

Study of formulation development and drug manufacturing

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Submitted: 25-11-2023

Accepted: 05-12-2023

ABSTRACT- Formulation development play an important role in the manufacturing of pharmaceutical product or medicine. Formulation development is very essential for curative and success of pharmaceutical product by providing quality protection and efficiency. Many types of formulation development relate to the product development procedure like as research and discovery of the new drugs and many types of trials manufacturing and various tests after market approval. Every drug product prepared by making the trial formulations because many types of difficulty occur during the manufacturing of drug. In this article the role of formulation development in the manufacturing of the drugs, pre formulation studies clinical trials SOP handling and procedure of drug manufacturing can be understand and recognized by all.

Keywords-Formulation, Clinical trials, Excipients, Bioavailability, Validation.

I. INTRODUCTION

Pharmaceutical formulation is the process in which the active pharmaceutical ingredients is mixed with the excipients and all other the components by determining the particle size of the granules polymorphism solubility and PH and become the useful medicinal product. Development of drug is very high trend in the drug manufacturing industries and biotechnology industries. Scientists of formulation development must determine the most suitable route to achieving effective and useful drug delivery based on the needs of patient the optimize the quality of formulations based on the knowledge of the Product and medicines bioavailability and processing requirements^[1,2]

Formulation development is determined the optimum dosage form the composition of ingredients and methods of manufacturing which is fundamental part of pharmaceutical product development. This is a difficult challenge that only 10% of new drugs is developed successfully in preclinical formulation and reached into the

market. Similar challenges also occur for generic pharmaceutical industries. When any new drugs is developed then the drug is not developed in final stage but the active pharmaceutical ingredients or excipients are identified by many types of researches. The best way to deliver the active pharmaceutical ingredients to its site is called pharmaceutical formulation. In modern pharmaceutical formulation is challenge faced by the biotech companies the new drugs which is to be developed is tested first in human clinical trial. Formulation development is also very important factor of drug development in the future marketing^[3,4]

The formulation development is the key of pharmaceutical product development that is determined by the success of the pharmaceutical product pharmaceutical formulation development involves the design of the drugs composition, structure, administrations methods and process of manufacturing. During the manufacturing of pharmaceutical product the active pharmaceutical ingredients should proper combination with the various chemical ingredients.



Definition –Pharmaceutical formulation development means discovery of a new drug to the successful development of new drug product. The Scientists must be determined the most suitable route of administration based on patients need and desirable effects. Pharmaceutical formulation is the process in which the active pharmaceutical

ingredients is mixed with the excipients by determining the Physical, chemical and mechanical properties of drug substances. And results of drug stability studies^[6]

Pharmaceutical formulation development is the process in which the various chemical substances is combined and mixed with active pharmaceutical ingredients and formed a pharmaceutical product which shows desirable effects is called pharmaceutical formulation development.

History-Discovery of drug and development has very long history. In ancient times drugs were not uses for the physical remedies but drugs was also associated with the religious and spiritual healing. The modern times the drugs derived mainly from the plant sources and animal material and minerals. The drugs were discovered with errors and trials experimentation and observation of animal and human reactions. The discovery of drugs and development started following the scientific technics after 1800s. From then many types of drugs discovered and developed in large scale manufacturing plants.^[5]

The first medicine is invented in 1804 by a german scientists Friedrich Sertuner. This drugs is made from the natural sources. The first synthetic drug is developed in 1869 is chloral hydrate shows the action of sedative and hypnotic. The first antipyretics and analgesics produced by the acetanilide and phenacetin. In the starting of twentieth century firstly the barbiturates family of drugs is developed.^[7]



The drug development Process-The process of drug development can be divided in following type.^[8]

1. Discovery and development

2. Preclinical research
3. Clinical research
4. FDA review
5. FDA post-market safety monitoring

1. Discovery and Development- Drug discovery means how to drug was invented. Drug discovery is and development mainly started with the identification of active pharmaceutical ingredients of traditional medicines after some years classical pharmacology developed and finds the therapeutic effects of the drugs. Efficacy or potency, half life of drugs, bioavailability of drugs are improved in following steps.

- Target Identification and validation.
- Hit discovery process.
- Assay development and screening.
- High throughput screening.
- Hit to lead process.
- Lead optimization.
- Active pharmaceutical ingredients.

2. Preclinical research- Preclinical research starts with the in vivo research to determine the safety and efficacy of the drugs.

