Technology Transfer (solid oral) Dosage Form

By

Ved Prakash Purohit

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2018-2020

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CHAPTER -1

INTRODUCTION

1.1 TECHNOLOGY TRANSFER OF (SOLID ORALS) IN PHARMACEUTICAL INDUSTRY

Technology Transfer is the development of medicines, educational tools and health services for the availability to the public. Later it realizes that it is the practice of transferring scientific finding from one organization to another's for the development of drugs or medicines. Simply Technology Transfer is the intersection between science and business , by this process the basics of science research and fundamental discoveries has being developed into practical and commercial application and products[1-2].For the development of new medicinal product Technology Transfer play a important role by means, Technology Transfer is an critical and integral to the drug discovery. This process is very important for the elucidation of necessary information from R&D (Research & Development) to PDL (Process Development Laboratory) and the development of products which are existing to the production of commercialization. Technology Transfer is very helpful in terms of development of dosage form in various ways like it provide process more efficient , It helps in maintaining product quality or it helps to achieve standardized process which timely facilitates and more cost effective production[3-4].

Research scientist focused on the idea which is bit more advanced from a program which is research oriented to target commercialization. Generally the product development cost dramatically raises during the pilot scale-up and initial efforts during the production. In other words, the path for success is totally dependent on completion of Technology to the site of production at an affordable cost. The success of any program is dependent highly on communication effectiveness before its apply or implement on production. The ultimate goal of Technology Transfer that it become successful and to have evidences which are documented that the manufacturing instruction for drug substances and drug product are robust and it is effective in producing the drug substances and drug product complying the specification and Good manufacturing requirements[5].

In Industry like Pharmaceutical, Technology Transfer means it is an action of information transfer and necessary technology to realization of design, Quality of Drugs during manufacturing. The primary consideration to be addressed in effective technology duration and during Technology Transfer with well equipped plans and involved process and these plans must be originally devised and once prepared, it must be communicated to the involved departments in research, at the level of corporate and the site of production. Technology Transfer does not mean the actions which are taken once by the transferring party towards the Transferred party, but it is the continuous exchange of information between both parties to maintain the product manufacturing. To assure the quality of product , it is desired that what, when and why information and it should be transferred to where and by whom and how it is to be transferred , then knowledge sharing and information which is relevance to Technology Transfer to each other between stake holders which are related to drug or product manufacturing [1,7-8].

Vertical Transfer is referred to the Transfer of Technology from Research i.e. Basic Research to the development of drugs as well as production respectively and on the same time Horizontal Technology transfer refers to the movement and technology which is use in one place or it may be in context of another place. In today scenario where business is globalise and Liberalised, setting many Technology development chains are linked by Transferor and Transferee. Technology Transfer has also been used to refer the technology movements from one Laboratory to Large scale Industry, developed to developing countries. The significance of technology Transfer in world economy arises from its capacity to provide developing countries with new technology that can improve efficacy and efficiency and contribute to the economic growth of world.

Technology Transfer is not only the product transferring but also the knowledge which has been used for its application. Technology Transfer may be accomplished by diversity of agents and through variety of mechanism. The agents can be organisation in the receiving country such as business firms, Government agencies or universities. Agents may also be foreign organisation such as foundations, firms, and also non profit universities. Research and Development (R&D) plays an important role in creating Technologies, but not always important benefits are being transferred to people who are needy and therefore for this reason the Technology Transfer need

arise. The important and ultimate goal of Technology Transfer is to have the Technology widely used and for this reason it is written into Laws, regulations, codes and standards. Key player which includes in this is spenders, users, dosers, producers and enablers [9].

Licensing which is important phenomenon of Transfer that has gained pharmaceutical industry momentum by which drug companies can contribute to R&D (Research & Development). Technology Transfer is usually considered as dissemination of drug information, matching the needs with technology and adoption of items for new users. Different models have been used to help the industry plan and managed Technology Transfer projects. The agreements of Technology Transfer between developed and developing are useful at some extent to making technology available to people in developing countries easily and economically. Drug industry is driven by Technology, intensive Research, High Risk-high Profit, and Long Process and tedious. For the various medicines development it took several years and billions of dollars are spent on them. In case of pharmaceutical formulation, it requires billions of dollars to come out with the new chemical entity in several years. Drug companies get benefit by collaborating with institution that give basic research, which further took by Pharmaceutical Industries[6, 11-12].

Importance of Technology Transfer to Drug Industry:

- Because of compressed time to market expectations, process development and commercial production is the critical path.
- For Drug companies it always Vulnerable Time.
- It leads to "reinvention of the Wheel'' because of Loss of Knowledge and Experience.
- It confused responsibilities.
- Most important it Delayed approvals.

For facilitating timely and cost effective technology transfers,

- It is handled by group of People who has clear idea how to bridge the Technology Transfer for an application of Technology receiver of any scientific concept or it was the process for new situation or circumstances.
- License agreement and setup the ventures and shared partnership for both risk and rewards to bring new Technology to Market.
- It should be able to handle (any formulation /specialized preparations) Technology Transfer as well as Development of analytical method.

- This should be in terms that the assurance of Technology Transfer being safely completed ,The process being runs as expected (yield, purity, cycle time, etc.), On time (product launch), On budget and with No “CRISIS” situations.

1.2 TECHNOLOGY TRANSFER

In the drug Industry, Technology Transfer it refers to the process that is required for the progress from drug discovery to manufacturing or it is defined as the process by which a Technology developer makes its Technology available to commercial partner that would simply Technology driven. Technology Transfer is the knowledge, Know- How and why Transfer, Simply based on the principle of building business which is profitable for its owners and stake holder. A drug company get the profit by diffusing Technology which is brand new through the entire company [13]. Drug Technologies which are better designed, meets the needs of developing countries and their stake holder. Technology which has been transferred must meet the demands and the needs of the people and market. It is a two sided process and has been emphasise that Technology Transfer to be successful and both parties should achieve benefit and interest to be acknowledged by both parties. In simple Term Technology Transfer is simply sharing of Technology, government facilities to be developed usually with the public and private sector. Generally there are two types of Technology Transfer, Vertical and Horizontal. Vertical Transfer refers to the Transfer of Technology from R&D to manufacturing. Thus this follows the stages of invention being progressive and on the same time innovation and development. As a name indicates, Vertical Transfer can be within one organization or it can be phase Transition between institute and Production Company. On the same time, Horizontal transfers refer to Technology establishment that is being transferred from one operational environment to another. This type of Transfer is used by drug companies for maximize the benefit or return from their Technology. There is a pattern of Horizontal Transfer is more common when technology is being transferred from developed to developing countries. The Japanese type Transfer Technology direct investment must be more beneficial than American type for balanced economy development and growth of developing countries in terms of Trade. Technology Transfer mainly refers to the training of Labourers and production managers. It seems that it is not possible without the corporation of people in the host country. For the faster improvement in productivity there has been Transfer of Technology. If the technology gap is large, it is very difficult for the establishment of enclaves. The technology is already commercialised and it simply purpose is to technology being disseminate and to extend its application and there is usually no improvement until unless these needs to be modified to suite the circumstances with keep in mind the environmental regulations[14-15].

Types of technology are given in figure 1

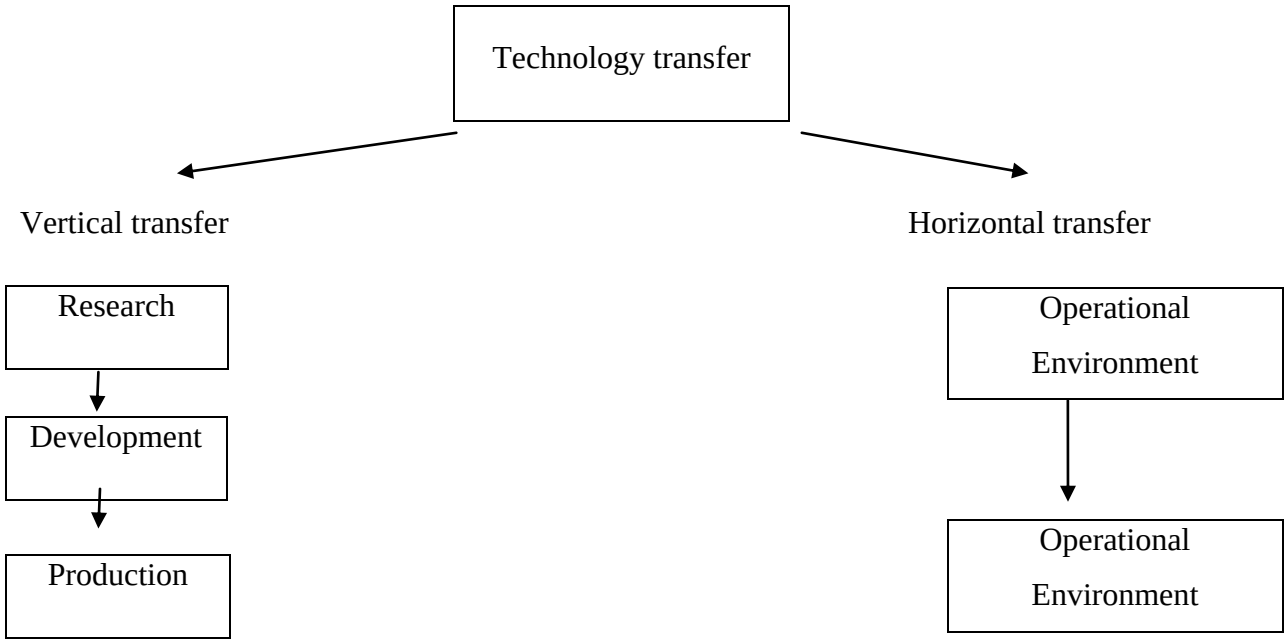


FIGURE 1: REPRESENTATION OF DIFFERENT TYPES OF TECHNOLOGY TRANSFER

1.2.1 Technology transfer to pharmaceutical industry

For any nation the development of Economy depends on the growth and development of the its economic entities such as organisation which are business inclined .In order for any drug organisation to succeed and grow. It has maintained a edge which is Technology driven in this competitive global business environment and this can be accomplished by either technological innovations or through any technological adaptation. The Technology which is acquired is transferred to different units or department of organisation and which are located at different geographic Location which includes to simplify necessary information to Technology Transferred from R&D to actual production by eliminate various production obtained during R&D ; to elucidate production places and to exemplify procedures which are specific and point

of concern for the two type of Technology which is being transferred through R&D to formulation of drug and the technology transferred which is related to post marketing changes in formulation places . Scientist has categorized technology into three category: product, process & management.

Product Technology is the ideas or set of ideas embodied in the product and it is the idea involved in the product manufacturing, whereas management technology is the managerial procedures associated with the product selling. Basic approach to Technology which is being transferred is as follows: The first step is simply we have to find out the industry representative who is interested in the formal methods, believes there is potential benefits of such methods and willing to work with organization. The next step is to find our normal procedures which are being applied for the normal methods for an applicable application. The main steps for technology transfer are given in figure 2.

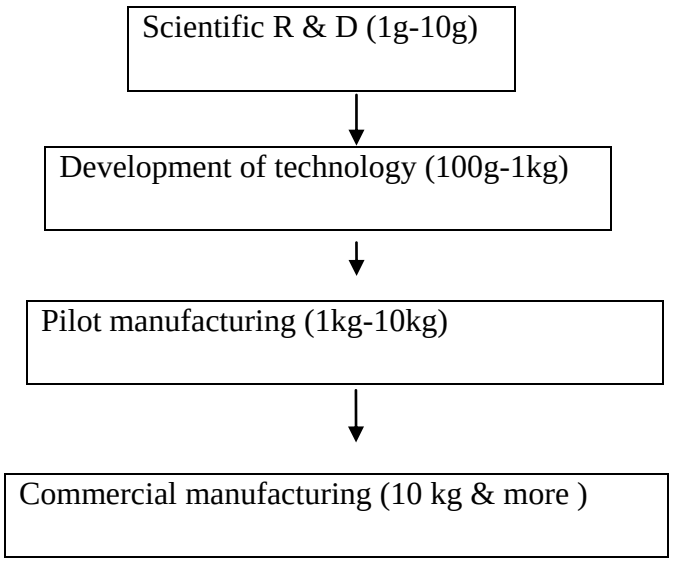


FIGURE 2: REPRESENTATION OF MAIN STEPS FOR TECHNOLOGY TRANSFER

Management of Technology Transfer involves not just involve the transfer of managers with their skills but also the transfer of managerial culture which is company specific. Management is the variable that affects the Transfer of Technology Process. The failure of Technology Transfer efforts has been process of management and this failure is just because of the poor planning and not having proper training of people at the bottom and it is said that the successful transfer of the management technology can be important factor for the economic development improvement.

1.3 CONCEPT OF CONTAINMENT IN PHARMA MANUFACTURING:

Containment- In a lay-mans' term it indicates to restrain anything from spreading all over. The same concept is applicable to the field of Pharma manufacturing also. Since Pharma manufacturing involves the manufacturing of dosage forms which include the handling of materials which have the property of eliciting pharmacological response/ material that are considered to be hazardous to humans in nature. Those drugs which are hazardous include which are used in cancer treatment, drugs which are antiviral properties, hormones and some which are bio-engineered drugs and other miscellaneous drugs. It gives rise to the need of containment concept to avoid un-necessary exposure to such pharmacologically active materials. The target is to manufacture the different dosage forms in an environment which allows minimum exposure to the Drug by the use of specially designed equipments.

Generally all drugs which are chemically synthesized have toxic side effect but there are few drugs which are relatively show lesser toxicity at very low dose. The toxicity level reflects the non - toxic to the toxic effect action in patient at minimum dose. According to author sergent et al. The dose of 10mg/day in Rat which produce serious toxicity, developmental toxicity , or any kind of toxicity which is relevant to reproductive toxicity has been used by drug companies to develop occupational exposure limits of less than 10microgram after applying uncertainty factor.OEL range typically established for drugs is poisonous or potent toxic drugs in the drug industries[16..]

As per the guidelines the occupational exposure limit (OEL) has been defined for various pharmacologically active substances. OEL refers to the maximum concentration of the material if present in the working environment is well tolerated and is considered to be safe for the health of the working people. Based on the potency of the drugs, the OEL limits have been defined for them, and the target is to maintain the working environment by the virtue of its design to achieve an OEL well below the defined limit.

OEL becomes very critical in case of handling of highly potent/hazardous drugs –e.g. Anticancer drugs, Immunosuppressant, Hormones etc.

Where and how we can find the drug toxicity information[16]

The hazardous drug precisely comprehensive, it is routinely used or likely to be used by practice which is generally being used locally and plasticised. some of the resources that any can use to evaluate the hazardous effect of a drug include :

- The MSD – it is material safety data sheets.
- Packing Leaflets – Product Labelling which is being approved by the US FDA
- Health Related warnings from drug manufacturers; FDA and other groups of professional and drug organisation.
- Case studies published in media and journals.
- Evidence-based recommendations from faculties to meet the proper criteria of hazardous drugs.

To have a control over the OEL becomes very essential in such cases in order to provide a safe working environment. Two do so either one or a combination of the below mentioned techniques are employed:

1. The use of specialized gowning systems

2. **PPE**: Personal protective equipment. Items such as gloves, gowns, respirators, goggles, face shields, and others that protect individual workers from hazardous physical or chemical exposures Using a self contained breathing apparatus- e.g. PAPR (Powered Air Purifying respirator).



3. Using biological safety cabinets (BSC) maintained at negative pressure to avoid maximum generation of powder dust in the external environment-e.g. Isolators.

Bio safety cabinets (Isolators***:*** It is a specialized type of safety cabinet which are sealed or is supplied by microbial air through a system which are retentive filtration system(HEPA minimum) and decontaminated time on time. When it is closed an isolator which is being used only decontaminated the isolator which is interface or when it is necessary used or it rapidly transfer the ports for the transfer of material. Whenever it is open, it allows the material which is ingress and /or egress in nature and help in material to be opened that have been designed and validated to the transfer of containments or air which is unfiltered in nature for the adjacent environment. For aseptic processing an isolator can be used for containment of potent compounds or for simultaneous asepsis containment. There are isolator which are designed and get operated with in the isolator to be conducted through attached rubber gloves without any compromisation of asepsis and/or containment are used to provide containment and which are used to provide primary environment in the laboratory when the investigation is being potentially used for infectious material .

Category 1 BSC: It is a cabinet in which occupied negative pressure and generally which is open. The air which is exhaust from the cabinet pipe is filtered by high efficiency particulate air filter (HEPA).Biological safety which is categorized in category 1 BSC will provide a protection which is environmental protected but there is no protection of product.

Category II BSC: It is open front, biological cabinet laminar flow cabinet which is ventilated. It also has cabinet provides the HEPA filtration, the re-circulated air flow within the space of work. The air which is exhaust is also filtered by HEPA filtered. Thus it shows that the product protection, environment, personnel will comes in category II bio safety cabinet.

Category II, Type A: It cannot be ventilated, which makes this suitable for the use in laboratory rooms which cannot be ducted. It is acceptable for the use of low to high agents which are at moderate risk in the absence of chemicals which are toxic volatile ridiculously which are volatile in nature.

Category II, type B1: It must be vented, with the air exhausted from cabinet to 30%. This cabinet which is being used with etiologic agents which are treated with minute quantity of chemical which are toxic in nature and the trace amount of radio nuclides which are required for microbiological studies by the condition that work has been done in the exhausted portion of cabinet or if the chemical which are present are there at any cost will not interfere with the study work when circulated in the air in downfall motion.

Category II, Type B2: It should be totally exhausted with air. Exhausted with 100% of air through a duct, this must be used by the agents which are etiologic and are treated with chemicals and radio – nuclides which is required for the micro biological studies.

Category II, Type B3: 70% of the air is exhausted from the cabinet which must be ventilated. It is also used with etiologic condition which is being treated with toxic chemical entities and trace quantity of Radio nuclides.

Category III: The ventilated cabinet which is totally enclosed. The operation within category III are being conducted through rubber gloves.[17]

4. Drug-transfer device (Closed) : It is an device which prohibits mechanically the transfer of the environment contamination into different different system and the drug which are hazardous in nature or vapour which are concentrated outside the system.

5. Using equipments which require minimum manual interventions to avoid exposure.

1.4 MANUFACTURING ORAL SOLIDS BY THE PROCESS OF WET GRANULATION :

For systemic effect the drug administration by oral route is the one of the most important method of administration of drug. Tablets which represent a unit and it is a form of dosage in which one dose of drug is accurately placed .There always be advantage when we compared liquid dosage form with solid dosage form because they are more expensive to ship and breakage and shipment always be more serious problem with liquid as compared to tablets. In the two solid form, the tablets and the capsule. The tablets have more number of advantages as compared to capsules. One major advantage of tablets over capsule which proved significantly that the tablets is an essential tamper proof dosage form. The most important advantage is: It offers the greatest capabilities of all oral dosage form. There is least content of variability and greatest dosage precision. They are cost effectiveness and easiest and cheapest to package and ship of all oral dosage form. Better suited for large scale production and provide greatest ease of swallowing with the least tendency for hangup in stomach

Table 1: Granulation Techniques

Process	Wet granulation	Dry granulation
Equipments used	5 machines	2 machines
Number of operations	Several depending on granulation process More clean up Less GMP	One
Energy Consumption	High, especially Single pot processor	Lower
Space/Building requirements	High	Lower
High Labour Input	Highest cost	Lower

Owing to its better process control and feasibility, wet granulation is one of the most common form used in the formulation of solid oral dosage forms i.e. Tablets.

