Report On

Industrial Training at Pacific Pharmaceuticals Ltd.

By

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ID:16146012

An internship report submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

Department of Pharmacy

Brac University

September 2020

Declaration

It is hereby declared that

1. The internship report submitted is my own original work while completing degree at Brac University.
2. The report does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The report does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Syeda Tazia Sraboni
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Supervisor's Full Name & Signature:

Professor Dr.Eva Rahman Kabir
Chairperson, Department of Pharmacy
Brac University

Letter of Transmittal

Professor Dr. Eva Rahman Kabir

Chairperson,

Department of Pharmacy,

Brac University,

66 Mohakhali, Dhaka-1212.

Subject: Submission of the Industrial Training Report Titled “Industrial Training at Pacific Pharmaceuticals Ltd”.

Dear Madam,

It is an immense pleasure for me to submit to you the industrial training report titled “Industrial Training at Pacific Pharmaceuticals Ltd”. My main incentive was to prepare this report according to your guidelines and in accordance with your directions. I hope that I have done a satisfactory job considering my level of experiences and capabilities and have been able to relate the fundamental things with realistic applications.

Moreover, I am extremely thankful for the opportunity that you gave me to express my ability and I intently hope that you will like the work that I have done.

Sincerely yours,

_____

Syeda Tazia Sraboni

16146012

Non-Disclosure Agreement

This agreement is made and entered into by and between Pacific Pharmaceuticals Ltd and undersigned student at Brac University.

Acknowledgement

At first, I would like to thanks to Almighty God for his favors as I have got chance to complete the industrial training in Pacific Pharmaceuticals Ltd.

I would like to express our gratitude to all those who gave us the opportunity to complete this in-plant training. I want to give thanks to the Authority of Pacific Pharmaceuticals Ltd. for giving me permission to commence this in-plant training in the first instance, to do the necessary work and to use departmental data. I also thanks to the Professor Dr. Eva Rahman Kabir (Chairperson, Department of Pharmacy) Brac University, who gave and confirmed this permission and encouraged me to go ahead with our training.

My most warm thanks to Mr. Samir Chandra Audhya QA Manager, for his unfailing personal and professional support to me during in-plant training. Thanks to Mr. Dipankar Paul Asstt. Manager QC, Mr. Sonjoy Mohan Mozumder, Production Manager, Mr. Md. Faysal Ikbal , Deputy Manager Product Development Department. Mr. Manoj Kumar Sarkar Administration, Mr. Ekramul Haque Rokon Deputy Manager Engineering Section, also tried their best to train me properly.

I particularly acknowledge and give special thanks to my training coordinator Miss. Asma Akter Kakuli. For her stimulating suggestions and encouragement help in all the time of training and writing of this report.

I also thanks to the contribution of all Officers, Technicians, and Workers who tried their best to help me during in-plant training.

Syeda Tazia Sraboni
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Executive Summary

This is the report about in-plant training that we have completed in Pacific Pharmaceuticals Ltd.

Subject like Pharmacy demands practical knowledge in the own field. Industrial training program is one of the most important parts of a student studying in a dynamic subject like Pharmacy. For gathering complete knowledge about pharmacy there is no alternative for In-plant or industrial training program which must be accomplished by every student of pharmacy after his/her final year B. Pharm. examination. This training is conducted by different pharmaceutical industries in our country. By this training, each pharmacy student can achieve practical knowledge and they can correlate the theoretical knowledge with the practical knowledge. Thus he/she can develop him/herself completely for pharmacy related job.

For this purpose we have completed our in-plant training in Pacific Pharmaceuticals Ltd. which ensures manufacturing & marketing of essential medicines with highest quality by following GMP, GLP, cGMP, and ISO-9001 : 2008 (Quality Management System) & ISO 14001 : 2004 (Environmental Management System) by all the modern technologies. The main dosage form manufacturing by the respective company is solid as tablet & capsule, powdered as dry syrup and liquid as syrup, suspension & Semi solid as, ointment, cream. To maintain cGMP, every procedure & equipment have its own "STANDARD OPERATION PROCEDURE". My training program was from 20th August to 2nd September, 2020. During this period, I have visited in every section under the direct supervision of related officers.

Keywords: GMP, cGMP, ISO, GLP, EMS

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List of Acronyms

BMR	Batch Manufacturing Record
BOM	Bill of Materials
BPR	Batch packaging record
RM	Raw Materials
PM	Packaging Materials
GMP	Good Manufacturing Practice
GCP	Good Clinical Practice
SOP	Standard Operating Procedure
QS	Quality System
HVAC	Heat Ventilation Practice
QC	Quality Control
IO	Installation Qualification
LAL	Limulus Amoebocyte Lysate

Chapter 1

1.1 INTRODUCTION

Pharmacy is the science and technique of preparing and dispensing drug. It is a health profession that links health sciences with chemical sciences and aims to ensure the safe and effective use of pharmaceutical drugs.

Medicine is directly related to human life and therefore, its manufacturers have massive social responsibility of providing safe and effective medication. For this purpose, pharmaceutical industry develops, produces, and markets drugs or pharmaceuticals licensed for use as medications. Pharmaceutical companies can deal in generic or brand medications and medical devices. They are subject to a variety of laws and regulations regarding the patenting, testing, and ensuring safety and efficacy and marketing of drugs.

To gather the complete knowledge about pharmacy there is no alternative for the in plant or industrial training program which must be accomplished by every student of pharmacy department after the finishing of the final exam of B. Pharm course. This training is conducted by the pharmaceutical industries in our country. In-plant is very important in pharmacy education to achieve practical knowledge for every student. Its co-ordinates between theoretical and practical knowledge about pharmaceutical industry as well as pharmacy profession. Thus he/she can develop himself/herself completely for pharmacy related job. To be an industrial pharmacist every graduate must have a practical experience on developing formulation, manufacturing, quality control and industrial management.

Pacific Pharmaceuticals Ltd. gives service to the Nation & Mankind by manufacturing and marketing ethical finished pharmaceuticals having belief in super quality. Pacific Pharma ensures the proper way of manufacturing, documentation, validation of each part of single product & marketing of essential medicines with high quality by following cGMP by all the modern technologies.

.Leader in Oral Antidiabetic Sector For About One Decade. Pacific Pharma is one of the leading and fast-growing pharmaceutical companies in Bangladesh, involved in the service to the nation and mankind by manufacturing and marketing ethical finished pharmaceuticals having belief in super quality.Right from the inception, quality is the passion of Pacific Pharma. In the backdrop of increasingly intensive demand of quality products, Pacific Pharma today is

well equipped with state-of-the-art technological facilities complying cGMP having innovative spirit to build an image as a superior quality drug manufacturer.

Pacific pharma is the only pharmaceutical company which is marketing all pediatrics lifesaving drugs just at cost price.

Mission Vision:

Mission:

Service to the Nation & Mankind by manufacturing and marketing ethical finished pharmaceuticals having belief in super quality.

Vision:

Pacific Pharma today is driven by its vision not only to be the ICON in the country's pharma sector through ethical and pragmatic approach of marketing but also aspires to become one of the key players in the untapped pharmaceutical markets in Afro-Asian and neighboring countries.

1.2 Human Resources Department

The company represents a unique mix of experienced professionals with solid background in marketing & sales of medicines. More than 700 employees are enrolled in the company who are working in the factory (A devoted loyal workforce totaling around 150 people mans the factory, out of whom 55 qualified professionals are working in the Production, Quality Assurance and Product Development Department), different Sales Centers, Head Office and in the Field (Over 350 highly professional marketing personnel of Pacific Pharma are representing the company in every important area of Bangladesh to ensure promotion of it's products).

1.3 Marketing

Marketing is the core of a company and teamwork is the secret of marketing success, which has become a part of the company's culture. Teamwork shapes the future of the company's marketing as well as the future of Pacific itself. Today because of the high level of competence, the marketing team of Pacific represents the best that a pharmaceutical company can strive for.

It represents a unique mix of experienced professionals with solid background in marketing & sales of medicines. Many of the company's products now hold coveted positions with the major market shares in their respective therapeutic groups.

The Marketing Division of Pacific consists of

Sales Department
Product Management Department
Marketing Surveillance Department
Market Information Services Department
Training Department.

1.4 Plant

Quality Policy

The management of Pacific Pharma is committed to implement the following quality policies in all levels to attain super quality products:

 To attain level of excellence in product quality with the acquisition of state-of- the-art equipment and facilities.

 To enhance skills, potentialities, and competency of human resources through planned training program.

 To comply strictly with the WHO recommendations on cGMP regulations.

 To consistently achieve customers' satisfaction by ensuring steady quality of products and services.

 To procure most of the raw materials from FDA approved vendors who maintain Drug Master Files (DMF).

1.5 Production

The newly built plant of Pacific Pharma at Kanchpur has the arrangement for manufacturing products in various dosage forms that include facilities to produce Tablets, Capsules in Hard Gelatin Shells, Soft Gelatin Capsules, Liquids, Dry Syrups and Palletizations. The operations relating to the manufacture, processing and packaging of penicillin products have been designed to be carried out in a separate building equipped with segregated facilities. The

arrangement for operations relating to the manufacture, processing and packaging of products including the requisite utility facilities belonging to Cephalosporin's and General Groups have been kept segregated and independent from each area section-wise having individual airlock system.

Distribution

Distribution Channel

Distribution is one of the vital parts of any marketing organization. It plays a very significant role for achieving the desired sales growth. The distribution system of Pacific consists of 03 (Three) depot offices at Dhaka, Comilla & Bogra and sales offices at district headquarters in the country.

Dhaka Depot (Central)

5, Wyre Street

Wari, Dhaka - 1203

Comilla Depot

Kandirpar, Comilla

Bogra Depot

Moiz Miar Bagan Bari,

Kanchgari.

Head Office:	**Factory/Plant:**
5, Wyre Street Wari, Dhaka - 1203	Plot No: 11 & 12 BSCIC Industrial Estate Kanchpur, Sonargaon, Narayangonj, Bangladesh

Chapter 2

PRODUCTION

- 1.2 Tablet Section.
- Liquid Section (General & Antacid)
- Capsule Section (General & Cephalosporin)
- Soft Gelatin Capsule & Semi Solid Section (Cream, Ointment & Gel)
- Dry Syrup / Suspension Section (General & Cephalosporin)
- Penicillin Section (Capsule, Dry Syrup & Suspension)

Tablet section

2.1 Tablet:

Tablet may be defined as the solid unit dosage form medicament or medicaments with or without diluents and prepared either by molding or by compression. They vary greatly in shape, size and weight which depends upon the amount of medicament and the mode of administration.

Most commonly the tablets are disk shaped with convex surface, but they are also available in special shapes like round, oval, cylindrical, oblong, square, triangular etc. Tablet for oral administration may weight from 0.2 to 0.8 gm including the diluents.

