Good Manufacturing practices In Tablets Manufacturing

[1]Miss Khose Shivani.B., [2]Dr. Khedkar Amol N, [3]Prof. Garud Neha. S, [4]Prof. Lagad Rutuja, [5]Phuke Jyoti.R

[1]Research Scholar [2]Principal, [3]Assistant Prof.
Saikrupa Institute Of Pharmacy, Ghargoan, Ahmednagar-413728 Maharashtra
Corresponding Author: Miss Khose Shivani.B.

***Abstract*- The part of quality assurance, known as good manufacturing practice (GMP), ensures that goods are manufactured and continuously monitored to meet the quality standards required for their intended use and marketing authorization. GMP regulations contain the minimum requirements that food or drug manufacturers must meet to ensure that their products are safe for consumers and do not pose a risk.**

A set of rules, procedures and recommendations known as Good Manufacturing Practices (GMP) governs the production of medicines and medical products, medical devices, food and in vivo and in vitro diagnostics. Globally recognized, GMP stands for Pharmaceutical Manufacturing Management and Quality Control Testing. People working in the pharmaceutical industry should generally know how good manufacturing practices or GMPs have been in place. Most of the orders were implemented because of sad events and to prevent the recurrence of disasters. Understanding GMP and the history of GMP is essential to achieving and maintaining GMP compliance. This review focuses on the history, present and future of GMP.

The holder of the manufacturing license must ensure that the medicines are manufactured in a way that meets all safety, quality and efficacy standards, is fit for purpose and does not pose a risk to patients. Top management is responsible for achieving this quality goal, which requires the participation and commitment of employees from many departments and levels of the organization, as well as suppliers and distributors. A comprehensive quality assurance system that includes good manufacturing practices, quality control and quality risk management is necessary to reliably achieve the quality goal. Its effectiveness must be fully verified and documented. Each component.

Information-

The Government of India has amended the drugs and cosmetics rules 1945 on June 1988 and prescribed GMPs under Schedule M. Schedule M has two parts, part 1 and part 2, GMP guidelines come under par 1.

The Schedule M has been revised and brought more or less to the level of WHO GMO text.

Although there are number of them, all guidelines follow the basic principles:

1. Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
2. Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of product and drug are the validated as necessary.
3. Instructions and procedures are written in clear and unambiguous language.

[Good Documentation Practices]

4. Operators are trained to carry out the processes and document procedures.

Information about tablets-

A tablet is a wirelessly portable, touchscreen-equipped personal computer. Generally speaking, tablets are larger than smartphones but smaller than notebook computers. Most people agree that Alan Kay of Xerox came up with the concept of tablet computing when he drew it out in 1971.

Benefits [1, 2, 5, 6].

1) Tablets are a unit dosage form that provide the most precise dose and least variability in content of all oral dosage forms.
2) It is cheapest and easiest to package and strip them.
3) Affordable.
4) Compact and lighter.
5) Out of all oral dosage forms, possessing the highest chemical and microbial stability.

Objectives of GMP.

To reduce dependence of one another.
To enable each organization, schedule its operations independently of another.
To obtain a reasonable utilization of people and equipment.
Maximize customer services.
Longer production runs.

Requirements in tablet manufacturing

General requirements: Location and surroundings
Building and premises
Water System
Disposal of waste

Warehousing area

Warehousing areas shall be designed and adapted to ensure good storage conditions.
Receiving and dispatch bays shall protect materials and products from adverse weather conditions.
There shall be a separate sampling area in the warehousing area for active raw materials and excipients.
Segregation shall be provided for the storage of rejected, recalled or returned materials or products.[3]

Production area

The production area shall be designed to allow the production preferably in onflow and with logical sequence of operations
Pipe-work, electrical fittings, ventilation openings and similar services lines shall be designed, fixed and constructed to avoid creation of recesses.[2]

Ancillary areas

Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.
Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users.[4]

Quality control area

Quality Control Labs shall be independent of the production areas. Separate area shall be provided each for physic-chemical, biological, microbiological or radioisotope analysis.
The design for the laboratory shall take into account the stability of construction material and ventilation. Separate air handling unit and other requirements shall be provided for biological, microbiological and radioisotope testing areas.[5]

Personnel

The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage and / or active pharmaceutical products.
The head of the Quality Control Laboratory shall be independent of the manufacturing unit.
Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced.
Number of personnel employed shall be adequate and in direct proportion to the workload. Health, clothing and sanitation of workers
A high level of personal hygiene shall be observed by all those engaged in the manufacturing processes.[7]

Manufacturing operations and controls

All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority.
The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labeled with the name of the product, batch number, batch size and stage of manufacture.
Products not prepared under aseptic conditions are required to be free from pathogens like Salmonella, Escherichia coli, etc. [6]

Sanitation in the manufacturing premises

The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material.
The manufacturing areas shall not be used for storage of materials, except for the material being processed.