TABLE 2 : THE WORKING PRINCIPLE OF WET GRANULATING EQUIPMENTS-RMG/SINGLE POT PROCESSOR:

The basic working principle for an RMG and single pot processor remains same. The additional feature being the online drying and dry screening option offered by the single pot processor along with containment.

Step	**Brief description**	**Measured variables/control parameters**	**Impact on the product**
Dry mixing	The materials loaded into the equipment are mixed together with the help of an agitator/mixer	Agitator speed- RPM Mixing time- minutes	Ensures proper and uniform mixing of the ingredients.
Binder addition- Manually or by automatic feeding system.	The binder or the granulating fluid is fed into the equipment while keeping the agitator on running mode to ensure the uniform distribution of the liquid.	Agitator speed- RPM Binder addition time- minutes. Binder addition rate	Ensures proper distribution of the granulating fluid.
Wet mixing/ kneading	After the complete addition of the liquid, the wet mass is further mixed using the agitator and either keeping chopper on or off to further ensure proper binding of the materials.	Agitator speed- RPM Wet mixing time- minutes. End point mixer torque/ Mixer power/ Amperage. The chopper if applied helps to break the larger lumps-chopper speed (high/low).	To impart sufficient binding strength to the powder and formation of granules.
Drying of granules	To remove the liquid added during granulation to from dry granules.	Depending upon the mechanism of drying. Vacuum- mBar. The applied vacuum increases the rate of evaporation of the liquid by lowering the pressure inside the bowl. Heating-Temperature Microwave-Joules Transflow- nL/minute- to provide fluidization to the powder bed. Swinging- to and fro motion to further enhance fluidization of granules. Chopper/Mixer- optional Moisture content of dried	Proper drying of granules so that the granules contain the optimum moisture content as per the product requirement.

		granules- LOD (loss on drying %w/w)	

Single Pot processor with automatic feeding system for Binder/granulating fluid and provision for online quadro-co-mill. All the equipment related parameters are controlled by a PLC control. Once the dry mix is loaded , the final dried and milled granules are unloaded into the bins in a fully contained manner.

Rapid Mixer granulator- Requires human interventions due to which the containment cannot be maintained.

The drying of granules of the RMG require unloading into Fluidized bed dryer Bowls which are then connected to the FBD for the purpose of drying-containment breach, not suitable for hazardous drugs.

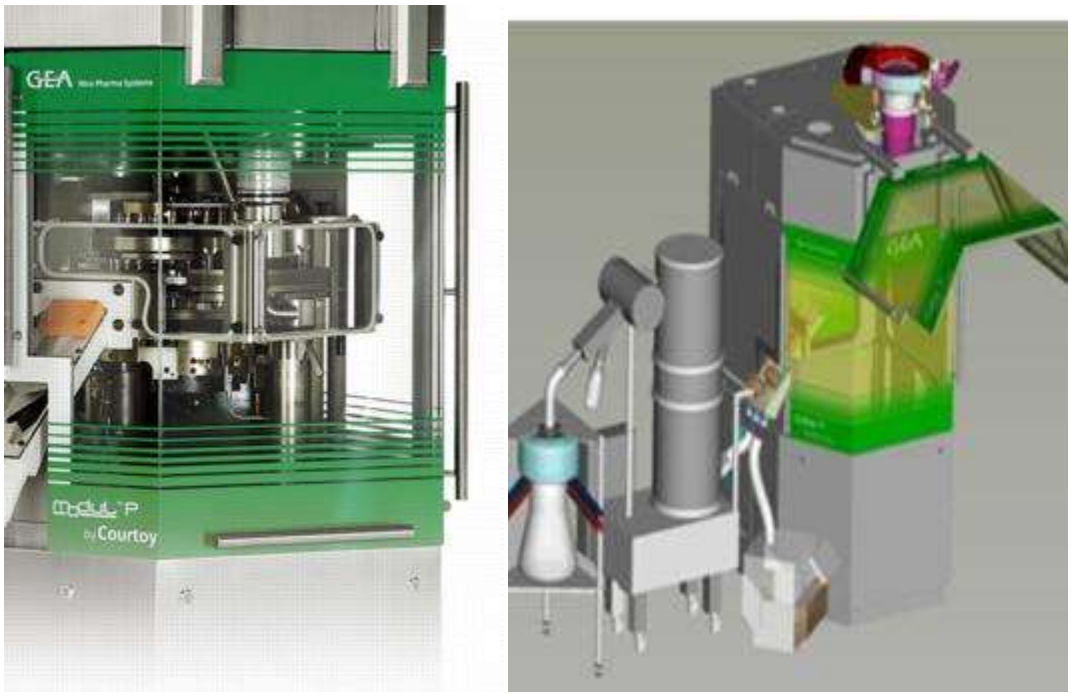
TABLE 3 : COMPARISON BETWEEN SINGLE POT PROCESSOR AND RAPID MIXER GRANULATOR

Single pot Processor	**Rapid Mixer Granulator**
Use-wet granulation equipment	Use-wet granulation equipment
Loading of material- By use of contained poly bags/ vacuum feed thereby causing minimum exposure of materials to the external environment.	Loading of material- Manually, causing exposure of materials to the external environment.
Binder addition- By use of binder feeding mechanism making use of a pump. The system is a closed and automatic one.	Binder addition- Manually through the opening meant for the purpose.
Drying- online drying system present which allows the drying of the granulated mass in the single pot processor itself.	Drying- The granulated mass is to be unloaded from the RMG and charged into a suitable drying equipment like FBD- material exposure.
Dry screening- certain systems are available which are fitted with online Quadro-co-mill which is used for the dry screening of the dried granules using suitable screen. The dried granules are then unloaded into bins without any exposure to external environment.	Dry screening- after drying in FBD, the materials are then put for dry screening using a suitable dry screening device like co-mill.
Material loss- minimal	Material loss- comparatively Higher.
Material Exposure- minimal	Material Exposure- high.

Miscellaneous- Equipments that are usually a part of fully contained manufacturing facility.

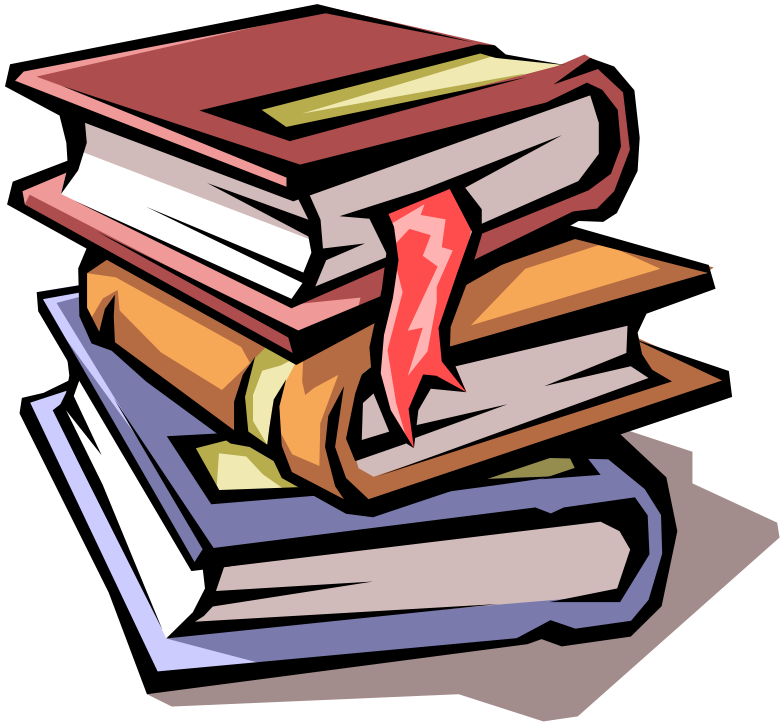
In-process bulk Containers (IBC)- Designed with pneumatic valves which cannot be opened manually. The containers fit directly under the single pot processor for the unloading of dried and milled granules. **The bins are designed to directly fit over compression and capsule filling machines provided with the bin feed systems e.g. Courtoy compression machine- no need to manually load material into the hopper of these machines- no containment breach.**

Bin-blender



Courtoy compression machine with bin feed mechanism on the top of the machine. The entire compression module is maintained under negative pressure to avoid dust generation to the external environment- full containment.

In the present study, technology Transfer of film coated tablets was done for scale up. For this study, the basic information and required data were obtained from R&D and then all the parameters were optimized for scale-up and then further exhibit batches were taken and evaluated.



CHAPTER -2

LITERATURE REVIEW

2.1 LITERATURE REVIEW

Research scientist believes that the integration of overall process is said to be best process. In drug companies Technology Transfer is very important for the successful progress of product development from the research development. There are many level which are synergized and for development process which is a type of duration with in Technology and for this lot of decision

were taken at different level ,this layer includes layer at business level ,layer of chemistry , layer of chemical reaction ,layer of separation ,layer of recovery of heat and the layer of utility system. The consideration which has been addressed during impressive Technology are the number of process involved following i.e. layout and defined process.

A mandatory devised plan must be organized in the step of process and once this prepared this plan must be transferred to the parties which are involved in Research and Development at the higher level and at the manufacturing site. This critical path depends upon the completion of Transfer of Technology to the shop floor at the least minimum cost. At the bottom ,Technology Transfer is basically is the flow of knowledge from one person to another person and communication of basic Research to applied technology or this flow of information can be through education and scientific journals. If we touch the legal aspects one rule that strike to middle is that the Licence management in respect to legal rights to adopt technologies in context but its level of human that surpass the reality at economic and managerial level, either there is need of corporation of many individual person to make a successful formulation weather is a formulation of Tablet,any transdermal patch. Technology Transfer success directly depends upon crucially on the skill adaption and ethical practice in the organization[18-19].

The process of Technology Transfer from which the basic applied discoveries has been developed into commercially practical products. Some time flow of the basic Technology is very simplified For example; whatever problem arises at the bottom shop floor give rise to modern idea that contribute in fundamental advances. The close link between few sectors of basic Research and production experts contribute to competitiveness as well as advancement. The product development goes through many stages of the early phase of clinical trials that is not require less than dose of 100 units proof to concept studies .At early stage of development of powder form and formulation of capsule can be approached manually. Organization should carry out all kind of innovations so that they can change in their external and internal surroundings .Scale up which is important and can be occur at various stage .We at small scale development (Laboratory level) from 0.2 to 1.5 kg and can up to 5-10 kg and then 100 kg on a larger pilot scale. On a larger pilot scale with larger equipment or with a continuous processing on pilot scale equipment. There have been many steps involved in small scale at the laboratory level. There has been Technology capabilities which includes the planning i.e. Project Planning to Learning. In

India like developing countries, in order to enhance the Transfer of Technology is carried out the order to enhance the local Technological Capabilities[20-21].

A approach can be implemented at the level of sub batch where increase in scale to production would involve the increasing number of manufacturing at the level of sub division on the pilot scale equipment. In development of Transfer of Technology which is highly complex problem. Technology Transfer contributes principles of quality by design (QbD) by identifying the critical quality attributes. The determining factor for success or failure at the scale up[20-21] depends upon the formulation development and the process of design experiments a well as understanding of critical and non critical parameters for different operation. Criteria for estimates the level of international technologies Transfer which includes: The Technology Transfer cost, the important technology assimilation and for the importing enterprise and economy. The transfer of technology has been indigenous role for major breakthrough in industry at scale up level.

During the Time of scale up, the technology Transfer and the knowledge transferred that had been gathered during at the small scale drug development of the product and the involved process. It has been realized that good communication is critical for drug formulation and process transfer. It is very important to consider the environment of formulation and system when developing drug and its associated process and at the same time the equipment and the excepient that has been used now it's been seen that it is necessary and important factor to consideration during the early phase of drug formulation development, so that it can be transferred to the production area in the firm and it will be available for its bioavailability**,** safety, and its efficacy, Machine operators are focused on segment of process so that process can run smoothly[5].Effective transfer of Technology helps us to provide efficient process and maintain the product quality. The process of drug development provide a clear understanding of significantly the effort for development process that involved in research in drug formulation to production at commercial stage.

There are various Technologies reviewed for the manufacturing dosage form. There are process which include different technologies and methods for mixing and compression and coating of solid dosage form as well as different methods for solutions and emulsions and for sterile products. Technologies at the level of manufacturing is acceptable for the up gradation of drug quality as it is designed at Research and development level and it assured transferred of quality

between contract giver and acceptor. To assure the quality of drug it is very important to designed and make sure 5W and 1 H that is what when and why and this information is transferred to where and by whom and how to transfer ,then shared knowledge and Transfer of Technology information for each other between different stake holders with in the firm.

2.2 REASON FOR TECHNOLOGY TRANSFER

In Technology Transfer the direct investment it is very important for any country choose very smartly what industry type and technology has been received by them. There may be reasons why any Technology Transfer developer might be considers the availability to another person to exploit and in fact and instead of Technology exploiting itself and these are following :

2.1.1 Progress development by forming parties of the technology to its market: The Technology Transfer developer might have the technology resources for drug development.e.g.Animal studies and toxicity study but there are the chances they does not have the resources for technology to step up for the phase of clinical as well as regulatory and must be collaboration through another organization to take it to the next step of the market

2.1.2 Partnership with manufacturing capability: The Technology developer may take the technology to a development state so that it can be ready for market, but it does not have the manufacturing capabilities for the product and it must be partner with those firms which does not have the capabilities.

2.1.3 Partnership and alliance with marketing and capability of distribution: The Technology developer must develop the technology and approvals for the regulatory and registration for product to be sold, & it lacks the channel of distribution and marketing for its marketing capabilities and collaboration with another firms what does have the capabilities.

2.1.4 Management in field with respect to its application: In the field of diagnostic,the application of the technology developer might be sufficient for the managing the technology transfer and might grant for its commercial partner for the application exploitation to another person , the technology developer creates income from the different rule of exploitation within the Technology that might take place the different field.

2.1.5 Not having capability for commercial: The Technology developer might be any college / University or it can be funded Research institute which does not have the commercial capabilities at all, and they need to collaborate with organisation. In drug companies' products exploitation, Product need to market with the feature of the industry[9].

2.2 THE PROCESS BEHIND TRANSFER OF TECHNOLOGY

In phase II clinical study the phase of quality of design almost said to be completed. For realization quality of design there are various manufacturing standards and test which has been established in reviewing the production process in any firm. If there is designed variation in validation studies, definitely it upgrades the product quality and the firm production Technology of Transfer mainly because of action which is taken into the developmental phase to realize the designed quality and if there is a condition that communicate the Transfer of Technology and would take place in such changes in place of production area. The process is classified into three phase i.e. Phase of Research, Phase of Development, and Phase of Production.

2.2.1 Phase of Research

2.2.1.1 Designed Quality : The designed quality for drugs which are legitimatised into the final stage of product which ultimately corresponds to designed properties and elimination of function such as Adverse drug Reaction , efficacy improvement , distribution during assurance of stability, its dissolution rate , disintegration of drug , which is based on the data which is derived from its chemical and physical properties . For designed substances for designed the stated material .The reaction and the drug specification are very important consideration.

2.2.2 Phase of Development in Factory

2.2.2.1 Research at the level of production: For the drug manufacturing the designed qualities, which is a requirement for the controlling quality control and different methods for manufacturing and variability detection for secure the drug stability in the phase of validation which is performed for production of designed drug within the firm which is on basis of scale experiment at the small scale.

2.2.2.2 Role of quality and dossier specification: Establishment of drug specification which is done on the basis of determined quality of product and which is required to vary the adequate specification for the quality of product. In brief , the quality and the product specification is

definitely to ensure as well as the designed quality for pre – determined dossier and the assured for the quality manufacturing and it specify the product as well designed by quality .

2.2.2.3 Desired consistency for the product manufacturing and validation: Product development and its indication at the pre clinical stage and designed quality which should by reproducible at the manufacturing quality of definite product. For this reaction which transferee always keep in mind the development change always understand the manufacturing or production charge and appropriate establishment of method which is evaluated to determined method whether this product meet the requirement meets the quality of design[8].

2.2.2.4 Transfer of Technology to production from R&D: Information which is technical transferred of this information is necessary for the realization for formula which is designed for manufacturing and facility which is designed and related to the production. Finally, this information collectively called as R&D report.

2.2.3 Phase of Production

2.2.3.1 Validation & Production: End step that is production of product is applied and implemented after study of validation. Validation study makes sure that what we are manufacture consistently in production mainly on formula of transferred manufacturing with higher stability. The department of research is responsible of the technology transfer and person should take the responsibility for validation study.

2.2.3.2 Communication the feedback from Transfer to Technology and production of marketed products: Developing information technology for the products which are developed and obtained from the data which are limited and evaluation of quality which has been development of establishment which is not always sufficient for the area. It is very demandable and desired to giving feedback and communicates the information obtained from the repeated production. In addition to this it is important appropriate to modify the various establishment of standard before the information comes to the transferee party. .

2.3 REASON FOR DOCUMENTATION OF TRANSFER OF TECHNOLOGY

The documentation of Transfer of Technology is interpreted with the indicated documents of Transferred Technology for both transferring and transferred parties. The data which is raw and

documented should be prepared, accordingly compiled and always available .Once firm felt the need on the same time it can be traceable. For making successful the transfer of technology assigned task and responsibilities should be clear and there should be criteria for the transfer of technology compilation. The department of QA should be a process of conformation for its all kind of Technology documentation.

2.3.1 Transfer of Technology in firm: The element which is most significant for successful Transfer of Technology is a communication which is entirely closed and which held between transferring and transferred parties. Therefore, Transfer of Technology within firm should be established and included and composed with both of parties members, scope of work for each parties, it should be classified and ensured the information feed with the organization which complies with Good Manufacturing Practice.

2.3.2 Report of Research and Development: For the realization of quality assurance in all stages from the development of drug to production of drug. Documents which are technical transferred simultaneous have product concern for the documents should be considered. The report of development is a kind of file which is a group or set of information for technical and development department is in charge for its documentation. This report is a documented file which indicates the rationale for the designed quality for drug substances and for the specification of drug and method which are applied at the test level. The file should be approved and duly inspected. The drug development in R&D phase is not pre requisite for the approval of tests. This can be used as inspection of pre- approved for the design of new drug.

The information which is exemplified to be continue in the development for the new product, the data which is in database for a drug substance and for the product at the stage for early phase of development to approval of final application, same is for the raw material and designed content for the synthetic route for routine dosage form and designed formula, production batches, methods for test of drug substances and intermediates new entities and rationale for the raw material.

2.3.3 File for the specification of product: The specification of product which is a compilation of information that sure the firm or any drug companies for the definite specification as well as the manufacturing for the method evaluation of product for its desired quality. The specification

of product should be checked at regular interval and make desired change at various levels which is obtained after the start of production of product.For any desired new product from the firm and reported development would be used as specimen in the specification file.

