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## Research Paper

# Technology Transfer And Evaluation Of Critical Process Parameters In Manufacturing Of Levofloxacin

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### ABSTRACT

The Aim of this work is to identify the Critical process parameters and optimized then to achieve robust process. Objective of work is to ensure high quality and stable manufacturing of developed and manufacturing products, it provide framework for capturing the technical information need for product manufactured and compliance with regulatory guidelines. In this article we focused on Technology transfer, there goals, scope of technology transfer and optimization of critical process parameters in manufacturing of Levofloxacin tablet dosage form. In optimization parameters dry mixing, wet mixing, %LOD, Compression parameters of machine are optimized and keeping it fixed in Exhibit batch and successfully transferred the Process from R&D to manufacturing site.

### INTRODUCTION

In order to develop new products and make them available to the public, such as medicines, educational tools, electronic devices, safety equipment, and health services, technology transfer is the process of moving scientific discoveries from one organization to another. The relationship between the fields of business, science, engineering, law, and government is technology transfer.[1-2] Technology transfer plays a crucial role in the process of finding new drugs and developing new medical products. This process is important for to elucidate necessary

information for technology transfer from R & D (Research & Development) to PDL (process development laboratory). Technology transfer aids in the development of dosage forms in a number of ways, including process efficiency, product quality maintenance, and the achievement of standardized procedures, all of which contribute to timely and economical production.[3-4]

### GOALS OF TECHNOLOGY TRANSFER: [5] According to ICH Q10 guidelines

1. Is an important stage in the process of development that leads to successful commercial manufacturing?

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2. To employ all of the information acquired as the foundation for the manufacturing control strategy, the process qualification methodology, and ongoing continuous improvement.
3. The transfer of knowledge about products, processes, and analytical methods between development and manufacturing locations.
4. To guarantee that process and parameter variability are adequately managed and robust enough to withstand the demands of a commercial production setting. To confirm that the parameters set during development remain within the designated design space and/or are modified during scale-up

#### **STEPS INVOLVES IN TECHNOLOGY TRANSFER PROCESS [6]**

During development of a formulation, it is important to understand the procedure of operations used, critical and non-critical parameters of each operation, production environment, equipment and excipient availability should be taken into account during the early phases of development of formulation.

##### **A. Development of technology by R&D. (Research Phase)**

- (a) Design of procedure and selection of excipients by R&D – Selection of materials and design of procedures is developed by R&D on the basis of innovator product characteristics.
- (b) Identification of specifications and quality by R&D – Quality of product should meet the specifications of an innovator product.

##### **B. Technology transfer from R&D to production (development phase):**

R&D gives the product development laboratory a technology transfer dossier (TTD) document that includes all of the following formulation and drug product information:

- (a) Master Formula Card (MFC) – Includes product name along with its strength, generic

name, MFC number, page number, effective date, shelf life and market.

- (b) Master Packing Card – Gives information about packaging type, material used for packaging, stability Profile and shelf life of packaging.
- (c) Master Formula – Describes formulation order and manufacturing instructions. (Process order and environment conditions.
- (d) Specifications and Standard Test Procedures (STP'S) – Helps to know active ingredients and
- (e) excipients profile, in-process parameters, product release specifications and finished product details.

#### **OPTIMIZATION AND PRODUCTION**

##### **Validation studies**

It is carried out to confirm that the process can stabilize the product using the transferred manufacturing formula before production is put into action. Validation studies are carried out to confirm that the process can stabilize the product using the transferred manufacturing formula before production is put into action.

