0.53	2.02	0.76	0.63	0.81

Batch No.	**% Dissolution of Metformin**							
	Z3				**Innovator**			
Time (min)	**15**	**30**	**45**	**60**	**15**	**30**	**45**	**60**
Sr. No.								
01	71	99	99	101	68	96	96	97
02	71	99	100	102	66	93	94	95
03	73	97	98	100	69	96	96	96
04	74	99	101	101	58	96	96	95
05	70	99	99	100	59	96	96	96
06	69	100	100	101	62	95	95	95
Avg.	71.3	98.8	99.5	100.8	63.6	95.3	95.5	95.6
% RSD	2.61	0.99	1.05	0.74	7.32	1.24	0.87	0.85

The comparative evaluation of validation batches dissolution data with innovators dissolution data was graphically represented as



Graph No.7.03: DISSOLUTION PROFILE COMPARISON OF METFORMIN 1000 mg FILM COATED TABLETS

Discussion:

The dissolution profile of validation batches were complying with that of innovator dissolution data satisfactorily.

The desired weight buildup & dissolution profile get at all above set critical coating parameters for three batches. The blisters are found to be complying with specified tests of blister packing.

The all above results clearly shows consistency & reproducibility of all critical parameters for film coating & blister packing operations.

7.3.07 Finished product release specification:

The following test was performed on finished product (Metformin Hydrochloride 1000 mg film coated tablets). The results of three packed batches was found as:

Table No. 7.34: FINISHED PRODUCT RELEASE SPECIFICATIONS

Test	**Specifications**	**Z1**	**Z2**	**Z3**
Description	**White, biconvex, oblong film-coated tablet.**	Complies	Complies	Complies
Individual weight variation	**(Between 1265.78 mg & 1399.02mg)**	1326.1	1326.4	1328.3
Hardness	**NLT 4.0 kg/cm^2**	Complies	Complies	Complies
Thickness	**Between 7.10 mm -7.90 mm**	7.83 Mini:7.70	7.82 Mini:7.77	7.84 Mini:7.6

		Max:7.98	Max:7.92	2 Max:7.91
Disintegration time	**All six tablets should disintegrate completely within 30 minutes**	8.24	8.56	9.04
Assay	**As per current I.P. 2014**	Complies	Complies	Complies
Dissolution	**Dissolution Profile comparison with innovator sample**	Complies	Complies	Complies
Uniformity of mass	**When 20 tablets are weighed not more than two of the individual weights deviate from the average weight by more than ± 5.0 % w/w and no tablet deviates by more than ± 10.0 % w/w than ± 10.0 % w/w**	Complies	Complies	Complies

Discussion:

All the above results show that, the test required for finish product release of Metformin 500 mg film coated tablets was found to be within specification.

7.3.08 Summary:

The validation study of Metformin 1000 mg tablets were carried out by considering critical parameters at each unit operations. The following critical steps were considered during three validation batches.

a) Granulation & drying:

The granulation & successive drying step of granules were found to be stable, consistent & reproducible for three consecutive batches at following parameters. This is evident from comparison of powder data of technology developer with obtained results of three batches given in Table No. 7.25.
The validated critical process parameters of granulation & drying steps are as follows

- **Spray rate:** 300-500 g/min
- **Fluidization air CFM:** 600-1300
- **Inlet tem:** 43-54ºC
- **Bed temp:** 33-39ºC
- **Atomization pressure:** 04
- **Drying time:** 07 min
- **LOD:** 1.5-3% w/w

b) Blending & lubrication:

The blending & lubrication step was found to be satisfactory stable, consistent & reproducible at following parameters. This is evident from content uniformity test results of consecutive three batches as given in Table No. 7.26 & 7.27.

The validated parameters for blending & lubrication steps are as follows.

- **Pre lubrication time**: 15 min
- **Lubrication time:** 05 min
- **Blender speed:** 10 RPM

c) Compression:

The Metformin 1000mg tablets compression data was found stable, consistent& reproducible at following parameters. This is evident from in process testing & content uniformity data of three consecutive batches as per Table No. 7.28, 7.29 & 7.30.