2.3.4 Desired plan for Transfer of Technology: The plan for Transfer of Technology which includes: the items in plan, the technology for which content to be Transferred, procedure which is detailed in dossier for the transferring of technology for the judgement criteria for the completion of Transfer of Technology. The party which is transferring before its implementation to the technology will be its reach agreement for its content with the party which involved and play the role as transferee.

2.3.5 Report design with respect to Technology:.There should be report after each file of completion to Transfer of Technology after complete action which is taken by the plan and evaluated the complete data which is judgemental through pre determined criteria for both parties transferring and transferred parties are documented the transfer of technology ; however this should reach the mention agreement for its content.

2.3.6 Result Verification for the Transfer of Technology: At the manufacturing site the technology completion and before its transferring the product it should verify the appropriate method for the product testing and simultaneously for the product audit which is manufactured after from the meeting the Transfer of Technology for its quality which is pre determined and maintained the desired results[4,22-23] and record for the firm . Transfer of Technology dramatically change the activity of various aspects in all over the world and the technologies which is relevant to development to development of drug which has been changed dramatically over the years primarily in the field of biotechnology and medical research[24-25].

2.4 MODELS IN TECHNOLOGY TRANSFER[26-27]

Research scientist find the transfer of Technology very complex process which requires the clear set for ensuring the technology for its seller and purchaser of Technology which already understand its application for its part in implementation for maximizing the party benefits. Due to high invention the complex difficulties in transferring the technology. There are different models which come in picture for facilitating the planning for firm implementation. The various models are:

2.5.1 Bar-Zakay model: In 1971, Bar – Zakay designed a model of Technology Transfer which is based on the approach of project management. Author divides the process of Transfer of Technology into four stages namely: search, adaptation, Implementation, and Maintenance stage. He showed the activities, the point of decision for milestone in each of their stage of model a shown in figure. The half upper part of the model showed the activities and requirement of the transferor for the donor and lower part which is responsible for transferee or the recipient. The carried activities which are associates with specifying the detail class of model and the significance of both the parties i.e. transferor and transferee which acquired the specific skill and help the organization for future forecasting in planning and find all the relevant project related to intelligence which emphasized in long term in organization. There has been term which is being used the term Donor for the giving impression on behalf of owner of the Technology for giving all the assets out of alestic reasons and for this reasons and the terms which have been used must be avoided.

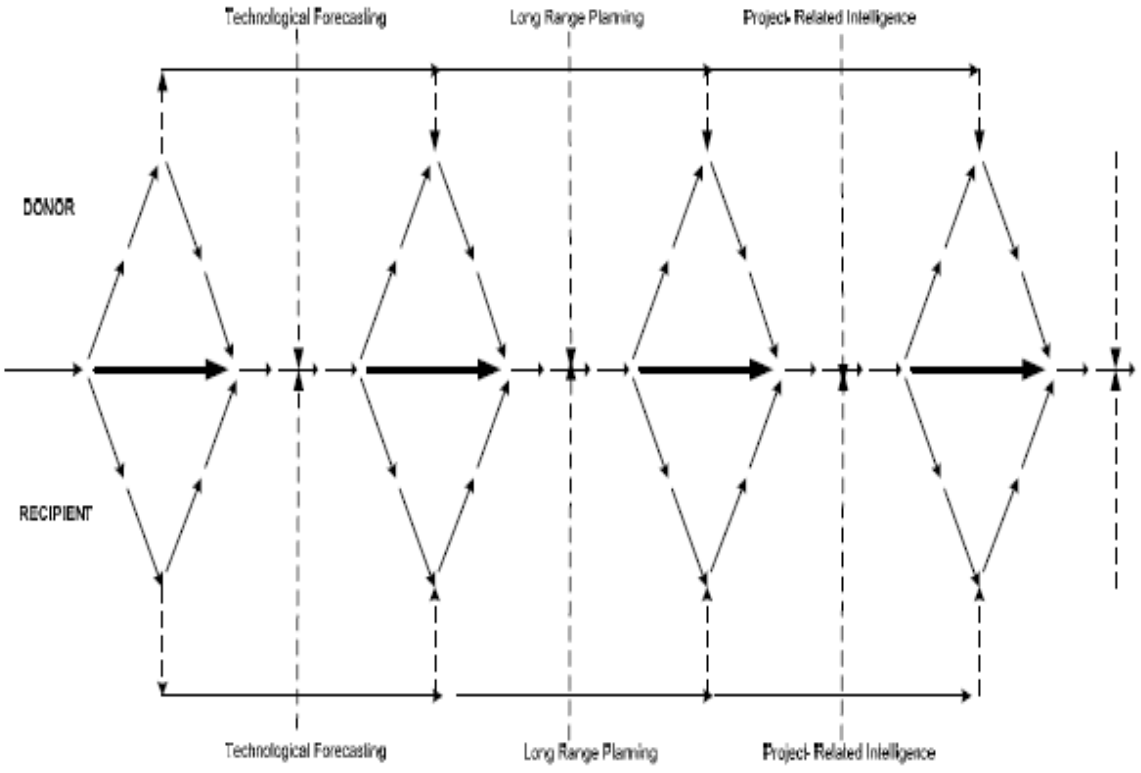


FIGURE 3 . THE BAR-ZAKAY MODEL OF TECHNOLOGY TRANSFER.

The model also go through:

The outcomes and learning from the Bar –Zakay model are following:

• Author find that there is Technology Transfer which is comprehensively examined the complete process from Search to the past implementation..

• This approached procedure can be implemented in the project of Technology Transfer.

• When even the project terminated at any time it is very important to have points that the activities which are running during Transfer of Technology can be strengthened and corrected.

2.5.2 Behrman & Wall ender Model: In 1976, according to the author it has been proposed that and said that it is a process of seven stages and a TT which is more related for multinational companies. The following are the seven stages:

•The proposal of manufacturing and arrived planning to its decision for any location in any business case including the assessment of good resources.

• Technologies which are meant for product designed id transferred.

• In any firm the infrastructure development and related aspects of construction, all these details are plant specified in reference to the new Technology for the product development.

•New start-up in manufacturing arena.

• To suit local conditions the strengthening production system is always a lining process and it must be adapted at very lesser time.

• With keep in mind, there should be improvement in Technology of the product for its skill.

•For the strengthening the relationship between the transferor and the transferee there must be external support for the Technologies.

The weakness of this model is that the stage which comprises of three phase and it is that dependency i.e. reinforcement all the project related to Transfer of Technology which is develop by the transferor

And the stages like fifth and sixth there is scope of transferee to improve and assimilate the process and the product technology. It emphasize the Transfer of Technology which does not stop and the commencement of production and unless until if there is a foster mechanism with project which cannot be considered to be delivered. Following are the lessons which can be learnt from Behrman and Wall ender Model:

• Any product which is relevant to the formulation does not end with any kind of commencement.

• Any transferor of technology which is not finished by with its formulation commencement.

• The Transfer of Technology cannot be said successful which make the explicit to measure into its place which definitely ensurly assimilated within firm

.**2.5.3 The Dahlman and Westphal Model:** In 1981**,** The Dahlman and Westphal carried out the work in the country of Korea and they experienced quick environmental changes in the year of 1980 in the Eastern part and proposed its nine phase of model as follows:

• In the establishment of viability of project there would be analysis of Technical as well economically information to carry out the feasibility at pre investment level.

• To carry out the feasibility study there must be preliminary identification of Technology.

• To carry out the bio medical study which involves the process preparation, layouts, energy balance, the particular design specification of the factory and which includes machinery and technologies which is transferred to its core level.

• To carry out the study which involve the preparation of all type of plans i.e. civil engineering for the plant facility, included its construction and the specification and all type of constructive identification for the technology which is peripheral which is needed to make all the differences for the effective transfer with in factory.

• To carry out the entire market supplier for the controlling and assembling the plant and the machinery for the work coordination among various parties.

• For execution and training thee educational plan the supplier of the technology for its workers who employed in Technology transfer project.

• Plant construction.

• For the commencing plant operation.

•Developing the trouble shooting and arrangements to solve the problem in design and operation as it shown that in early decades of operation.

This model is considered to be one step model beyond the Behrman and wall ender model in great emphasis on transferee involvement in all high stages of engineering. It may not be true as many developing countries.

The important lessons which we learn from this model are following:

• The Transfer of Technology assignments that is considered to be best suited for study of sequential perspective.

• Such Transfer of Technology projects requires heavy resource of commitments for the defined feasibility study.

• Whatever the transferee is involved there should be right planning from the beginning.

• It is very important for the plant transferee for sound engineering and skill related to the project management without which TT cannot manage efficiently.

2.5.4 Schlie, Radnor and Wad model: In 1987 schlie et al proposed the theory of model which consists of delineates seven type of elements which influence the planning and implementation and eventually success of a model of Transfer of Technology project. These elements are following:

• The person within firm which generally is transferor that is entity of the firm and its objective is to sell the technology.

• The entity which is intent to buying the technology is a transferee.

• Mainly the technology which is being transferred.

• The mechanism which is chosen by the transfer of technology.

•The environment which is created by transferor is the immediate of set of circumstances conditions in which the transferor is operating. Attributes which is influence by transferor environment is effectiveness of transfer process which includes towards the business and economy and stability of the firm.

•The environment of transferee which is the set of immediate conditions which comes under the operations of transferee. Attributes of the environmental transferee who influence the capacity of absorptive included physical and organizational infrastructure skills, availability, attitudes and commitment to the project transfer and the technological status and the orientation towards the business, the economic status and the stability.

• The environment which includes the surrounding of both transferor and transferee. There is an environmental layer at the regional , sub regional , and at the global layer and it is sais that the immediate operating operation of the transferee and transferor in the transfer of technology , by the condition if there is not a supportive greater environment at the cross border and at the international technology transfer that may be effected adversely. The factors in the greater environment such as political relationship between different countries, the rate of exchange, climate, negotiation at the trade level. The levels at the technology and the intellectual property status with influence the Transfer of Technology project success. .

It's been found that this model is also valid in today business scenario. The way they manifest however it change with time .The weakness of this model is that it offers neither a single guide lines for transferee that in which condition what transferee should do.

The lesson that emerges with this is following:

• The changes that have taken place in the global business have made its impression for the managers of transfer of technology to have insights on the transferee and in the transferor environment and the environment for the planning and for the implementing of project of the technology transfer.

• The Transfer of Technology and the choice depends upon the based of sophisticated understanding of these six elements.

2.5.5 Chantramonklasri Model: The model of Dahlman and westphal advanced and improved by the scientist chantramonklasri in 1990, this scientist propose the five phase of the model. The following highlight is the chantramonklasri model as follows:

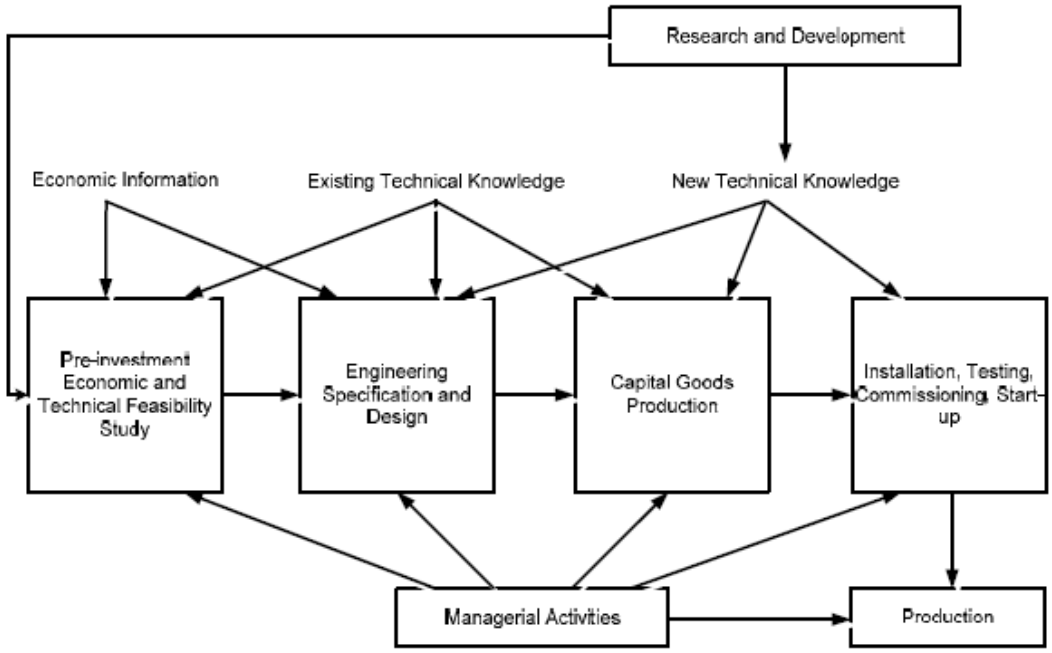


FIGURE 4 : CHANTRRAMONKLASRI MODEL OF TECHNOLOGY TRANSFER

• In study of feasibility there must be carrying out the pre – investment.

• The specification for the developing of engineering and the steady of feasibility based on these models.

•Organisation should commence the goals for the production based on the specification of engineering and designed which has been developed.

• Project Commissioning and start for the including the workforce comprehensiveness.

•commence the production for commercial and there is two phases which comes under and this model are not valid for clearing whether the requirement of goods can be produced or not and if yes then the transferee of settings comes under the arrangements which includes the technology

transfer which is needed for the manufacturing. While it is said that it is valid in large for the advancement of the technology in the country. As it is final that the model proposed by Dehlman and west phal Model There re elements are missing in negotiation and in assimilation. The lesson which can be learnt with case in similar to those in model of Dahlman and west phal.

2.5.6 UNIDO Model: The UNIDO (1996) model, proposed ensuring effectiveness by Transferring of Technology there are steps which are needed; the step included the search, evaluvation , negotiation and execution and adaptation and absorption of technology. A model is proposed by the Durrani et al. (1998) which consisting of five elements:

• The requirement and establishment of the market place.

• The trace and to identify the technological solutions.

• To classify and identification of technological solutions.

• The sources establishment for this the acquisition of technology is desired.

• Acqusion decision should be finalised by transferee

The model end with the effectiveness of contingent model for the transfer of Technology while author emphasis on transfer of technology ,with this model the key elements of this process of transfer

It was the year 2000 The scientist Bozeman has proposed the significant Transfer of Technology model which emphasis on the transfer of technology from the universities and small scale laboratory of Government .The model is also relevant to the inter firm Transfer of Technology and the key elements of the Transfer are :

• The involvement of Transferor.

• The mechanism behind the Transfer of Technology.

• The object being transferred.

• The recipient of transfer.

• The environment needed for the technology.

Model also emphasises that the estaiblishment of Technology need for the transfer of technology and the identification for need of multiple source of technology for enabling the betterment of transferor. There are six out the Door which are proposed for the measures of Transfer of Technology. There are impact on the market for the development on the economy , with opportunistic lost ans scientific development for the economic capitalwhich is developed by human for the Transfer of Technology.

2.5.7Sharif and Haq Model: The model proposed the potential concept for the technological distance between transferor and transferee and in this case the effectiveness of transferor is very low. It has been suggest that and observed that the first look of transferee is become for its potential transferor. It has been said that and find the one which the potential technological difference from different practical point of view and firm leave to the transferor at the organizational level that may indulge at every information that could not be essential for its potential concept.The greatest importance for the difference is that it play a crucial important for this difference is that it play crucial important difference for the concept of incorporating the potential development in dealing the Transfer of Technology .

2.5.8 Raz et al. : Author introduced the technological model which catch up the shows how leader of Transfer of Technology that assist the technological rate for the development of technology which follows the initial phase of capability technology gap with fast learning phase in the advancement gap which is consider to very minute in scenario like today in world of Technology. **Klein and lim** Author said that the transfer of Technology have a critical role in the advancement of Technology at different level.

2.5.9 Roger's model: This model also known as Model of Dissemination and suggest that the Transfer of Technology with specialized role which turns into knowledge to the use of willing once in the organisation the production complete the link that established the new technology will go from expert to non-expert. This model later describes by the **Gibson and Slimor**. According to them it is prime concern to select technology and make sure the technology is available to a receptor that can understand the potential use of the technology, but the main disadvantage of this model was one way communication.

2.5.10 Knowledge Utilization model: This is another important model which is based on the role which is important for the communication that is in between the technologies of developer and user for the importance of barrier which is faced by the organisational level for the transfer of technology.

2.5.11Communication model: This model describes the technology transfer is an ongoing process and important which involves the two way process of interactive and continuously and by the same time it exchange the set of idea amongst the people of organisation which are involved for the Transfer of Technology .

2.5.12 Gibson and Slimor's model: purposed that technology transfer involves the three Levels:

a. Level One (Technology Development)

b. Level Two (Technology Acceptance)

c. Level Three (Technology Application)

Technology Development level considered as the most important level, in which transfer is generally carried out in which transfer means research reports and general articles. Technology acceptance indicates that it is the duties of developer to make certain technology that can be easily understand by the receptor. Technology application includes the commercialization of the technology to the market. This model equates with the knowledge utilization model.

2.5.13 Malik's model: This model is based on the intra firm technology transfer. For the attempt of Transfer of Technology the link between transmitter and receiver depends upon the both parties. Communication, understanding and trust are the important factors which should be considered for a proper technology transfer.

2.5.14 Lin and Berg model: Author proposed a Model which is as effective for the Transfer of Technology. By the various phenomena the impact of the International Technology Transfers includes: Technological nature which is Transferred the experience at the level of international and for the cultural differnce.

2.5.15 Putranto et al: According to the Author the Transfer of Technology which emphasis on the given view point and by the end of Transfer of Technology which is generally divides into the various stages

- Preparation
- Production
- Operation
- Evaluation

All stages which is being mention here help in the proper technology transfer and technology investment.

2.5.16 Dagfous: He introduced conceptual model for technology transfer who pays more attention on the technology as well as transfer of Knowledge. Transfer of Technology is learning process by which is generally transferred from one entity to another by a proper communication. The different stages given by this model are: prior knowledge, learning process, project stage, intended benefits and unintended benefits.

2.5.17 Haris & Haris: Author proposed the M type model which shows that how this framework will be used as the model effectiveness for the Transfer of Technology at the international level that is from one domain to another. The proposed five models are Man, Machine , Management , Medium and Mission.

2.5.19 Simkoko model: Author emphasises on Transfer of Technology which in the construction industry of developing country. The different factors are presented by this model are project delivery system, project characteristics, project management teams, transfer program client characteristics, design and construction technologies project performance[7,28].

2.6 PROCEDURE FOR THE TRANSFER OF TECHNOLOGY

It is described by the three phases and it is the procedure for the technology and transfer of knowledge to manufacturing which is described as following:

2.5.21Beginning: From the beginning there has to be a form of agreement between donor and receptor for the concerning the manufacturing of new entity which is filled by drugs , excipients and which is lead by the final commercialization product for the market there are side which is

appoint and known as the receptor should encourage with different department of quality with strict regulatory affairs background and there should be meeting between the representative of both the level of donor and receptor side of the firm in the production area.