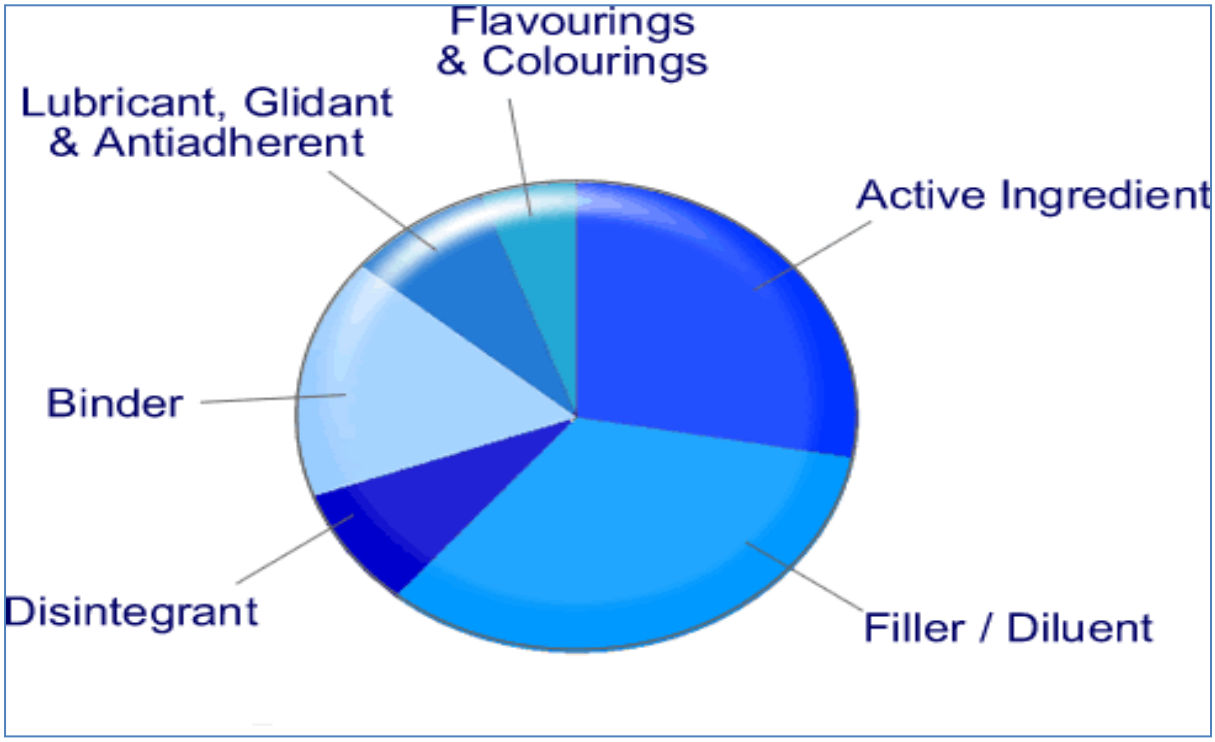


Fig1: Common ingredients of a tablet

2.2 Tablet Design and Formulation:

1. **Diluents:** when the quantity of the drug for an individual dose is very small and it is not practicable to compress such small amount in the form of a tablet then the inert substance which are added to increases the bulk of powders to be easily compressed are known as diluents.
   example: lactose, sodium chloride, starch, mannitol etc.

2. **Binders:** some substance which are available in the crystalline form can be compressed directly but majority of the drug will have to be converted to granules before compression. The agents used powdered substance are known as binders.
   example: acacia, gelatin, methyl cellulose, tragacanth etc.

3. **Granulating Agents:** Granulating Agents are the substance which are added to powders during granulating process to convert fine powders into granules. The quantity of proper granulating agent to be incorporated is critical.
   example: water, tragacanth, acacia, syrup, alcohol etc.

4. **Disintegrating Agents:** Disintegrating agents or disintegrators are the substance or a mixture of substances which are added to tablets to facilitate their disintegration or breaking apart into small particles in GIT after administration, thus facilitating dissolution. Generally, two types of disintegrating are used:
   a) Substance which swells up when they meet moisture.
   b) Substance which reacts with effervescence when they meet moisture.
   example: maize starch, potato starch, cmc, veegum, agar etc.

5. **Lubricants:** Lubricants are the substance which are added to granules before compression to improve the flow of granules from the hopper to the die cavity by reducing interparticle friction, to present adhesion of the powders to the surface of dies and punches thus reducing wear and tear of dies and punches and to facilitate the ejection of the tablet from the die cavity after compression.
   example: magnesium stearate, calcium stearate, stearic acid talc etc.

6. **Glidants of flow promotes:** Glidants are intended to promote flow of the tablet granulation or powder materials by reducing the interparticle friction. The most used glidants are:

   Example: talc, corn starch, aerosol etc.

7. **Coloring Agent*:*** the use of colors and dyes in tablet making has served three purposes:
   - ***a)*** Distinguishing of color drugs.
   - ***b)*** Product identification.
   - ***c)*** Production of a more elegant product.

   example: FD & C Red No. 2(amaranth), FD & C Green No. 3 (Green) etc

8. **Flavoring Agent:** flavors can be used to mask unpleasant taste and odor of active ingredients and improve the elegance to the tablet. flavoring agents are added to all lozenges, chewable tablets, and effervescence tablets.

   example: Orange oil, Cinnamon oil, Methanol, Vanillin etc

9. **Sweetening Agent:** Sweetening agents are added to the tablets which required to be dissolved in the buccal cavity. To make the ingredient more palatable. Especially in chewable.

   example: mannitol, sucrose, lactose etc

In tablet production there are several steps involved which are following:

1. Dispensing
2. Weighing
3. Dry mixing
4. Wet mixing
5. Wet granulation
6. Drying
7. Dry granulation
8. Lubrication & Blending
9. Discharge
10. Coating
11. Blistering (Primary packaging)
12. Secondary Packaging

2.3 Granulation

Granulation may be defined as a size enlargement process which converts small particles into physically stronger and larger agglomerates to facilitate compression for the production of tablet. All the materials are received from the dispensing unit and granulation is performed. For suitable granulation, it is required to have 30-40% powder and 60-70% granules and also 15% moisture in compressing particles.

2.4 Purposes of Granulation:

1. To produce tablets of appropriate size.
2. To prevent segregation of the constituents in the powder mix.
3. To improve the flow properties of the powder mix.
4. To improve compression nature of powder.

Method of Preparation Tablets in Pacific Pharmaceuticals Ltd.

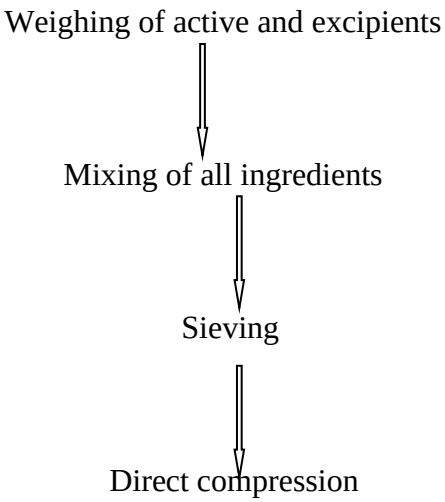
There are three methods by which compressed tablets can be prepared.

1. Direct Compression.
2. Dry Granulation.
3. Wet Granulation.

Fig 2:FBE-250

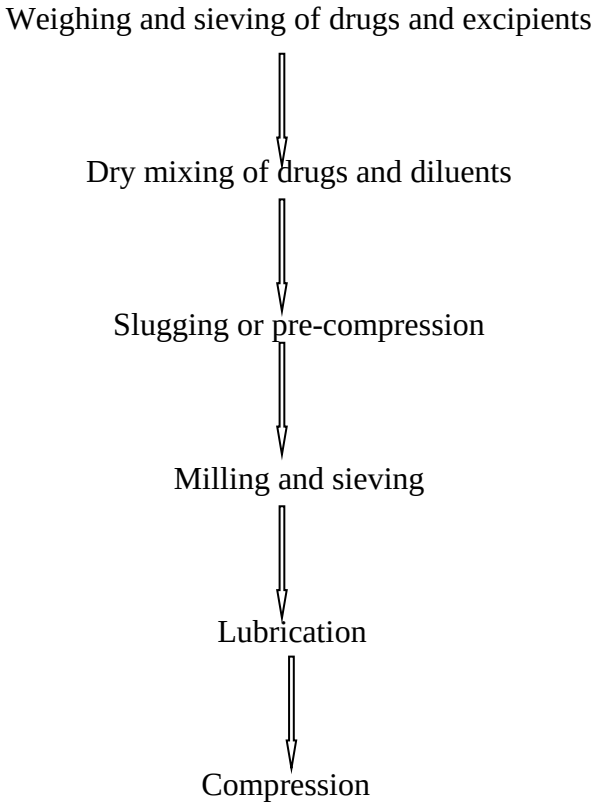
Direct Compression:

The materials which are available in crystalline form and have free flowing and binding characteristics can be compressed directly. But most of the drugs cannot be compressed easily in this way because sometimes they produce tablets which may not disintegrate. To overcome this difficulty directly compressible vehicles can be the drug and compressed. Such vehicles include spray dried lactose, mannitol, microcrystalline cellulose, calcium phosphate etc. The drugs which can be compressed directly are sodium chloride, sodium bromide, ammonium bromide, methenamine etc. these materials possess necessary cohesive and flow properties thereby they can be easily compressed.



2.5 Dry Granulation

This method is also known as slugging, precompression or double compression method. This process is used when the product needed to be granulated may be sensitive to moisture and heat. Dry granulation. Two methods are used for dry granulation. The more widely used method is slugging, where powder is recompressed, and the resulting tablet or slug are milled to yield the granules. The other method is to recompress the powder with pressure rolls using a machine.



2.6 Wet Granulation

This is most widely, and general method used in preparation of tablets. In this method granulation meets all the qualities required for a good tablet. Materials which are destroyed by moisture and excessive heat cannot be prepared by this method.

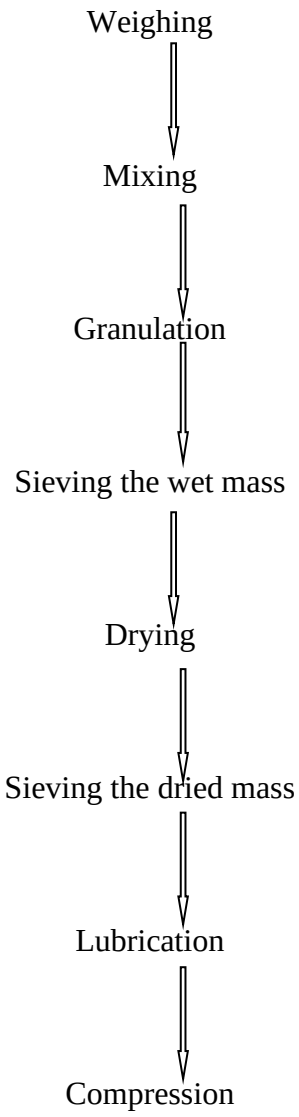


Table 1: Used Machineries at Pacific Pharma. during granulation:

Serial no.	**Name of machine**	**Source**	**Purpose**
01	Fluid Bed Equipment (FBE), Section 1: 125L, Section 2: 250L, Section 3: 500L.	P+am Glatt, India.	For granulation.
02	Multimill Cum Vibro Shifter (Section 3)	MYTH Industries, Bangladesh.	Size reduction & Seiving.
03	Paste Maker	MYTH Industries, Bangladesh.	Make slurry for granulation.
04	Vibro Shifter	MYTH Industries, Bangladesh.	For Seiving.
05	Multimill	MYTH Industries, Bangladesh.	Size reduction.
06.	Drum dryer	MYTH Industries, Bangladesh	For mixing.
07	Cone blender	MYTH Industries, Bangladesh.	For lubrication.

Diagram of Tablet Compression:

Granules (previously made)

↓

Transfer of granules in the Hopper of tablet press machine

by hand or auto powder/granules loader

↓

Rising of upper punch & dropping of lower punch

↓

Filling of die cavity through feed frame

↓

Removal of extra granules by scrape off plate

↓

Coming down of upper punch for compression to produce tablet

↓

Raising of both upper & lower punches to certain extent

↓

Ejection of tablet with the help of take-out plate

↓

Conventional Uncoated Tablets of desired shape and size

Fig 3: *Cadpress-II*

Table 2:Compression Machineries :

Serial no.	Name of machine	Source
01.	Cadpress-II (Section 3)	Cadmach, India.
02.	Rimek, Unik-I FC (Section 2)	India.
03.	Cadmach, CMB 40 (Section 1)	India.
04.	Clit-27 Station (Section 1)	India.

2.6 Manufacturing defects in Tablet:

During the routine production of tablets so many defects arise with the finished tablets which may be due to either some faults in the formulation or in the tableting equipment and sometimes due to both reasons. These defects are described below:

Problems	Causes	Remedy
01. Binding in the die	I. Poor lubrication. II. Low flow properties.	I. Uniform Lubrication. II. Uniform drying.