The following table compares different parameters obtained during three validation batches even at different machine speed & hopper level.

Table No. 7.35: VALIDATION BATCHES COMPRESSION RESULTS

Parameters	**Specification**	**Observed value**	
		Mini.	**Max.**
WT variation	**(1218.24 - 1346.48 mg)**	1257	1324
Thickness	**(7.1 to 7.9 mm)**	7.51	7.74
Hardness	**NLT 4.0 Kg/cm^2**	Complies	Complies
DT	**NMT 15 min.**	0.089	0.13

d) Film coating:

The following coating parameters were found stable, consistent & reproducible during three validation batches, which is evident form finished product release specification data & dissolution data comparison as per Table No. 7.31.

The coating parameters found during three validation batches were compared with the given specifications as following:

Table No.7.36: VALIDATION BATCHES COATING RESULTS

Parameters	**Specification**	**Observed value**	
		Mini.	**Max.**
Spray rate:	**10-60 g/min**	25	49
Inlet temp.	**60-70°C**	64.6	68.2
Bed temp.	**42-46°C**	41.9	44.1
Air pressure	**03-06 kg/cm2**	04	04

e) Blister packing:

The following parameters were found to be consistence & reproducible during three validation batches for blister packing.

- **Sealing temperature (ºC):** 170±20

- **Forming temperature (°C):** 150±20
- **Machine speed:** 70-110

This result of all three batches & its critical steps clearly shows consistency & reproducibility of parameters and all results. Hence the manufacturing method of Metformin Hydrochloride 1000 mg Film Coated tablets say validated at above parameters & equipments.

7.4 STABILITY STUDIES

The samples were charged for stability, accelerated stability studies were conducted as per ICH Guidelines. The samples were analyzed at initial, 1 month, 3month intervals. The result has been tabulated in following Tables:

Table No. 7.37: STABILITY STUDIES RESULTS OF METFORMIN HYDROCHLORIDE 500 mg FILM COATED TABLETS

Test	Specifications	Initial	3 Month	6 Month
Description	White, biconvex, oblong film-coated tablet.	Complies	Complies	Complies
Assay %	As per current I.P. 2014	Complies	Complies	Complies
Dissolution %	Dissolution Profile comparison with innovator sample	Complies	Complies	Complies
Water content%	01-04%w/w	1.56	1.54	1.55
Avg. wt.	671.2 ± 5 %(Bet. 637.64-704.76 mg)	653-690	650-690	652-694
Hardness	NLT 4.0 Kg/cm^2	Complies	Complies	Complies
DT	NMT 15 min.	7.55	7.56	8.0
Impurities	As per current I.P. 2014	Complies	Complies	Complies

Discussion:

The sample of Metformin Hydrochloride 500 mg film coated tablets was found to be stable after 6 Month accelerated stability storage condition.

Table No.7.38: STABILITY STUDIES RESULTS OF METFORMIN HYDROCHLORIDE 850mg FILM COATED TABLETS

Test	Specifications	Initial	3 Month	6 Month
Description	White, biconvex, oblong film-coated tablet.	Complies	Complies	Complies
Assay %	As per current I.P. 2014	Complies	Complies	Complies
Dissolution %	Dissolution Profile comparison with innovator sample	Complies	Complies	Complies
Water content%	01-04%w/w	1.66	1.65	1.64
Avg. wt.	(Between 1074mg -1145 mg)	1103	1101	1102

Hardness	NLT 4.0 Kg/cm^2	Complies	Complies	Complies
DT	NMT15 min.	7.57	7.58	8.02
Impurities	As per current I.P. 2014	Complies	Complies	Complies

Discussion:
The sample was found to be stable after 6 month accelerated stability storage condition.