2.5.22Transfer: The content of packaging and production and direct relation with the product quality with the process achievement as well as the protection of health and environment with agreed plan on both sides. Definitely there is framework sets with the Transfer of Technology process take place with in the area of production therefore it is set to be designed with in measure in order to meet the requirements of both parties with characterisation of Transfer of Technology Projects. The covered area for the development of covering phase like pharmaceutical ingredient and data which is scientific literature , The pharmaceutical development , specification related to material , the specified product and the procedure related to the production of product with utmost care of the production of document.

2.5.23 Analytical development: This includes the procedure for the sampling and validation. On the same way it is very relevant for concerning the material safety for its intermediate products for manipulation and exposition simultaneously for the protection of staff as well as its stability and reactivity for its transport elimination for t he given and circumstances for the toxicity in respect to environment by the products.

2.5.24 Result: The Transfer of Technology is in hierarchical manner and the team leader meetings for all the person in charge for the step which are described previously that is reaching on agenda which is full of action for the establishment for the Transfer of Technology process and after the all sequential process which is being completed , the revision which is took place with issue on documentation phase that will confirm the Transfer of Technology which has been concluded agreeably In the initial phase, the process of Transfer and the responsibility for the control and whatever changes occur in correspondent procedure for both sides but there is a side of donor with keep in mind the authority for sanctioning them. By the end the Transfer of Technology the changes in the sanction goes to the other receptor side[29-31.] The transfer of technology from R & D to production involves various manufacturing processes which are shown in figure 5.

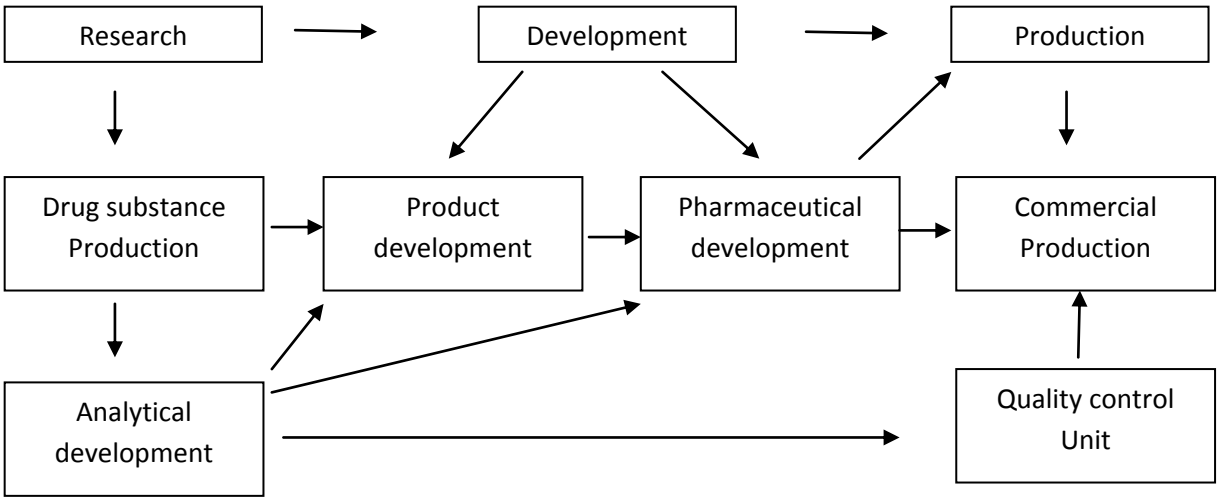


FIGURE 5: REPRESENTATION OF VARIOUS MANUFACTURING PROCESSES DURING TECHNOLOGY TRANSFER

CHAPTER -3

AIM & PLAN OF WORK

3.1 AIM AND OBJECTIVE :

A. Filing of the drug in different markets for approval :

To understand the procedures/steps involved in the Filing of a drug product in different markets for approval through an effective technology transfer.

B. Minimizing the risks during production run

The Transfer of Technology helps us to give efficiency and full control and finally maintenance in the quality of product. The new drug development is tedious and time consuming which is passed through many stages. The process in development with equipment and process needs millions which is depending on the group of population which is treated separately.Whaterver product is being transferred through technology needed a formula which is validated from the Research and Development Team. The process of scale up which involves the drug manufacturing that increases the batch size with in larger equipments and required continuous processing on the stage of pilot scale.

It is very important to consider the desired environment and the process for the formulation with respect to the equipment and excipient etc.For the process of smooth running of production there must be focused approach from the end of Operators.

3.2 PLAN OF WORK

A typical work plan for an effective technology transfer shall cover following mentioned activities:

The technology transfer starts from the thought process behind the selection of the formulation and dosage form that is to be manufactured. The particular dosage form that is to be commercialized may be an existing product which is already being manufactured by one of the existing manufacturers or a new molecule which has been identified by an innovator and needs to be developed into a particular pharmaceutical dosage form. The primary steps involve the preformulation studies to be performed by R&D and a series of developmental trials to finally arrive at a conclusion that product developed is ready to be transferred to that location followed by a series of activities as listed below:

- Collection of data from R&D
- Review of Technology Transfer Dossier (TTD)
- Arrangement of different equipments and ingredients
- Batch fabrication and division
- Scale up batch (granulation, blending, compression and coating)
- Evaluation of granules, tablets and % age of coating material coated.
- Exhibit batches (granulation, blending, compression and coating).

CHAPTER - 4

EXPERIMENTAL WORK

4.1 COLLECTION OF DATA FROM R&D :

Different batches were taken in Research & Development (R&D) for trial purposes. Information from R&D to Process Development Laboratory (PDL) was transferred in the form of Technology Transfer Dossier (TTD) for optimization of parameters. Studied drug was coded as WH because of industrial patent.

4.2 TECHNOLOGY TRANSFER DOSSIER (TTD):

TTD contained all the information of drug product as given below:

Master formula card (MFC)
Master Packaging Card (MPC)
Master formula
Standard Test Procedures
Specifications
Development report
Packaging development report

4.2.1 Master formula card (MFC)

MFC included Product name along with its Strength, Generic name, MFC number, Page number, Effective date, shelf life, market, packaging details, storage conditions, precautions for personnel safety as well as for the product safety. Ingredients details with pharmacopoeial status along with the specifications numbers, brand names/grades along with approved vendors label claim and a brief manufacturing detail. Formula per unit strength is given in table 4.

Table 4 : Details of formula per unit strength available from R&D

S.No.	Ingredients	Qty. (mg/tablet)	Vendor
INTRAGRANULAR			
1	WH(API)	2.50	Natco Ltd. India
2	Lactose Monohydrate	65.00	DMV International, Holland
3	Maize starch	10.00	National Starch, USA
4	Hypromellose	2.00	Dow Chemicals, USA
EXTRA GRANULAR			
5	Microcrystalline Cellulose	16.00	FMC, USA
6	Sodium starch glycolate	3.00	DMV, Holland
7	Colloidal anhydrous Silica	0.50	Evonik Degusssa, Germany
8	Magnesium stearate	1.00	Mallinckrodt, USA
COATING MATERIAL			
9	Opadry Yellow	3.00	Colorcon Asia Ltd, India

This table provided the amount of Active Pharmaceutical ingredient(API) and excipients used for individual strength. This data helped us for calculating the quantities of each ingredient as well as API.

4.2.2 Master Packaging Card (MPC)

Master packaging card provided the information of product regarding its strength, packing type, packaging material details, storage conditions, vendors, shelf life and market for which these formulations are to be introduced.

4.2.3 Master Formula (MF)

MF contained the Formulation Order (FO) and Manufacturing Instructions(MI). FO provided the order by which a ingredients should be dispensed along with their specification and batch numbers and SAP codes . MI provided the instructions which were considered during small scale R&D batch. Different environmental conditions were also given along with it.

Stipulated Environmental conditions

Relative humidity (%RH) & temperature(°C) should be maintained to increase the stability profile of the drug as specified in TTD. Environmental conditions were maintained during small scale R&D batches and different recommendations were given for scale-up and exhibit batches because of moisture sensitive nature of the drug. The different environmental conditions of different operations were checked from time to time. Recommendations are given in table 5.

TABLE 5: STIPULATED ENVIRONMENTAL CONDITION RECOMMENDATIONS

S.No.	Operation	Recommendation
1.	Dispensing Temperature (°C) Relative Humidity(%)	 Not more than 27 Not more than 50
2.	Fabrication Temperature (°C) Relative Humidity(%)	 Not more than 27 Not more than 50
3.	Compression Temperature (°C) Relative Humidity(%)	 Not more than 27 Not more than 50
4.	Coating Temperature (°C) Relative Humidity(%)	 Not more than 27 Not more than 50

Different manufacturing instructions given in TTD e.g sifting, granulation, drying, blending, compression and coating are as below : Proper gowning should be there, the area and machine should be clean and inspect before starting the operation, the final blend storage area should meet the environmental specifications, the visual inspection should be there so that there is no chance of contamination of previous product. The transportation of blend from blend storage area to compression area should handle with care. The weight of blend before compression should be checked, tooling , hopper and metal detector should be visually checked. The area should be within the range of environmental conditions.

4.2.4 Batch Fabrication

Batch fabrication was done by various operations e.g. sifting, granulation, compression and coating. Different recommendations were given in TTD with the use of these recommendations parameters were adjusted.

4.2.5 Development Report

This report contained the method of development as well as process development. Process development and commercial production were on critical path because of compressed time-to market expectations

4.2.6 Packaging development report

This information provided details about packaging development to the concerned technology transfer person for executing the function

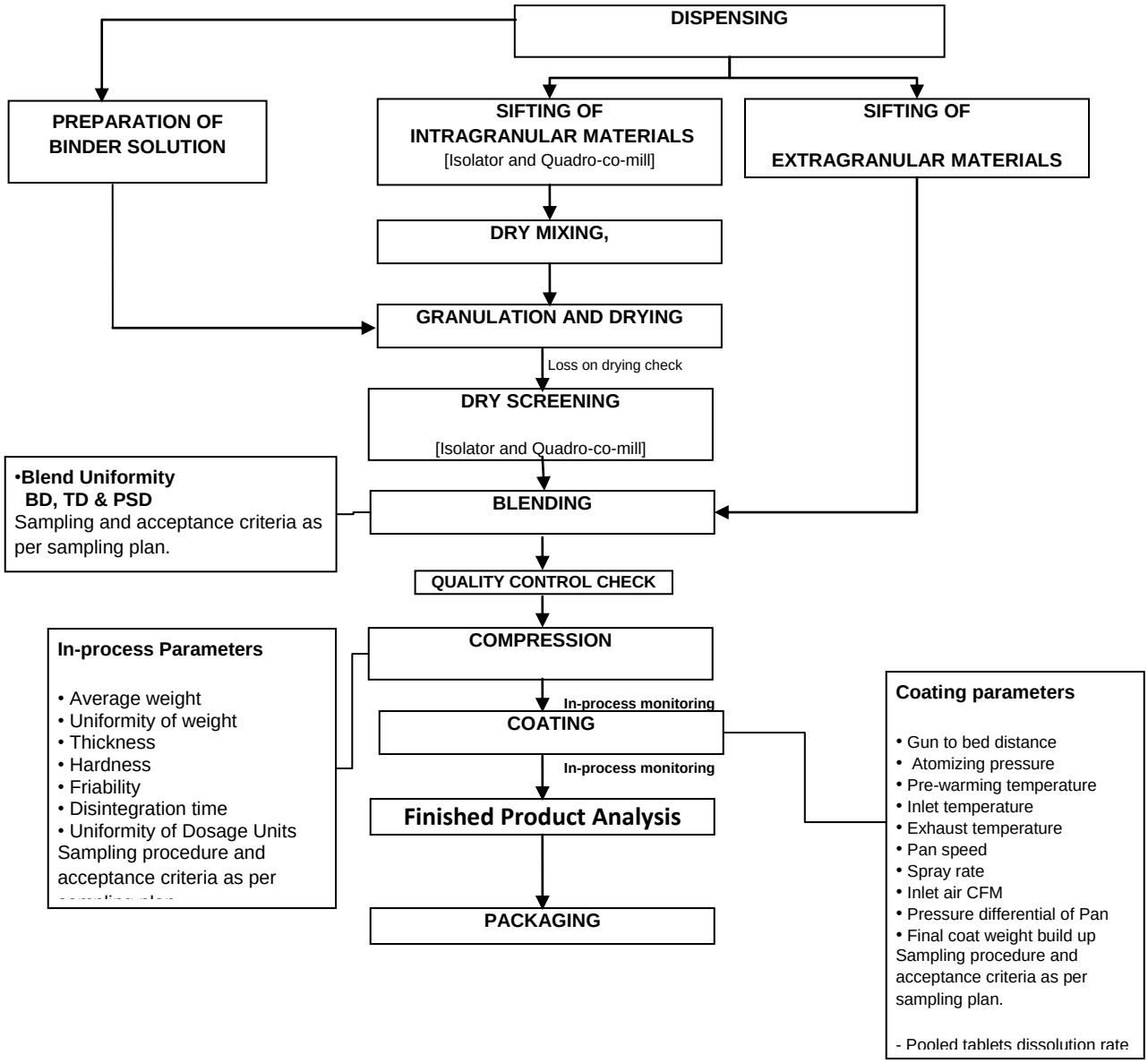
4.3 SCALE-UP

Scale up followed after getting all information from R&D. It involved the transfer of technology and the transfer of knowledge. From sifting to film coating each process had its own set of challenges. The development of robust formulation and process through the use of Design of Experiments (DoE) as well as understanding the critical v/s non-critical parameters for each operation were be major determining factors for success v/s failure on scale-up. The following chapter focused on the same of the scale-up issues and considerations for several unit operations that may be utilized during the manufacture of solid dosage forms. Full scale commercialization includes: Active Pharmaceutical Ingredient (API), Drug product (dosage form or delivery system), analytical methods.

4.3.1 Considerations of different parameters for scale-up: Before starting scale-up, we also considered different parameters that should be optimum for successful technology transfer. These were : Flexibility, Cost, Dependability, Innovation and Product Quality. It was important to realize that good communication was critical for formulation and process transfer to be successful.

4.3.2 Selection of method : The method for batch fabrication was selected on the basis of data given from R&D. Granulation ,blending, compression and coating were critical parameters for technology transfer. The steps used for fabrication as shown in Figure 5.

FIGURE 6 : SCHEMATIC REPRESENTATION OF THE UNIT OPERATIONS INVOLVED IN THE PRODUCT MANUFACTURING ALONG WITH CRITICAL IN-PROCESS QUALITY CONTROL CHECKS.



4.3.3 Setting of Stipulated environment conditions for Scale-up : Relative humidity (%RH) & temperature (°C) were maintained to increase the stability profile of the drug as

according to TTD. They were checked time to time. Dry Bulb temperature & Differential pressure (DP) were checked before and during each operation is given in Table 6.

TABLE 6: ENVIRONMENTAL CONDITIONS DURING MANUFACTURING & PROCESSING OF DIFFERENT OPERATIONS .

S.No.	Operation	Observation
1	Dispensing Temperature (°C) Relative Humidity (%)	 21- 23 34-37
2	Sifting Temperature (°C) Relative Humidity (%)	 22-24 31-35
3	Granulation , drying & dry screening Temperature (°C) Relative Humidity (%)	 23-24 33-37
4	Blending Temperature (°C) Relative Humidity (%)	 22-23 36-38
5	Compression Temperature (°C) Relative Humidity (%)	 22-24 34-36
6	Coating Temperature (°C) Relative Humidity (%)	 21-23 35-39

4.3.4 Selection of quantities for batch

It was designed according to the equipment capacity and availability in the plant. The batch size was 15.00 kg. The quantity of each ingredient was calculated on the basis of formula per unit strength given in TTD is given in table 7.

TABLE 7: BATCH SIZE CALCULATION

Batch Size = 150000 tablets

S.No.	Ingredient	Quantity (kg)			
		Lot A	Lot B	Lot C	Lot D
1	WH	0.095	0.095	0.095	0.094
2.	Lactose Monohydrate	2.437	2.437	2.437	2.435
3.	Maize starch	0.375	0.375	0.375	0.375
4.	Hypromellose	0.075	0.075	0.075	0.075
5.	Microcrystalline cellulose	2.269			
6.	Sodium starch glycolate	0.425			
7.	Colloidal anhydrous silica	0.071			
8.	Magnesium stearate	0.542			
9.	Opadry yellow	0.450			

The batch was fabricated till granulation and drying in four lots due to capacity constraint of Single Pot Processor. The quantity of API was adjusted based on assay and potency and quantity of filler was compensated accordingly

4.3.5 Batch Fabrication

Batch fabrication generally included various operations as per the flow chart given above e.g. sifting, granulation, drying, dry screening, blending, compression and coating The various unit operations were carefully monitored as per a predefined protocol and the parameters and their observations were recorded as per the details given below in table 8

TABLE 8 : EQUIPMENTS USED ALONG WITH THEIR MAKE,MODEL AND CAPACITY

S. No.	Equipment Name	Equipment No.	MAKE/MODEL/CAPACITY
1	Isolator	BEPRISO02/BEWHISO02	Klenziads/L(1900+1150) H-2100
2	Single Pot Processor (UP 75)	BEPRSPP03	Collete NV, GEA Pharma Systems/75 Lit.
3	Quadro-co-mill	BEPRQDM02	Ganson/U-05
4	Bin Blender	BEPRBBL01	Buck Systems, GEA Pharma Systems 100 L
5	Tablet Compression Machine	BEPRRCM02	Courtoy,GEA Pharma Systems /Module - P
6	Mechanical Stirrer	BEPRMCS01/02/03	Remi / Ganson
7	Coating Machine	BEPRGAC03	Ganson /Dual 24/36

4.3.6 Procedure for batch fabrication

1. The Intragranular material API, Lactose, and Maize starch were mixed together and sifted through Quadro co-mill using a suitable screen.
2. Extra granular Microcrystalline cellulose, Sodium Starch Glycolate, Colloidal Anhydrous silica and Magnesium stearate were sifted sifted through Quadro co-mill using a suitable screen.
3. Binder solution was prepared by adding Hypromellose (HPMC 5 cps) in a suitable qty. of purified water.
4. The material of step 1. Were then loaded into the pot of the single pot processor and dry mixing was done.
5. To the dry mix of step 4, the binder solution of step 3 was added and granulation was done.
6. The wet mass of step 5 was then further granulated for sufficient time to obtain granules of sufficient strength.
7. The granules of step 7 were then put for drying for suitable time period , so that terminal moisture content of the granules was not more than 2.0% w/w.
8. The dried granules were then screened using Quadro-co-mill using a suitable screen. The steps 1-8 were then repeated for all the remaining lots.
9. All the lots were then mixed together in asuitable blending device for suitable period of time.
10. To the mixed granules of step 9 extragranular Microcrystalline cellulose, Sodium Starch Glycolate and Colloidal Anhydrous silica were added and blending was done.
11. To the blend of step 10 Magnesium stearate was added final blending done.
12. The final blend of step 11 was then put for compression.
13. The compressed tablets were then coated using Opdadry yellow to obtain a weight gain of 3.0%.