- Absorption, distribution, metabolism, and excretion related information.
- Mode of action and potential benefits of drugs.
- Route of administration and dosage form.
- Adverse effects of drugs.
- Effectiveness compare to other similar drugs.

3. Clinical research-Clinical research include the clinical trials and volunteer studies of drugs to improvement the drugs for patient use.

- Phase 1-healthy volunteer study of drugs.
- Phase 2-and phase 3 studies in the patient population.
- Doses studies.
- Safety and efficacy studies.
- Pharmacokinetic analysis.
- Bio analytical method development and validation.

4. Food and drug administration review-When a new drug is formulated for best efficacy and safety and results. The drug is advance forward for food and drug administration review then the FDA review and approved or not approved

and The drug application submitted by the drug manufacturing company.

- NDA /ANDA / BLA Application.
- FDA Approval.
- Drug registration.

5. **FDA Post-market safety monitoring**-FDA requires the drug manufacturing industries to monitoring the safety of its drug by using the FAERS database.(FDA adverse event reporting system)

Formulation of drugs-Mainly drugs are formulated in following forms-

1. **Tablet Formulation**
2. **Capsule Formulation**
3. **Powder Formulation**
4. **Oral Solutions Formulation**
5. **Injectable Solution Formulation**
6. **Others Formulations**

Tablet formulation- There are 3 most common methods of tablets manufacturing-^(9,26)

1. Wet granulation
2. Dry granulation
3. Direct compression methods



1. **Wet granulation**-Wet granulation process involve following step-

Dispensing , weighing , milling and mixing the APIs with the powdered excipients.

Preparation of binder solution

Mix the binder solution with the powders

Wet screen the powders into granules using a mess screen

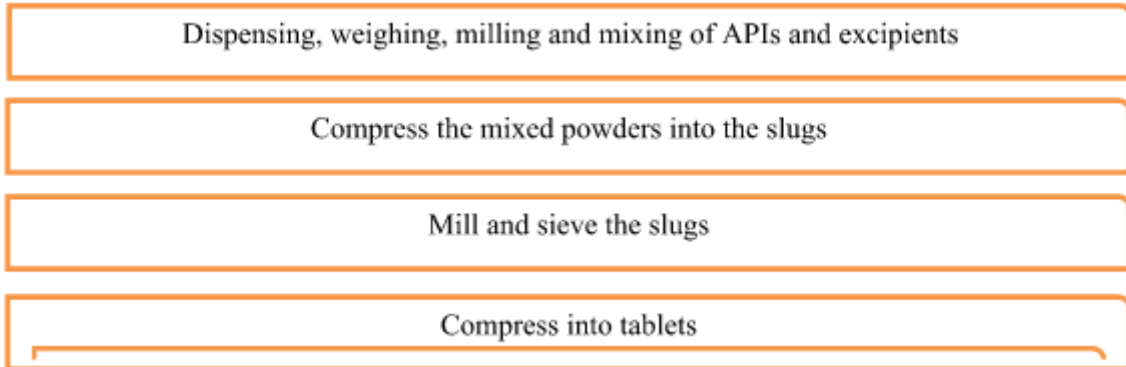
Dry the moist granules

Use dry screening for size granulation

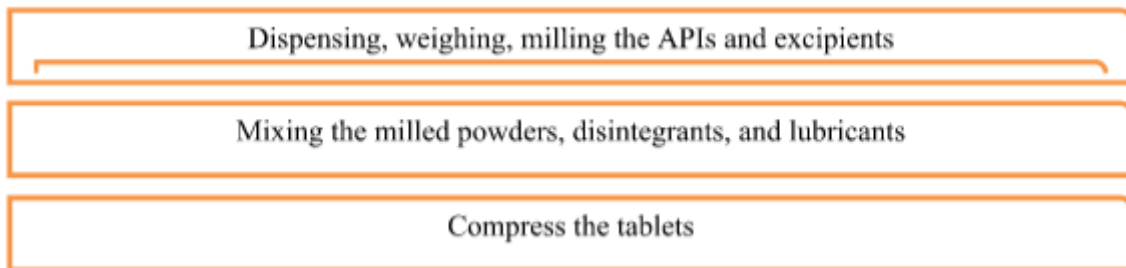
Mixing the dried granules with lubricant and disintegrants