Table No.7.39: STABILITY STUDIES RESULTS OF METFORMIN HYDROCHLORIDE 1000mg FILM COATED TABLETS

Test	**Specifications**	**Initial**	**3 Month**	**6 Month**
Description	White, biconvex, oblong film-coated tablet .	Complies	Complies	Complies
Assay %	As per current I.P. 2014	Complies	Complies	Complies
Dissolution %	Dissolution Profile comparison with innovator sample	Complies	Complies	Complies
Water content%	1.5-3.0%w/w	2.10	2.09	2.07
Avg. wt.	(Between 1265.78 to 1399.02mg)	1327	1326	1326
Hardness	NLT 4.0 Kg/cm^2	Complies	Complies	Complies
DT	NMT 15 min.	8.49	8.50	8.52
Impurities	As per current I.P. 2014	Complies	Complies	Complies

Discussion:
The sample was found to be stable after 6 month accelerated stability storage condition.

CHAPTER-7
CONCLUSION

Metformin Hydrochloride 500 mg, 850 mg, 1000 mg film coated tablets was prepared using FBE granulation technology on lab scale size. This study was carried out through a systematic plan; critical parameters were optimized to engender a stable & robust manufacturing process.

This project involves international technology transfer, which has been transfer within Grampus Laboratories, Kala Amb, H.P. The data provided by technology supplier was studied extensively to understand product comportment, tribulations were taken on lab scale size & additionally verified feasibility of technology on available sets of facilities and equipments. The critical process variables studied extensively during tribulation batches

The validation study of Metformin Hydrochloride 500 mg, 850 mg, 1000 mg film coated tablets were carried out by considering critical parameters at each unit operations. The granulation & successive drying step of granules were found to be stable, consistent & reproducible. The blending & lubrication step was found to be satisfactory stable, consistent & reproducible. The compression data was found

stable, consistent & reproducible. The following coating parameters were found stable, consistent & reproducible during three validation batches, which is evident from finished product release specification data & dissolution data comparison.

The dissolution profile of Metformin Hydrochloride 500 mg tablets are better than Metformin Hydrochloride 850 mg & 1000 mg tablets.

The friability of Metformin Hydrochloride 1000 mg tablets are better than Metformin Hydrochloride 500 mg & 850 mg tablets.

The disintegration profile of Metformin Hydrochloride 500 mg tablets are better than Metformin Hydrochloride 850 mg & 1000 mg tablets.

The uniformity of mass of Metformin Hydrochloride 1000 mg tablets are better than Metformin Hydrochloride 850 mg & the uniformity of mass of Metformin Hydrochloride 850 mg tablets are better than Metformin Hydrochloride 500 mg tablets.

The result of all three batches & its critical steps clearly shows consistency & reproducibility of parameters and all results. Hence the manufacturing method of Metformin Hydrochloride 500 mg, 850 mg, 1000 mg Film Coated tablets are validated at above parameters & equipments.

Three validation batches of commercial scale batch size were taken successfully and monitored the in-process critical parameters for commercial batches. Metformin Hydrochloride tablets were manufactured within specified Limits for meeting all quality attributes and loaded for stability study.

The samples were charged for stability, accelerated stability studies were conducted as per ICH Guidelines. The samples were analyzed at initial, 1 month, 3 month intervals.

The accelerated stability data was found after three months and found to be satisfactory & data matches with previous test results.

The overall successful three consecutive validation batches of Metformin Hydrochloride film coated tablets (500, 850 & 1000 mg) verifies the international technology transfer success.