4.3.7 Selection of sampling location: Prior to the scale-up activity a detailed monitoring and sampling plan was designed to carry out the study in a systematic way.

The following parameters of the unit operations to be studied / monitored / evaluated and documented

- **<u>Sifting</u>:**
  - Screen size
  - Speed (hertz)

- **<u>Dry mixing, Granulation & Drying</u>:**

  - **Dry Mixing**
    Mixer Speed
    Mixing Time
    Chopper Speed
    Bowl Pressure
    Bowl Temperature
    Chopper Flip-Flop

  - **Binder addition**
    Chopper Speed
    Mixer Speed
    Chopper Flip Flop
    Bowl Pressure
    Bowl Temperature
    Binder addition Time

  - **Mixing after Binder addition**
    Chopper Speed
    Mixer Speed
    Chopper Flip Flop
    Bowl Pressure
    Bowl Temperature
    Extra water addition Time

Quantity of extra water added

- **Wet Mixing**
  Mixer Torque
  Mixer Power

- **Dry Screening:**
  - Screen size
  - Milling Speed

- **Blending:**
  - Blender Speed
  - Blending Time

- **Compression:**

  Thickness
  Hardness
  Average Weight
  Mode
  Turret speed
  Feeder speed (feeder 1 rpm/ feeder 2 rpm)
  Pre compression force
  Max final compression force
  Mean force (in Mode 2)
  Bottom pre compression height
  Bottom final compression height
  Fill Depth
  Ejection Force (Higher limit)
  Correction Factor (in %)
  % Weight deviation of mean value
  Cam used

- **Film Coating:**
  - Coating parameters
    - Prewarming Inlet Temperature
    - Prewarming Exhaust Temperature
    - Inlet Temperature
    - Exhaust Temperature
    - Pan Speed
    - Spray Rate
    - Gun to bed Distance
    - Bed temperature
    - Inlet air CFM
    - Atomizing air pressure
    - Pressure differential of pan
  - Final coat weight build-up

TABLE 7 : MONITORING SAMPLING PROCEDURE AND ACCEPTANCE CRITERIA

Process ProcessVariables / Validation Study	**Sampling Stages**	**Tests to be Performed**	**Approx. Sample size**	**Acceptance Criteria**	**Responsibility**
Blending time	5+ 20 + 5 min.	Blend Uniformity (Individual Assay)	**2 sets of 10 samples each between 100 – 300 mg. Submit 1 set for analysis and**	**Mean of all the individual values should be within the range of 90.0 – 110.0 % of the**	Production / PDL/ QA / QC
		Bulk density, Tapped density and Particle size distribution	Approx. 120 g of the final blend to be sampled for physical characteristics evaluation.	Recommendation Bulk Density should be 0.55 – 0.75 g/cc. Tapped Density should be 0.60 – 0.90 g/cc.	
Uniformity of dosage units (By Content Uniformity)	Start, Middle & End of Compression	Uniformity of dosage units (By Content Uniformity)	Approximately 120 tablets at each stage	Acceptance Value should not be more than 15.	
Machine Speed Study	Low, optimum and high speed	**Individual weight**	Not less than one revolution output	97-103 mg	
		Thickness	Minimum 20 tablets at each speed	3.1 – 3.5 mm	
		Hardness	Minimum 20 tablets at each speed	20 – 80 N	
		Friability	Minimum 6.5 g/100 rev. at each speed	NMT 1.0 % w/w	
		Disintegration time	Minimum 6 tablets at each speed	NMT 15 min	

Sampling Stages	Tests to be Performed	Approx. Sample size	Acceptance Criteria	Responsibility	Manufacturing Stages
Full level **Middle level** **Low level**	**Individual weight**	Not less than one revolution output	97-103 mg	Production / PDL/ QA / QC	Blending
	Thickness	Minimum 20 tablets at each speed	3.1 – 3.5 mm		
	Hardness	Minimum 20 tablets at each speed	20 – 80 N		
	Friability	Minimum 6.5 g/100 rev. at each speed	NMT 1.0 % w/w		
	Disintegration time	Minimum 6 tablets at each speed	NMT 15 min		
Pooled tablets	12 units dissolution rate profile (10, 15, 30 and 45 min).	A pooled sample of 2 sets of 30 coated tablets, representing all 6 locations of coating pan (as specified in section 6.3) to be collected at the end of coating operation and submitted for analysis. **Submit 1 set for analysis and retain another sets as contingency.**	Dissolution Rate Profile: As per current approved Finished Product Specifications not less than 75 % (Q) of the labeled amount of API is dissolved in 45 min.		Compression

Manufacturing Stages	**Process Variables / Validation Study**
Compression	Hopper / Powder supply tube Study
Coating	Dissolution rate profile

FIGURE 7 : LOCATION OF THE SAMPLES TO BE TAKEN FROM BIN BLENDER

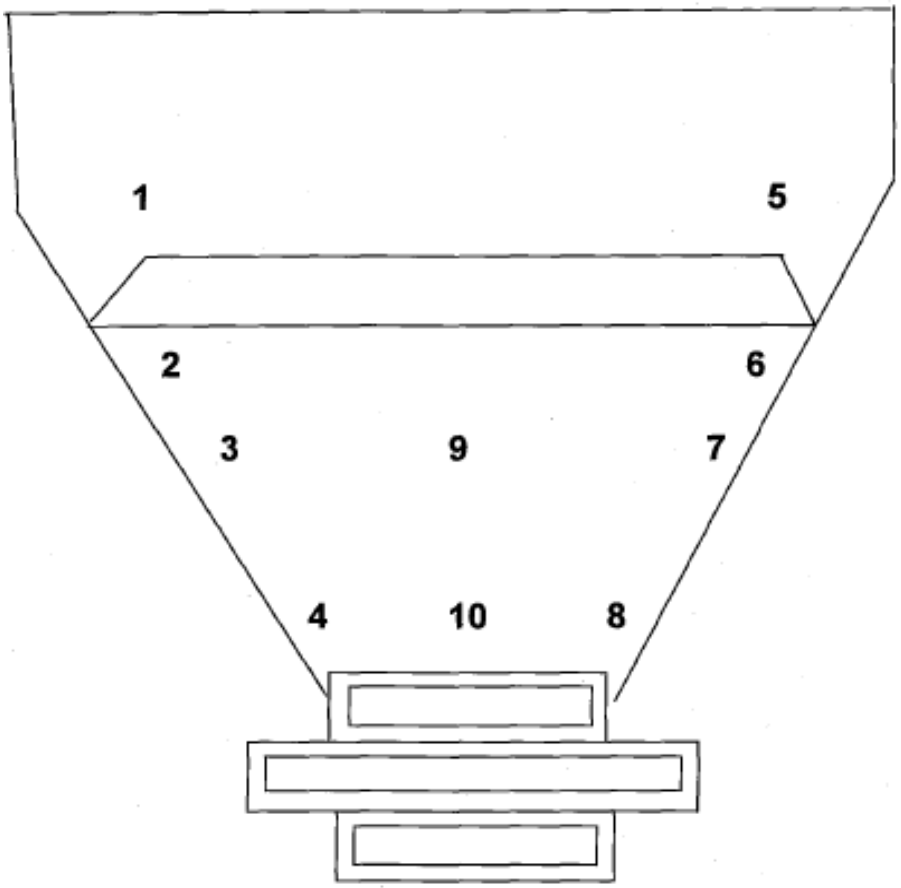

1
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FIGURE 8: LOCATION OF THE SAMPLES TO BE TAKEN FROM FILM COATING PAN

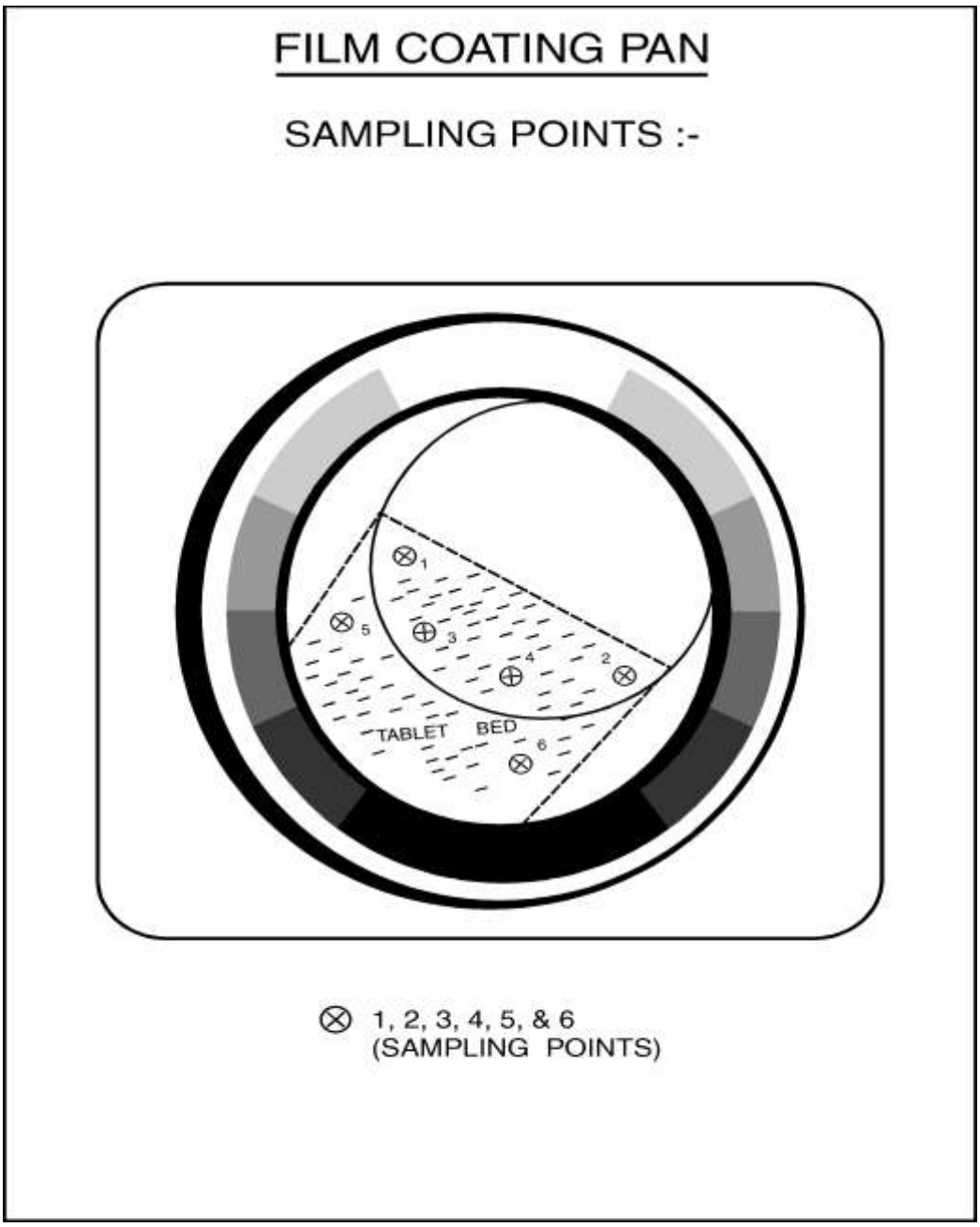


TABLE 10 : BATCH FABRICATION DETAILS

S. No.	Operation	Details	Observations			
1	**Sifting**	Equipment used	← Quadro – Comil →			
		Screen Used & mill speed	←Screen 018 R (0.018 inch) and 30 Hz (Intragranular materials) → ←Screen 018 R (0.018 inch) and 50 Hz (Extra granular materials) →			
2	**Granula-tion & Drying**	Equipment used	← Single Pot Processor →			
		LOTS	**Lot A**	**Lot B**	**Lot C**	**Lot D**
		Dry Mixing time	7 min.	3 min.	15 min.	10 min.
		Mixer speed (rpm)	400	400	400	400
		Chopper Speed	0	0	0	0
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	964 - 969	961 - 967	968 - 970	968 - 970
		Bowl Temp. °C	24.6 – 39.3	25.3 – 32.8	34.1 – 35.3	29.6 – 30.5
		Binder addition time	2 min.	2 min.	2 min.	2 min.
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	0	0	0	0
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	960 - 961	963 - 965	960 – 963.1	963 – 965.2
		Bowl Temp. °C	23.7 - 24	24.8 – 25.6	24.8 – 29.6	29.1 – 30.5
		Water Addition time	1 min.	1 min.	1 min.	1 min.
		Mixer Speed (rpm)	300	300	300	300
		Wet mixing time (sec.)	30 +30	60	60	60
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	0	0	0	0

		Chopper Flip-Flop	Off	Off	Off	Off
		End Point Mixer Torque (Nm)	5	5	4	5
		Bowl Pressure (mBar)	960	963	961	963 - 964
		Bowl Temp. °C	23.7	27	31	34 – 34.2
		Drying time (min.)	60	100	56	60
		Inlet temp (°c)	60	60	60	60
		Vacuum (milli bar)	60	65,60	60	60
		Blow Back Interval (sec.)	600	600	600	600
		Trans Flow	Off	Off	Off	Off
		Microwave (%)	60	70 ,60	60	60
		Product Temp.	60	60	60	60
		Tilting	Continuous	Continuous	Continuous	Continuous
		Mixer on time	1 sec.	1 sec.	1 sec.	1 sec.
		Swinging	On	On	On	On
		Swinging position	1	1	1	1
		Swinging mixer left	3	3	3	3
		Swinging mixer right	3	3	3	3
		Bowl offset temp.	0	0	0	0
		Circuit	Bowl & lid	Bowl & lid	Bowl & lid	Bowl & lid
		End Point Product Temp.	57	57	57.1	57.1
		LOD at 105°C for 10 min (%w/w) from four locations as per protocol	1.70, 1.77, 1.77, 1.49	1.52 , 1.42 , 1.67, 1.47	1.74, 1.64 1.51, 1.51	1.41, 1.39, 1.25, 1.52
3	**Dry**	Equipment Used	← Quadro–co–mill →			
		Screen Used	←Screen 040 G (0.040 inch) →			

	Screening & Milling	Mill Speed (Hz)	25	25	25	25
4	**Blending**	Equipment used	← V – Blender →			
		Blender Speed (rpm)	20	20	20	
		Blending time (min)	5 + 20+5			

4.3.8 Evaluation of powder blend

Angle of repose : The angle of repose signifies the flow properties of powder blend were determined by funnel method. The height of funnel was adjusted in such a way that the tip of funnel just touch the apex of the heap of powder. The powder blend was accurately weighed and allowed to flow through a glass funnel onto a clean surface. The diameter of the powder cone so formed was measured and angle of repose was calculated using the following equation

$\tan \theta = h/r$

Where h is the height of the powder and r is the radius of the powder cone. Angle of repose with its flow ability is given in Table 11.

TABLE 11: RELATIONSHIP BETWEEN ANGLE OF REPOSE AND FLOW ABILITY

Angle of repose	**Flow ability**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density : Loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity 0f 28-35 gm of powder from each formula was poured into a 50 ml graduated cylinder via funnel and volume was measured.

Tapped Density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus, which was operated for a fix number of taps i.e 350. LBD and TBD were calculated using the following formulae:

LBD = Weight of powder/volume of powder

TBD = Weight of powder/tapped volume of powder

Compressibility index : The compressibility indexes of the formulation blends were determined using Carr's index formula

Carr's compressibility index (%) = [(TBD-LBD) X 100] / TBD

Carr's compressibility index with its flow ability is given in Table 12.

TABLE 12 . RELATIONSHIP BETWEEN % COMPRESSIBILITY AND FLOW ABILITY

% Compressibility	**Flow ability**
≤ 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very Poor
>38	Very, very poor

4.3.9 COMPRESSION DETAILS :

TABLE 13 : COMPRESSION MACHINE PARAMETERS DETAILS

S. No.	Parameters	Observations		
1	Mode	1/2		
2	Turret speed (tablets per minute)	390	1300	2080
3	Precompression force (daN)	120	120	120
4	Max. final compression force (daN)	1113	1113	1113
5	Bottom pre compression height (mm)	5.07	5.07	5.12
7	Bottom final compression height (mm)	4.64	4.69	4.71
8	Mean Force (daN)	700	750	760
9	Fill Depth (mm)	5.12	5.24	5.24
10	Ejection force (higher limit) daN	80		
11	Correction Factor	25 %		
12	% Deviation of mean value	20		
13	No. of tablets to reject in case of bad a tablet	1		
14	Feeder speed (feeder 1 rpm/ feeder 2 rpm)	12/24	12/24	12/24
15	Cam used	12		

4.3.10 EVALUATION PARAMETERS FOR COMPRESSED TABLETS

TABLE 14 : IN PROCESS CHARACTERISTICS OF COMPRESSED TABLETS

S. No.	Parameter	Specification	Observations
1	Average Weight (mg)	100±3	99.8 -99.9
2	Uniformity of Weight	±5	-0.2 TO -0.1
3	Thickness (mm)	3.3±0.2	3.31 – 3.40
4	Hardness (N)	50±30	46 – 71

5	Friability (%w/w)	NMT 1.0	0.05 – 0.09
6	Disintegration Time (min.)	NMT 15	2’51’’ – 3’ 03’’

A. Weight variation test

To find out the weight variation, 20 tablets were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value.The specifications for tablets to pass the weight variation test as per Indian pharmacopoeia are mentioned in Table 15.

TABLE 15: SPECIFICATIONS FOR WEIGHT VARIATION IN TABLETS AS PER INDIAN PHARMACOPOEIA (IP)

S.No.	Average weight of tablets	% Deviation
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

B. Hardness

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. The hardness is directly related to the disintegration of the tablet. Hardness is sometimes termed as crushing strength; the apparatus which was used for calculating hardness was **Schleuniger Tester.** Hardness increases with increasing die fills and decreases with lower die punch. Lubricants can affect tablet hardness when they are used in too high concentration or mixed for too longer period

Figure 9 : Schleuniger tester for hardness

Method: The **Schleuniger tester** operates in horizontal position. An anvil was driven by an electric motor pressed the tablet at a constant load rate against a stationary anvil until the tablet breaks. The breaking value was recorded by the instrument.