02. Capping & Splitting	I. Capping is caused due to air in the granule II. Wear & tear of punches and dies.	I. Reducing the speed of the machine. II. Proper granules and required number of fine powders must be used to avoid capping.
03. Picking & Sticking	I. Spray rate too high II. Inadequate drying condition III. Pan speed too low IV. Inadequate atomization of coating liquid V. Poor distribution of coating liquid	I. Decrease spray rate. II. Increase drying condition III. Increase pan speed. IV. Increase atomizing air pressure/volume.
04. Weight Variation	I. Poor flow of granules to the die. II. Due to size variation. III. Poor lubrication.	I. Uniform particles size. II. Increased flow properties.
05. Mottling	I. Different colors in drugs & excipients. II. Over drying.	I. Drying at low temperature. II. Changing the solvent system

2.7 Tablet Coating

Coated tablets are tablets covered with one or more layers of mixtures of various substances such as natural or synthetic resins, gums, gelatin, inactive and insoluble fillers, sugars, plasticizers, polyols, waxes, coloring matter authorized by the competent authority and

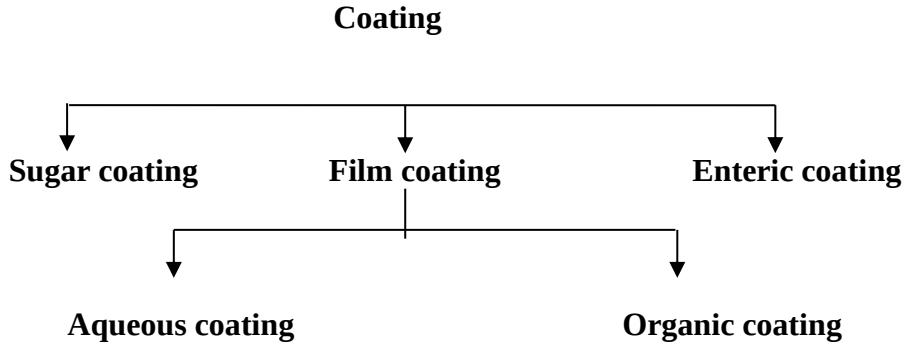
sometimes flavoring substances and active substances. The substances used as coatings are usually applied as a solution or suspension in conditions in which evaporation of the vehicle occurs. When the coating is a very thin polymeric coating, the tablets are known as film-coated tablets.

Reasons for coating tablets:

To improve the pharmaceutical elegance of the product by use of special colors.

- To mask the unpleasant taste, odor, or color of the drug.
- To control the release of the drug from the tablet.
- To provide physical and chemical protection for the drug.
- To protect moisture sensitive drugs from moisture.
- To control dust of the tablet.
- To protect the drug from the gastric environment of the stomach with an acid resistant enteric coating.
- To incorporate another drug or adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
- To improve the pharmaceutical elegance by use of special color or contrasting printing.

Classification of Coating: Mainly three types of coating. They are as follows:



For coating following process are done in Pacific Pharmaceuticals Ltd.

a. Film coating materials:

i. Hydroxy propyl methyl cellulose

ii. Polyethylene glycol

iii. Methylene chloride

b. **Enteric coating materials:**

❖ **Sub-coating:**

i. Aqua-p mix

ii. Isopropyl alcohol (IPA)

iii. Methylene chloride

❖ **Top coating**:

1. Acryl eze

Fig 4: *Neocota (coating machine)*

Important critical parameters of coating solution:

- Pump speed
- Pan Rotation
- Bed Distance
- Negative Pressure
- Inlet Air Temperature
- Outlet Air Temperature
- Atomizing Air Pressure
- Fluid Return Volume
- Nozzle Distance from the Tablet Bed.

Table 3: Coating machineries:

Serial no.	Name of machine	Source
01.	Gansons (Section 1)	India.
02.	Neocota-36 (Section 2)	India.
03.	Neocota-48 (section 3)	India.
04.	Colloidal Mill	Cadmach, India.

Common problems associated with tablet coating:

1. **Logo bridging:**

Cause:

I. Inadequate adhesion of film coating
II. Inadequate design of logo (e.g. too detail/fine logo)

Remedy:

I. Modify core formulation to include more hydrophilic ingredients
II. Increase core porosity
III. Using formulation with increased adhesion property.
IV. Increase area within the embossing and modified angles.

2. **Core erosion:**

Cause:

I. Inherent softness or high friability of core.
II. Excessive pan speed in coating process.
III. Spray rate too low.
IV. High sensitivity of core to moisture as coating is applied.

Remedy:

I. Increase mechanical strength of core.
II. Decrease pan speed.
III. Increase spray rate.

3. **Edge chipping/erosion:**
4. **Cause:**

I. Low mechanical strength of coating
II. Excessive pan speed
III. Low solid content in coating liquid
IV. Low spray rate
V. Sharp edges on tablets
VI. Worn tablet punches

Remedy:

I. Using formulation with increased mechanical strength
II. Decreased pan speed
III. Increase solid content in coating liquid
IV. Decrease spray rate
V. Use modified punch design

5. Picking & sticking:

Cause:

I. Spray rate too high
II. Inadequate drying condition
III. Pan speed too low
IV. Inadequate atomization of coating liquid
V. Poor distribution of coating liquid

Remedy:

I. Decrease spray rate.
II. Increase drying condition.
III. Increase pan speed.
IV. Increase atomizing air pressure/volume.
V. Increase number of spray gun.

6. Cracking:

Cause:

I. Low mechanical strength of coating, exacerbated by inadequate plasticization, excessive pigmentation.
II. Core has significantly different thermal expansion characteristics than coating.
III. Extended strain relaxation of core after compaction.

Remedy:

I. Selecting formulation with increased mechanical strength and elasticity properties.
II. Avoid use of mineral type fillers (e.g. $CaCO_3$, $CaSO_4$, $MgCO_3$ etc.)
III. Extend holding period of tablets prior to submitting them to coating process.

7. Peeling:

Cause:

I. Low mechanical strength of coating
II. Poor adhesion of coating to tablet surface

Remedy:

I. Using ingredients of improved mechanical strength.
II. Using ingredients with improved adhesion properties.

8. Orange peel/roughness:

Cause:

I. Viscosity of coating liquid is too high
II. Poor atomization of coating liquid
III. Excessive drying condition
IV. Over wetting (causing coating too rub)

Remedy:

I. Decrease solid content of coating liquid
II. Increase atomizing air pressure/volume
III. Decrease inlet air temperature/flow rate
IV. Decrease spray rate

9. Twinning:

Cause:

I. Spray rate too high

II. Pan speed too low

III. Inappropriate tablet shape

Remedy:

I. Decrease spray rate

II. Increase atomizing efficiency

III. Increase pan speed

IV. Select new tablet shape that decrease chances of flat surfaces coming into contact during application of coating liquid. (e.g. avoid capsule shape tablet with thick side wall)

10. Tablet-to-tablet color variation:

Cause:

I. Too little coating applied

II. Inadequate mixing of tablet during coating

III. Poor opacity (or hiding power)

IV. Solid content of coating liquid too high

V. Insufficient number of spray gun

Remedy:

I. Increase quantity of coating applied

II. Increase pan speed/increase improve baffle system

III. Reformulate coating with respect to colored ingredients or use an opacified white pre-coat.

IV. Decrease solid contents of coating liquid.

V. Increase number of spray gun.

Flow Chart of Blister Packing:

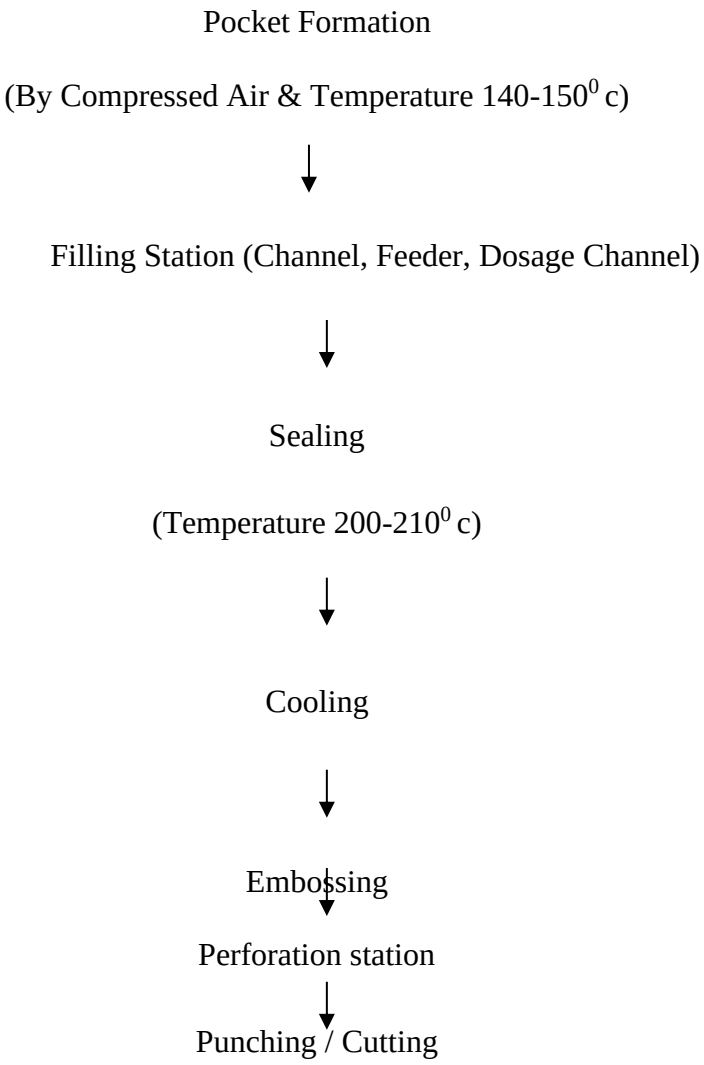


Table 4: Blister Machineries used in Tablet Section:

Serial no.	Name of machine	Source
01.	Rapid Pack, RP-230 CT (Section 3)	India.
02.	Rapid Pack, RPE-250 (Section 2)	India.
03.	Rapid-Pack, MACH 1$^+$ (Section 1)	India.