REFERENCES

1. Agalloco, J., Carleton J., (2008), Validation of Pharmaceutical process. Why Validation?. *Informa Healthcare: NY*, 3rd Edition, p. 3.
2. Ahmed, S.U., Nani, V., Wadgaonkar D., (2005). Scale up process validation & Technology Transfer, Generics Drug Product Development: Solid Oral Dosage form, *Marcel Dekker, New York*, 143, pp. 95-136.
3. Bankar, G.S., Anderson, N.R., (1986a). The Theory and Practice of Industrial Pharmacy, *Varghese Publishing House. Bombay*, pp. 293-342.
4. Bankar, G.S., Anderson, N.R., (1986b). The Theory and Practice of Industrial Pharmacy, *Varghese Publishing House. Bombay*, pp. 343-348.
5. Bankar, G.S., Anderson, N.R., (1986c). Tablets, The Theory and Practice of Industrial Pharmacy, *Varghese Publishing House. Bombay*, pp. 375-378.
6. Berry, I.R., (2007a). Technology transfer consideration for Pharmaceuticals, Encyclopedia of Pharmaceutical Technology, *Informa Healthcare, New York/ London.*, 6, pp. 3717-3723.
7. Berry, I.R., (2007b). Technology transfer consideration for Pharmaceuticals, Encyclopedia of Pharmaceutical Technology, *Informa Healthcare, New York/ London.*, 6, pp. 3611-3612.
8. Bretnall, A. E., Clarke, G. S., (1998a). Metformin hydrochloride. Analytical Profile of Drug Substances, *Academic press, California*, 25, pp. 243-294.

9. Bretnall, A. E., Clarke, G. S., (1998b). Metformin hydrochloride, Analytical Profile of Drug Substances, *Academic press, California*, 25, pp. 341-345.
10. British Pharmacopoeia, (2007).*British Pharmacopoeial commission, London*, p. 2739, 1347.
11. Bolton S., (1997), Optimization Technique Pharmaceutical Statistics, *Marcel Dekker, New York*, pp. 590-626.
12. Chao, A. Y., Forebes, F. J., Johnson, R. F., (2003a). Prospective Process Validation, Pharmaceutical Process Validation, *Marcel Dekker, New York/Basel*, 129, pp. 7-12.
13. Chao, A. Y., Forebes, F. J., Johnson, R. F., (2003b). Prospective Process Validation, Pharmaceutical Process Validation, *Marcel Dekker, New York/Basel*, 129, pp. 31-33.
14. Cheng, L. C., (2004). Biowaver Extension Potential to BCS Class III high solubility-Low permeability drugs: Bridging evidence for Metformin immediate release tablet. *European Journal of Pharmaceutical Sciences*, 22, pp. 297-304.
15. Davis, S. N., (2006a). Insulin, oral Hypoglycemic Agents & The Pharmacology of Endocrine Pancreas, The Pharmacological Basis of Therapeutics, *McGraw-HILL Medical Publication Division, New York/Chicago/London*, pp. 1613-1639.
16. Davis, S. N., (2006b). Insulin, oral Hypoglycemic Agents & The Pharmacology of Endocrine Pancreas, The Pharmacological Basis of Therapeutics, *McGraw-HILL Medical Publication Division, New York/Chicago/London*, pp. 1656-1658.
17. Dosage Form. *(http://en.wikipedia.org/wiki/dosage-form.).*
18. Dosing *(http://www.drugs.com/drug_dose.).*
19. European Pharmacopoeia/ Supplement 5.2, (2006a). *Council of Europe, Strasbourg*, pp. 2003-2004.
20. European Pharmacopoeia/ Supplement 5.2, (2006b). *Council of Europe, Strasbourg*, pp. 2015-2017.
21. FB Granulation.(*http://www.glatt.com/e/16_downloads/pdf/fbe-pro_e.pdf*) .
22. Glodek, M., Lin, C.S., Taylor, R.J., (2006a), Process robustness- A PQRI white paper. *Pharmaceutical Engineering.* 26, pp. 1-10.
23. Glodek, M., Lin, C.S., Taylor, R.J., (2006b), Process robustness- A PQRI white paper. *Pharmaceutical Engineering.* 26, pp. 21-23.
24. Glodek, M., Lin, C.S., Taylor, R.J., (2006c), Process robustness- A PQRI white paper. *Pharmaceutical Engineering.* 26, pp. 33-35.
25. Hinak T., (2000), Granulation and Scale-up Issue in Solid Dosage Forms Development. *An Pharm Rev.*, 3(4), pp. 33-36.
26. ICH Harmonized Tripartite guideline." Stability Testing of New Drug Substances and Products".Q1 a (R2), August 2003.
27. Indian Pharmacopoeia, (2014), *Indian Pharmacopoeial Commission, Gaziabad*, pp. 2187-2188.
28. International Technology Transfer -By design. (*http://www.pharmapubs1.com/ITT-Ronald_Snee_Tunnell-1-4.pdf)* 02/06/2009.
29. Kumar, V., (2000a). Direct compression Metformin hydrochloride tablets .*U S Patent 06117451*. pp. 12-14.
30. Kumar, V., (2000b). Direct compression Metformin hydrochloride tablets .*U S Patent 06117451*. pp. 36-37.