C. Thickness

The thickness of the tablet can be monitored and controlled. The thickness of a tablet is the only dimensional variable related to the process. At a constant compressive load, the thickness varies with changes in die fill with particle size distribution, while in constant die fill; thickness varies with variation in compressive load. The thickness was measured by **sliding caliper scale**

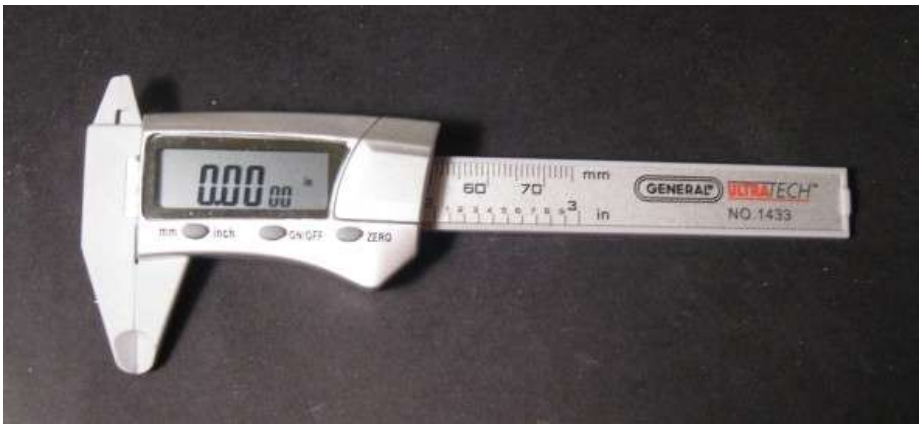


Figure 10 : Sliding calliper scale for thickness

D. Friability

The **friability test** is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the **Roche friabilator** shown in figure 11

Figure 11 : Roche friabilator for friability testing

Method : A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

E. Disintegration

For most tablets, first important step toward dissolution is breakdown of the tablet into smaller particles or granules, process is known as **Disintegration.** For this purpose we used **Tablet Disintegration tester** which is also known as United States Pharmacopoeia (USP) device is shown in figure 12.

Figure 12 : Disintegration tester

The USP device to test disintegration uses 6 glass tubes that are 3 inches long, open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test for disintegration time one tablet was placed in each tube and the basket rack was positioned in 1L beaker of water at 37°C±2°C such that the tablets remain 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. A standard motor driven was used to move the basket assembly containing the tablets up and down through a distance of 5-6 cm at a frequency of 28-32 cycles/minute. The disintegration time of each tablet was NMT 15 minutes.

4.3.11 In Vitro Dissolution Studies

In vitro dissolution studies of the core tablets were carried out in the 500 ml 0.1 N Hydrochloric acid to assess the drug release from core tablets after disintegration of tablets. At the end of the time periods 10 ml of sample was withdrawn from each dissolution flask filtered through Watmann filter paper and samples were suitably diluted using dissolution medium and analyzed for API specifications with their standard values used as shown in Table 16

TABLE 16. DISSOLUTION TEST PARAMETERS FOR CORE TABLETS

S.No	Specifications	Standard Values
1	Apparatus	Ph. Eur II
2	Speed	25 rpm
3	Volume of media	500 ml for dissolution medium
4	Dissolution media used	0.1 N Hydro Chloric Acid
5	Stirrer	Paddle type
6	Aliquot taken at each time interval	10 ml
7	Temperature	37 ± 0.5°C

4.3.12 Coating details

In a clean stainless steel vessel equipped with mechanical stirrer purified water was taken and adjusted all parameters as according to recommendations given in TTD. Transfer of coating suspension to the coating machine was done and operation of coating started with the setting of machine parameters as given in Table 17-18

Table 17: Parameters for film coating of tablets

Sr. No.	Parameter	Observations													
1	Equipment used	45 – 50													
2	Pre-warming Inlet temp(°C)	35 – 40													
3	Pre-warming Exhaust temp(°C)	60	61	63.7	62	64	62.7	50	55	53	55	60			
4	Exhaust temperature (°C)	49.7	48.1	48.7	46.7	47.6	47.4	40.4	41.1	40.4	42.7	45			
5	Pan speed (rpm)	4	5	5	5	5	5	4	5	6	6	7			
6	Spray Rate (g/min.)	35	35	35	35	35	35	35	35	35	35	35			
7	Atomizing air pressure (kg/sq. cm)	2.0	2.0	2.4	2.4	2.0	2.0	2.0	2.0	2.0	2.0	2.5			
8	Peristaltic pump rpm	3	3	3.5	3.5	3.5	4	4	4	4	4	3			
9	Spray gun distance (from the bed) (cm)	22	22	22	22	22	22	22	22	22	22	22			
10	Inlet Air CFM	222	295	269	234	187	207	02	269	295	238	207			
11	Pressure Differential	28	9	10	6	7	6	18	19	18	20	21-22			
12	Bed Temp.	50	49	47.7	42.4	44.6	40.8	40.1	34.3	34.9	34.3	45.6			
13	Final Coat weight build-up (% w/w)	3.3 %													

TABLE 18: PARAMETERS FOR DRYING OF FILM COATING OF TABLETS

S. No.	Parameters	Machine parameters set
Drying of tablets		
1	Pan speed	3-7
2	Inlet temperature (°C)	50-60
3	Drying time (min.)	10

Initially the weight of 300 tablets (100 tablets each from 3 different locations) were done , taking mean and check the weight gain.

4.4 RECOMMENDATIONS FOR EXHIBIT

After the successful completion of the scale up batch of the product, the parameters were freezed for the exhibit batches. Exhibit batches were taken for filing purposes in different regulatory agencies. Exhibit batches were planned to be taken as per the following recommendations

TABLE 19 : RECOMMENDATIONS FOR GRANULATION

Stage	**Parameters**	**Proposed**
Dry mixing	Mixer speed	400 rpm
	Chopper	off
	Mixing Time	10 minutes
	Bowl pressure	900 -999 mBar
	Chopper Flip - Flop	Off
	Mixer power	0
Binder Addition	Mixer speed	300 rpm
	Chopper	Off
	Addition Time	2 minutes
	Bowl pressure	900 -999 mBar
	Chopper Flip - Flop	Off
	Mixer power	0
	Quantity of Additional Purified Water	0.090 kg
Kneading	Mixer speed	300 rpm
	Chopper	Off
	Mixing Time	60 seconds
	Bowl pressure	900 -999 mBar
	Mixer torque	4 – 6 Nm
	Chopper Flip - Flop	Off
	Mixer power	0

Drying	Mixer on time	1 sec
	Chopper	Off
	Bowl pressure(mBar)	60
	Blow back interval (sec)	600
	Microwave forwarded power (kW)	60 %
	Product temperature	60°C
	Swinging	ON
	Swinging Position	1
	Swinging Mixer left	3
	Swinging Mixer Right	3
	Circuit	Bowl & lid
	Temperature	60°C
	Bowl Offset temperature	0
	Chopper Flip-Flop	OFF
	LOD at 105°C for 10 min (%w/w)	NMT 2.0
	End point product temperature	55 -60 °C
Dry Screening	Quadro Comill Speed	25 hertz
	Screen	040 G

- **Blending :**

Final blending of sifted material was done in V-blender for 20 minutes for pre- lubricated blend and for 5 minutes for the lubricated blend respectively. Unit dose samples were withdrawn from 10 different locations of Blender at the end of final blending and were sent for analysis as per the protocol, results are within the specified acceptance criteria. Based on the results of Blend uniformity of the final blend the total mixing time proposed for the exhibit batch would be 20 minutes and 5 minutes for Pre-lubricated and lubricated blend respectively

- **COMPRESSION :**

In order to ascertain the machine speed, the bulk blend was compressed on 26-station compression machine (Courtoy compression machine) with different speeds (viz. 390, 1300 & 2080 tablets/min.). The tablets compressed at different speed were checked for physical parameters as well as subjected for Content Uniformity testing. The tablets compressed at different hardness of compression low, optimum & high hardness (viz.30 - 40 N,50– 68N 60 – 70 N respectively) were checked for physical parameters and Dissolution profile.

Basing on the results of the Content Uniformity and Dissolution data the proposed parameters for the exhibit batch would be as given below.

TABLE 20 : RECOMMENDATIONS FOR COMPRESSION PARAMATERS

Parameters	Target	Range
Average Weight (mg)	100	97 - 103
Uniformity of weight	Not Applicable	±5.0 %of average weight
Thickness (mm)	3.3	3.1 – 3.5
Hardness (N)	50	20 – 80
Machine Speed (Tablets per minute)	1300	390 – 2080
Pre compression Force (daN)	120	80 -200
Max. final compression force (daN)	NA	600 -1500
Feeder 1 speed rpm	12	10 - 15
Feeder 2 speed rpm	24	20 - 30
Mean force(in mode2) (daN)	750	600 - 900
Bottom pre compression height (mm)	NA	4.0 – 6.0
Bottom final compression height (mm)	NA	3.0 – 6.0
Fill depth (mm)	NA	4.0 – 7.0
Ejection force (higher limit) (daN)	80	50-120
Correction factor (in %)	25	20 - 30
% weight deviation of mean value	20	15 - 25
No. of tablets to reject in case of a bad tablet	1	
Cam used	NA	F8/ F12

COATING :

- Film coating for tablets was carried out by using coating machine. The coating operation was smooth and the product is uniformly coated. The final coat weight build up was observed –

Stages	Final Coat Weight Build-up Limits	Observed
Film Coating	3.0 % ± 0.5 %w/w	3.8

- Samples of coated tablets collected were subjected for evaluation of different physical parameters, Content Uniformity and Dissolution Rate Profile.

- On performing the coating activity up to the weight build up of 3.8 % Logo Bridging was observed. Hence the proposed final coat weight build up for the exhibit batches would be 3.0 %±0.5%.

- During the coating operation peeling effect was observed at low pan rpm and hence it was decided to increase the pan rpm.

- Based on the results of Content Uniformity and dissolution testing the final proposed parameters for the exhibit Batch would be as follows

Table 21: Recommendations for Coating Parameters

Parameters	Target	Range
Atomizing Pressure	3	2 – 5
RPM of peristaltic Pump	3	3 – 4
Pre-warming Inlet temperature	40 – 50 C	
Pre-warming Exhaust temperature	35 – 40°C	
Inlet Temperature Set	55 – 65° C	
Exhaust Temperature	48 °C	45 – 55 °C
Pan Speed	3 – 10 rpm	
Spray Rate (g/minute)	35	30 - 50

Final Coat Weight Build up	3.0 %w/w	2.5 – 3.5 % w/w

4.5 EXHIBIT BATCHES

After taking scale up batch of the product exhibit batches were taken. Exhibit batches were done for filing purposes in different regulatory agencies. Three batches of same size (15.00 kg) were done as were already done in scale up batch

4.5.1 Setting of stipulated environment conditions for Exhibit batches

Relative humidity (% RH) and temperature(°C) were maintained within limits to increase the stability profile of the drug. They were checked time to time as shown in Table 22.

TABLE 22: ENVIRONMENTAL CONDITIONS DURING MANUFACTURING & PROCESSING OF DIFFERENT OPERATIONS DURING EXHIBIT BATCHES .

S.No.	Operation	Setting
1	Dispensing Temperature (°C) Relative humidity (%RH)	 21-24 35-45
2	Sifting Temperature (°C) Relative humidity (%RH)	 22-24 35-40
3	Granulation Temperature (°C) Relative humidity (%RH)	 22-24 35-40
4	Dry screening Temperature (°C) Relative humidity (%RH)	 21-24 35-40
5	Blending Temperature (°C) Relative humidity (%RH)	 22-24 35-40
6	Compression Temperature (°C)	 22-26

	Relative humidity (%RH)	35-45
7	Coating Temperature (°C) Relative humidity (%RH)	 21-24 35-40

5.4.2 Selection of quantities for Batch X, Y & Z

Batch X was a first exhibit batch, which was of similar batch size as all other batches. The batch size of batch X, Y and Z was 15.00 kg same as Scale up batch the quantity of each ingredient was calculated and given in table 23.

TABLE 23: BATCH SIZE CALCULATION FOR EXHIBIT BATCHES

S.No.	Ingredient	Quantities (kg) for Batch X, Y & Z			
		Lot A	Lot B	Lot C	Lot D
1	WH	0.094	0.094	0.094	0.094
2.	Lactose Monohydrate	2.435	2.435	2.435	2.435
3.	Maize starch	0.375	0.375	0.375	0.375
4.	Hypromellose	0.075	0.075	0.075	0.075
5.	Microcrystalline cellulose	2.400			
6.	Sodium starch glycolate	0.450			
7.	Colloidal anhydrous silica	0.075			
8.	Magnesium stearate	0.150			
9.	Opadry yellow	0.585			

TABLE 24 : BATCH FABRICATION DETAILS OF EXHIBIT BATCHES

Batch No. X

S. No.	Operation	Details	Observations			
1	**Sifting**	Equipment used	← Quadro – Comil →			
		Screen Used & mill speed	←Screen 018 R (0.018 inch) and 30 Hz (Intragranular materials) → ←Screen 018 R (0.018 inch) and 50 Hz (Extra granular materials) →			
2	**Granulation & Drying**	Equipment used	← Single Pot Processor →			
		LOTS	**Lot A**	**Lot B**	**Lot C**	**Lot D**
		Dry Mixing time (min.)	10	10	10	10
		Mixer speed (rpm)	400	400	400	400
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	956	950	959	958
		Bowl Temp. °C	22.6	31.3	22.9	29.2
		Binder addition time (min)	2	2	2	2
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	955	951	961	958
		Bowl Temp. °C	23.5	30.2	23.3	28.3
		water Addition time (sec.)	60	60	60	60
		Mixer Speed (rpm)	300	300	300	300
		Wet mixing time (sec.)	60	60	60	60
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		End Point Mixer Torque (Nm)	5	5	5	6
		Bowl Pressure (mBar)	954	952	973	958
		Bowl Temp. °C	24.4	31.1	23.9	29.2

		Drying time (min.)	65	59	61	59
		Temperature (°c)	60	60	60	60
		Bowl pressure (milli bar)	60	60	60	60
		Blow Back Interval (sec.)	600	600	600	600
		Trans Flow	NA	NA	NA	NA
		Microwave forwarded power (%)	60	60	60	60
		Product Temp.	60	60	60	60
		Mixer on time (sec)	1	1	1	1
		Swinging	On	On	On	On
		Swinging position	1	1	1	1
		Swinging mixer left	3	3	3	3
		Swinging mixer right	3	3	3	3
		Bowl offset temp.	0	0	0	0
		Circuit	Bowl and Lid	Bowl and Lid	Bowl and Lid	Bowl and Lid
		End Point Product Temp.	57.5	57.7	57.3	57.5
		LOD at 105°C for 10 min (%w/w)	1.90	1.73	1.63	1.75
3	**Dry Screening & Milling**	Equipment Used	← Quadro – Comil →			
		Screen Used Mill Speed (Hz)	←Screen 040 G (0.040 inch) and 25Hz →			
4	**Blending**	Equipment used	V- Blender (40 L)			
		Blender Speed (rpm)	20	20	20	
		Blending time (min)	5 + 20 + 5			

Batch No.: Y

S. No.	Operation	Details	Observations			
1	**Sifting**	Equipment used	← Quadro – Comil →			
		Screen Used & mill speed	←Screen 018 R (0.018 inch) and 30 Hz (Intragranular materials) → ←Screen 018 R (0.018 inch) and 50 Hz (Extra granular materials) →			
2	**Granulation & Drying**	Equipment used	← Single Pot Processor →			
		LOTS	**Lot A**	**Lot B**	**Lot C**	**Lot D**
		Dry Mixing time (min.)	10	10	10	10
		Mixer speed (rpm)	400	400	400	400
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	958	959	960	959
		Bowl Temp. °C	25.3	23.6	23.7	34.2
		Binder addition time (min)	2	2	2	2
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	959	961	959	959
		Bowl Temp. °C	25.1	23.9	33.9	32.3
		water Addition time (sec.)	60	60	60	60
		Mixer Speed (rpm)	300	300	300	300
		Wet mixing time (sec.)	60	60	60	60
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		End Point Mixer Torque (Nm)	6	5	6	6
		Bowl Pressure (mBar)	973	968	970	963
		Bowl Temp. °C	26.2	25.1	36.1	33.7
		Drying time (min.)	86	60	58	67
		Temperature (°c)	60	60	60	60

		Bowl pressure (milli bar)	60	60	60	60
		Blow Back Interval (sec.)	600	600	600	600
		Trans Flow	NA	NA	NA	NA
		Microwave forwarded power (%)	60	60	60	60
		Product Temp.	60	60	60	60
		Mixer on time (sec)	1	1	1	1
		Swinging	On	On	On	On
		Swinging position	1	1	1	1
		Swinging mixer left	3	3	3	3
		Swinging mixer right	3	3	3	3
		Bowl offset temp.	0	0	0	0
		Circuit	Bowl and Lid	Bowl and Lid	Bowl and Lid	Bowl and Lid
		End Point Product Temp.	57.1	56.7	57	57.1
		LOD at 105°C for 10 min (%w/w)	1.34	1.86	1.42	1.56
3	**Dry Screening & Milling**	Equipment Used	← Quadro – Comil →			
		Screen Used Mill Speed (Hz)	←Screen 040 G (0.040 inch) and 25Hz →			
4	**Blending**	Equipment used	V- Blender (40 L)			
		Blender Speed (rpm)	20	20	20	
		Blending time (min)	5 + 20 + 5			

Batch No.: Z

S. No.	Operation	Details	Observations			
1	**Sifting**	Equipment used	← Quadro – Comil →			
		Screen Used & mill speed	←Screen 018 R (0.018 inch) and 30 Hz (Intragranular materials) → ←Screen 018 R (0.018 inch) and 50 Hz (Extra granular materials) →			
2	**Granulation & Drying**	Equipment used	← Single Pot Processor →			
		LOTS	**Lot A**	**Lot B**	**Lot C**	**Lot D**
		Dry Mixing time (min.)	10	10	10	10
		Mixer speed (rpm)	400	400	400	400
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	957	969	962	949
		Bowl Temp. °C	23.5	30.5	25	31.5
		Binder addition time (min)	2	2	2	2
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		Bowl Pressure (mBar)	955	952	957	952
		Bowl Temp. °C	23.8	29.5	24.8	30
		water Addition time (sec.)	60	60	60	60
		Mixer Speed (rpm)	300	300	300	300
		Wet mixing time (sec.)	60	60	60	60
		Mixer Speed (rpm)	300	300	300	300
		Chopper Speed	Off	Off	Off	Off
		Chopper Flip-Flop	Off	Off	Off	Off
		End Point Mixer Torque (Nm)	6	5	6	5
		Bowl Pressure (mBar)	968	958	988	955
		Bowl Temp. °C	24	30.3	26.3	31.6
		Drying time (min.)	63	66	76	71

		Temperature (°c)	60	60	60	60
		Bowl pressure (milli bar)	60	60	60	60
		Blow Back Interval (sec.)	600	600	600	600
		Trans Flow	NA	NA	NA	NA
		Microwave forwarded power (%)	60	60	60	60
		Product Temp.	60	60	60	60
		Mixer on time (sec)	1	1	1	1
		Swinging	On	On	On	On
		Swinging position	1	1	1	1
		Swinging mixer left	3	3	3	3
		Swinging mixer right	3	3	3	3
		Bowl offset temp.	0	0	0	0
		Circuit	Bowl and Lid	Bowl and Lid	Bowl and Lid	Bowl and Lid
		End Point Product Temp.	57.4	58.1	57.1	57.8
		LOD at 105°C for 10 min (%w/w)	1.65	1.49	1.49	1.47
3	**Dry Screening & Milling**	Equipment Used	← Quadro – Comil →			
		Screen Used Mill Speed (Hz)	←Screen 040 G (0.040 inch) and 25Hz →			
4	**Blending**	Equipment used	V- Blender (40 L)			
		Blender Speed (rpm)	20	20	20	
		Blending time (min)	5 + 20 + 5			

Tablet Compression

TABLE 25 : COMPRESSION PARAMETERS DETAIL

S. No.	Parameters	Observations		
		Batch X	**Batch Y**	**Batch Z**
1	Mode	1/2		
2	Turret speed (tablets per minute)	1300 - 1308	1300	1300
3	Precompression force (daN)	120	120	122
4	Max. final compression force (daN)	633	663	1382 – 1385
5	Bottom pre compression height (mm)	5.06 – 5.08	5.05 – 5.08	5.07
7	Bottom final compression height (mm)	4.61 – 4.64	4.57 – 4.66	4.65 – 4.68
8	Mean Force (daN)	735 – 737	688 – 798	723 – 794
9	Fill Depth (mm)	5.23 - 5.28	5.32 – 5.35	5.35
10	Ejection force (higher limit) daN	80		
11	Correction Factor	25		
12	% Deviation of mean value	20		
13	No. of tablets to reject in case of bad a tablet	1		
14	Feeder speed (feeder 1 rpm/ feeder 2 rpm)	14-15/15-30	12/24	13/26
15	Cam used	F12		

Film Coating

TABLE 26 : COATING PARAMETERS DETAIL

Sr. No.	Parameter	Observations		
		Batch X	**Batch Y**	**Batch Z**
1	Equipment used	← Film Coating Machine →		
2	Pre-warming Inlet temp(°C)	45	45	45
3	Pre-warming Exhaust temp(°C)	35	37	37
4	Inlet temperature (°C)	57.8 – 64.5	58.4 – 63.4	59.5 – 61.1
5	Exhaust temperature (°C)	47.8 – 52.7	46.2 – 53.5	48.1 – 50.7
6	Pan speed (rpm)	5.0 -6.0	5.0	5.0 – 5.5
7	Spray Rate (g/min.)	30	40	30
7	Atomizing air pressure(kg/sq. cm)	3.0 – 3.4	3.2 – 3.3	3.0 – 3.3
8	Peristaltic pump rpm	3.5 – 3.8	3.0 – 3.8	5.0
9	Spray gun distance (from the bed) (cm)	21	21	21
10	Inlet Air CFM	756 – 1130	870 - 974	690 - 891
11	Bed Temp.	51.1 – 57.4	49.5 – 56.9	50.3 – 52.2
12	Final Coat weight build-up (% w/w)	2.62	2.83	2.71

CHAPTER – 5

RESULTS AND DISCUSSION

5.1 SCALE UP

5.1.1 Batch fabrication- It generally included various operations as per the flow chart given above e.g. sifting, granulation, drying, dry screening, blending, compression and coating The various unit operations were carefully monitored as per a predefined protocol and the parameters and their observations were recorded.