Raw materials

The licensee shall keep an inventory of all raw materials to be used at any stage of manufacture of drugs and maintain records as per Schedule U.
All incoming materials shall be quarantined immediately after receipt or processing and materials shall be checked to ensure that the consignment corresponds to the order placed.
All incoming materials shall be purchased from approved sources under valid purchase vouchers.
Raw materials in the storage area shall be appropriately labeled. Labels shall be clearly marked with the following information:

Designated name of the product and the internal code reference, and analytical reference number;
Manufacturers name, address and batch number.
The status of the contents and the manufacturing date, expiry date and re-test date.

Equipment.

For effective operations, the tablet production department shall be divided into four distinct and separate sections as follows: -

a. Mixing, Granulation and drying section.
b. Tablet compression section.
c. Packaging section (strip/blister machine wherever required).
d. Coating section (wherever required).

Area minimum additional area of thirty square meters for coating section for basic installation and ten square meters for ancillary area is recommended.
The manufacture of effervescent and soluble/dispersible tablets shall be carried out in air-conditioned and dehumidified areas.

Documentation and records

Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply these rules and approved, signed and dated by appropriate and authorized persons.
Documents shall specify the title, nature and purpose. The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable.

Quality assurance

The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that:

e. The pharmaceutical products are designed and developed in a way that takes account of the requirement of Good Manufacturing Practices and other associated codes such as those of Good Laboratory Practices and Good practices.
f. Adequate arrangements are made for manufacture, supply and use of the correct starting and packaging materials.
g. The finished product is correctly processed and checked in accordance with established process.

2. INSTRUMENTS USED IN PHARMACEUTICAL INDUSTRIES FOR MANUFACTURING OF TABLETS

Rapid Mixer Granulator
Double Cone Blender /Mechanical Shifter
Spray Coating Machine
Rotary Tablet Press
Tablet Counting Machine
Polishing Machine
Automatic Tablet Printing Machine
Strip Packing Machine.

Rapid mixer granulator: Rapid mixer granulator is widely used instrument in pharmaceutical manufacturing. It is used to mix the pharmaceutical ingredients and make the granules before compression and also called as shear mixer.[8]

Rapid mixer granulator

Double cone blender: Double cone blender is an efficient and versatile machine for mixing of dry powders and granules homogeneously. [8]

Double cone blender

Spray coating machine: Coating machine coats the external surface of a tablet using a thin film of coating material.[17]

Rotary tablet press: The basic principle behind the tablet compression machine is hydraulic pressure.

Tablets are formed by compression of granules.[17]

Tablet counting machine: A tablet counting machine is a versatile assembly of systems that work as a unit for accurate counting.[16]

Tablet counting machine

Tablet Polishing Machine: Tablet polishing machine is used for sugar and film coating of tablets.[8]

Automatic Tablet Printing Machine: Inkjet printing is a recent method, which gained acceptance in pharmaceutical industry. It offers great versatility in terms of printing schemes and multiple colors, complex logos and machine-readable codes. [16]

Automatic tablet printing machine

Packing Machine: Strip packing machines are designed to handle a wide range of products with utmost precision and speed upto 2400 units per minute.[17]

3. QUALITY CONTROL TEST PERFORMED FOR API Diclofenac sodium)

INTRODUCTION:

Diclofenac belongs to NSAIDs category.