##### **Scale up for production**

During the small-scale development of the product and processes, scale up entails the transfer of technology. When developing a process, it is imperative to take the production system and environment into account. For the formulation of a solid dosage form, various procedures are used, such as dispensing, sifting, blending, compaction/dry granulation/wet granulation, compression, and coating. Pharmaceutical experts can easily become engrossed in the specific step of the manufacturing process that they are directly responsible for, from blending to film coating. Operators concentrate on keeping their segment of the production process running smoothly. But the whole manufacturing line can be improved, even before production begins, if technology transfer is implemented thoughtfully. Effective technology

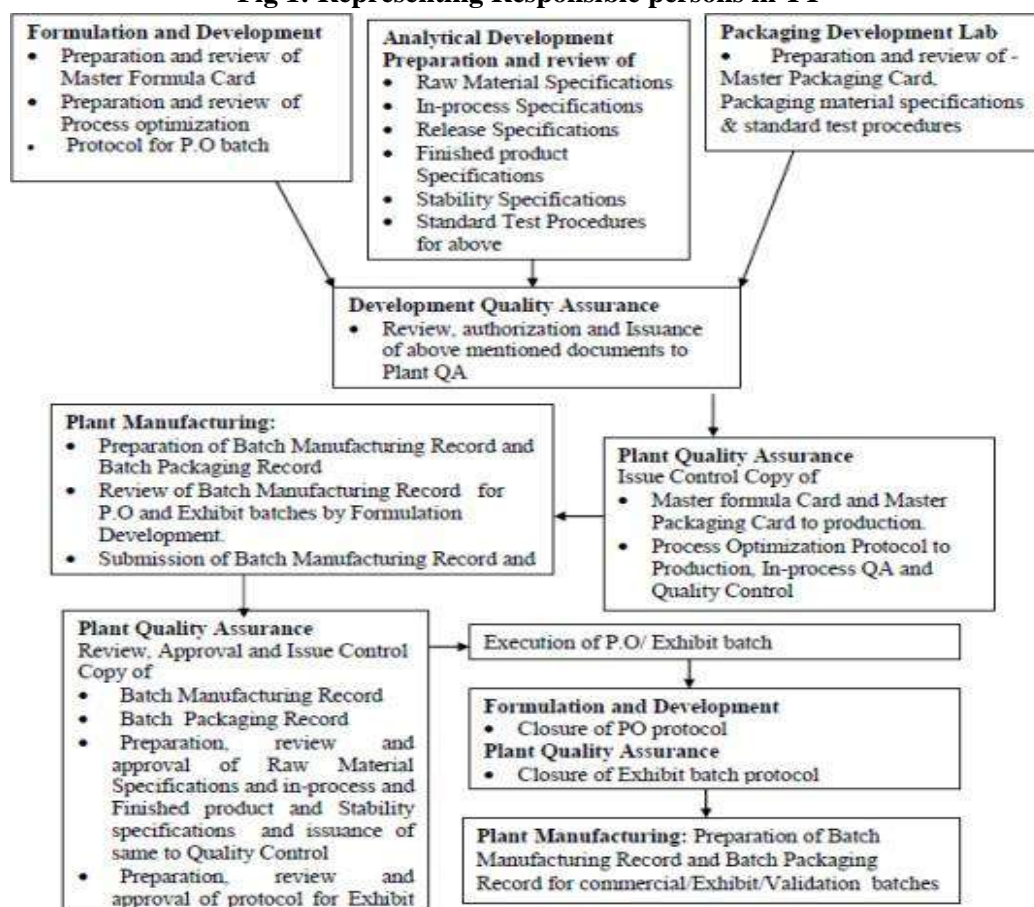


transfer helps to provide process efficiency and control and maintain product quality

Technology transfer team members	Responsibilities
Process technologist	Central focus for transfer activities
	Collates documentation from the donor site
	Performs initial assessment of the transferred project for Feasibility, Compatibility with site capabilities and Establishes resource needs
QA representative	Reviews documentation to work out compliance with marketing authorization (MA)
	Reviews analytical strategies with QC to work out capability, instrumentation training requirements
	Initiates conversion of donor site documentation into local systems or format
	Initiates or confirms regulatory needs, e.g., an amendment to manufacturing license; variations to MA if method changes needed, etc.
Production representative	Reviews process instructions (with process technologist) to verify capacity and capability