5.1.2 Granulation Cycles – granulation was performed in four lots and the characteristics of the granules of the four lots are as given below in table 27

TABLE 27 : PHYSICAL CHARACTERISTICS OF INDIVIDUAL LOTS

(A)

S. No.	**Parameters**	**Observations**			
		Lot A		**Lot B**	
01.	Screen no.	040 G (25 Hertz)			
02.	Bulk Density (g/cc)	0.625		0.58	
03.	**Sieve Size**	**% Retained**	**% Cumulative Retained**	**% Retained**	**% Cumulative Retained**
	# 44	18	0	22	0
	# 60	17	35	13	35
	# 85	42	77	42	77
	# 100	16	93	14	91
	Pan	7	100	9	100

(B)

S. No.	**Parameters**	**Observations**			
		Lot C		**Lot D**	
01.	Screen no.	040 G (25 Hertz)			
02.	Bulk Density (g/cc)	0.63		0.64	
03.	**Sieve Size**	**% Retained**	**% Cumulative Retained**	**% Retained**	**% Cumulative Retained**
	# 44	24	0	22	0
	# 60	10	34	8	30
	# 85	39	73	33	63
	# 100	20	93	17	80
	Pan	7	100	20	100

5.1.3 Blending – The four lots along with extra-granular materials were blended together and results of the final blend were as given below in table 28-30

TABLE 28 : PHYSICAL CHARACTERIZATION OF FINAL BLEND

S. No.	Parameters	Observations	
01.	Bulk Density (G/cc)	0.61	
02.	Tap Density(G/cc)	0.73	
03.	**Sieve Size**	**% Retained**	**Cumulative % Retained**
	# 44	16.92	16.92
	# 60	17.91	34.83
	# 85	26.13	60.96
	# 100	7.71	68.67
	Pan	26.62	95.30

Unit dose samples were collected from pre-defined sampling locations of the blender and evaluated for uniformity of mixing at various time intervals of blending. The results obtained are tabulated below

TABLE 29: BLEND UNIFORMITY STUDY OF PRE- LUBRICATED BLEND

S. No.	Sampling Location	Individual Assay(%)		
		10 min.	**15 min**	**20 min**
1	Location I	101.3	100.1	101.2
2	Location II	103.1	101.5	98.0
3	Location III	103.7	98.7	100.1
4	Location IV	102.3	97.1	99.8
5	Location V	104.5	102.2	98.9
6	Location VI	101.0	102.9	97.4
7	Location VII	99.8	101.5	99.5
8	Location VIII	99.4	100.5	98.8
9	Location IX	100.7	100.1	98.1

10	Location X	99.9	103.3	98.9
Mean		**101.6**	**100.8**	**99.1**
Minimum		**99.4**	**97.1**	**97.4**
Maximum		**104.5**	**103.3**	**101.2**

TABLE 30 : BLEND UNIFORMITY STUDY OF LUBRICATED BLEND (FINAL BLEND)

S.No.	Sampling Location	Individual Assay(%)
		5 min.
1	Location I	99.6
2	Location II	97.1
3	Location III	96.9
4	Location IV	100.1
5	Location V	96.4
6	Location VI	96.8
7	Location VII	99.4
8	Location VIII	98.5
9	Location IX	98.0
10	Location X	94.6
Mean		**97.7**
Minimum		**94.6**
Maximum		**100.1**
RSD		**1.74**
Pooled sample		**101.2**
Water by KF of pooled sample (%w/w)		**2.2**

5.1.4 Compression : The final blend was then put for compression using approved tooling and samples were collected during the entire compression run for in-process testing and for quality control tests for evaluation of various challenge studies. The results of the samples submitted are as given below in table 31-34:

TABLE 31 : CHARACTERISTICS OF COMPRESSED TABLETS

S. No.	Parameter	Specification	Observations		
			Machine Speed		
			Low	Optimum	High
			390 Tabs/min	1300 Tabs/min	2080Tabs/min
1	Average Weight (mg)	100 ± 3	100.1-103	99-103	99-100
2	Uniformity of Weight	± 5% of average weight	+0.10 to + 3.0	-1.0 to + 3.0	-1.0 to 0.00
3	Thickness (mm)	3.3 ± 0.2	3.28 - 3.50	3.28 – 3.36	3.24- 3.31
4	Hardness (N)	20 -80	57 - 73	58 - 68	49 - 72
5	Friability (%w/w)	NMT 1.0	0.18	0.17	0.16
6	Disintegration Time (min.)	NMT 15	2’38”	2’48”	2’45”

TABLE 32 : CONTENT UNIFORMITY STUDY OF COMPRESSED TABLETS

Unit No.	Individual Assay (% of label claim)		
	Speed of Compression (tablets/minute)		
	Low speed (390)	Optimum Speed (1300)	High Speed (2080)
1	97.7	99.4	105.2
2	100.5	98.7	102.7
3	101.2	97.9	100.2
4	99.9	99.5	96.4
5	100.9	99.8	101.9
6	97.1	100.1	101.5
7	101.6	95.7	101.1
8	100.8	99.0	102.3
9	98.3	100.1	100.8
10	100.5	100	98.7
Mean	**99.8**	**99**	**101.1**
Minimum	**97.1**	**95.7**	**96.4**

Maximum	**101.6**	**100.1**	**105.2**
Acceptance value	**3.8**	**3.3**	**5.6**

TABLE 33: DISSOLUTION RATE PROFILE OF COMPRESSED TABLETS:

(A): Low hardness

Unit No.	**% Dissolution**			
	10 min.	**15 min.**	**30 min.**	**45 min.**
1	91	97	99	100
2	93	98	99	99
3	95	95	96	96
4	91	96	97	98
5	91	95	96	96
6	96	96	96	97
Mean	**93**	**96**	**97**	**98**
Minimum	**91**	**95**	**96**	**96**

Maximum	**96**	**98**	**99**	**100**
SD	**2**	**1**	**1**	**2**

Acceptance Criteria: Not less than 80% of labeled amount of API is dissolved in 45 min and for all other time points there shall not be any acceptance criteria

TABLE 33: DISSOLUTION RATE PROFILE OF COMPRESSED TABLETS

(B): Optimum hardness

Unit No.	**% Dissolution**			
	10 min.	**15 min.**	**30 min.**	**45 min.**
1	98	96	97	97
2	100	101	102	101
3	101	101	102	102
4	101	100	101	101
5	99	100	100	100
6	96	98	99	99

Mean	**99**	**99**	**100**	**100**
Minimum	**96**	**96**	**97**	**97**
Maximum	**101**	**101**	**102**	**102**
SD	**2**	**2**	**2**	**2**

Acceptance Criteria: Not less than 80% of labeled amount of API is dissolved in 45 min and for all other time points there shall not be any acceptance criteria

.

TABLE 33 :DISSOLUTION RATE PROFILE OF COMPRESSED TABLETS

(C): High hardness

Unit No.	% Dissolution			
	10 min.	**15 min.**	**30 min.**	**45 min.**
1	91	97	98	99
2	95	99	100	100
3	95	98	99	99
4	97	101	102	102

5	92	97	98	98
6	91	96	98	99
Mean	**94**	**98**	**99**	**100**
Minimum	**91**	**96**	**98**	**98**
Maximum	**97**	**101**	**102**	**102**
SD	**3**	**2**	**2**	**1**

Acceptance Criteria: Not less than 80% of labeled amount of API is dissolved in 45 min and for all other time points there shall not be any acceptance criteria

TABLE 34 : CONTENT UNIFORMITY AND DISSOLUTION DATA OF COMPRESSED TABLETS (POOLED SAMPLE)

Content Uniformity **Dissolution data**

Unit No.	Individual Assay (% of label claim)	Unit No.	Individual Assay (% of label claim)
1	97.9	6	99.8
2	99.0	7	100.3
3	101.7	8	101.3
4	99.8	9	99.9
5	98.2	10	98.6
Mean	**99.7**	**Acceptance Value**	**3.0**
Minimum	**97.9**		
Maximum	**101.7**		

Unit No.	% Dissolution (in 45 min.)
1	96
2	101
3	104
4	100
5	96
6	97
Mean	**99**
Minimum	**96**
Maximum	**104**

5.1.5 Coating :

The compressed tablets were then coated using Opadry yellow suspension to an approximate weight gain of 3.0% over the average weight of compressed tablets. Samples of coated tablets

were submitted for analysis as per the specifications and the results found are as given below in table 35-36 :

TABLE 35 : CONTENT UNIFORMITY STUDY OF COATED TABLETS

Unit No.	Individual Assay (% of label claim)
1	99.6
2	99.0
3	102.8
4	98.1
5	101.0
6	97.8
7	102.0
8	101.7
9	101.4
10	99.2
Mean	**100.3**
Minimum	**97.8**
Maximum	**102.8**
Acceptance Value	**4.2**

Criteria: **Acceptance than 15**

Acceptance value not more

TABLE 36: DISSOLUTION RATE PROFILE OF COATED TABLETS (POOLED SAMPLE)

Unit No.	% Dissolution			
	10 min.	**15 min.**	**30 min.**	**45 min.**
1	96	99	99	98
2	97	98	97	98
3	98	100	98	99
4	98	98	99	99
5	96	96	97	97
6	98	97	99	99
Mean	**97**	**98**	**98**	**98**
Minimum	**96**	**96**	**97**	**97**
Maximum	**98**	**100**	**99**	**99**
SD	**1**	**1**	**1**	**1**

Acceptance Criteria: Not less than 80% of labeled amount of API is dissolved in 45 min and for all other time points there shall not be any acceptance criteria.

5.2 EXHIBIT BATCH EXECUTION:

The exhibit batches were also fabricated in the same manner as scale up batch.

5.2.1 Granulation Cycles – granulation was performed in four lots.

5.2.2 Blending – The four lots along with extra-granular materials were blended together and results of the final blend were as given below in table 37-39

TABLE 37 : PHYSICAL CHARACTERIZATION OF FINAL BLEND

S. No.	Parameters	Observations					
		Batch X		Batch Y		Batch Z	
01.	Bulk Density G/cc)	0.61		0.59		0.65	
02	Tap Density (G/cc)	0.73		0.66		0.71	
03.	**Sieve Size**	**% Retained**	**Cumulative % Retained**	**% Retained**	**Cumulative % Retained**	**% Retained**	**Cumulative % Retained**
	# 44	16.92	16.92	18.32	18.32	15.36	15.36
	# 60	17.91	34.83	15.66	33.98	18.90	34.26
	# 85	26.13	60.96	23.7	57.68	27.30	61.56
	# 100	7.71	68.67	11.35	69.03	10.68	72.24
	Pan	26.62	95.30	28.86	97.89	25.13	97.37

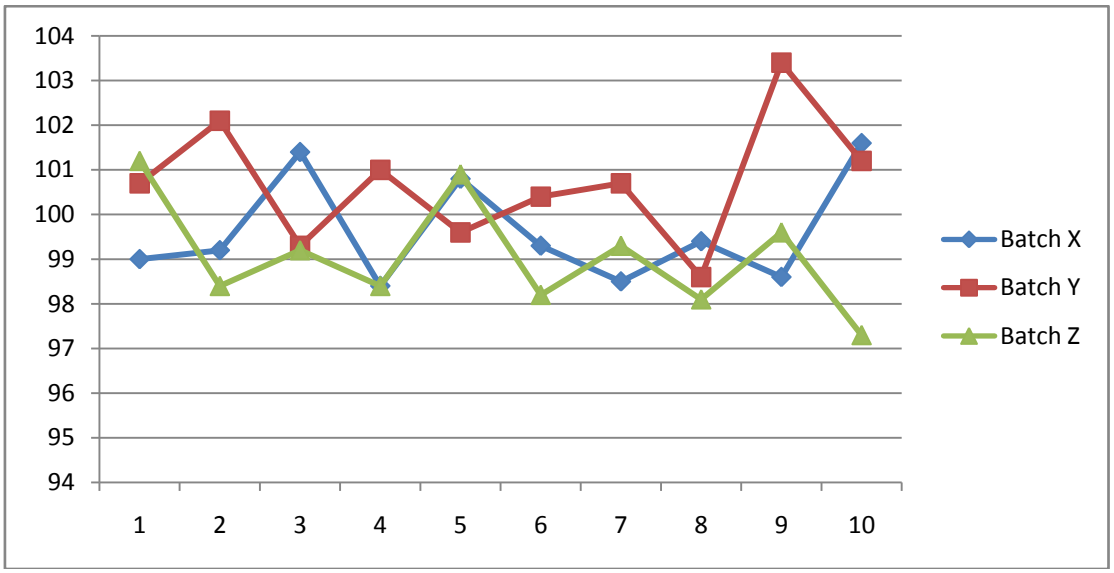
TABLE 38: BLEND UNIFORMITY STUDY FOR PRE LUBRICATED BLEND

S. No.	Sampling Location	Individual Assay(%)		
		Batch X	**Batch Y**	**Batch Z**
1	Location I	100.1	102.1	99.8
2	Location II	100.4	102.6	99.9
3	Location III	101.0	102.9	98.4
4	Location IV	99.2	102.8	97.9
5	Location V	100.3	100.3	98.7
6	Location VI	99.8	100.6	99.0
7	Location VII	103.2	100.8	101.8
8	Location VIII	99.8	99.8	98.9
9	Location IX	99.2	98.9	97.9
10	Location X	101.5	98.8	97.9
Mean		**100.5**	**101.0**	**99.0**
Minimum		**99.2**	**98.8**	**97.9**
Maximum		**103.2**	**102.9**	**101.8**

TABLE 39 : BLEND UNIFORMITY STUDY FOR LUBRICATED BLEND (FINAL BLEND)

S. No.	Sampling Location	Individual Assay(%)		
		Batch X	**Batch Y**	**Batch Z**
1	Location I	99.0	100.7	101.2
2	Location II	99.2	102.1	98.4
3	Location III	101.4	99.3	99.2
4	Location IV	98.4	101.0	98.4
5	Location V	100.8	99.6	100.9
6	Location VI	99.3	100.4	98.2
7	Location VII	98.5	100.7	99.3
8	Location VIII	99.4	98.6	98.1
9	Location IX	98.6	103.4	99.6
10	Location X	101.6	101.2	97.3
Mean		**99.6**	**100.7**	**99.1**
Minimum		**98.4**	**98.6**	**97.3**
Maximum		**101.6**	**103.4**	**101.2**
RSD		**1.20**	**1.37**	**1.26**

FIGURE 13: COMPARISON OF BLEND UNIFORMITY RESULTS FOR LUBRICATED BLEND OF THE EXHIBIT BATCHES



5.2.3 : Compression : The final blend was then put for compression using approved tooling and samples were collected during the entire compression run

TABLE 40 : COMPRESSED TABLETS CHARACTERISTICS

S. No.	Parameter	Specification	Observations		
			Batch X	Batch Y	Batch Z
1	Average Weight (mg)	100±3	99.8 -99.9	98.8 – 99.7	99.1 – 100.3
2	Uniformity of Weight	±5	-0.2 TO -0.1	-0.2 to -0.3	-0.9 to +0.3
3	Thickness (mm)	3.3±0.2	3.31 – 3.40	3.30 – 3.41	3.30 – 3.39
4	Hardness (N)	50±30	46 – 71	50 - 68	51 – 74
5	Friability (%w/w)	NMT 1.0	0.05 – 0.09	0.05 – 0.07	0.03 – 0.14
6	Disintegration Time (min.)	NMT 15	2’51’’ – 3’ 03’’	2’06’’ – 2’58’’	2’34’’ – 3’

TABLE 41 : CONTENT UNIFORMITY STUDY OF COMPRESSED TABLETS

Batch No. X

Unit No.	Individual Assay (% of label claim) at different Stages of Compression		
	Start	**Middle**	**Towards end**
1	101.0	100.7	97.8
2	101.4	100.4	98.2
3	101.0	100.8	98.5
4	99.1	101.8	98.8
5	99.5	99.8	103.7
6	101.0	96.4	98.8
7	99.0	102.1	100.1
8	98.4	97.7	100.6
9	98.6	98.4	103.4

10	99.4	102.1	100.9
Mean	**99.9**	**100.0**	**100.1**
Minimum	**98.4**	**96.4**	**97.8**
Maximum	**101.4**	**102.1**	**103.7**
Acceptance value	**2.7**	**4.6**	**5**