It is phenyl acetic acid derivative.

pH: 7 to 8.5

Storage: Preserved in tight, light resistant containers. Molecular weight: 318.1 g/mol. [19] Use**:**

Osteoarthritis

Ankylosing spondylitis Non –articular rheumatism spot injury

Pain and inflammatory disease as gout. [9]

STRUCTURE:

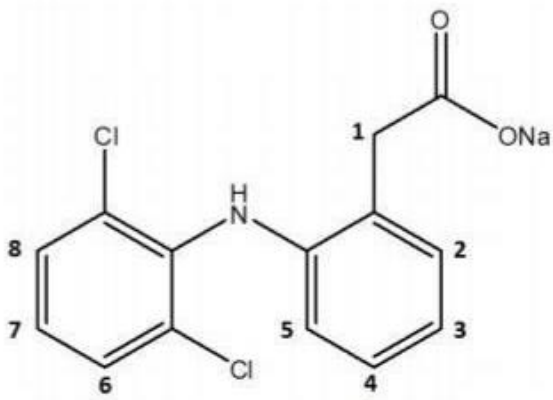


Figure 1: Chemical structure of diclofenac sodium.

Sodium[o-(2,6-dichloroanilino) phenyl] acetate [13]

QUALITY CONTROL TEST FOR DICLOFENAC

Retention time of the Diclofenac peak in a chromatogram of test solution correspond to that of the resolution solution as obtain in the test of chromatographic purity. (19)

The residue obtains by igniting it response to the flame test for sodium <191>. [19]

Color of solution:

A one in 20 solution of it in methanol is colorless to faintly yellow, and the absorbance of the solution, determined in a 1cm cell at 440 nm, is not more than 0.50, methanol being used as the blank [19]

Clarity of solution:

The solution prepared as directed under color of solution is not significantly less clear than an equal volume of methanol contained in a similar vessel and examined similarly.

Loss on drying:

Dry it at 105° to 110° for 3 hrs. it loses not more than 0.5% of its weight.

Assay:

Dissolve about 450 mg of Diclofenac sodium, accurately weighed, in 25 ml of glacial acetic acid, and titrate with 0.1N perchloric acid VS, determining the end point potentiometrically. Perform a blank determination and make any necessary correction. Each ml of 0.1N perchloric acid is equivalent to 31.81 mg of Diclofenac sodium.[19]

Preparation of granules by wet granulation

Wet granulation: -

The process of adding a solution to powder involves the wet massing to dry powder particle using a granulating fluid Wet granulation forms granules binding powder together with binders. The metho of introducing the depends on its solubility and on the components of mixture.[10] Binder used in the wet granulation are:

1. Starch
2. Cellulose derivatives A] Hydroxypropyl cellulose

B] Hypromellose

3. Povidone [12]

Formula: -

(Table No.-1)

Ingredients	Quantity for 1 tablet	Quantity for 30 tablets
Diclofenac sodium	100 mg	3g
Starch paste	75 mg	2.5g
MCC	310 mg	9.3g
Magnesium stearate	10 mg	0.3g
Talc	5 mg	0.15g

Procedure

Preparation of Starch paste: -

2.5g of starch was dissolved in 25 ml of distilled water, heated the solution to become viscous, then 25 ml of more water was added to the solution and dissolved. After complete mixing more 50 ml of distilled water was added, heated the solution to dissolve it well and cooled it down.

Procedure For granulation: -

Required quantity of diclofenac sodium and MCC were taken accurately in a mortar and starch paste slurry added to it, all the ingredients were mixed well. Poured the mixture and collected it well.

Wet mass was passed through sieve no.12 and dried in hot air oven at 60^0 C for 15 minutes.

The dried granules were passed through sieve number 16 and the granules retained on sieve number 20 get collected. Fines of 10 % incorporated to retained granules. Required quantities of magnesium stearate and talc added to granules, mixed in polyethylene bag by shaking it for 30 minutes. After proper mixing we had followed the process for tablet compression.

2. **Quality Control Tests for Prepared Granules**

Particle Size Determination:

Size affects the average weight of tablet, Disintegration Time, Weight Variation, Friability, Flow ability, Drying Rate etc.

The Mean Particle Diameter of Diclofenac Sodium is 20.96 micrometer

The Method for Determining Size and Shape sieving.

Sedimentation Rate iii. Microscopy (SEM) iv. By Light Scattering.

Surface Area:

It is not commonly used for granules but generally used for drug Substances.

Most method used is gas absorption & air permeability.

In gas absorption gas is absorbed as monolayer on particles this is in term of calculated & converted to surface area.

In air permeability method the rate of air permeates a bed of powder, is used to calculate surface area of powder sample.