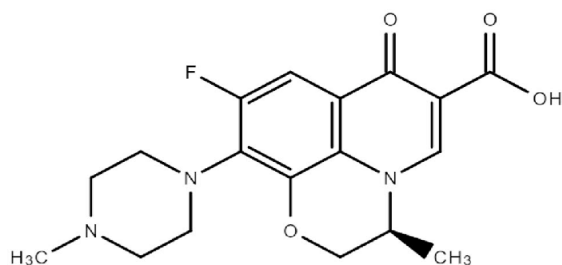
Technology transfer team Members and Their responsibilities.[7]

**Fig 1: Representing Responsible persons in TT**



Flowchart for technology transfer for process Optimization and Exhibit batches. [7]

**Description of Drug and material**



**Figure 3: Representing Structure of Levofloxacin**

Chemically speaking, Levofloxacin is known as (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl piperazine-1-yl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. Its molecular weight is 361.368 and its molecular formula is C<sub>18</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>4</sub>. (1), Its freely soluble in water, organic solvent ethanol, butanol, acetic acid and ethyl acetate. [17-19]

Pharmacology and MOA: Levofloxacin is a broad-spectrum antibiotic that is active against both gram positive and gram-negative bacteria. Its

**List of equipment's used for process as per specified by GMP.**

**Table no 1: Representing equipment used in Process**

Sr No	Stage of manufacturing	Equipment	Supplier	Qualification
1	All applicable stages	Weighing balance	Jaypan & metler	Qualified
2	Granulations	Rapid mixer granulator	Sainath	Qualified
3	Drying	FBD	Pam glatt	Qualified
4	Sizing	Combo mill	RP Products	Qualified
5	Sifting	Vibratory sifter	Gansons	Qualified
6	Blending & Lubrications	Conta blender	RP Product	Qualified
7	Compression	Rotator compression machine	Sejonj	Qualified

Process flow diagram and Critical process parameters which have to be optimized

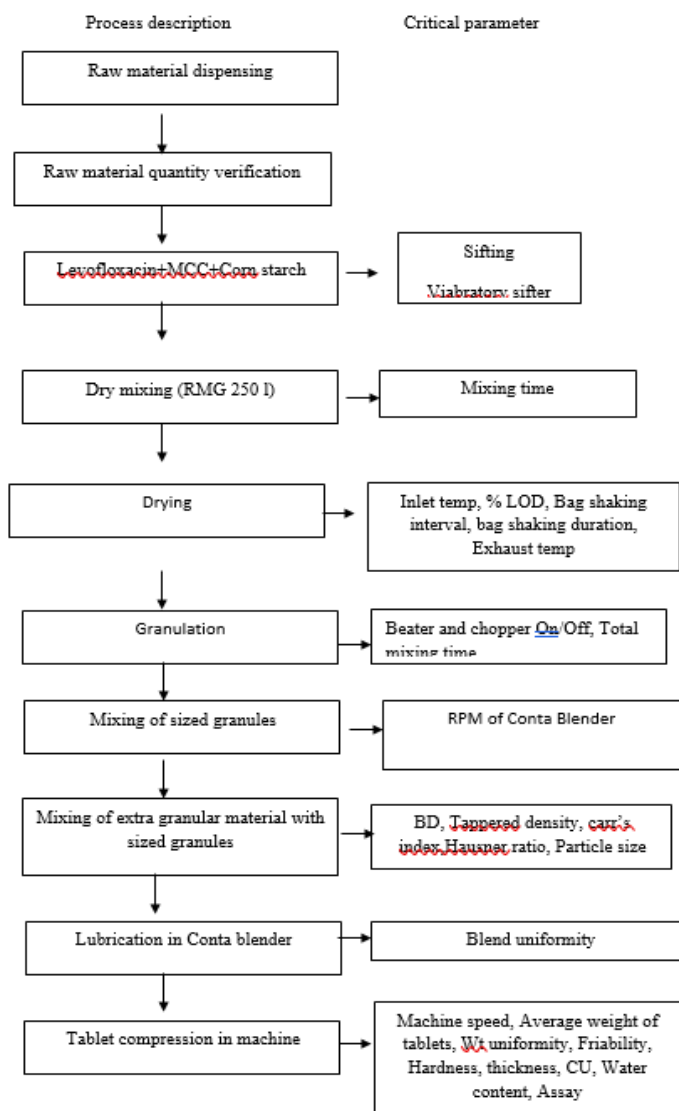
function by inhibiting DNA gyrase and thereby inhibiting cell division.