Compress the granules into tablets

2. **Dry granulation-** Dry granulation methods involve following process-



3. **Direct Compression-** Direct Compression method involve following process-



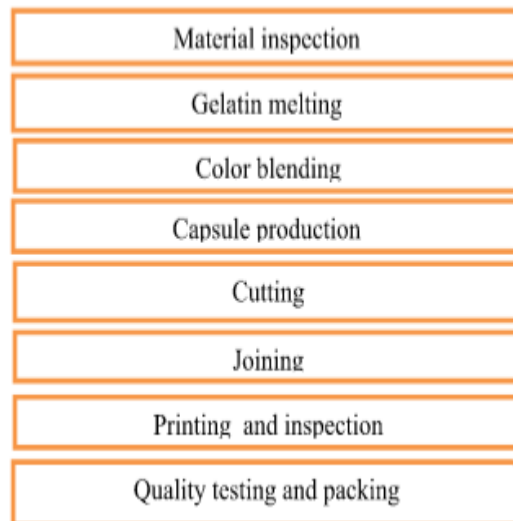
Capsule formulation- Capsule is solid dosage form in which drug substance is filled within the hard gelatin cell of soft gelatin cell the cells of capsule is made up of gelatin

Type of capsule-

- Hard gelatin Capsule
- Soft gelatin Capsule

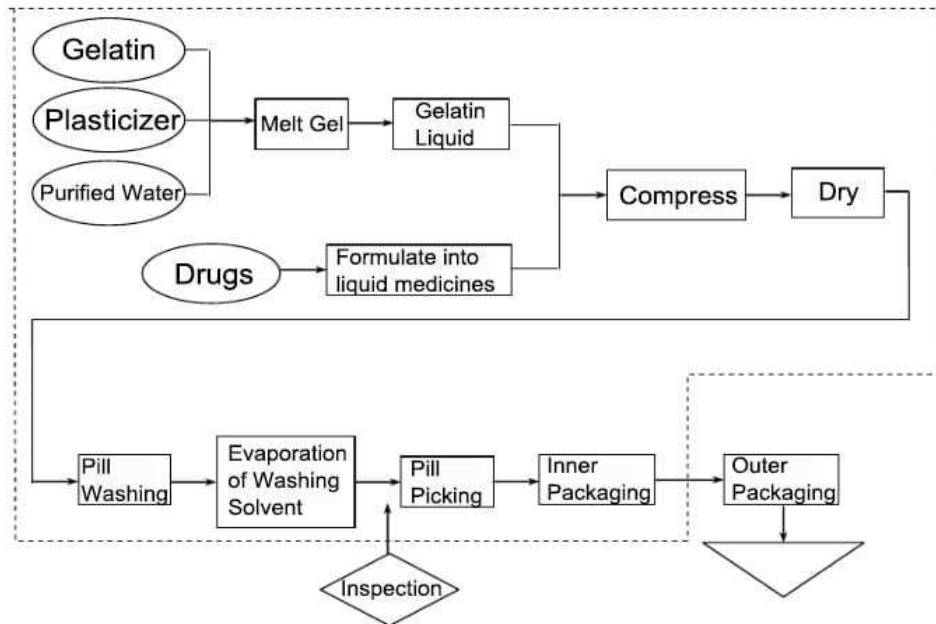


• **Hard gelatin capsule-** Hard gelatin capsule is prepared by following process⁽¹⁰⁾



• **Soft gelatin capsule-** Soft gelatin capsule are smooth in nature and required some ingredients like as glycerin to obtain soft texture. Liquid or semisolid medicaments is filled in soft gelatin capsule. Soft gelatin capsule are widely prepared for nutritional substances.^(11,12,40)