Density

Density may influence compressibility, tablet porosity & dissolution.

Dense hard granules may require higher load to produce cohesive compact to reduce free granules seen on the surface of tablets.

Increase Compressibility, Increase Disintegration Time, Dissolution, if Disintegration Time is slower dissolution is indirectly hampered.

Dense granules have less friability but cause a problem in releasing the drug.

The Density of Diclofenac Sodium is 1.4 g/cm3.

There are three methods to determine density:

a) Bulk Density

Bulk density is given by equation, $\rho_b = M / V_t$

- ρ_b is bulk density of granules,
- M is mass of granules in gm,
- V_t is volume of granules in measuring cylinder in ml.

More compressible bed of particulate – less flowable powder or granules.

If less dense/compressible – more flowable powder or granules.

True\Tapped density

Tapped/true density is given by equation,[13] $\rho_t = M / V_t$

ρ_t bulk density of granules,

- M is mass of granules in gm
- V_t is volume of granules in measuring cylinder after tapping in ml.

The Range of tapped density for Diclofenac Sodium is 0.4281 to 0.4841 g/ml **c)**

Granular density

It is determined by Pycnometer method.

Two methods are used to determined granular density.

In one intrusion fluid used-Mercury, and other.

Granular Density (D) = M / V_{IP} -V_i Where,

- V_{IP} is Total volume of Pycnometer,
- V_i is Volume of intrusion fluid (ml)

Granule Strength & Friability:

They are important because they affect:

a) Change in particle size distributions of granulation

b) Compressibility into cohesive tablets

Granule strength & friability are measured by:[14]

c) Compressive Strength

d) Using Friability Measurements.

Flow Properties:

It is an ability of the granule to flow from hopper to die cavity for tablet uniformity

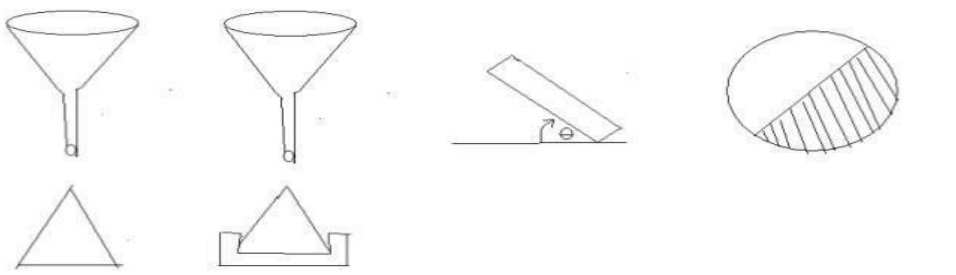
Flow properties of granules are determined by measuring 3 parameters:

e) **Angle of Repose:**

The angle of repose of Diclofenac Sodium ranges from 21.22 to 34.22 ▪ It is measured by two methods: 1) Static angle of repose

2) Dynamic angle of repose

Its equation is, tan **θ = h/r**. Were, θ – Angle of repose, h – Height of pile, r – Radius of pile.



Fig(1) Fixed height **Fig(2) fixed base cone** **Fig (3) Tilting angle** **Fig (4) Rotating cylinder**

SVERI's COP,PANDHARPUR. 20

Hausner's Ratio

The range for Diclofenac is 1.12 to 1.16

Hausner's ratio was related to interparticle friction and as such could be used to predict powder flow characteristics. It showed that powder with low particular friction such as coarse sphere had ratio of approximately 1.2, whereas more as cohesiveness- less free flowing powders such as flaks have Hausner's ratio greater than 1.6.

Formula: **Hauser's ratio = Tapped density / Bulk density**

Compressibility Index

It is directly related to the relative flow rate cohesiveness & particle size.

It is simple fast & popular method of presiding powder flow characters

The range for Diclofenac Sodium is 11.13 to 14.26%

It can be obtained from bulk density measurements is the % Compressibility index I.

Formula:

% Compressibility index = Tapped density – Bulk density / Tapped density X 100.

Were,

- I is % Compressibility index,
- V is Volume occupied by powder/ granules after tapping,
- Vo is volume of powder/granules

Moisture content:

Generally, the granules contain 2 % moisture. It is required for the binding of the powder or granules during compression in die cavity. The range for Diclofenac Sodium is 1.02 to 1.08 %.