**Polymer profile:**

- 1) Croscarmellose sodium: Its Synonym is Crossed linked carboxymethylcellulose sodium and Chemical name Cellulose, Carboxymethyl ether. Its functional category is tablet and capsule disintegrant.
- 2) Hypromellose: Its Synonym is Benceel MHPC and Chemical name Cellulose Hydroxypropyl methyl ether. Its functional category is Bioadhesive material.

**MATERIAL AND METHOD:**

In manufacturing of Optimization batches, the active drug with raw material in specific grade are taken .It includes Levofloxacin hemihydrates, Lactose monohydrate, croscarmellose cellulose, hypermellose, microcrystalline cellulose, etc and the equipment's used for manufacturing of tablets.



**Figure 4: Representing Critical process parameters and manufacturing steps**

In manufacturing of Levofloxacin, initially the selection of vendor for raw material was done by R &D unit of industry Kandewali, Mumbai. They synthesized the kilo size batch in the supervision of TT Person. All the list of raw material and list of critical process parameter are collected in documentary form, the major documents are as follows

1) MMD (Master manufacturing documents): This document contains the list of raw material and manufacturing method. BMR was prepared by using MMD given by R&D.

2) DPAD (Drug product analytical Data): This document gives information about the analytical data like absorbance, Dissolution chromatographic data.

### **Manufactured of Optimization batches of Levofloxacin tablets 250 mg, 500 mg and 750mg.**

Common blend was prepared and bifurcated into three strength i.e 250,500 and 750mg respectively. 102Kg common blend prepared of Batch No EQJ20019, This was bifurcated into three strength as follows

**Table no 2: Representing First Optimization batch details**

Strength	Batch no	Batch size	No of Tablets
Levofloxacin 250mg	EQK20019	17 kg	50000
Levofloxacin 500mg	EQK20019	34kg	50000
Levofloxacin 700mg	EQL20019	51kg	50000

Similarly, Second batch EQJ20029 with batch size 102.00 kg. This was bifurcated into three strength as follows

**Table no 3: Representing Second Optimization batch details**

Strength	Batch no	Batch size	No of Tablets
Levofloxacin 250mg	EQK20029	17 kg	50000
Levofloxacin 500mg	EQK20029	34kg	50000
Levofloxacin 700mg	EQL20029	51kg	50000

Third batch EQJ20039 having common blend batch size is 318.240 kg and it is bifurcated into three strength as follows

**Table no 4: Representing Third Optimization batch details**

Strength	Batch no	Batch size	No of Tablets
Levofloxacin 250mg	EQK20039	53 kg	150000
Levofloxacin 500mg	EQK20039	106.0kg	150000
Levofloxacin 700mg	EQL20039	159.120kg	150000

## Results obtain in optimization batches

### 1. Dry mixing

**Table no 5: Representing % Blend uniformity in Optimization batches.**

Batches	Time of sampling	Location of sampling	%Blend uniformity
EQJ20019	5	Top front	101.4
	10	Top right	105.0
	15	Top back	100.7
EQJ20029	5	Top front	100.2
	10	Top right	100.2
	15	Top back	99.4
EQJ20039	5	Top front	100
	10	Top right	100.6
	15	Top back	100.1

After reviewing above data it was concluded that dry mixing to be done for 10 min in the exhibit batch.

