IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

ADVANCE FORMULATION DEVELOPMENT TECHNIQUES

Assistant Professor:Miss Swati Aher.
[2]*Student, Nisha A.Sathe ,Divya .D.Kudal,Matoshri Institute of Pharmacy, Dhanore,Nashik*
[3]*Student,Shubham D.Hembade Matoshri of Institute of Pharmacy,Dhanore ,Yeola,Nashik*

Abstract : Formulation development scientists must determine the most appropriate route to achieving effective drug delivery based on patient need, then optimize the formulation's characteristics based on a knowledge of the drug product's bioavailability and processing requirements. Drug formulation is one of the most critical aspects of the pharmaceutical development process. If a drug cannot be delivered in a stable form that is acceptable to the patient, it is unlikely to find a sizable market, and it may not even go beyond Phase I clinical trials. The science of drug formulation revolves around the configuration of best possible potent agent that is highly efficacious without adverse effects, To achieve the desired final quality of tablets and improve the production efficiency, it is necessary. However, this aspect seems to be unexpectedly ignored in terms of reviews published so far. Therefore, it is the major focus in this review and was summarized and discussed based on the quality by design (QbD) concept.CGMP,SOP Of Different Instrument & Identification And Characterization Of Drug By Using FTIR,DSC,UV.

KEYWORDS: GRDDS ,CGMP, SOPs, UV, FTIR,DSC

INTRODUCTION

1. INTRODUCTION TO FORMULATION DEVELOPMENT:

Because it ensures product quality, safety, and efficacy, formulation development is a crucial component of pharmaceutical research and is necessary for both therapeutic and commercial success. [1]The multi-step process of pharmaceutical formulation involves combining the active medication with all other ingredients while taking pH, solubility, polymorphism, and particle size into account to create the ultimate useful medicinal result. [2]The success, lifetime, and patentability of a medicinal product can all be determined by its formulation. To improve their product development, businesses employ personnel, development guidelines, and this formulation. [1]recise dose forms are taken into consideration throughout the creation of pharmaceuticals in order to guarantee stability and efficient product distribution. Finding the ideal pharmaceutical dosage form, content, and manufacturing technique is the aim of formulation development. There are many different kinds of pharmaceutical dose forms, such as oral, liquid, powder, controlled, and sustained drug medications. [3]

I.Definition:

The successful creation of a commercial drug product is correlated with the discovery of a novel drug substance, according to pharmaceutical formulation development. Based on patient demand, formulation development experts must choose the best course of action for obtaining successful drug administration. They must then optimize the formulation's properties by understanding the therapeutic product's bioavailability and processing needs. [1]

II.History:

Dhanvantari were the once who initially popularized Ayurveda, a mythical medicine from Hinduism. The German chemist Friedrich Serturner created the first medicinal medication in contemporary history in 1804. Up to the middle of the 19th century, natural medications were used. Chloral hydrate, the first synthetic medicine, was created in 1869. Pharmaceutical enterprises use coal-tar distillation to obtain organic compounds, making them the opposite of the textile and synthetic coloring industries. Silicon and aspirin, two extracts from the white willow tree bark, were used to cure fever and inflammation. [1]

The process of preparing a medication in a particular dosage form that is appropriate for patient administration is known as pharmaceutical formulation. [4

2. CONCEPT OF CGMP:

Definition:

CGMP stands for current good manufacturing practices. The FDA defines current good manufacturing practices as procedures to guarantee appropriate planning, oversight, and management of manufacturing facilities and processes in the pharmaceutical and other FDA-regulated industries. These systems are made to assist organizations in ensuring that pharmaceutical items have the proper identification, potency, purity, and quality. [5]

Importance of CGMP:

CGMPs are essential for patient safety in high-risk professions. Through stringent testing, CGMP compliance guarantees the safety and efficacy of drugs. Production procedures as well as instruction. Testing is not enough to ensure quality because most batches can be reused. [5]

Objectives:

1) To create a dosage form that is safe, stable, and effective.
2) To offer pertinent data for the purpose of creating a novel medication delivery method with improved bioavailability.
3) To determine the novel drug's physicochemical characteristics.
4) To produce the relevant data required to create safe dosage forms that can be produced commercially. [6]

Pillars of CGMP:

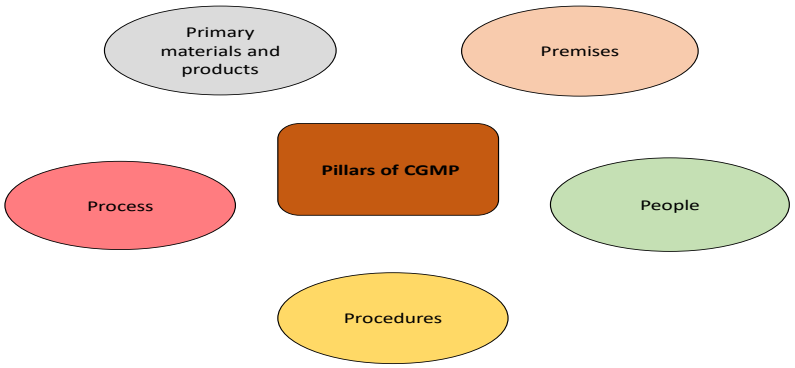

Fig 1: Pillars of CGMP

Products and primary materials:

Subpar primary materials might result in defects because they are the fundamental building blocks used to create a finished good. A master recipe and routine testing are necessary for quality assurance according to GMP requirements.

Premises:

To avoid cross-contamination, mishaps, and fatalities on the premises, cleanliness, appropriate equipment storage,calibration,documented,protocols,ongoingvalidationarecrucial.

People:

Strict adherence to production rules, frequent performance reviews and evaluations, skilled, well-trained personnel, and regular training in sanitation, recordkeeping, labeling, and equipment handling are all necessary for GMP success.

Procedures:

To make sure they understand their responsibilities, employees get recorded training, job evaluations, and quizzes during onboarding and the yearly refresher.

Processes:

Profit is the result of successfully adhering to all five Ps. GMP guarantees product fit and regulatory compliance, fostering a reliable reputation and fostering expansion and success. [5]

3. STEPS IN FORMULATION DEVELOPMENT:

A. Drug Characterization and Validation:

A drug's characterization and validation are crucial since they have an impact on the finished product.

B. Study of Drug Additive Compatibility:

The likelihood that a drug formulation will be successful and that the drug will have an effect both increase with the compatibility of the addition.

C. Formulation Development:

The process of developing a formulation involves combining chemicals with an excipient to create pharmaceuticals.

D. Formulation Optimization:

At this point, formulations such as vaccines are created; compared to conventional formulations, these formulations have undergone a great deal of research and require a great deal of knowledge.

E. Evaluation of Formulation:

By replacing some formulation components, such as the solvent, the assessment studies contribute
To improving the formulation that has already been completed.

F. Research on Stability:

It also contributes to extending the formulation's shelf life and encompasses testing the formulation to achieve greater stability. [7, 8, 9]

4. REQUIREMENT LISTING AND PROCUREMENT:

a) Purchasing medications and excipients needed for particular formulations:

The generic name, dosage form, strength, basic unit, basic package size, basic package in the outer packets, specification of containers, suggested price for the basic unit, and any further specifications are all listed on the selection list, which is created by an approved committee.

b) Purchasing tools and apparatus for formulation and analysis:

It is the process of purchasing supplies of tools and equipment from suppliers, whether public or private, the manufacturer, or their representatives, such as distributors. [6]

MODULE: 2 BASIC TECHNIQUES

1. SOP Handling:

Standard Operating Procedures (SOPs) are written guidelines that specify a regular or recurring task that an organization performs. Sometimes the terms "SOP" are used interchangeably with terms like workbooks, protocols, and directions. [10]

Functions of SOP:

- A potent catalyst that promotes better organizational outcomes and performance.
- SOPs are designed to establish a procedure's accepted practice and quality level.
- The foundation of any high-quality system.
- SOP is a required course of study.[11]

A) Preparation of SOPs for different instruments and equipment:

SOP is a documented, step-by-step guide that outlines how to carry out the necessary actions to finish a task. It is necessary for all parties involved to do these actions. [12]

Procedure of SOP:

The materials required for achieving that goal are listed, along with all necessary actions that must be performed sequentially. All users of the devices, including researchers, lab staff, students, and instructors, are required to read and understand the entire SOP. This is intended to be dynamic and will be updated frequently. Mentioning commercial products or brand names does not indicate approval or recommendation of their use. [13]

2. Various equipment and instruments handling:

a) Tablet compression machine:

Fig 2: Tablet Compression Machine

Operating procedure for tablet compression machine:

1. Clean the compression machine, including the AL Handling Unit. Check return filters for leaks and integrity. Notify quality control for rinse water and swab sampling.
2. After quality control approves, label the equipment "cleaned," apply food-grade oil inside the chamber, and mark it "to be cleaned" for maintenance. Clean the turbine with 70% isopropyl alcohol before getting quality control's permission.
3. Replace the "cleaned" label with the machine's status label, including product and batch info, before starting compression. Set and test punch and machine settings in accordance with the SOP and batch records.
4. Verify batch info on granule containers, set up the machine per tablet specs in the batch record, and destroy initial tablets as per SOP.
5. Store initial tablets labeled "useful residue" for future use. Stop compression when the hopper is nearly empty, handle the remaining residue, weigh, document, and refill containers with compressed tablets.
6. Clean and label outer containers with batch info for storage. Remove and clean materials and records from the previous batch, marking the setup "to be cleaned" for the next batch. Clean and store the punch set and tools in the cabinet.
7. Verify tablet settings and ensure calibration of instruments. Use fresh water for each disintegration test and discard the old water.[14]

b) Tablet Coater:

Fig 3: Tablet coating machine

Operating procedure of tablet coating machine:

1. Ensure the coating pan is clean before starting.
2. Connect the air blower hose to the pan.
3. Measure the required weight of material and transfer it to the pan, warming it with warm air as it rotates.
4. Apply the coating solution to the material while it rotates, ensuring it dries with warm air until the desired coating level is achieved.
5. Once coating is complete, transfer the coated material to a clean polyethylene-lined stainless steel container and label it appropriately.[15]

c) Capsule filling machine:

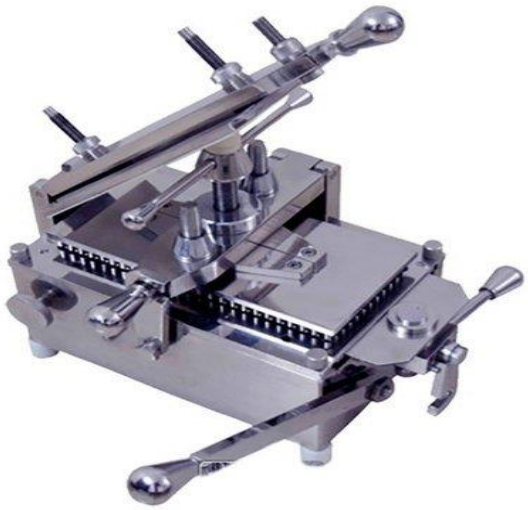

Fig 4: Capsule Filiing Machine

Operating procedure of capsule filling machine:

1. **Locking Plate Open**: Place the adapter on the Caps Tray and ensure the Cam Lever is at 3 o'clock.
2. **Capsule Setup**: Lay down the capsule bodies and CapsiCards® on the adapter, then push capsules into the tray using the Pusher.
3. **Prepare CapsiCards®**: Remove cardboard and modify as needed.
4. **Secure Filler**: Close the Filler Locking Plate by turning the two tabs.
5. **Lock Bodies**: Gently pull the Cam Lever towards the post to secure the capsule bodies without crushing them.
6. **Separate Capsules**: Press down on the grips and raise the Caps Tray to separate the capsules, tightening the cam lever if necessary.
7. **Check Capsules**: Ensure some capsules aren't locked if only a few fail to split.
8. **Release Capsules**: Allow the bodies to fall into the filler and adjust them if uneven, then place the Powder Tray on the Filler.
9. **Add Powder**: Pour powder into the filler, spreading it with the powder spreader, and tamp as needed.
10. **Vibration and Tamping**: Use tapping and optional vibration to settle the powder; avoid holding the filler by the lifting plate.
11. **Tamping**: Use a tamper to add more powder and continue distributing.
12. **Remove Powder Tray**: Take out the powder tray and reattach the Caps Tray to the Filler.
13. **Lock Capsules**: Press down on the locking plate and lift the lifting plate to lock the capsules, repeating as needed.
14. **Locking Process**: Turn the Caps Tray over and use the Capsule Locker to lock the capsules until you hear a snap.
15. **Final Check**: Ensure all capsules are locked using the locked capsule indicator, ensuring it doesn't obstruct any locked capsules.[15]

d) Fluidized Bed Dryer:

Fig 5: Fluidized Bed Dryer

Operating procedure of fluidized bed dryer:

- Before starting, the production officer must label the equipment or area with activity status (product name, B. No. Stage) and notify the IPQA officer for line clearance. Adjust the FBD bowl beneath the chamber.
- Turn on the main power, apply 2.5 to 3.5 kg pneumatic pressure to lock the bowl by opening the compressed air valve, and open the steam and bypass valves to drain condensed water during steam drying.
- Close the condensed valve and adjust the steam valve to achieve the desired air inlet temperature. Set the timer according to batch production records (BMR) and ensure the FBD bowl and exit are not airtight.
- After shaking, remove the container and rack its contents. Reset the product container and continue drying, sampling granules as needed. Once drying is complete, turn off the steam valve and let the material air dry to room temperature.
- Shake the FBD bag to settle its contents. Release compressed air to remove the FBD bowl, then take out the product container. Clean and label the equipment.

- Inspect the FBD bag for integrity, checking for tears, holes, and undamaged stitches, as well as the corners and corner stitches.

- Inspect the FBD bag before and after use, recording findings in the usage record as per Annexure II. Clean the equipment according to the SOP after the operation.[15]

e) Extruder and Spheronizer:

Fig 6: Extruder and Spheronizer

The technique of extrusion involves pushing material—such as pharmaceuticals or other materials—through a series of dies to form desired forms. Pharmaceutical items can be quickly and easily shaped into small spheres, or spheroids, with a diameter of between 0.5 and 10 mm by a technique called spheronization, also called maramuerization. [16]

MODULE 3: EXPERIMENTAL

1. Preformulation study and preparation of preformulation data sheet:

a. Introduction to preformulation, goals and objectives, study of physicochemical characteristics of drug substance.

1. Introduction to preformulation:

In the years 1950 and early 1960, preformulation investigations developed. The process of rationally developing dosage forms for a pharmacological substance begins with preformulation testing. Studying the physical and chemical characteristics of a pharmacological ingredient both by itself and in combination with excipients is what is meant to be understood. [17]

2. Goals:

- To determine the physicochemical property of a novel drug substance.
- To determine its physicochemical characteristic.
- To establish the kinetic rate profile of a novel pharmaceutical substance.
- To establish whether the novel drug material is compatible with the widely used excipients.[18]

3. Objectives:

- To provide the formulator with important data.
- To decrease problems with excipient compatibility.
- To increase the bioavailability of medicines.
- To create attractive dose forms that are dependable, effective, and safe.[19]

4. Study of physicochemical properties of drug:

A) Physical characteristics:

1. Organoleptic properties:

Color: The quality of a substance should be attractive and established using instrumental procedures or visible means that varies between batches. [20]

Odor and taste: Since their stability and bioavailability, which are influenced by excipients, scents, colors, and flavors, drug compounds that cause skin irritation should be handled carefully. [21

2. Bulk characteristics:

a) Flow properties:

The most significant characteristic of powder that determines cohesiveness in terms of angle of repose, Hausner's ratio, and Carr's index is this one. [22]

- **Carr's index:**

$$\text{Carr's index} = \frac{Tape\ density - Bulk\ density}{Tape\ density} \times 100$$

- **Hausner's ratio:**

$$\text{Hausner's ratio} = \frac{Tape\ density}{Bulk\ density}$$

- **Angle of repose:**

$$\text{Tan } \theta = h/r$$

Where, h = Height of pile of surface,
r = Radius of circle. [22]

b) Density:

Density are the most important pharmaceutical properties that can be derived from the information on particle size distribution, particle shape, and surface area. Density can be defined as ratio of the mass of an object to it's volume. [23]

$$D = \frac{M}{V}$$

Where, D = Density,
M = Mass,
V = Volume.

c) Compressibility:

Compressibility measures how much a powder reduces in volume under pressure, while compatibility indicates its ability to form a tablet with a specific tensile strength.