Percentage of moisture is calculated by using "moisture Balance" or "Imbalance".

IR Balance consist of simple balance which is placed I to the casing in which the IR bulb is attached which produce heat inside the chamber.

% of moisture is calculated by,

% moisture content = Initial wt. – Final wt./ initial weight X 100.

Percentage:

% fines mean amount of powder remained in the granules.

Generally, the amount is 15 % of fines

% fines can be calculated by using sieve method.

% fine should not be more than 15%.

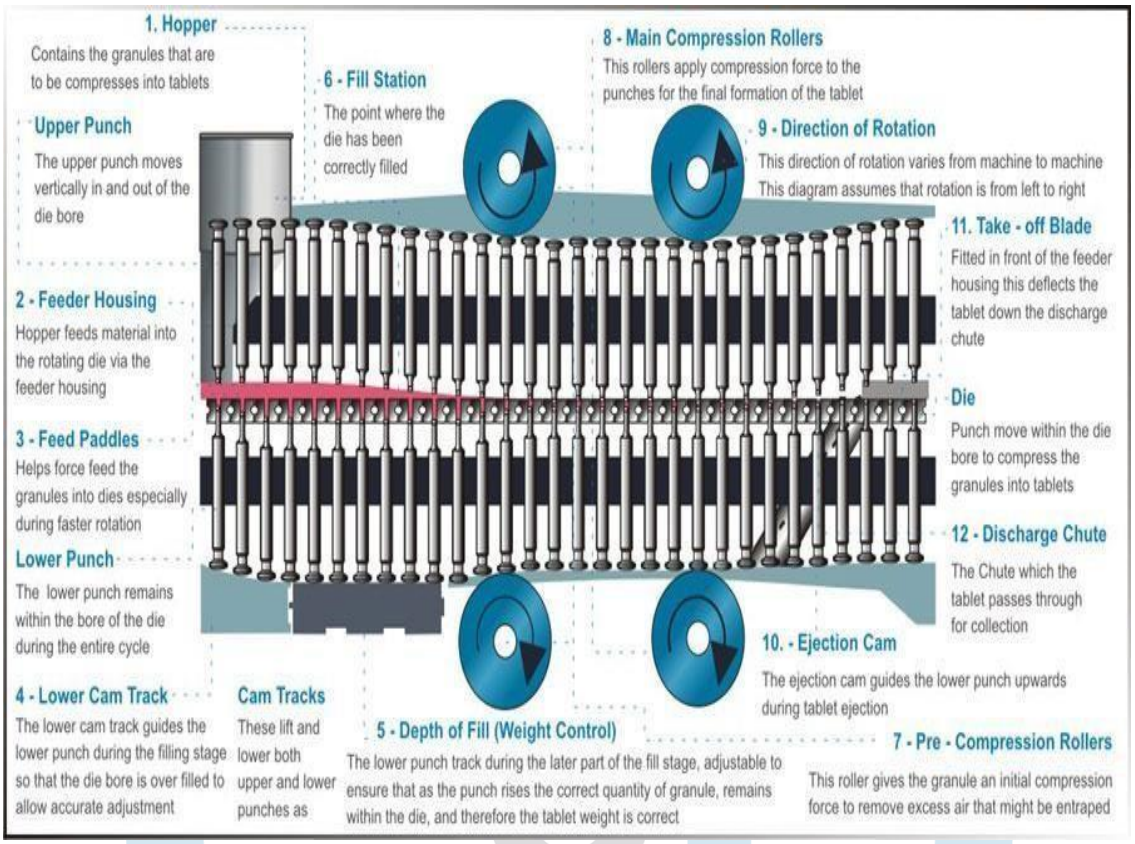
. TABLET COMPRESSION

Diclofenac sodium tablets are being formed by compressing the granules using the compression machine. A tablet formation takes place by the combined pressing action of two punches and die.

Principles of tablet compression machine

The principle behind the tablet compression machine is hydraulic pressure. This pressure is transmitted unreduced through the static fluid. Any externally applied pressure is transmitted via static fluid to all the directions in the same proportion. It is also makes it possible to multiply the force as needed.[14]

Components/Functional Parts of a Rotary Press:



(Compression machine)

Hopper – The hopper holds the granules/powder mixture (API plus excipient) that are to be compressed into tablets.
Die cavity This is where the powder granules are compressed into tablets and it determines -

a. The diameter of the tablets.
b. The size of the tablets.
c. To some extent the thickness of the tablets.