Wet mixing is done in RMG Granulator and recorded the ammeter reading of impeller at the end of granulation point.

### 2. Wet mixing:

**Table no 6: Representing Granulator parameters in Optimization batches.**

Batches	Time	Optimized parameters
EQJ20019	03	Beater :slow Chopper : off
	03	Beater :slow Chopper : off
EQJ20029	04	Beater :slow Chopper : off
	04	Beater :slow Chopper : off
EQJ20039	04	Beater :slow



		Chopper : off
	04	Beater :slow Chopper : off

After reviewing above data it was concluded that WET mixing to be done by keeping Beater in slow, fast and slow speed with chopper remain off in throughout process, it gives optimum granules.

### 3. Drying

Drying of optimization batches was carried out in FBD and optimized the different parameters like inlet temperature, exhaust temperature, bag shaking interval duration, and % LOD.

**Table no 7: Representing % LOD in Optimization batches.**

Batches and location of sampling	Batch no and % LOD		
	EQJ20019	EQJ20029	EQJ20039
Left	2.7	2.8	2.8
Right	2.7	2.7	2.7
Center	2.7	2.7	2.7
Front	2.8	2.7	2.7
Back	2.7	2.8	2.8
composite	2.7	2.8	2.7

After reviewing above data it was concluded that %LOD was found NMT 1.2% .It was recommended for the exhibit batch.

### 4. Sizing:

The dried granule were milled through 1.2mm screen using combo mill with co mill screen at speed 550 rpm in first optimization batch and 250-350RPM in second and third optimization batch.

**Table no 8: Representing % LOD in Optimization batches.**

Batches and density	Batch no and % LOD		
	EQJ20019	EQJ20029	EQJ20039
Bulk density	0.617	0.61	0.82
Tapped density	0.769	0.79	0.62

It was found suitable to mill the dried granules through 1.2mm screen using Co-mill. The same was recommended for milling purpose in the Exhibit batch.

### 5. Prelubrication:

Prelubrication was done in V blender at 10+ 1rpm for mixing of extra granular material with sized granules. In that Microcrystalline cellulose, crospovidone, colloidal silicon dioxide was sifted through sieve through #40 then mix in the

optimization batches. In order to optimize the mixing time, mixing was carried out for 5, 10, 15 minutes. Following table indicate % of blend uniformity of collected from different sampling location in RMG.

**Table no 9: Representing % Assay of Blend uniformity in Optimization batches.**

Location of sampling & Minute	EQJ20019			EQJ20029			EQJ20039		
	5 Min	10Min	15 Min	5 Min	10 Min	15 Min	5 Min	10 Min	15 Min
Top Front	106.7	100.0	100.7	98.8	100.5	100.7	98.1	98.2	98.0
Top Left	104.45	104.3	102.5	99.3	99.3	100.6	96.1	96.0	98.6
Top Back	104.5	104.8	102.4	96.8	99.6	100.7	94.9	94.9	99.3
Top Right	104.5	104.8	100.4	98.6	100.8	99.3	96.1	96.1	99.9
Bottom Front	104.5	105.7	101.4	98.2	98.9	100.6	95.0	95.0	98.5
Bottom Left	104.0	102.8	103.5	98.2	99.7	101.2	95.9	95.9	99.8
Bottom Back	105.2	102.7	105.1	96.4	100.5	99.6	96.3	96.3	98.6
Average	104.7	103.8	102.5	98.1	99.6	100.5	96.3	96.3	99.0
%RSD NMT 5%	0.8	1.7	1.4	1.0	0.7	0.7	1.1	1.2	0.5

After reviewing above data it was decided to carry out Prelubrication for 10 minutes in the Exhibit Batch.

#### 6. Lubrication:

Pre lubricated blend was lubricated with magnesium stearate for 2 minutes in V Blender at 10+1 rpm. % Blend uniformity(% assay) was found within specification and satisfactory. Following table represent the data.