We observed the following tablets in Tablet section:

Brand name	Generic name
01. Metfo Tab. 500mg	Metformin Hydrochloride 500mg
02. Metfo Tab. 850mg	Metformin Hydrochloride 850mg
03. Sugatrol Tab.	Acarbose
04. HPR-DS	Mefenamic Acid
05. Cal-D	Cholecalciferol
06. Cetam Tab.	Paracetamol

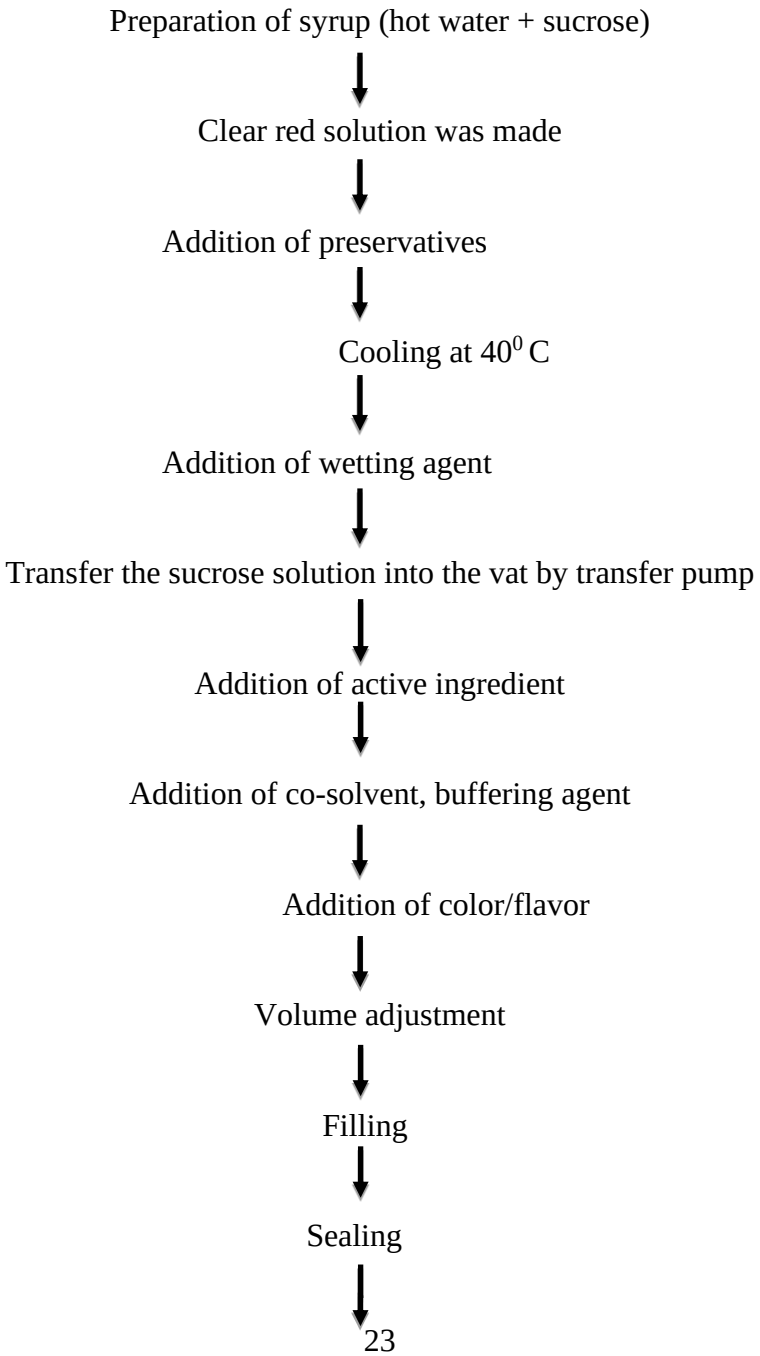
2.7 LIQUID SECTION

A solution is a clear, homogeneous mixture that is prepared by dissolving a solid, liquid or gas in another liquid.

Syrup:

Syrup is a viscous concentrated sugar, such as sucrose, in water or other aqueous liquid, combined with other ingredient, such a solution is used as a flavored vehicle for medications.

Diagram of Syrup Preparation:



Labeling

↓

Packaging

Suspension:

Suspension are the biphasic liquid dosage form of medicament in which the finely divided solid particles ranging from 0.5 to 5.0 micron are suspended or dispersed in a liquid or semi-solid vehicle. The solid particles constitute the discontinuous phase whereas the liquid vehicle constitutes the continuous phase. Suspension are mainly used for oral administration.

Preparation of Paste for Suspension:

Glycerin & RO water taken into a vat

↓

Emulsifier on

↓

Dispersed & Suspending agents mixed

↓

Preservatives

↓

Paste Prepared

Cooling for 7-8 hour

Preparation of Suspension:

Cool Syrup (Previously prepared for suspension)

↓

Addition of active ingredient + Paste into a vat

↓

Sweetening Agents

↓

Coloring/Flavoring Agents

↓

Suspension prepared.

↓

Volume adjustment

↓

Filling

↓

Sealing

↓

Labeling

↓

Packaging

Excipients used in Liquid:

a. Flavoring agent: orange flavor, banana flavor.
b. Emulsifying agents: avicel RC 591, CMC etc.
c. Coloring agents: eurocent ponceau 4R color
d. Sweetening agents: sucrose, lactose, aspertin , Sorbitol etc.
e. Suspending agents: CMC, Veegum.
f. Preservatives: MPS, Sodium benzoate, PPS.
g. Antifoaming agents: polysorbate 80 .

Problems Associated with Oral Liquid Dosage Form:

- Microbial contamination
- Sedimentation
- Phase separation
- Cake formation
- Color may be changed
- P^H Change
- Potency
- Viscosity

Table 5:Instruments used in Liquid Section

Name of machine	**Manufacturer**	**Purposes**
01. Vat (100 L, 200 L, 300 L , 400 L, 500 L, 2000 L)	MYTH Industries, Bangladesh.	To Mixed ingredients
02. Online Filling & Sealing Machine	ROTOFIL, India	Bottle washing, drying, filling, sealing, labeling & packaging
03. Sealing machine	MYTH Industries, Bangladesh	Seal bottle.
04. Double Nodule filling machine	MYTH Industries, Bangladesh	Filling bottle
05. Bottle Dryer	MYTH Industries, Bangladesh	Dry bottle
06. Inline Homogenizer (2000 L)	Bectochem, India	Mixer

07. Paste Maker	MYTH Industries, Bangladesh	Hot water, glycerin etc
08. Colloidal mil	Clit , India	Mixer
09. HAPA filter	India	Air filter
10. Emulsifier	MYTH Industries, Bangladesh	Emulsifying

Condition required during Manufacturing of Liquid:

- **Relative Humidity**: Not more than 55 %
- **Temperature**: Below 30°C

Liquid we observed:

Product	**Active**
01. Livax Solution	Lactulose conc. Solution
02. Broxolit P/D	Ambroxol HCl
03. Fexodin suspension	Fexofenadine
04. Magmil suspension	Magnesium Hydroxide
05. Cetum suspension	Paracetamol

OBSERVATION:

- Cleanliness & environment are strictly maintained.
- Temperatures are maintained.
- Purified water is used.

- Microbial contamination is maintained.
- Separate bottle washing and drying room.
- All machines are operated according to standard operating procedure (SOP).
- Machines are calibrated timely.

2.8 CAPSULE SECTION

Capsule:

These are solid dosage form of medicaments, in which drugs is enclosed in a practically tasteless, hard, or soft soluble container or shell made up of a suitable form of Gelatin.

Several categories of capsules are:

1. Hard Gelatin
2. Soft Gelatin
3. Special Types of Capsules

    a) Enteric Coated Capsules
    b) Sustained Release Capsule
    c) Rectal Capsules
    d) Capsules for Packing of Ophthalmic Ointments

Capsule Shell:

These capsules are made up of gelatin blends, small number of certified dyes, plasticizers, and preservatives.

Gelatin:

Gelatin is heterogeneous product derived by hydrolytic extraction of animal's collagen. The sources of gelatins including animal bones, hide portions and frozen pork skin.

There are two basic types of gelatin

TYPE A:

Derived from acid treated precursor that exhibits an iso-electric point at pH-9. It is manufactured mainly from pork skin.

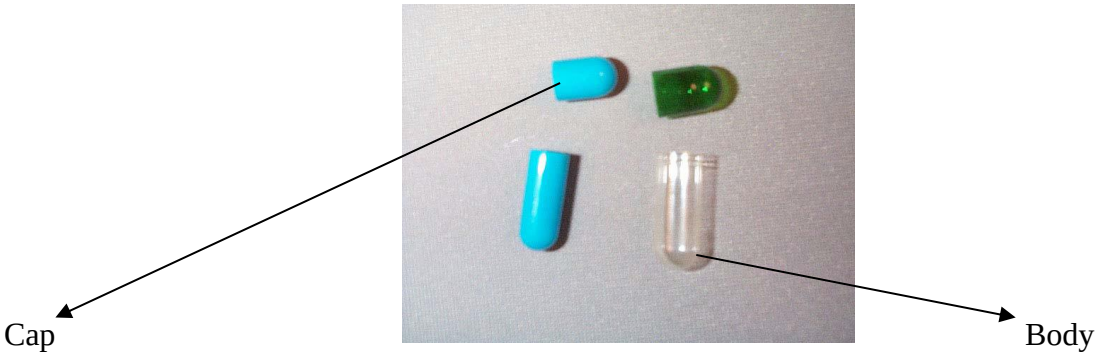
TYPE B:

Derived from alkali treated precursor that exhibits an iso-electric point at pH-4.7. It is manufactured mainly from animal bones.

Hard Gelatin Capsule:

Hard gelatin capsules are used for filling the solid substance. Hard gelatin capsule shells are made up of two cylindrical halves, one slightly large in diameter but Shorter in length this piece is called cap and one slightly short in diameter but large in length is called body. These capsules are usually made up of a base containing plasticizers and water. This base also contains preservatives, colors, flavors and sugars. Hard gelatin capsule may fill with pellets or placebo.

Parts of Hard Capsule



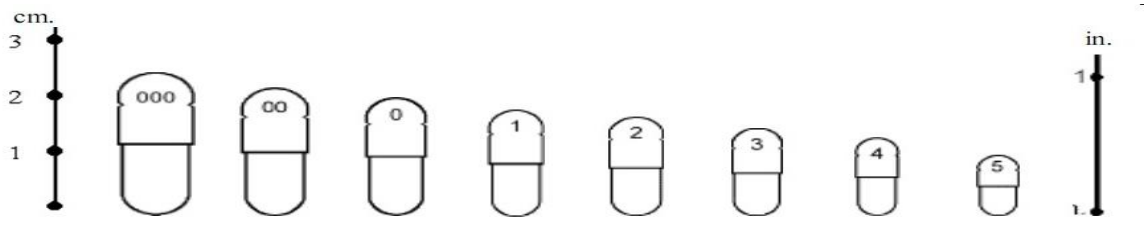


Fig: Shapes of Capsule.

a. The largest size of the capsule is No: 000.
b. The smallest size is No: 5.
c. The standard shape of capsules is traditional, symmetrical bullet shape.

Table 6: Size of Capsules

Size	Volume in ml	Size in mm
000	1.37	26.3
00	0.95	23.7
0	0.68	21.8
1	0.50	19.2
2	0.37	18.3
3	0.30	15.3
4	0.21	14.7
5	0.15	11.9

Hand operated hard gelatin capsule filling:

Empty Capsules are filled into loading tray

↓

Then placed over the bed

↓

By operating the handle capsule bodies are locked and caps are separated in loading tray by operating the lever.

↓

Weighted amount of the drug to be filled

↓

Place the caps holding tray in position and press

↓

Unlock the caps and bodies of the capsules

↓

Remove the loading tray and collect the filled capsules in a tray

Fig 6: *hand filling machine & Polish Machine*

Four size hard gelatin capsules are manufactured in pacific pharmaceuticals:

- 00
- 0
- 1
- 2

Fig 7: Automatic Capsule Filling Machine (Pam-

Table 7: Machineries used for Hard Gelatin Capsules & Cephalosporin Capsules:

Name	Source
01. Auto Loader	Pharma Chem Industries, India
02. Hand Filling Machine	Pam Pharmaceutical & Allied Machinery Company Pvt. India
03. Automatic Capsule Filling Machine (Pam-AF 90T)	ACG Pam Pharma Technologies Pvt. Ltd. India

04. Automatic Capsule Filling Machine (Pam-AF 25T)	ACG Pam Pharma Technologies Pvt. Ltd. India
05. Octagonal Blender	Sams Machine Tools, India
06. RPE-250 (Blister Machine)	Rapid-Pack, India
07. Polish Machine	Pam Pharmaceutical & Allied Machinery Company Pvt. India
08. Pam Pac (Blister Machine)	Pam Pac Machines Ltd. India

Observed Product:

1. Prazo 20 mg
   Active: Omeprazol 20 mg.
2. Trifix 200 capsule
   Active: Cefixime trihydrate.

Soft Gelatin Capsule & Semi Solid Section (Cream, Ointment & Gel)

A.Soft Gelatin Capsule:

Soft gelatin capsules are single unit dosage form consisting of a flexible shell and normally a semi liquid or liquid filling. The term 'Soft gelatin capsules' is commonly abbreviated to 'Soft gels'

Typical shapes and fill volumes of soft capsules:

Shape	Typical fill Volume (ml)
Round	0.05-6 (mainly small volumes)
Oval	0.05-7 (mainly large volumes)

Oblong	0.1-20
Torpedo-shaped	0.1-20
Tube-like	0.1-30 (mainly large volumes)

Manufactured shapes in Pacific Pharmaceuticals:

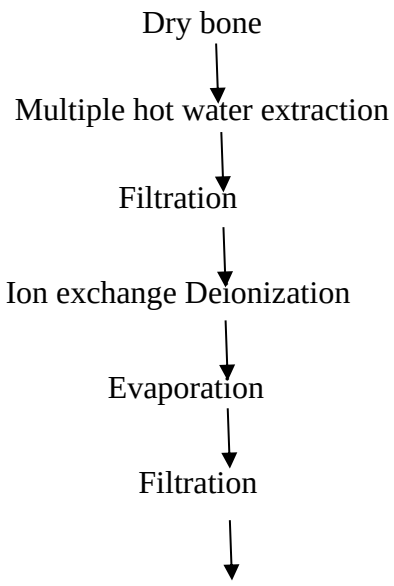
01. Oval
02. Oblong

Formation of Soft gelatin:

Typical soft gels shells may contain other components than gelatin mentioned here as per requirement of the specific formulation:

03. Gelatin: Most commonly Type B is Used.
04. Plasticizer: Glycerin, sorbitol, propylene glycol etc.
05. Opacifiers: Titanium dioxide etc.
06. Flavors
07. Preservatives
08. Sugars: For chewable soft gels.