Feed paddle helps to force the feed/ the granules into the dies especially during faster rotation.
Punches This comprises the upper and the lower punches. They move within the die bore to compress granules into tablets.
Lower cam track This guides the lower punch during the filling stage so that the die bore is overfilled to allow accurate adjustment.
Cam tracks This guides the movement of both the upper and lower punches. ▪ **Dept of fill/capacity control** This adjusts the lower punch track during the latter part of the fill stage to ensure that the appropriate quantity of granules remains within the die prior to compression.
Pre-compression rollers this roller gives the granules an initial compression force to get rid of excess air that might be entrapped in the die.
Main compression this roller applies the final compression force needed for the formation of tablets.
Ejection cam Guides the lower punch upwards facilitating the ejection of tablets from the die cavity after compression.
Take-off Blade – This is fitted in front of the feeder housing and it deflects the tablet down the discharge chute.
Discharge chute – This is where the tablet passes through for collection after being deflected by the take-off blade.[18]

Advantages of Rotary Press

High productivity can be gained with a minimal amount of labor while saving money.
Rotary press has an output of between 9000-234000tab/hour thus saves time and meets up with the high demand of tablet dosage form.
The powder-filled cavity can be automatically managed by a moving feeder.
Rotary press decreases waste of valuable formulation in non-specific tablets.
The machine allows independent control of both weight and hardness.[16]

Multi-Station Press

Multi-station press is a mechanical device that unlike the single punch tablet press has several tooling stations which rotates to compress granules/powder mixture into tablets of uniform size, shape (depending on the punch design), and uniform weight.
It was developed to increase the output of tablets.

In rotary press, the compaction force on the fill material is exerted by both the upper and lower punches leaving the powder granules to be compressed in the middle. This is known as accordion type of compression.
The capacity of a rotary tablet press is determined by the rotation speed of the torrent and the number of stations on the press.

Working of tablet compression machine:

I. Filling and dosing of the Dies:

The material to be pressed reaches the rotary or gravity feeder from the material supply.
The fill cam below the feeder pulls the lower punches down by a fixed amount and the dies are filled with material.
The quantity of the material filled in is larger than the actual amount required i.e.
excess dosing is done.
Thereafter, the dosing units lifts the lower punches until only.[17]

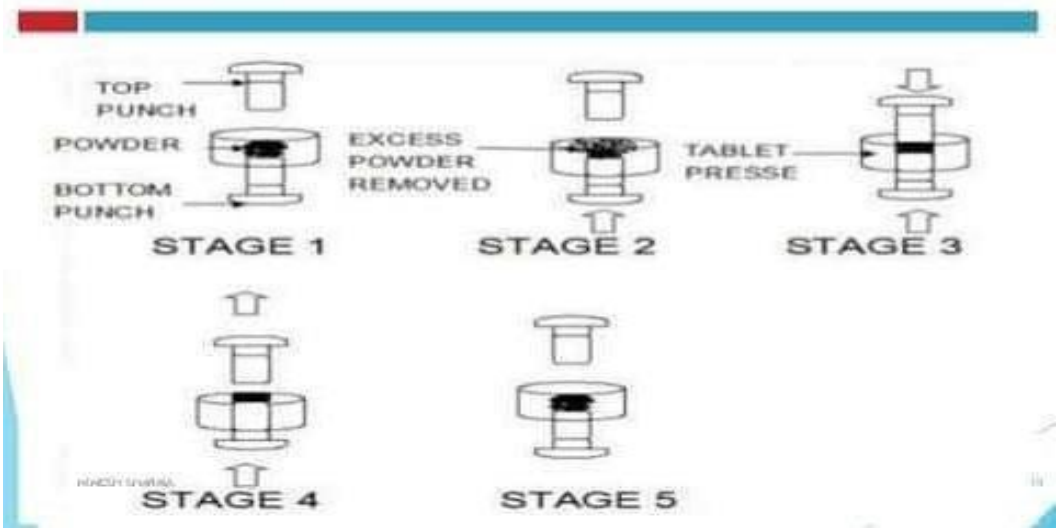
II. Compression of the tablet:

After that, the upper CAM course lowers the upper punch until the upper punches are inserted into the dies.
The lower punches are guide to the pre-compression CAM, they are inserted a little more into the dies and the material is pre-compressed and the slugs are forms. The tablets reach their final height and hardness.[4]

III. Ejection and exit of the tablets:

After the compression, the upper cam course pulls the upper punches into their top position and simultaneously the ejection device lifts the lower punches until the tablets are ejected from the dies.
The tablet stripping device strips the tables off the lower punches and passes them on to the discharge chute and compressed tablets were collected.