**Table no 10: Representing % % Assay Blend uniformity in Optimization batches.**

Sampling location & Time(Min)	EQJ20019	EQJ20029	EQJ20039
Top Front	103.6	103.1	99.5
Top Left	103.6	98.2	97.8
Top Right	101.8	98.9	98.5
Top Back	104.4	101.2	99.2
Bottom Front	103.4	98.0	97.5
Bottom Left	104.4	101.0	98.5
Bottom Back	103.2	99.6	97.89
Average	103.5	99.8	98.5
%RSD NMT 5%	1.7	0.7	1.2

All the data mentioned above, it was decided to carry out lubrication for 2 min in the exhibit batch.

#### 7. Compression:

Compression was performed on double rotary compression machine as per specification.

Following challenges were carried out during compression in optimization batches.

- Machine speed challenge test
- Hardness challenges test



In it three optimization batches were compressed and carried out the machine challenge and hardness test. At initially in first and second optimization batches sticking and picking defects is observed due to the moisture in the blend .After

keeping LOD NMT1.2% the problem was solved and fixed the machine RPM and Hardness in range. Following table represent the optimized parameters obtained in third optimization batches of Levofloxacin tablets.

**Table no 11: Representing Machine challenge and Hardness challenge test in Optimization batches.**

Parameters	EQK20039	EQL20039	EQM20039
Uniformity at Low RPM	1.6-1.5	2.0-1.4	2.0-1.4
Uniformity at At High RPM	1.4-1.2	1.5-1.5	1.5-1.5
Hardness at low RPM	84-100	157-167	157-167
Hardness at High RPM	85-97	133-177	133-177
Thickness low RPM	4.61-4.67	6.34-6.44	6.34-6.44
Thickness High RPM	4.56-4.60	6.32-6.40	6.32-6.40
Friability low RPM	0.2	0.2	0.2
Friability at High RPM	0.1	0.1	0.1
DT at low RPM	3 min 20 sec	6min 10 sec	6min 10 sec
DT at High RPM	3 min 40 sec	10 min 30sec	10 min 12sec
% Uniformity low RPM	100.0-102.6	94.2-103.9	94.2-103.9
% Uniformity RPM	100.4-101.9	97.7-102.4	97.7-102.4

## 8. Coating:

Coating of Levofloxacin tablets was carried out in SFC-100 Coating machine. It was processed in three stages, it include Preheating, coating and drying. Different coating parameters like inlet

temperature, Product bed temperature, Pan speed, spray rate, gun to bed distance and finally % eight gain was studied and finalized in exhibit batch of Levofloxacin.

### Summary of Parameters optimized and final for exhibit batch of Levofloxacin tablets

**Table no 12: Representing Summary of Parameters Optimized for Exhibit batch.**

Parameters	Exhibit Batch specification
Dry Mixing	10 min
Wet mixing	End point of granulation Beater 018-023& Chopper 001-002
Drying	LOD NMT1.2%
Sizing	1.2mm screen with Co mill
Pre lubrication	10 min
Lubrication	RSD NMT5%
Compression machine speed	250-750 mg tablet 15-70RPM
Hardness	250mg tablet 70-120N 500mg 120-180N 750mg 130-200N
Coating Parameters	
Inlet temperature(C)	50 $\pm$ 5
Product bed temperature(C)	40 $\pm$ 5
Pan speed	2-5 rpm
% Weight gain	3.0

## CONCLUSION



Levofloxacin 250mg, 500mg and 750 mg film coated tablets was prepared using FBE Granulation technology on lab scale size. This study was carried out through a systematic plan, critical process parameters were optimized in three optimization batches and parameters fixed in commercialization batch to produce stable and robust manufacturing process. The overall successful three consecutive batches of Levofloxacin film coated tablets verify the successful technology transfer from R&D to Manufacturing site.

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