Batch No. Y

Unit No.	Individual Assay (% of label claim) at different Stages of Compression		
	Start	**Middle**	**Towards end**
1	100.2	101.4	102.4
2	101.4	99.9	98.9
3	99.4	98.7	98.6
4	98.0	100.3	101.6
5	101.3	99.3	102.5
6	101.5	102.3	99.8
7	102.8	99.9	103.4
8	100.6	100.7	99.4
9	98.3	100.4	100.8
10	102.9	100.0	100.6
Mean	**100.6**	**100.3**	**100.8**
Minimum	**98.0**	**98.7**	**98.6**
Maximum	**102.9**	**102.3**	**103.4**
Acceptance value	**4**	**2.4**	**3.9**

Batch No. Z

Unit No.	Individual Assay (% of label claim) at different Stages of Compression		
	Start	**Middle**	**Towards end**
1	100.7	101.4	98.8
2	99.5	99.9	101.9
3	101.8	100.1	104.1
4	100.4	98.7	98.1
5	98.3	96.9	100.1
6	101.8	100.3	102.5
7	100.0	99.1	99.1
8	100.0	100.6	100.1
9	100.8	98.4	101.0
10	101.0	97.8	101.4
Mean	**100.5**	**99.3**	**100.7**
Minimum	**98.3**	**96.9**	**98.1**
Maximum	**101.8**	**101.4**	**104.1**
Acceptance value	**2.6**	**3.3**	**4.4**

TABLE 42 : DISSOLUTION RATE STUDY OF COMPRESSED TABLETS AT DIFFERENT STAGES OF COMPRESSION

Batch No. X

Unit No.	% Dissolution (In 45 min.)		
	Start	**Middle**	**Towards end**
1	99	95	98
2	100	97	97
3	97	100	98
4	98	99	102
5	100	100	100
6	96	99	100
Mean	**98**	**98**	**99**
Minimum	**96**	**95**	**97**
Maximum	**100**	**100**	**102**

Batch No. Y

Unit No.	% Dissolution (in 45 min.)		
	Start	**Middle**	**Towards end**
1	101	98	97
2	97	100	96
3	97	96	99
4	97	99	99

5	102	99	95
6	99	98	98
Mean	**99**	**98**	**97**
Minimum	**97**	**96**	**95**
Maximum	**102**	**100**	**99**

Batch No. Z

Unit No.	**% Dissolution (in 45 min.)**		
	Start	**Middle**	**Towards end**
1	94	97	96
2	97	95	97
3	97	96	97
4	95	98	99
5	96	94	97
6	99	98	98
Mean	**96**	**96**	**97**
Minimum	**94**	**94**	**96**
Maximum	**99**	**98**	**99**

TABLE 43 : DISSOLUTION RATE PROFILE STUDY OF COATED TABLETS

Batch No. X

Unit No.	% Dissolution							
	10 min.		15 min.		30 min.		45 min.	
	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2
1	98	97	98	99	97	99	98	100
2	100	97	101	98	101	98	102	98
3	97	97	95	98	98	98	98	99
4	97	101	98	101	98	102	98	102
5	98	99	98	99	99	100	99	100
6	98	99	99	99	99	100	100	100
Mean	**98**	**98**	**98**	**99**	**99**	**100**	**99**	**100**
Minimum	**97**	**97**	**95**	**98**	**97**	**98**	**98**	**98**
Maximum	**100**	**101**	**101**	**101**	**101**	**102**	**102**	**102**
SD	**1**	**2**	**2**	**1**	**1**	**2**	**2**	**1**

Batch No.Y

Unit No.	% Dissolution							
	10 min.		15 min.		30 min.		45 min.	
	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2	Set 1	Set 2
1	88	97	90	97	90	99	94	97
2	93	98	95	98	95	99	96	99
3	99	99	100	100	101	100	101	100
4	94	99	95	100	96	100	97	101
5	97	96	98	96	99	100	100	102
6	98	96	99	96	99	97	99	98
Mean	**95**	**98**	**96**	**98**	**97**	**99**	**98**	**100**
Minimum	**88**	**96**	**90**	**96**	**90**	**97**	**94**	**97**

Maximum	**99**	**99**	**100**	**100**	**101**	**100**	**101**	**102**
SD	**4**	**1**	**4**	**2**	**4**	**1**	**3**	**2**

Batch No. Z

Unit No.	**% Dissolution**							
	10 min.		**15 min.**		**30 min.**		**45 min.**	
	Set 1	**Set 2**	**Set 1**	**Set 2**	**Set 1**	**Set 2**	**Set 1**	**Set 2**
1	87	91	89	92	90	95	94	98
2	92	91	94	92	94	93	95	94
3	97	91	98	92	99	93	100	93
4	94	92	98	93	96	94	96	95
5	92	93	93	94	94	94	94	95
6	93	97	94	97	95	98	95	99
Mean	**93**	**93**	**94**	**93**	**95**	**95**	**96**	**96**
Minimum	**87**	**91**	**89**	**92**	**90**	**93**	**94**	**93**
Maximum	**97**	**97**	**98**	**97**	**99**	**98**	**100**	**99**
SD	**3**	**2**	**3**	**2**	**3**	**2**	**2**	**2**

FIGURE 14: COMPARISON OF THE PERCENTAGE DRUG DISSOLUTION OF 12 UNITS (COATED TABLETS) AT 45 MINUTES.

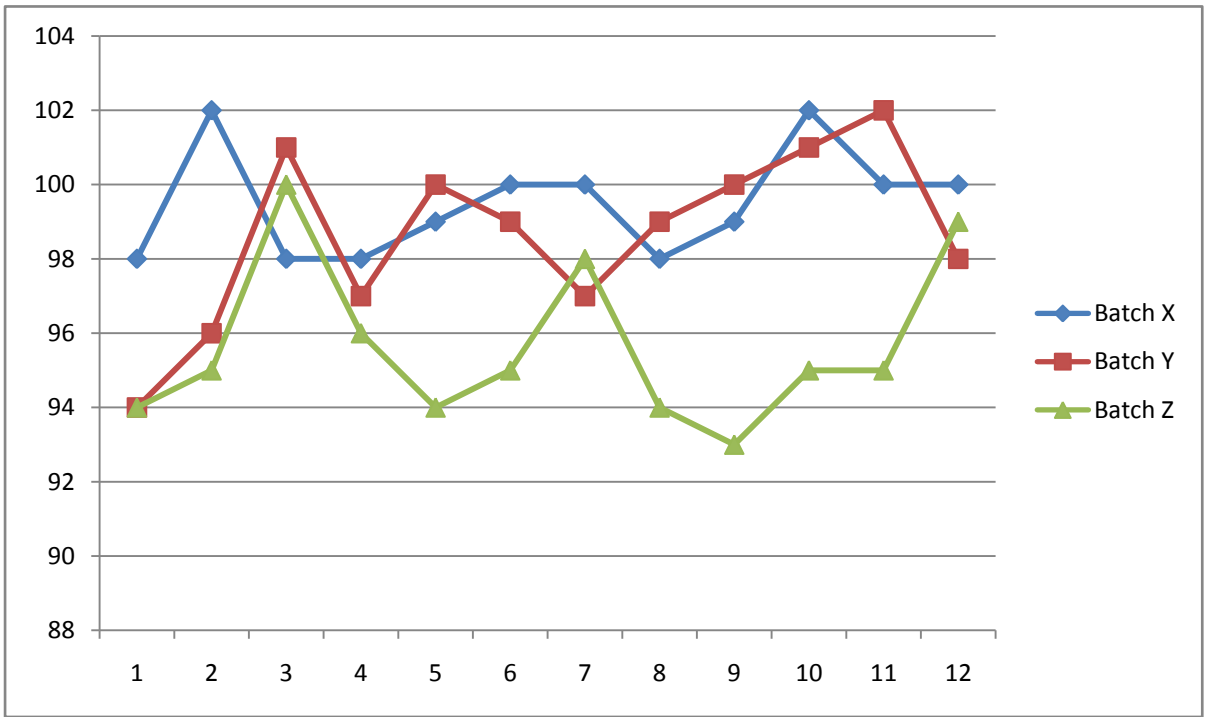


Table 44 : Final Yield of X,Y,Z batches

S. No.	Stage	Observation		
		Batch X	Batch Y	Batch Z
1	Final Blend (%)	97.33	98.0	97.33
2	Compressed Tablets (%)	89.30	90.73	91.07
3	Coating (%)	87.74	89.81	89.56

CHAPTER-6

SUMMARY AND CONCLUSION

6. SUMMARY AND CONCLUSIONS:

In pharmaceutical industry, Technology transfer includes the transfer of data in the form of technology transfer dossier (TTD) from R&D to PDL and then finally to production for the commercial manufacturing of the dosage form. In the present study we followed the technology transfer of tablet dosage form which belongs to potent molecules i.e. the product was to be manufactured in a containment facility with full attention to personal protection.

The entire event of technology transfer involved the manufacturing of one scale up batch as per the recommendations of the technology transfer dossier for the optimization of process parameters.

After the successful completion of the scale up batch and evaluation of the analytical samples, exhibit batches were planned for the filing of the product as well as for the validation of the manufacturing process.

The test batch of API Tablets 2.5 mg involved monitoring of the manufacturing process of three test batches. The observations made during monitoring activity are summarized as follows

- **BLENDING:**
  - Unit dose samples withdrawn at the stage of Pre lubrication and Final Blending show good blend uniformity. For the final blend individual results and the mean are well within the specified acceptance criteria of 90.0 - 110.0 %, with a maximum RSD of 1.37 %.
    The results are reproducible and consistent for all sampling locations. The blend homogeneity is found to be independent of location of sampling.
  - Analytical results of representative In-Process sample of final blend are consistent. The results conform to the predetermined In-process Specifications.

- **COMPRESSION :**

  - The bulk blend was compressed on Tablet Compression Machine (Courtoy compression machine). Samples of tablets collected during compression run were subjected for evaluation of different physical parameters.
    The observed data reveals that the physical parameters of the compressed tablets are consistent.

  - Further, the Uniformity of Dosage Units and Dissolution data of the tablets sampled at different stages of compression is satisfactory and conforms to the acceptance criteria i.e. acceptance value should be NMT 15, with a maximum Acceptance Value of 5.0

- **FILM COATING:**

  - Film coating for tablets is carried out by using Film Coating Machine. The coating operation is smooth and the product is uniformly coated with the parameters specified in Master Formula. The final coat weight build up observed is 2.62 – 2.83 % w/w against the recommended limit of 2.50 % – 3.50 %w/w.

    The batch representative samples of coated tablets tested for Dissolution show no significant variation between the batches. Tablets of all the batches comply to specification of NLT 80% of labeled amount of API is dissolved in 45 min.

- The finished product results of the batches comply to the laid down Product Release Specifications.

Conclusion

The overall review of results shows consistency and reproducibility. These results demonstrate that the manufacturing process was under control throughout all the stages of manufacturing. The collated data clearly indicates Process Consistency and Reproducibility in yielding the product that meets predetermined attributes for the product.

Recommendations for Validation/Commercial Batches :

- **GRANULATION:**

Stage	Parameters	Proposed
Dry mixing	Mixer speed	400 ± 2 rpm
	Chopper	off
	Mixing Time	10 minutes
	Bowl pressure	900 -999 mBar
	Chopper Flip - Flop	Off
	Mixer power	0
Binder Addition	Mixer speed	300 ± 2 rpm
	Chopper	Off
	Addition Time	2 minutes
	Bowl pressure	900 -999 mBar
	Chopper Flip - Flop	Off
	Quantity of Additional Purified Water	0.090 kg
Kneading	Mixer speed	300 ± 2rpm
	Chopper	Off
	Mixing Time	60 seconds
	Bowl pressure	900 -999 mBar
	Mixer torque	4 – 6 Nm
	Chopper Flip - Flop	Off
	Mixer power	0
Drying	Mixer on time	1 sec
	Chopper	Off
	Bowl pressure (vacuum) (mBar)	60 ± 5

	Blow back interval (sec)	600
	Microwave forwarded power (kW)	60 %
	Product temperature	60°C
	Swinging	ON
	Swinging Position	1
	Swinging Mixer left	3
	Swinging Mixer Right	3
	Circuit	Bowl & lid
	Temperature (bowl & lid)	60 ± 3 °C
	Bowl Offset temperature	0
	Chopper Flip-Flop	OFF
	LOD at 105°C for 10 min (%w/w)	NMT 2.0
	End point product temperature	55 -60 °C
Dry Screening	Quadro Comill Speed	25 hertz
	Screen	040 G

COMPRESSION :

Parameters	Target	Range
Average Weight (mg)	100	97 - 103
Uniformity of weight	Not Applicable	±5.0 %of average weight
Thickness (mm)	3.3	3.1 – 3.5
Hardness (N)	50	20 – 80
Machine Speed (Tablets per minute)	1300	390 – 2080
Pre compression Force (daN)	120	80 -200
Max. final compression force (daN)	NA	600 -1500
Feeder 1 speed rpm	12	10 - 15
Feeder 2 speed rpm	24	20 - 30
Mean force(in mode2) (daN)	750	600 - 900
Bottom pre compression height (mm)	NA	4.0 – 6.0
Bottom final compression height (mm)	NA	3.0 – 6.0
Fill depth (mm)	NA	4.0 – 7.0
Ejection force (higher limit) (daN)	80	50-120
Correction factor (in %)	25	20 - 30
% weight deviation of mean value	20	15 - 25
No. of tablets to reject in case of a bad tablet	1	
Cam used	NA	F8/ F12

COATING :

Parameters	Target	Range
Pan size	600 mm	
Spray gun to bed distance	22	18-25
Atomizing Pressure	3	2 – 5
Pre-warming Inlet temperature	40 – 50 C	
Pre-warming Exhaust temperature	35 – 40°C	
Inlet Temperature Set	55 – 65° C	
Exhaust Temperature	48 °C	45 – 55 °C
Pan Speed	3 – 10 rpm	
Spray Rate (g/minute)	35	30 - 50
Final Coat Weight Build up	3.0 %w/w	2.5 – 3.5 % w/w

1. Mahboudi M, Ananthan BR. Effective factors in technology transfer in the Pharmaceutical industries of Iran: A Case Study. The IUP Journal of Knowledge Management. 2010; 8(1, 2):99.

2. Bendis R, Byler E. Creating a National Innovation Framework, Building a Public-Private Support System to Encourage Innovation. Science progress, 2009.

3. Reamer A, Icerman L, Youtie J. Technology Transfer and Commercialization: Their Role in Economic Development, 2003, 10-16.

4. Feifei YUE, Yigming YUE. Research on Technology Transfer in the Pharmaceutical Industry, Technology Transfer Journal of Tongji University. Natural Science. 2008, 11-14.

5. Steenhuis HJ, De Boer SJ. Differentiating between types of technology transfer: the technology building. International Journal of Technology Transfer and Commercialization. 2002; 1(1-2):187-200.

6. Ghafaripour A. Fundamental Concepts for Technology Transfer Process, Industries Ministry, Tehran, 1999.

7. Gupta. Technology Transfer in pharmaceutical industry: An overview. Novel Science International Journal of Pharmaceutical Science. 2012; 1(7):430-434.

8. Steenhuis HJ. International Technology Transfer: Building Theory from a multiple Case-Study in The Aircraft Industry, Doctoral Thesis, University of Twente, the Netherlands, 2000.

9. Gorman ME. Types of knowledge and their roles in technology transfer. Journal of Technology Transfer. 2002; 27:219-231.

10. Gibson M. Pharmaceutical Preformulation and Formulation: A Practical Guide form Candidate Drug Selection to Commercial Dosage Form, Interpharm/CRC Press, A division of Taylor and Francis Books Inc, FL, USA, 2001,

11. Liebowitz S. PhD. Pharmaceutical Technology Transfer: Pre and Post NDA Submission. Pharm Tech Conference, 1995.

12. Patel DS, Nadiad. Technology Transfer an Overview of Pharmaceutical Industry. Int Biopharm Association Publ. 2009; 2(4):2-8.

13. Patil RP. Technology Transfer in Pharmaceutical industry: Objective, Issues and Policy Approaches. Int J Pharma Res Dev. 2010; 2(10):43-48.

14. Singh A, Aggarwal G. Technology Transfer in Pharmaceutical Industry: A Discussion. Int J Pharma Biosci, 2009; 1(3):1-5.

15. Green S, Warren P. Technology Transfer in Practice, Sue Horwood Publishing Limited, Storrington West Sussex, UK, 2002,

16. Al Ali S. Developing countries and technology transfer. ~ 240 ~ The Pharma Innovation Journal International Journal of Technology Management. 1995; 10(7-8):704-713.

17. Al Ghailani HH, Moor WC. Technology Transfer to developing countries. International Journal of Technology Management. 1995; 10(7, 8):687-703.

18. Ali S, Pandit V, Chander S. Technology Transfer in Pharmaceuticals. Int Res J Pharm. 2012; 3(6):43-48. 19. Reddy NM, Zhao L. International technology transfer: A review. Research Policy. 1990; 19(4):285-307.

20. Osman Gani AAM. International technology transfer for competitive advantage: A conceptual analysis of the role of HRD. Competitiveness Review 1999; 9:9

21. ISPE Good practice guide, Technology transfer, Tampa, FL, International Society for Pharmaceutical Engineering, 2003.

22. Jandia MS, Sreedhar D, Ligade VS, Pise A, Udupa N. Facts of Technology Transfer: A perspective of Pharmaceutical Industry. Ind J of property rights. 2008; 13:28-34.

23. Ramanathan K. The role of technology transfer services in technology capacity building and enhancing the competitiveness of SMEs, Mongolia National Workshop on "Subnational Innovation systems and Technology Capacity-building Policies to Enhance Competitiveness of SMEs." Organized by UN- ESCAP and ITMRC (Mongolia), Ulaanbaatar, Mongolia, 2007, 27-33.

24. Robinson RD. The international transfer of technology, Theory, issues, and practice, Cambridge, MA: Ballinger Publishing Company, 1988.

25. Souder WE, Nashar AS, Padmanathan V. A guide to the best technology transfer practices. Journal of Technology Transfer. 1990; 15:1-2.

26. Teece DJ. The market for know-how and the efficient international transfer of technology. Annals American Academy of Political and Social Science. 1981; 45(8):81- 96.

27. Sexton F. Effective and efficiency knowledge transfer from R&D to manufacturing, Purdue Pharma's SMC meeting, 2004.

28. Arrow K. Classificatory note on the production and transmission of technological knowledge. American Economic Review. 1969, 244-250

29. Autio E, Laamanen T. Measurement and evaluation of technology transfer: Review of technology transfer mechanisms and indicators. International Journal of Technology Management. 1995; 10(7, 8):643-664.

30. Technology Atlas Team, Components of technology for resources transformation. Technological Forecasting and Social Change. 1987; 32:19-35.

31. Donald. Transfer of Process from Development to Manufacturing. Drug Information Journal. 1998; 32:19- 26.

32. Akhavan A. Technology Transfer to Developing Countries: The Iranian Experience, Ph.D. Dissertation, University of Bradford UK, 1995.

33. Ortega AJ, Arce NA, Sequeda F, Gribenchenko I. Management of Innovation and Technology Transfer Process Between University and Industry. The Mater Res Cent Case in Universidad del valle, Colombia. 2009; 2:7- 8.

34. Godkin L. Problems and practicalities of technology transfer: a survey of the literature. International Journal of Technology Management. 1988; 3(5):587-603.