The stages in the compression cycle are shown in figure



(Working of Compression machine)

Procedure:

500mg of granules were accurately weighed, 12mm flat surfaced punches were used to compress the tablets.
Accurately weighed amount were poured in the die cavity, the volume of the die cavity was adjusted, so that 500mg of granules could be appropriately filled into the die cavity.
The compression force of tablet compression machine was adjusted, the tablet was compressed between upper and lower punches.
Hardness of the prepared tablet was evaluated and checked whether the compression force was proper or not.
Since, tablet hardness was in proper range, further all tablets were compressed at same compression force and compressed tablets were collected.

7. Quality control test for Tablets:

General Appearance:

Size, shape and thickness
This is important to facilitate packaging and to decide which tablet compressing machine to use.
Organoleptic properties:
Which include color, taste and odor of the tablets.

(Table No.-2)

Official test	**Non-official test**
Content of API	Tablet hardness or crushing strength
Uniformity of weight	Friability
Uniformity of content	Tablet thickness
Disintegration test	
Dissolution test	

I. Content of API:

Analysis of API is usually carried out using spectrophotometry or High – performance liquid chromatography [HPLC].

II. Uniformity of weight:

It is performed by weighing individually 20 tablets.

Sample complies with USP standard. If not more than 2tablets are outside the percent limit and if no tablet differs by more than 2-time percent limit. [12]

(Table No.-3)

Average weight of tablets	Deviation (%)	Number of tablets
Less than 80 mg	±10.0 ±20.0	Minimum 18 Maximum 2
80mg to 250 mg	± 7.5 ± 15.0	Minimum 18 Maximum 2
More than 250 mg	± 5.0 ± 10.0	Minimum 18 Maximum 2

III. Uniformity of content:

It is required for all coated and uncoated tablets containing less than 50mg of an active ingredient comprising less than 50%of the weight of one dosage unit. Nine of 10 must contain labeled amount 15%and none exceed 25%.

Disintegration time:

It is the time required for tablet to break into particles the disintegration test is measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through 10 mesh screens.[12]

IV. Dissolution test:

Dissolution is the process by which a solid enters a solution.

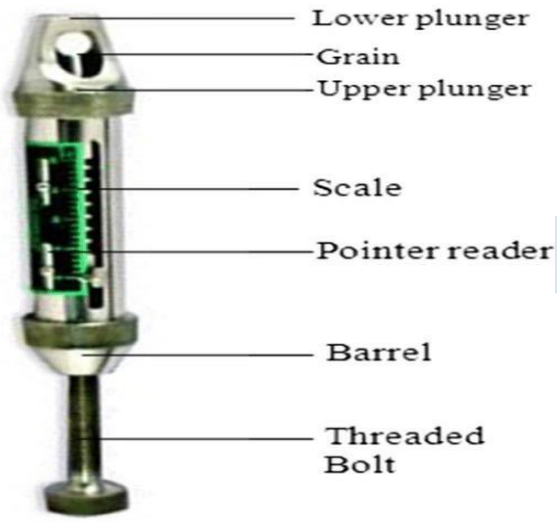
The dissolution rate is defined as the amount of drug substance that goes into solution per time under standardized conditions of liquid/solid interface, temperature and solvent composition [7]

V. Tablet hardness or crushing strength:

This measures the degree of force in [kg and pound or arbitrary unit] needed to fracture tablet.

It is usually checked by Monsanto, stokes hardness tester, strong Cobb tester and Pfizer hardness tester.

$$\text{Tablet Tensile Strength} = \frac{2\,(\text{Breaking Strength})}{\pi(\text{Diameter})(\text{Thickness})}$$



(Tablet Hardness Machine)

VI. Friability:

It is tendency of tablets to powder, chip. Or fragment and this can affect the elegance appearance, consumer acceptance of tablet, and also add to tablet's weight variation or content uniformity problems.