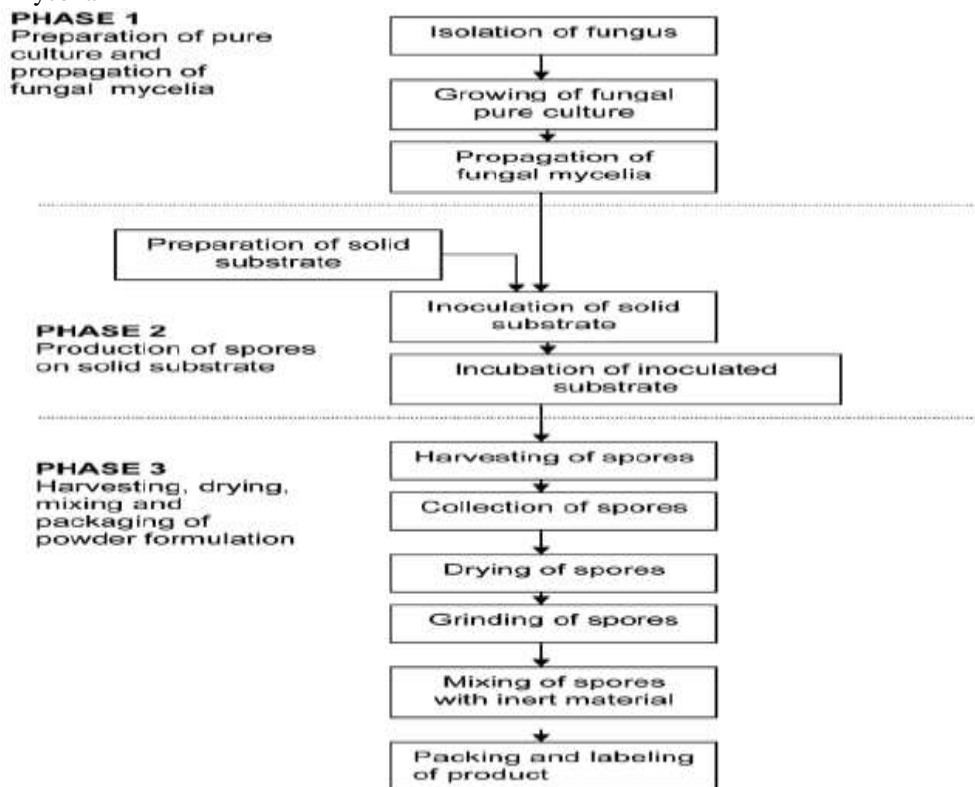
Soft Capsule Production Process



Powder formulation- Pharmaceutical powder formulation involve following phases^(13,39)

- Preparation of pure culture and propagation of fungal mycelia

- Production of spores and substrate
- Harvesting, drying mixing and packaging of powder formulation



Oral solution formulation- Oral solution formulation is a type of dosage form in which the medicaments is administered in liquid form.^(24,25)