Manufacturing of Soft Gelatin:



Final concentration

↓

Sterilization

↓

Polish filtration

↓

Chilling to set point

↓

Extraction

↓

Drying

↓

Milling

↓

Blending and packing.

Soft gelatin capsules we observed:

- Norad SG capsule
- E Soft capsule

Capsule Drying room condition:

Tem: 22-24^{0} c

Humidity: 18-20%

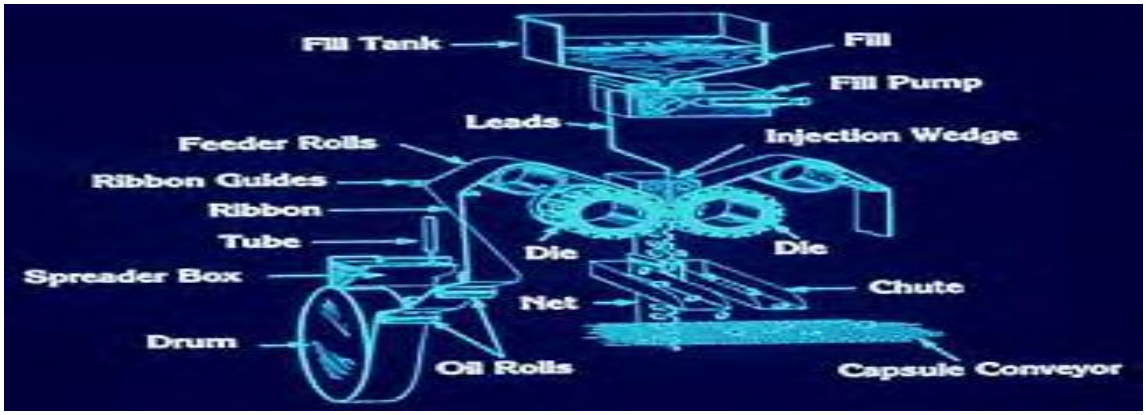


Fig 8: *Encapsulating Machine*

Table 8:Machineries used in Soft Gelatin Section:

Name	**Source**
01. Reactor / vat 200 L	MYTH industries, Bangladesh
02. Chiller machine	Masel,
03. Colloidal mill	Cadmach, India
04. Emulsifier	Myth industries, Bangladesh
05. Vat	Myth industries, Bangladesh
06. Triple Roller	India
07. SS vessel	Myth industries, Bangladesh
08. Plamtary mixer	India
09. Encapsulating Machine	Softesule private Ltd. India
10. Polisher	SMT, India
11. RP-250 PDA (Blister machine)	Rapid Pack, India

B.Semi-Solid (cream, ointment, and gel)

Ointment and Cream:

Ointment are semi solid preparations intended for topical application such as to provide protective and emollient effects on the skin or carry medicaments for treating certain topical ailments, to deliver drugs into eye, nose, vagina, and rectum.

Cream are water-incorporated less greasy ointments that are used to provide protective and emollient effects or deliver drugs to surface or interior layers of skin, rectum, and vagina.

Uses:

a) Tropical ointments and creams.
b) Ophthalmic ointments and creams.
c) Vaginal ointments and creams.
d) Rectal preparation.

Fig9: Fully automatic ointment cream manufacturing machine

Formation:

- Drug
- The base
- Stabilizer
- Preservatives
- Levigating agents

Manufacture:

Usually, levigating and fusion methods are employed for incorporating formation components into the base.

- Levigation involves simple mixing of base and other components over an ointment slab using a stainless-steel ointment spatula.
- A fusion process is employed only when the components are stable at fusion temperatures.

Ointments and creams containing white wax, yellow wax, paraffin, stearyl alcohol and high molecular weight PEGs are generally prepared by both levigation and fusion processes.

Observed ointments and creams are:

- Scabfre Cream

Active: Permethrin

Gels:

Gels are semisolid preparations that contain small inorganic particles or large organic molecules interpenetrated by a liquid. Gels made of inorganic materials are usually two-phase systems where small discrete particles are dispersed throughout the dispersion medium. When the particle size of the dispersed phase is larger, they are referred to as magmas. Gels made of organic molecules are single phase system, where no apparent physical boundary is seen between the dispersed phase and the dispersion medium.

Gelling Agents:

Many gelling agents are commercially available for the preparation of pharmaceutical gels. The following section lists some pharmacopeial gelling agents.

- Alginic acid
- Bentonite
- Calcium CMC
- Sodium CMC
- Carrageenan
- Gelatin
- PVA
- MC
- HEMC
- Propylene carbonate (PC)
- HPC
- HEC
- Glyceryl monooleate(GMO)
- Tragacanth etc.

Preparation:

Gels are relatively easier to prepare compare to ointments & cream. In addition to the gelling agent, medicated gels contain drug, antimicrobial, preservatives, stabilizers, dispersing agents and permeation enhancers. Some of the factors given below are essential to obtain a uniform gel preparation.

- Oder of mixing
- Gelling medium
- Processing conditions and duration of swelling
- Removal of entrapped air

Table 9: Machineries used in Semisolid Section:

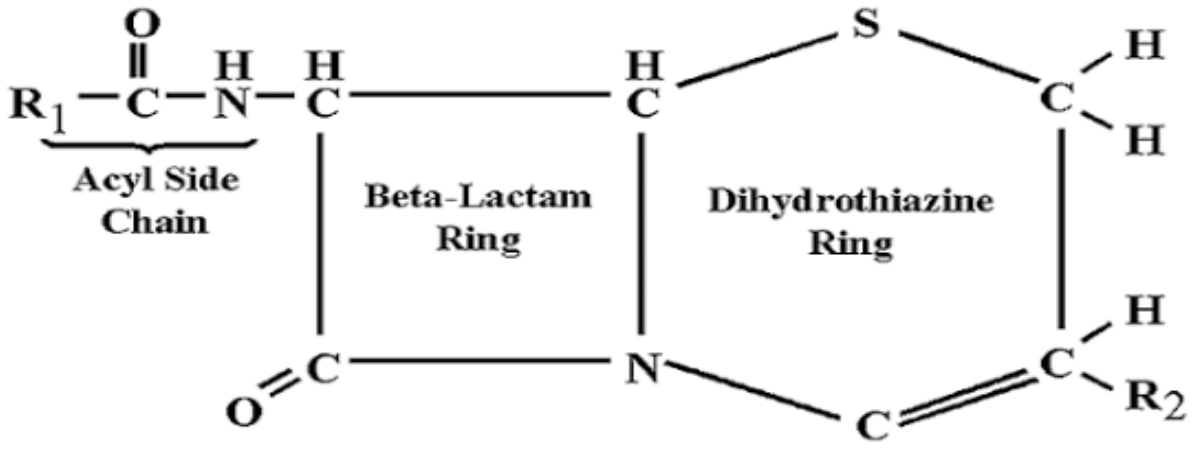
Name	Source
01. Water Phase	Precikot, Kothari, India
02. Wax Phase	Precikot, Kothari, India
03. Main phase, 100kg	Precikot, Kothari, India
04. Bump Pump	Precikot, Kothari, India
05. SS vessel	MYTH industries, Bangladesh
06. Tube filling machine GAB (LS-60)	WIMCO

D.Dry Syrup / Suspension Section (General & Cephalosporin)

Cephalosporin:

The cephalosporin are the largest and most diverse family of beta-lactam antibiotic. They are structurally and pharmacologically related to the penicillins. Cephalosporins have beta-lactam ring structure, infused to a 6-membrened dihydrothiazine ring. Thus, forming the cephem nucleus.

Cephalosporin compounds were first isolated from cultures of bacteria Cephalosporium acremonium found in a sewage outfall off the Sardinian coast in 1948 by Italian scientist Guiseppe Brotzu. The first agent cephalothin (cefalotin) was launched by Eli Lilly in 1964.



General Structure of Cephalosporins

Mechanism of action:

Cephalosporins are bactericidal agents and have the same mode of action as other beta-lactam antibiotics. All bacterial cells have a cell wall that protects them. Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls, which causes the walls to break down and eventually the bacteria die.

Peptidoglycan is a heteropolymer component of the cell wall that provides rigid mechanical stability. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin binding proteins (PBPs). PBPs bind to the D-ala D-ala at the end of muropeptides to crosslink the peptidoglycan.

Cephalosporins mimic the structure of the D-ala D-ala link and bind to the active site of PBPs, disrupting the cross-linking process. If the peptidoglycan fails to cross-link the cell wall will lose its strength which results in cell lysis.

Dry Syrup:

Dry powders for oral suspension are powder mixtures that require the addition of water (reconstitution) at the time of dispensing and are mostly for pediatric use. These are called dry syrups or reconstitute oral suspensions. They are prone to hydrolysis during extended exposure of moisture. They are to be reformulated by mixing with certain amount of boiled water and should be use up within certain periods (5 days at normal temperature).

Rationale

• Inadequate chemical stability of the drug in the aqueous vehicle.

• Avoid the physical stability problems like viscosity changes, conversion of polymorphic form, incompatibility, crystal growth, caking.

Commonly used Ingredients

Frequent:	**Infrequent:**
Suspending agent	Anti caking Agent
Wetting agent	Flocculating agent
Sweetener	Solid diluents
Preservative	Antifoaming agent
Buffer	Granule binder
Coloring agents	Granule disintegrant
Flavoring agents	Antioxidant
	Lubricant

The **Pacific Pharmaceuticals Ltd.** produces three different formulations for Dry Syrup

1. Powders for suspension
2. Powders for syrup
3. Powders for pediatric.

Areas in plant:

It is divided into two areas:

- Manufacturing area (blending or mixing area)
- Filling and Sealing area

Flow Chart for Dry Syrup:

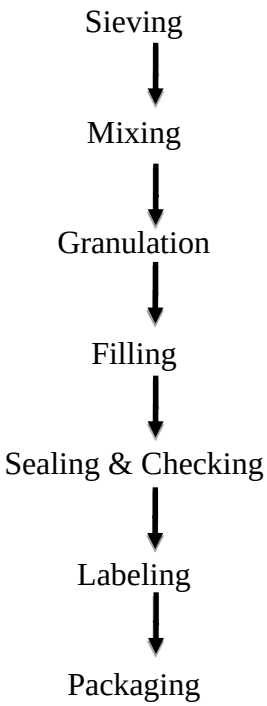


Table 10: Instruments used in Dry syrup / suspension section:

Name of Machines	**Source**
01. Agor Filler	Anchor, India.
02. Cone Blender	MYTH Industries, Bangladesh.
03. Tray Dryer	Indo German Pharma Equip, India.
04. Auto Sealing Machine	MYTH Industries, Bangladesh.