31. Lawrence, X.Y., (2008). Pharmaceutical Quality by Design: Product and Process Development, understanding, and control. *Pharmaceutical Research*. 25, pp. 781-790.

32. Lionberger, R. A., (2008). Quality by Design: Concept of ANDA's. *The AAPS Journal*. 10, pp. 268-275.
33. Manthan, D. J., (2008). Facets of Technology Transfer: A Perspective of Pharmaceutical Industry. *Journal of Intellectual property Right* .13, pp. 28-34.
34. Mehta, R.M., (2002a). Processing of Tablets, Pharmaceutics-I, *Vallabh Prakashan, Delhi*, pp. 237-238.
35. Mehta, R.M., (2002b). Processing of Tablets, Pharmaceutics-I, *Vallabh Prakashan, Delhi*, pp. 266-267.
36. Mehta, R.M., (2002c). Processing of Tablets, Pharmaceutics-I, *Vallabh Prakashan, Delhi*, pp. 282-284.
37. Mehta, R.M., (2002d). Processing of Tablets, Pharmaceutics-I, *Vallabh Prakashan, Delhi*, pp. 290-291.
38. Metformin hydrochloride. (*http://www.drugs.com/pdr/metformin-hydrochloride.html*.) 25/05/2009.
39. Michel Levin, (2006), Pharmaceutical Process Scale-Up, *Taylor and Francis Group, CRC Press New York*, pp. 199-220.
40. Parikh, D. M., Mogavero, M., (2005). Batch Fluid Bed Granulation, Handbook of Pharmaceutical Granulation Technology. *Taylor & Francis Publications, London/New York,* 154, pp. 247-249.
41. Panchal, H.A., Kumar, S., & Eqbal, T., (2012), Importance of Immediate Drug Release, *The AAPS Journal*. 15, pp. 118-145.
42. Pamglatt, (2009), Different Types of Granulation Techniques in Tablet Formulation, *Pharmaceutical Research*. 21, pp. 552-560.
43. Patel, J. K., (2009a). Aqueous-Based Film Coating of Tablets: study the effect of critical process parameters. *Pharma Tech Research*.1, pp. 235-240.
44. Patel, J. K., (2009b). Aqueous-Based Film Coating of Tablets: study the effect of critical process parameters. *Pharma Tech Research*.1, pp. 243-245.
45. Patel, R., Shah. N., Rathod, D., Dr. Rajesh, K. S., (2013a), Process Validation Of Metformin Hydrochloride and Glimepiride Bilayered Extended Release Tablet, *Pharmagene*, 1(3), pp. 13-19.
46. Patel, R., Shah. N., Rathod, D., Dr. Rajesh, K. S., (2013b), Process Validation Of Metformin Hydrochloride and Glimepiride Bilayered Extended Release Tablet, *Pharmagene*, 1(3), pp. 21-22.
47. Patel, R., Shah. N., Rathod, D., Dr. Rajesh, K. S., (2013c), Process Validation Of Metformin Hydrochloride and Glimepiride Bilayered Extended Release Tablet, *Pharmagene*, 1(3), pp. 26-27.
48. Pfeffer, F., (2006). Direct Compression Formulation and Process: *US Patent 20060210627*, p. 21.
49. Porter S., Verseput, R.P., Cunningham C.R., (1980), Process Optimization Using, Design of Experiments. *Pharm Tech*, 4(3), p. 66.
50. Rane, M., Parmar, J., (2009a). Tablet Formulation design and Manufacturing: Oral Immediate Release Application. *Pharma Times*, pp. 41-43.
51. Rane, M., Parmar, J., (2009b). Tablet Formulation design and Manufacturing: Oral Immediate Release Application. *Pharma Times*, pp. 21-24.
52. Rowe, R.C., Sheskey, P.J., and Weller, P.J., (2003), Handbook of Pharmaceutical Exceipients. *The Pharmaceutical Press*, London., 6, pp. 404-406.