Classification of liquid orals-

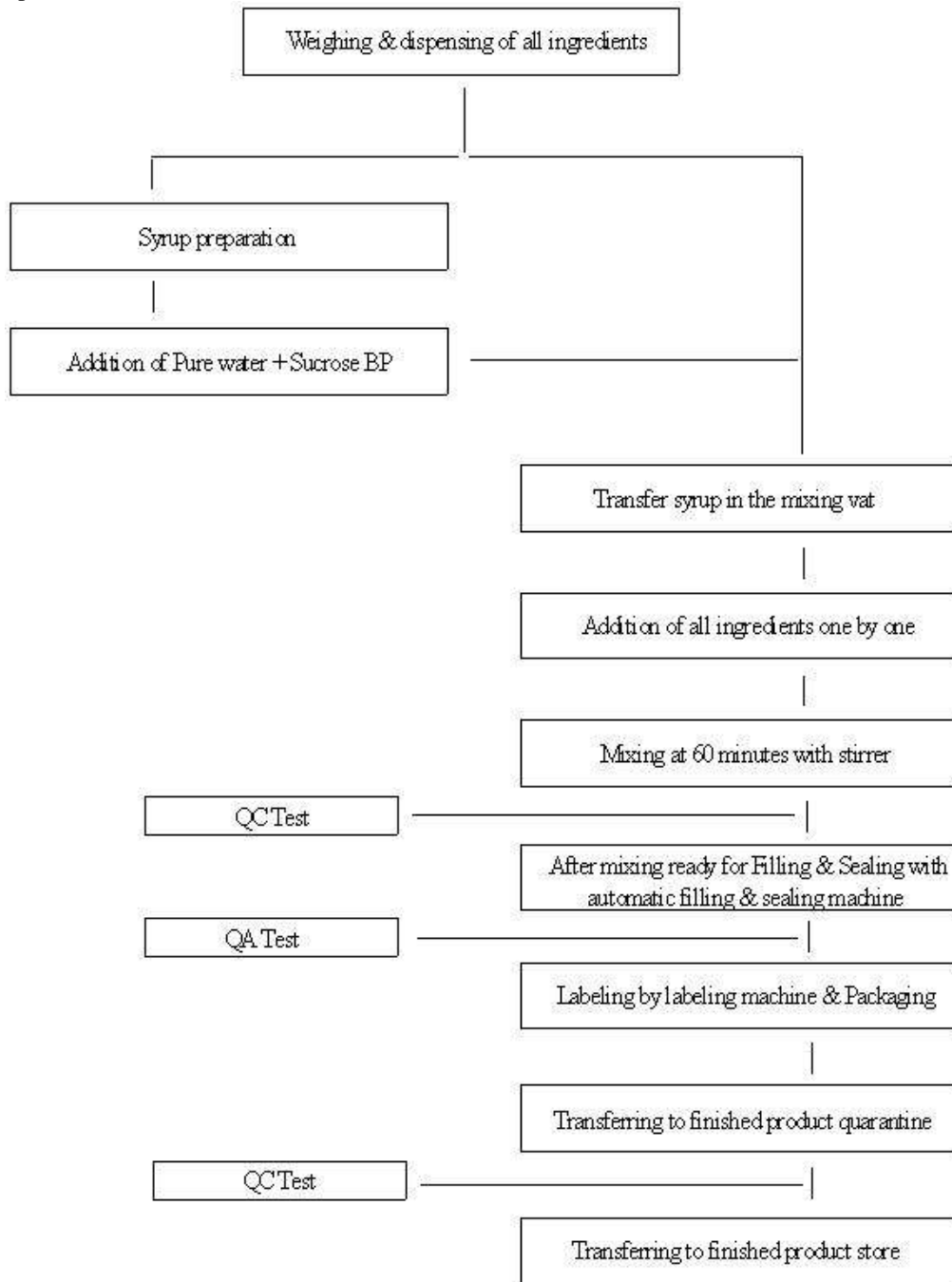
• **Monophasic liquids-**

- Solution elixir
- Syrup
- Liquid drops etc.

• **Biphasic liquids**

- Suspension
- Emulsions

Oral solution formulation- Oral solution preparation involve following steps-



Injectable solution or parenteral preparation-

Injectable solution are the type of dosage form which is administered into human body by intravenous, intramuscular, or subcutaneous injection. It is also called parenteral products. Injectable solution are not to administered orally⁽¹⁴⁾



Type of parenteral formulation-Based on the route of administration the parenteral products are following types-^(15,37,38)

- Intramuscular for muscle
- Intradermal into the skin
- Intravenous for veins
- Subcutaneous under the skin
- Intraosseous for bones
- Intraarticular for joints
- Intraarterial for arteries
- Endotracheal for down the trachea
- Intracerebral for brain
- Intracardiac for heart
- Intraspinal for spinal column
- Intrathecal for spinal fluid
- Intrasynovial for joint fluid area

Formulation of parenteral products-In the manufacturing of dry and liquid parenteral preparation the raw material, APIs, and packaging material should held in aseptic generally parenteral formulation involve following steps-

- Cleaning
- Filtration
- Filling
- Sealing
- Sterilization
- Packaging of Parenteral products

Cleaning- Cleaning is very important focus before, during, and after manufacturing of parenteral product to prevent the contamination. Before preparation of any product we sure that the equipment or machineries is clean.^(16,17)

Filtration- if the material is liquid then after dispensing it should filter. For clarify and removing the foreign particle down to 0.2 micro meter. Parenteral solution must have high purity and clarity.

Filling- After manufacturing filling of product into the container is sterilized by the filtration process and will not sterilized into the final container. The product must transferred from the bulk container they subdivided into those containers during the filling process and after filling in dose containers it should be sealed

Sealing- After filling the dose container the container should sealed under aseptic condition.

Sterilization- sterilization process should done after the sealing of dose container or final container.

Packaging of parenteral products- Parenteral products are filled in two type of containers-

- Glass containers
- Plastic containers

Glass containers- Glass container is composed of silicon dioxide with amount of various oxides ex. sodium, potassium, aluminium, magnesium, boron, and iron.

Plastic containers- Plastic packaging material is not easily breakable compare to glass container and weight is also reduced in large volume intravenous fluids currently uses the flexible bags of PVC or polyolefin

Other formulations-

Cream formulation- Creams are semisolid, viscous, and homogenous preparation intended for external application. Creams are manufactured by using of hydrophilic and lipophilic bases. Cream can be used for administering the drugs through the vaginal route. Cream may contain antimicrobial agent and preservatives and emulsifiers.^(33,34)

Production of creams- Creams are manufacturing by following methods.^(20, 27)

1. Weighing and measuring of raw materials used in the formulation of cream.
2. After that oil phase and aqueous phase is prepared at required temperature, stirring speed and time.