Room Condition:

- Room temperature: 25-30°C
- Relative humidity: Less than 55%

Observed Products:

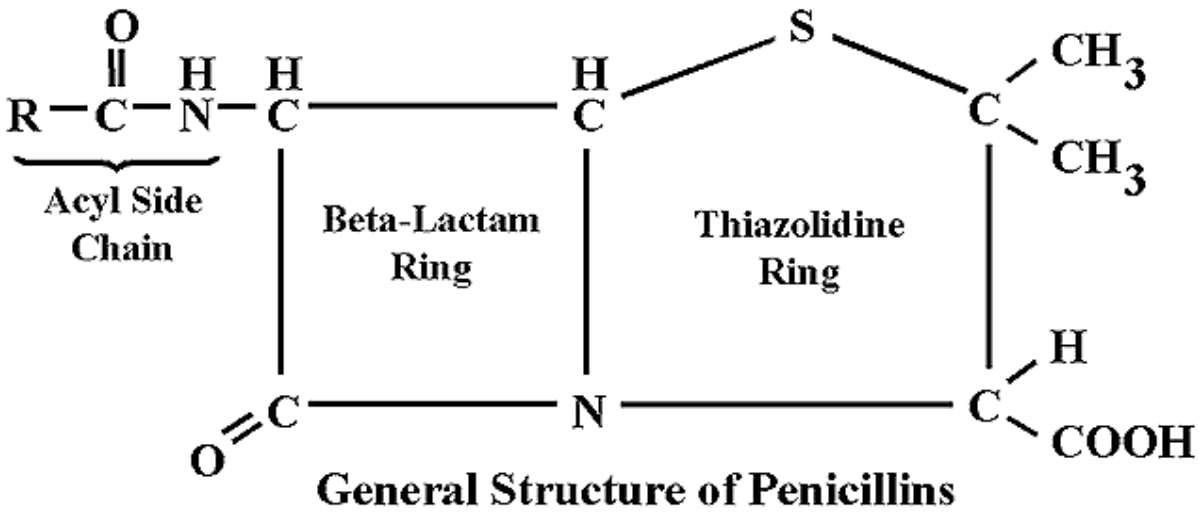
Brand Name	Active
01. Gigacef dry susp.	Cephradine
02. Gigacef P/D	Cephradine
03. Trifix dry susp.	Cefixime Trihydrate

Pacific pharmaceuticals Ltd is the only pharmaceutical company which is marketing all pediatric lifesaving drugs just at cost price.

E.Penicillin section (Capsule, Dry Syrup and Suspension)

Penicillin:

Penicillin is a group of antibiotics derived from penicillium fungi. Including penicillin G (intravenous use), penicillin V (Oral Use), Procaine penicillin And benzathine penicillin (intramuscular use).



Penicillin antibiotics were among the first drugs to be effective against many previously serious diseases, such as bacterial infections caused by staphylococci and streptococci. All penicillin are beta-lactam antibiotics and used in the treatment of bacterial infections.

In Pacific Pharmaceuticals Ltd. The operations relating to the manufacture, processing and packaging of penicillin products have been designed to be carried out in a separate building equipped with segregated facilities.

Machineries used:

Name of Machines	Manufacturer
01. Polishing machine (DP-100-P+am)	India.
02. Mack-1 (Blister Machine)	Rapid-Pack, India.

03. Hand Capsule Filling Machine	Pam, India.
04. Drum Dyer	MYTH industries, Bangladesh.
05. Auto Filler	Pam, India.

Manufactured Products:

1. Amocin capsule.
2. Amocin dry susp.
3. Stapkil capsule.
4. Stapkil dry susp.

Chapter 3:

WAREHOUSE

Warehouse is a place where all types of raw materials, packaging components and finished goods are kept separately. Since warehouse is normally the largest operation in the plant, in the term of area, special attention is needed on maintaining cleanliness, freedom from infestation and orderliness.

Pacific Pharmaceuticals Ltd have a good storage area which have sufficient capacity to allow orderly storage of the various categories of material and products, starting and packaging materials, intermediates, bulk and finished products, products in quarantine and released, rejected and returned or recall products.

Appropriate storage of materials is prerequisite for the manufacturing of quality pharmaceutical products. All the activities of warehouse must be performed in systemic and defined method to avoid confusion, material mix-up and to prevent determination or shortening expiry period or the materials.

Routine Works:

3.1: Arrival of Materials:

Raw and packaging materials arrive at the factory premises by different supplier with two copies of delivery chiller and invoice.

3.2: Invoice Checking:

The concern authority of the warehouse verifies the invoice and accordingly they will check whether by shipping mark is logged on the container or not.

Physical Inspection and Receipt/Discrepancy Report:

After completing the physical inspection of the raw materials, the materials are received based on SOP, if there is no discrepancy.

3.3: Quarantine Storage:

Raw and packaging materials are stored in this stage before the checking by the QC and approval from the QA.

3.4 Logbook Entry:

To entry the actual received quantity of materials into the logbook and copy to MIS dept., shipping dept. production planning (factory), warehouse.

3.5 MRR for Imported Items:

After receipt of materials MRR is completed and the quantity of materials undergoes computer entry to the final stock. Three copies of MRR sent to shipping dept., QC dept., and warehouse.

3.6 QC Sampling:

Warehouse authority will inform the authority for sampling, and after doing sampling and analyzing the QC will send the report to the QA.

3.7 QA Release/Reject:

Based on QC analysis and pass report QA give ‘release tag’ on each and individual container or box. If the material fails to pass QC test, QA give rejected tag or each and individual container or box.

3.8 MRR/Failed MRR:

Send copy to QC dept. shipping dept. and warehouse.

Disposition or released/reject material:

Released are placed in the release area for dispensing and rejected materials are placed in the rejected area until further decision for final disposition is made.

Dispensing:

Only the released materials are dispensed as per requisition of production dept. following respective SOP.

Distribution:

Most of the dispensed materials are carried and supplied to respective dept. by warehouse personnel.

Computer Entry or Requisition:

Inventory updating is done by computer entry issued requisition and copy to email for users.

Monthly Inventory Report:

Monthly updated inventory report is sent to MIS dept. A/C dept. and purchase dept.

Function of warehouse:

- To store raw materials.
- To serve as a temporary storage for finished products before going to the central depot followed by distribution.
- To supply the raw materials on the FIFO (First in First Out) basis to the production floor according to the process order.
- To store rejected materials before disposal.
- To supply the finished products to the market on the basis of FEFO(First Expire First Out)
- To maintain all the documents of every steps of production of a particular lot and its delivery to the depot.

- ❖ To check for the batch no. of vendors, manufacturing date, expiry date and quantity check before entry, although materials are always taken from approved source.
- ❖ To confirm complete security and prevention of pilfered of every material including the promotional.

PRODUCT DEVELOPMENT SECTION

R & D (Research & Development)

The Product Development Department of Pacific Pharmaceuticals Ltd., has been enriched with vast assortment of modern and sophisticated process equipment and machineries for designing, optimizing, and qualifying manufacturing processes within designed parameters, specifications and requirements. Product Development Department of Pacific Pharma follows specific plans for each design and development of its product in the form of "Product Development Project Plan" and it describes all required activities and identifies responsible person for implementation. The product development activities are executed by trained and experienced qualified personnel. The outputs of Product Development Department documented in the form of "Drug Master File"; which contains material specifications, procedures for manufacturing and packaging the products, test methods, acceptance criteria, product specifications in-process checking parameters, stability data, process validation data, safe usage, and storage data etc.

Purpose of Product Development:

- To develop safe and effective therapeutic options for undiscovered drug.
- To be the most protective product development center.
- Quality remains as essential attribute in all aspects and activities for the product.
- Always develop a new formula for old items.
- Preparation of BMR for a new product.
- To comply with camp requirement.
- Compatible with product line and dosage form.

Stages of Drug Development:

Any drug development process must proceed through several stages in order to produce a product that is safe, efficacious and has passed all regulatory requirements.

- Discovery
- Product Characterization
- Formulation, delivery, Packaging development
- Pharmacokinetics and disposition
- Preclinical Toxicology Testing and IND Application
- Bioanalytical Testing
- Clinical Trials

Fig 10: Quest-TC

Table 11: Machineries used in Product Development:

Name	Source
01. Quest-FB	ACG, India
02. Quest-TC (coating machine)	ACG, India
03. Clit 10 station (compression Machine)	Clit, India
04. Rimek Mini Press-II MR	India
05. Cone Blender	SMT, India
06. Mini Cap (capsule filling & sealing Machine)	Karnavati, India
07. KALWEKA series	Rimek, India
08. UV-Pharmaspace 1700	Shimadzu, Korea
09. Melting Point Determinant-SMP 10	Stuart
10. Toshiba GR-W41ET fridge	Malaysia
11. Filter press	Kothari, India
12. Hand P^H meter	Hanna, Romania
13. Vernier Caliper	China
14. Stability Chamber	Thermolab

Chapter 4:

RAW MATERIALS

Pharmaceutical raw materials comprise substrates or elements that are used for manufacturing different types of drug eg. cholecalcipherol, paracetamol, magnesium stearate, fluconazol, diclofenac sodium, penicillin, cephalosporin, etc. pharmaceutical excipients and ingredients or raw materials used to manufacture drugs are extracted from different types of sources. These sources could be natural or synthetic.

Pharmaceutical raw materials are essential to producing pharmaceutical drugs and include active pharmaceutical ingredients (API), also known as bulk active, are pharmaceutically active and have desired pharmacological effects on the body.

Pharmaceutical excipients are pharmaceutically inert substance which help in delivering the active ingredient. E.g. antiadherents, binders, coatings, disintegrants, fillers etc.

Storage of Raw Materials:

Goods Receiving of all incoming raw materials through invoice/challan.

↓

Inspection of all the containers for visible defects such as – damaged / torn container, broken security seal, missing label etc. In case of major abnormalities immediately inform Commercial and Accounts Department with intimation to general manager (factory).

↓

After complete inspection, transfer the consignment to quarantine area and affix quarantined tag.

↓

QC will collect sample as per procedure and sampling must be done in sampling must be done in sampling booth. QC will affix Sampling tag on the containers from where sample was collected.

If sample is approved. Then Approved materials must be transferred to approved / released material storage area and affix Released tag.

If sample are rejected/ Non-conformed. then Reject / Non-conforming materials must be separated from released material, reject material must be kept on reject area and non-conforming materials must be kept in non-confirming area.

In Pacific Pharmaceuticals Ltd. penicillin products have been designed to be carried out in a separate building equipped with segregated facilities.
Raw materials for Cephalosporin are also separate from general raw materials.

Table12: Instruments used in raw materials store:

Name	**Source**
01. Laminar air flow	Teknopak, India
02. Champ-II (Weight machine)	ONAUS, USA.
03. KEREN CB 6KI (Electrical balance)	alfa scientific co. Bangladesh
04. Cooling Cabinet 3000L	thermolab scientific equipments, India.

Chapter 5

PACKAGING MATERIALS

Pharmaceutical packaging must be carried out for the purpose of the safety of the pharmaceutical preparation to keep them free from contamination, hinder microbial growth, and ensure product safety through the intended shelf life for the pharmaceutical. Packaging is a critical tool in pharmaceutical industries for product delivery and regulatory compliance. In Pacific pharmaceuticals packaging done within a contamination free environment or clean room.