Fryolator determine friability by allowing the tablet to Rolland fall 6 inches within a rotating tumbling apparatus [19]

$$\text{Friability} = \frac{\text{w intial} - \text{w final}}{\text{w intial}} \times 100$$

Where, $W_{initial}$ = weight of the tablets before test (mg).

W_{final} = weight of the tablets after test (mg).

% Friability of tablets less than 1% is considered acceptable.

.

(Friability machine)

VII. Tablet thickness

Tablet thickness is determined by the diameter of the die

ii. The amount of fill permitted to enter the die cavity

iii. The compaction characteristics of fill material

iv. Force or pressure applied during compression.[11]

Result:

(Table No.4)

Sr. no	Evaluation parameter	result	remark
1.	Hardness	5kg/cm^2	Sufficient mechanical strength
2.	Thickness	3mm	Sufficient mechanical strength

8. SUMMARY

Good manufacturing practices is a quality control system which makes sure that every pharmaceutical product is adequately tested and further analyzed. GMP also control the quality of food, diagnostics, and ingredients in the drug, food and pharmaceutical devices used. The leche Q7 guidelines for GMP practice for API under appropriate system for managing quality. Pharmaceutical instruments play an important role in the tablet manufacturing process. The granulation process allows to improve the properties of powder, flow ability and compressibility due to the more regular shape and large size of granules than the original particles. Tablets are being formed by compressing the granules using the tablet compression method. The prepared tablets were evaluated for its official and non-official tests. In industry the personnel requirement during manufacturing of pharmaceutical tablets are production pharmacist, manufacturing chemist, analytical chemist, quality assurance manager, machine operator and mechanics.

The quality assurance is essential for ensuring that pharmaceutical products are manufactured to a safe and consistent standard. Quality control is the practice of ensuring consistent quality throughout a manufacturing process and also uniformity in a company's product. Tablets are evaluated by a variety of methods. Tablet hardness must be hard enough to withstand mechanical stress during packaging and handling by the consumer. Pharmaceutical packaging involves variety of materials which are carefully selected to preserve and protect the drug and enable the customer or the patient to use it safely.

REFRENCES:

1. PP Sharma et al., Good pharmaceutical manufacturing practice GMP, Rational and compliance, Vandana publication pct. Ltd;2006; page no312-316,481-484
2. Alan AC, International Pharmaceutical Registration, Pharma International Innovation Centre CH 4123 Allchin Switzerland, March 2000.
3. Deshpande SW et al., The drugs and cosmetics act 1940 & rules, 1945, Fifth edition,2009, Impression graphic.156-78.
4. EU/EMEA. www.emea.europa.eu, European Commission Enterprise And Industry Directorate- General Consumer goods Pharmaceuticals
5. Brussels et al., Guidelines to Good Manufacturing Practice
6. Medicinal Products for Human and Veterinary Use, Volume 4EU,25 October 2005.
7. Sharp J et al., Good pharmaceutical manufacturing practice, CRC Press, 2005.19258
8. https://www.pharmaceuticalmachinery.in/
9. Mbenga et al., Pharm Anal Chem Open Access 2016, 2:1
10. Roop K Khar's Vyas et al., Lachman/Lieberman's The Theory and Practice of Industrial Pharmacy, Fourth Edition page no 470-471,67-68
11. https://www.researchgate.net/publication/302870672_Quality_Evaluation_o diclofenac Formulations Manufacture ding DRC on go
12. http://www.pharmatips.in/Articles/Production/Wet-Granulation-Process-ForTabletManufactured (involving%20wet%20massing, %2C%20and% 20be%20non%2Disintegration Timeboxes.
13. Indian Pharmacopoeia-2007, Goof Indian Ministry of Health & Family Welfare,5th Edition, page no,171-179
14. www.pharmainfo.net
15. In Process Quality Control Tests (IPQC) for Pharmaceutical Products https://www.researchgate.net/publication/328264833_In_Process_Quality_Controlutetium QC_for_Pharmaceutical_Products
16. https://www.pharmapproach.com/quality-control-tests-for-tablets
17. http://www.saintytec.com
18. http://Rheonics.com
19. The United States Pharmacopoeia 38th Revision, NF 33rd Edition 2015, Vol-