3. Emulsification process is performed.
4. Packing and dispensing.

Eye drops-Eye drops is a medication that is directly administered into the eye Eye drops containing only saline and some time contain lubricant. Eye drop is used in the condition of allergies, infection, redness, and glaucoma^(21,35)



Production of eye drops- Eye drop preparation involve following steps-^(22,36)

1. Preparation of solution or vehicle which contain preservative, stabilizer, antioxidant, tonicity modifier etc.
2. Add active ingredients and other excipients and make up volume.
3. Clarification of the solution, filled into the final containers sealed and sterilized the eye drops.
4. Packaging and dispensing.

Inhalation preparation-Inhalation preparation are liquid or solid dosage form administered in aerosols or vaporization forms to the lungs to obtain a systemic or local effect⁽²³⁾

Type of inhalations- Inhalation are two types

- Moist/wet inhalation
- Dry inhalation



Inhaler production- There are some important factor that must be considered during manufacturing of inhaler

- Target action
- Therapeutic development
- APIs stability during the administration

Method of inhaler manufacturing process-

Metered dose inhalers production –

Cold filling method- In cold filling method The concentrated drugs, volatile propellants, and other excipients are mixed within the vessel under the pressure at low temperature.

Pressure filling method- In pressure filling method the concentrated drugs, volatile propellants and other excipients are mixed under the pressure within the vessel

Insulin preparation- Insulin preparation are intended for human or animal body by subcutaneous route insulin are prepared by suspension and solutions insulin preparation contain not less than 90.0 % and not more than 110.0% of the amount of insulin. Leonard Thompson was the first human that receive an injection of insulin

Production of insulin- Insulin production involve following steps -

- Human insulin preparation are sterile preparation used in the treatment of diabetes in the production of insulin the insulin producing gene is isolated.
- Human insulin producing gene is insert into the bacterial plasmid vector to formation of recombinant DNA.

- After that the recombinant DNA is introduced into the bacterial cell for the formation of recombinant bacterium.
- The recombinant bacteria is divided in the tank and produced human insulin. After that human insulin is extracted from the fermentation tank, purified and packed.^(18,31,32)

Pessaries—Pessaries are vaginal preparation that contain one or more active ingredients. Pessaries single dose and solid preparation have various shape suitable for introducing into the vagina. It is used in the treatment of stress urinary incontinence to stop urinary leakage or treat organ prolapse. It is also used as a method of contraception.^(23,30)



Production of pessaries- Pessaries are prepared by moulding. measures are taken in the pessaries manufacturing to ensure the appropriate particle size. The medicaments including various excipients are heated and convert into the liquid and poured into the moulds. After that cooling and solidify.

Suppositories-Suppositories are solid formulation suitable for rectal administration. Suppositories contain auxiliary substances like lubricant, diluents, absorbents, and antimicrobial preservatives and colouring agents.

Method of preparation of suppositories-Suppositories are prepared by mainly 3 methods.

1. **Hand rolling method**- Hand rolling method is the oldest method. In this method the APIs and excipients are mixed with the suppository bases and after that rolling by hand to provide the shape it is time consuming process.
2. **Compression molding method**- Generally suppositories are prepared by using this

method. The APIs and excipients are mixed with the suppositories base after that inserted into the power driven compression machine.

3. **Fusion molding**- Fusion method is performed by heating the mold in this method firstly the suppositories bases are melted and drug is dissolving in the melted base. After that inserted into the suppository mold. After that suppositories are removed from the mold.^(19,29)

II. CONCLUSION

Formulation development are cover the combination of APIs and excipients and convert into the suitable dosage form is called drug formulation. In above article the development of drugs and manufacturing methods of drug is discussed. Pharmaceutical formulation development are important challenge which is faced by the biotech companies it also developed the investigational medicinal product and success of a drug. Formulation development make easy to deliver the active substance to the target organ. In the modern drug development dosage form development often delayed due to insufficient quantities of active pharmaceutical ingredients are available. The novel approaches of formulation development helps to overcome the challenges in the requirements of labor, machineries, and materials during the formulation of drugs.

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