Packaging we observed:

05. Primary Packaging (Blistering)
06. Secondary Packaging (Unit Pack)
07. Tertiary Packaging (Master Pack)

Instruments used in packaging store:

- Superfold (Folding machine)
- Fully Automatic Overprinting Machine
  Source: MAC, India.
- Hand printing machine.
- Z-printer, source: markem imaje 9020

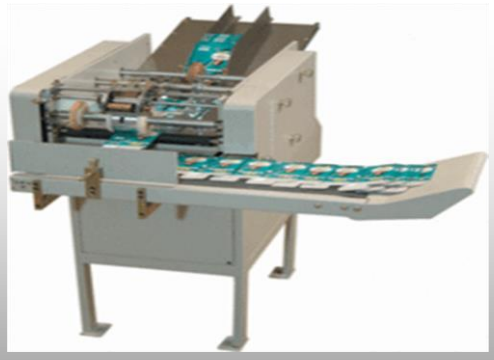


Fig11: Fully Automatic Overprinting Machine

Batch Coding Approval:

Product name → Product code no. → Batch no

↓

Batch size

↓

Pack size

↓

Mgf / expiry date

↓

MPR / IP (with vat)

↓

Qty. to be printed

Packaging materials we observed:

- Aluminum foil
- PVC (poly vinyl chloride
- PVDC (poly vinyl di-chloride)
- Insert
- Spoon , Cup, Droppers.
- Unit pack
- Master pack
- Tube for ointment
- Cap
- Labeling

Fig 12: Superfold Machine

Condition for Packaging materials:

- Temperature: 15-20^0 C
- Humidity: 45-70%

Fig13: master cartooning

FINISHED PRODUCT

A finished dosage form of a pharmaceutical product, which has undergone all stages of production, including packaging in its final container and labeling.

Facilities: Quarantine area, Release Area, separate area for products need to be stored under controlled temperature.

Storage Temperature: 15ºC to 20ºC and ambient

Activities: the major activity includes reception of finished goods in warehouse after production and distribution.

Finished Goods receive & Dispatch

Delivery of finished goods from production to warehouse with goods receiving note

↓

Checking of quantity of finished goods with the quantity mentioned in the good receiving note

↓

Transfer of finished goods to the quarantine area of warehouse

↓

Information entry in the finished good receiving register

↓

Released product to storage

↓

Requisition of Finished Goods

↓

Checking of availability of Finished Goods

↓

Sending request to Quality Assurance for release (if required)

↓

Arranging covered van for loading Finished goods

↓

Preparation of Delivery Challan, Issue voucher & gate pass

↓

Exit of Finished Goods Vehicle from Warehouse

Some important areas of Warehouse:

- **Cold room:** Temperature range 2 ^{o} c to 8 ^{o} c.
- **Cool area:** Temperature range 8 ^{o} c to 15 ^{o} c.
- **Control area:** Temperature range 15^{o} c to 20^{o} c and 15 ^{o} c to 25 ^{o} c.
- **Ambient area:** Temperature range 25 ^{o} c to 40 ^{o} c.
- **Non-conforming room:** The materials or product which are under special quality inspection and are not approved for use in production are generally kept in this area.
- **Reject materials or products room:** The materials or products which are rejected by quality control department are kept here until final disposition. Reject tag must be affixed on the containers before storing in this area.

Chapter 6:

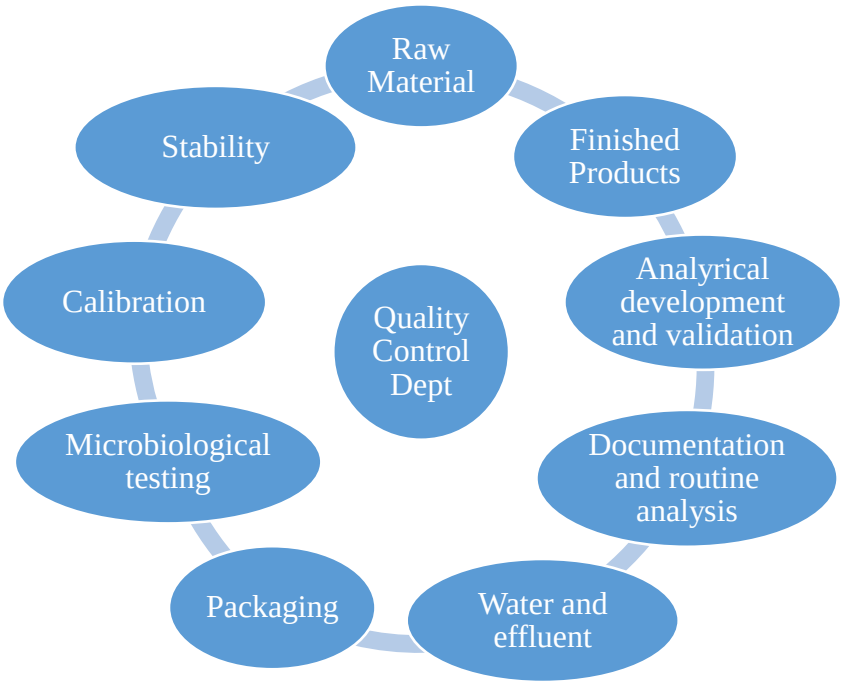
QUALITY CONTROL DIVISION

Quality control at Pacific Pharmaceuticals Ltd is to keep the quality up at their produces and responsible for the day-by-day control at quality within the company. This dept. is stuffed with scientist and technicians who assess and assure that entire production process has been completed satisfactory and satisfied all the aspects of GMP.

A quality control program for pharmaceuticals is concerned with the batch-to-batch uniformity of a product as well as ensuring that the final informing, safety, efficiency, and stability within established levels which meet all legal, professional and company standards.

Activities of Quality Control Department:

- Sampling the new raw and packaging materials arriving at the factory premises.
- Issuing release, reject or quarantine tag for each batch of raw material and final product.
- Assessment of intermediate products and bulk products to further processing.
- Performing all test procedure for all incoming samples according to the schedule.
- Maintaining batch wise full quality control tests records and signature of the persons who perform the test.
- Calibration and standardization of laboratory equipment's.
- Ensuring precision and accuracy of all testing methods.
- Research and development any method and its validation.
- Testing of any reform goods.
- Stability test for finished product.



Working Division in Quality Control:

- Analytical Section
- Microbiological Section
- Packaging Section
- Stability Study Section
- Routine Chemical Analysis
- Documentation

Analytical Section:

Analytical section of Quality Control dept. performs the tests.

- Chemical and physical analysis
- For raw material

Solid Raw Material:

- Identification
- %LOD
- Sulfated Ash
- Bulk density
- Heavy metals
- Impurities
- Melting point

Liquid Raw Material:

- Maximum test for solid
- Refractive Index
- Ph
- Weight per ml
- Viscosity

For Finished Product:

- Solid Prep
  - Description
  - Dissolution and Disintegration time
  - Weight Variation
  - Assay
- Liquid Prep
  - Weight per ml
  - Microbiological limit test
  - pH
- Semi-solid Prep
  - Microscopic Examination
  - Assay
- For Packaging Material
  - Description
    - Test
    - Color
    - Dimension
    - Weight (gm/mˇ)
    - Visual inspection for defects
    - Opacity and chemical test glass pack
    - Auditability

Good Manufacturing Practice (GMP):

In provides basic standard for the manufactures and form the basis of which each company builds its own system procedures to assure the product quality. Good manufacturing practices ensure that product consistently produced and controlled to the quality standard appropriate to

the intended use. There are several national and international GMP regulatory boards such as WHO, PIC, FDA, TGA etc.

GLP Rules and Regulation:

To ensure a wide range of testing disciplines the laboratory has some facilities which are discussed in GLP. The GLP functions involve:

Organization and Management:

Quality control dept. is a well-organized dept. It has the authority of approval or rejection of each batch of starting, packaging, and final materials based on testing.

Personnel:

Qualified and competent personnel are a key factor to ensure quality. They have three factors to ensure quality. They have three important characteristics:

- Education
- Experience
- Training

Equipment:

The laboratory is well equipped for performing all tests according to BP, USP. To maintain all equipment's and machineries following measure are taken:

- Every equipment has a logbook for record.
- Regular maintenance is done.
- All equipment's are calibrated at specified intervals.
- Most of the equipment and machineries relate to printers, thus there is no chance of manipulation.

Reference Standards:

Reference standards are substances with known purity on potency certified reference standard are available from many official sources.

Reagents:

To maintain reagent quality control department has taken following initiative-

Laboratory has complete list of all the reagents needed.

Why it is necessary:

An important parameter of Quality product is that the product must be free from microbial contamination. We are very careful about visible defect of a product but most often we forget that microbial contamination should also be considered.

It is necessary for following reasons:

- To provide control or suitable environment for the production.
- To provide chance to confirm product without microbial contamination.
- To ensure personal hygiene or health.
- To ensure suitable utility.
- To ensure sterility of sterile product.
- To ensure dehydrogenation of parenteral products.

All the above facts are essential for quality product. So microbiology dept. of Pacific Pharmaceuticals Ltd is an important supportive step of quality product.

Work Process:

Microbial Count	Water raw materials, bulk samples, finished product (sterile), packaging containers.
LALTest Sterility Test	Water, raw material other sterile products.
Environmental Study	All manufacturing and filling are including as aseptic filling room.
Validation	Steam and dry heat sterilizer, oven, cleaned equipment.
Personal Hygiene Test	Aseptic production area operators.
Bio-assay	Antibiotic raw materials and finished products.
Penicillin Cross Contamination Study	Penicillin in environment and in non-penicillin production area.

Tests performed in the microbiological department of Pacific Pharmaceuticals LTD.

- ✓ Limit test/ total microbial count test.
- ✓ Sterility test.
- ✓ Pathogen city test.
- ✓ Potency determination of antibiotic, such as erythromycin.
- ✓ Pyrogenic test/ LAL test (Limulus amoebocytes Iysate);
- ✓ Environmental monitoring which includes-
  - -Settle plate test.
  - -Air sampling test.
  - -Surface sampling test.
- ✓ Portable water test.
- ✓ Preservation efficiency test.
- ✓ Method validation test.

Agar media used for specified test:

- For fungal test: melt extract agar.

- For bacterial test. Tryp for soya agar Mac CONKEY agar (used for pathogenic bacteria).

  Temperature related with microorganism.
- For fungal 20-25°c (Cool Incubator)
- For bacterial 30-35°c (Worm incubator)
- For LAL test 37°c (Worm incubator)

Process of limit test:

Prepare sample solution at desired one

⇩

Placed in sterile Petridis

⇩

Poured in suitable media

⇩

Allowed to grow the microorganism by placing into overnight

⇩

Count colony number approved or reject considering the specification.

Process of LAL test:

⇩

LAL Reagent + LAL Reagent Water

⇩

Mix at 0.125 Eμ / ml (Endotoxin unit/ml) cone.

With the sample at the same conc.

⇩

Allowed to keep

⇩

It clots then pyrogen in present otherwise nut

If the result is positive, then perform the test in the same way to detect the quantity of pyrogen

If pyrogen level is below 0.125 mg/mL then the same is passed for further step.

Purpose of LAL test:

To detect the presence of pyrogen in parenteral preparation.

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Environmental Monitoring:

1. Monitoring personal hygiene
   -Contact plate method.
2. Monitoring surfaces
   -Contact plate method
   -Swab test
3. Monitoring of Airborn microorganism
   -Air sampling by RCs samples.

Water Analysis:

Rinse water of manufacturing vessel of LCD section and other used water analyzed for total bacterial count and presence of pathogens like coli forms and ***Pseudomonas aeroginosa***.

Packaging section:

In this section, following parameters of a packaging material are checked evaluated:

a) Description:
   1.Size 2. Inscription 3.Color.

b) Test:
   1. None 2. Label, claim 3. Price 4. Indication 5.

Chapter 7:

QUALITY ASSURANCE DIVISION

7.1 Introduction:

Quality Assurance covers all activities from design, development, production , installation, servicing to documentation It need the regulation of the quality of new material assemblies , products and components , servicing related to production and management production and inspection process.

7.2 Quality Assurance

Quality is not just an organizational facet, right from the inception it has been a passion. Today Pacific Pharma proudly claims to have the distinction to fly in the professional sky with quality wings. The Quality Assurance Division of Pacific Pharma is duly equipped with sophisticated modern instruments and appliances which are being supervised and run by qualified and skilled personnel. The Quality Assurance (QA) Division comprises of 03 (three) Departments i.e., Quality Control Department, Quality Compliance Department and Product Development Department.