53. Rohokale, B.S., Jadhav, V.M., Kadam, V.J., (2010), Studies in Prospective Process Validation of Metformin HCl Tablet Dosage Formulation. *International Journal of Pharmtech Research*, 2(3), pp. 1673-1678.
54. Setter, S.M., (2003). Metformin Hydrochloride in the treatment of Type-2 diabetes mellitus. *Clinical Therapeutics*. 25, pp. 12-16.
55. Shiromani, P. K., (2006a), Tabletting Tips. *Pharma & Bio Ingredients*. pp. 30-34.
56. Shiromani, P. K., (2006b), Tabletting Tips. *Pharma & Bio Ingredients*. pp. 38-39.
57. Shiva, S., Krishna, B., Goswami, T. (2009). Pharmaceutical Compositions of Metformin.*US Patent 20090124702*, pp. 214-216.
58. Srinivasan S., (2015), Granulation techniques and technologies: recent progresses, *BioImpacts*, 2015, 5(1), pp. 55-63.
59. Sweetman, S. C., (2007). Metformin Hydrochloride, Sweetman, S. C. (Ed.).The complete drug references, *Pharmaceutical Press, London/Chicago*, 1, pp. 411-412.
60. Tablet Coating & Trouble shooting, (2009a), (*http://online1.ispcorp.com/enUS/Media/Articles/Tablet%20Coating,%20Troubleshooting%20Appearance-Related%20Problems%20of%20Film-Coated%20Tablets.pdf*).
61. Tablet Coating & Trouble shooting, (2009b), (*http://online1.ispcorp.com/enUS/Media/Articles/Tablet%20Coating,%20Troubleshooting%20Appearance-Related%20Problems%20of%20Film-Coated%20Tablets.pdf*).
62. Tripathi, K. D., (2008), Essentials of Medical Pharmacology, *Jaypee Brothers Medical Publications, St Louis/Panama/New Delhi*, pp. 254-274.
63. U. S. FDA-"Guidance for Industry Process Validation: General Principle & Practices". Nov.2008.
64. U.S. FDA- "Guidelines on general principle of process validation" updated May 1987.
65. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Guidance for Industry, (2015) Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, *(http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.)*
66. United State Pharmacopoeia/ The National Formulary, 2007. *United State Pharmacopeial Convention, Rockville, MD*, USP30/NF25, pp. 242-243.
67. Vadnere, G.P., Sathe, B.S., Bharate, S.D., (2006). Prospective Process validation/ Premarket Validation: a focus on product development. *Pharma Times*. 38, pp. 20-23.
68. Wadwalkar, S., (2009). Fighting diabetes- the FMHG way. *PHARMA EXPRESS*. 15, pp. 27-28.
69. Wong, K., Mark, J.D., Sane, W.K., (2005a). Compositions and dosage forms for enhanced absorption of Metformin. *US Patent 20050158374*, pp. 21-24.
70. Wong, K., Mark, J.D., Sane, W.K., (2005b). Compositions and dosage forms for enhanced absorption of Metformin. *US Patent 20050158374*, pp. 39-43.