Quality Assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

QA = Product design + GMP + QC + Quality Goal Activities.

Amis of Quality Assurance:

- Create a more efficient, effective operation
- Increase customer satisfaction and relation

- Reduce audits
- Enhance marketing
- Improve employee motivation, awareness and moral
- Promote International trade
- Increase profit
- Reduce waste and increase productivity

Function of QA department:

- Warehouse
    - Visual inspection of incoming raw and packaging material.
    - Sampling of raw and packaging materials for the following test.
    - Amoy
    - Microbial test
    - Retention
    - Released Injection of raw and packaging material based on analysis.
- **Dispensing area:**
    - QA dispensing officer monitors dispensing process in the dispensing area and attaches dispensing card to materials.
- **In process checking:**
    - Solid department
    - Granulation area
    - Check machine cleanliness and room condition and permit line clearance
    - Check LOD of granulation
- **Compression area:**
    - Check machine cleanliness and room condition and give line clearance.
    - Initially some tablets are compressed to check general description, weight, hardness, thickness, friability, disintegration and dissolution time, organoleptic test for chewable tablets and after relevant parameter. In case of capsule initially some capsules are tilled to check weight.
- **Quarantine Area:**
    - Based on QC report the tablets are released for packaging.
- **Packaging Area:**

- Before packaging starts, the machine and rooms are checked for proper cleaning.
- During Packaging.
- QA department checker the following.
- Humidity of packaging area.
- Leak test of package.
- Appearance of tablet and capsule.
- Labeling of tripper and inner and outer cartoon.

Quality Assurance operation in LCO department in manufacturing site:

1. Before starting a new batch production room's cleanliness, manufacturing tank cleanliness, room temperature and % RH are checked.
2. After preparation in manufacturing tank the following are checked by QA department.
    - pH of Preparation
    - Viscosity
    - Assay
3. Filling and scaling
    - Proper Weight
    - Proper Volume
    - Cleanliness
    - Microbial test of scaled preparation
    - In case of suppository teak test is done
4. In Packaging area:
    - Batch Printing
    - Inner and shipping carbon at regular time interval.

Documentation:

Documentation is most important test of the quality assurance department. The purpose of documentation is to record import information with evidence G✕P requires that complete

and accurate record of all raw packaging materials, finished product, BMR, BPR, must maintain for any necessary forcing back of any time.

The following documents are maintained-

- Production sheet order
- BMR (Batch Manufacturing Record)
- BPR (Batch Packaging Record)
- Tablet/ Capsule inspection sheet
- Weight/ volume inspection sheet
- Coated tablet inspection sheet
- Leak test record sheet
- Packaging order sheet
- Retention sample quality

Develop Works:

- Problem analysis occurred during manufacturing and packaging
- Product complains handling and correcting measures are recommended

Retention Sample:

Quality Assurance preserve the sample of cover batch in the achieve rooms in normal temperature and process for reviewing the quality of product. In any complain comes from any source they check the sample of some batch staring in the archive room. Their samples are called retention sample. Retention sample are preserved for life plus one year. Batch history control, preservation and follow up.

Validation:

Validation is an integral part of as Quality Assurance. Validity maybe defined as a systematic study which help to prove that the system. Facilities and process perform the job adequately and consistently as specified, in more precise a validated operation is one which has been proved to have the potential for the uniform outcome meeting the required.

Instruments used in QC Section

Name of Machineries	Source
01. Ultrasonic cleaning bath	Spectralab, India
02. Leak test machine	
03. Tap Density tester	Elecrolab, India
04. Fume Cup board	Salil Enterprise, India
05. Heating Mantle	
06. Magnetism Heating Mixer/Stirrer	Labtech, Korea
07. Electrical balance	KERN & Sohn GmbH, Germany
08. Analytical/precision balance	KERN & Sohn GmbH, Germany
09. Viscometer	Brook Field
10. Auto titrator (karl fischer Titrator)	Overseas marketing co. ptv, ltd.
11. Heater	
12. Water Still	Labtech, Korea
13. Natural convection Oven	Labtech, Korea
14. Mettle Toledo (P^H meter)	
15. HPLC Prominence	Shimadzu, Japan
16. TOC (Total organic carbon) analyzer	Shimadzu, Japan
17. AAS (atomic absorption spectroscopy)	Shimadzu, Japan
18. UV-1650PC	Shimadzu, Japan
19. IR Prestige 21	Shimadzu, Japan
20. Dissolution Tester	Elecrolab, India
21. Disintegration Tester	Elecrolab, India
22. Digital Centrifuge	JP Selecta, spain
23. Electromagnetic Sieve Shaker	Elecrolab, India
24. Friabilator	
25. Tablet Tester	Campbell Electronics,
26. Muffle Furnace	
27. Auto Clave	Labtech, Korea
28. Colony Counter	Rocker
29. Microscope	
30. Refrigerator	Toshiba
31. Incubator	Labtech, Korea
32. Laminar Air Flow Clean Air Work Station	Teknopak
33. Conductivity Meter	Romania
34. Digital Hygro-thermometer	
35. Hand p^H Meter	Hanna, Romania

36. Gas Chromatography	Shimadzu, Japan
37. Chlorine Tester	Hanna, Romania
38. Water Hardness Tester	Hanna, Romania

Chapter 8:

MAINTENANCE

Engineering department is an important department in any pharmaceutical industry. It maintains all the mechanical devices and electricity in the pharmaceutical industry. The engineering department of Pacific Pharmaceuticals Ltd. proceeds with a group of skilled personnel. Engineering department is also concerned for maintenance of all production machineries.

Typical work activities:

- Designing maintenance strategies, procedures, and methods
- Planning and scheduling planned and unplanned work
- Diagnosing breakdown problems
- Controlling maintenance tools, stores, and equipment
- Monitoring and controlling maintenance costs
- Dealing with emergency and unplanned problems and repairs
- Writing maintenance strategies to help with installation and commissioning guidelines.

Maintenance engineers are also responsible for the continuous running of equipment and machinery. They are also involved in control and monitoring devices and occasionally in the manufacture of items that will help in maintenance.

Utilities include:

- ❖ Water Treatment Plant
- ❖ ETP (Effluent Treatment Plant)
- ❖ Generator
- ❖ Chiller & Boiler

Chapter 9: Water Treatment Plant

Water purification is extremely important to pharmaceutical industries. Suspended or dissolved particles, organic compounds, impurities, and other contaminants restrict the usage of tap water in laboratory application and scientific research. Some application can tolerate the presence of specific impurities in the water, but others such as HPLC require of most contaminants.

Test for Water Treatment Plant:

1. PH (5.5-7.0)
2. Chlorine test
3. Hardness test
4. Conductivity test
5. TDS (total dissolve solid)

9.1 HVAC System:

The main purpose of a heating ventilation, and air conditioning system are to help maintain good indoor quality through adequate ventilation with filtration and provide thermal comfort.

❖ **Purpose of HVAC:**

- To maintain specified temperature
- To maintain specific relative humidity.
- To remove dust particle from production area.
- To maintain proper airflow to the rooms ensuring that cross contamination does not occur.
- To prevent microbial contamination in some area by maintain particle size within the tolerance range.

HVAC instruments are:

- Air compression

  Atlas Copco, China

- Air Dryer
  Atlas Copco, China

- Air Dehumidifier

  Beam Techno services, India

CHILLER & BOILER

Chiller:

A chiller is a machine that removes heat from a liquid via a vapor-compression or absorption refrigeration cycle. This liquid can be circulated through a heat exchanger to cool air or equipment as required.

Chiller parameters:

- Chill water inlet temperature
- Chill water outlet temperature
- Cooling water inlet temperature
- Cooling water inlet temperature
- Dilute solution temperature
- HTG (High temperature generator)
- HTG vapor
- Stack temperature

Instruments:

Thermax, India.

Capacity:240 rt

Boiler:

Boiler is a device for generating steam. It consists of two principal parts:

1. Furnace: which provides heat, usually by burning a fuel, and the boiler proper, a device in which the heat changes water into steam.
2. Steam engine: which is driven by steam generated under pressure in a boiler.

Two most common types of boilers are

1. Fire-tube boiler
2. Water-tube boiler

We observed fire-tube boiler

Revotherm

Source: Thermax, India.

Capacity: 2 ton

9.2 ETP (EFFLUENT TREATMENT PLANT)

Pacific Pharmaceuticals are more concern about environment pollution. To protect the environment from industrial wastage they have set up ETP (Effluent treatment plant). They treat the effluent raw water coming from production area as wastage before discharge to the environment.

Chemical used in Effluent Treatment Plant:

1. Bleaching Powder
2. Lime
3. Potash Alum

Service:

ITEM	**CAPACITY**
Water (Potable)	100,000 Lit/hr.
RO Water	2000 Lit/hr.
DM Water	2000 Lit/hr.
Electricity	2.2 MW(Self generation)
Steam	2000 kg/hr.
Compressed Air	5700L/min
Effluent Treatment Plant	2000 Lit/hr.

Generator

Electricity supply is one of the most important jobs of engineering department in a pharmaceutical plant. A generator is a device that converts mechanical energy to electrical energy for use in an external circuit. Generators provide nearly all of the power for electric power grids.

Electricity supply flow is as follows:

Generator Start

↓

Electric Current produced

↓

Electric Current passes Control panel board through the cable

↓

Electric Current passes Low tension (LT) panel board

↓

Electric Current Distribution to factory

Pacific Pharmaceuticals Ltd use two gas generators

Company name: WAUKESHA Gas Generator.

Source: USA

Capacity: 1100 KW

Soft water and cool water are used to regulate the gas generators.

ADMINISTRATIVE

Administration consists of the performance or management of business and thus the making or implementing of major decision. Administration can be defined as the universal process of organizing people and resource efficiently to direct activities toward common goals and objectives.

Administrative Function:

The main function of this dept. is to run the plant smoothly by performing the following function:

- Recruitment of personnel with appropriate qualification and experience to fill all position that influences quality.
- Assist new employees to complete joining activity and ensure placement of newcomers.
- To arrange, induction- training program (orientation program) for new employee. Prepare and coordinate internship program for the students at different universities.
- Maintain and update personal files of all employees monthly. Such as confirmation of job increment, promotion, transfer and other letters is adjusted in the employee's file.
- Supervise and monitor employee monthly attendance, job carts, prepare monthly attendance summary and daily absent report etc.;
- Monitor and update leaves of plant employees. Each employee has a leave file which integrated all kinds of leaves;
- Inform managers and employees regarding personnel policies and procedure of the company.
- Asses the training need of personnel in light with cGMP and other work-related issues.
- Ensure proper implementation of labor laws applicable of factory employees.

- Disciplinary action including suspension punishment and termination.
- Ensure healthy labor management relationship for smooth production.
- Maintain liaison Govt. regulatory bodies. Ensure safety off all employees and company assets.

Chapter 10:

CONCLUSION

Pacific Pharmaceuticals Ltd. is one of the leading and fast-growing pharmaceutical companies in Bangladesh, involved in the service to the nation and mankind by manufacturing and marketing ethical finished pharmaceuticals having belief in super quality. Leader in Oral Antidiabetic Sector about One Decade.

This In plant training in Pacific Pharmaceuticals Ltd. has given us such a great experience about Quality Assurance Division, Production Division, Warehouse Department and Maintenance section also which is going on the company. After sinking for one month as a trainee in the pharmaceutical company we really feel fresh. It helps us to understand the exact mechanism of working at various department. It also helps us well to establish ourselves in the corporate world after completing our academic session.

Pacific Pharmaceuticals Ltd. Strictly follows the discipline, which is the key to their success and important in any organization level. The officers try hard and soul to lead the company forward.
This company has the great asset that is they are willing to do work as a unit, we feel proud to become a trainee of this company.