Cubic (NaCl)

Tetragonal (urea)

Rhombic[23]

Compression involves a reduction in bulk volume as a result of reduced gaseous phase. A closer packing of the powder particles as a result of rearrangement is the main mechanism for initial volume reduction. [24]

d) Polymorphism:

The terms used to refer to these different states include polymorphism. The physicochemical characteristics of each polymorphic form, such as solubility and melting point, can differ greatly and significantly affect a drug's stability and bioavailability. Additionally, polymorphism can affect the compression characteristics of drugs (e.g., paracetamol can occur in monoclinic or orthorhombic forms, the latter possessing preferable features of compaction). [25]

e) Hygroscopicity:A lot of pharmacological compounds have a tendency to absorb air moisture, especially salt versions that are soluble in water. Adsorption and equilibrium moisture content can be influenced by temperature, surface area, exposure, and moisture uptake processes in the atmosphere. [26]

3. Solubility Analysis:

The aqueous solubility of a drug molecule is influenced by several physicochemical properties, such as the partition coefficient and molecular surface characteristics that play a role in drug absorption. [27]Therefore, we anticipate and confirm a relationship between low solubility and poor absorption. [28][29]Compounds that are prone to hinder absorption and distribution have been identified through solubility and pH-solubility profiles. [30][31]

A. Dissociation Constant (pKa):

The pH at the retention site, the ionization equilibrium, and the lipid solubility of the unionized species. [25]

B) Chemical characteristics:

a) Hydrolysis:

Many pharmaceutical contain ester or amide functional groups, which undergo hydrolysis in solution. Examples of drug that tend to degrade by hydrolytic cleavage of and ester or amide linkage are anesthetics, anti-biotics, vitamins and barbiturates. [32]

b) Oxidation:

Electrons are lost during oxidation, which is defined chemically as the breakdown or termination of hydro peroxide, the transformation of iron from ferric (Fe3+) to ferrous (Fe2+), or any other process involving the presence of an electron acceptor, also referred to as an oxidizing agent.

c) Reduction: It is a much more common pathway for drug metabolism. The hepatic microsomes can't perform any of their many reductive chemical processes without NADPH.

d) Polymerization: It is a continuous chemical reaction that takes place between molecules. For example, the darkening of the glucose solution is due to the polymerization of breakdown. [33]

b. Identification and characterization of drug using FTIR, DSC and UV:

Drug-excipient compatibility research is essential for product stability, good quality, and preventing incompatibilities during manufacture. [34]

1) Differential Scanning Calorimetry (DSC):

DSC is a thermal technique used to analyze the physicochemical interactions between drugs and excitants.

Limitations:

1. DSC is not suitable for very small thermal changes.
2. It cannot detect compatibilities that arise after long-term storage.
3. New findings from incompatibility testing should be interpreted with caution. [34]

Applications:

1. We can utilize DSC to examine liquid crystals
2. To assess the oxidative stability of samples.[35]

2) Fourier Transform Infrared Spectroscopy (FT-IR):

FTIR analysis is an effective technique for assessing compatibility between a drug and its excipients, as it detects shifts in functional groups during interactions. [36]

c. Physical properties: Physical form (Crystalline & Amorphous), particle size, shape, flow properties, solubility profile, etc.

Physical form (amorphous & crystalline):

Amorphous pharmaceuticals have randomly organized molecules or atoms but have decreased stability within contrast to crystalline formations. Although crystalline medications are more stable and have consistent molecular lattice spacing, they are less water-soluble. [37]

1) Size of particles:

The following is an explanation of how particle size analysis is applied during the preformulation stage:

Reducing the particle size (increased surface area) can greatly boost the solubility when it's a big concern.

In the case of potent formulations, there is a major danger related to content consistency due to non-uniform particle size distribution. [38]

2) Flow Properties:

Proper flow of powdered drug substances is essential for effective tablet formulation. For hygroscopic materials, the flow properties can worsen due to absorbed moisture, which increases cohesiveness. Additionally, irregular particle size and non-uniform shape can disrupt the normal flow characteristics of the drug. [39]

Solubility profile:

The solubility profile is an essential preformulation analysis technique that evaluates formulation performance. It underpins the biopharmaceutics classification system and assists in the design of drug delivery systems.

Table no 1: Correlation of solubility and permeability with BCS class and associated approach in formulation development. [40]

BCS Class	Solubility	Permeability	Approaches in formulation development
Class 1	High	High	Conventional solid oral dosage form
Class 2	Low	High	Use techniques to improve surface area or improving solubility by addition of co-solvent or surfactant
Class 3	High	Low	Use of permeability enhances
Class 4	Low	Low	Use approaches of classes 2 and 3

d. Drug-excipient compatibility studies can be conducted using techniques such as DSC and FTIR.

DSC- Differential scanning calorimetry is a thermal method used to study how drugs and excipients interact by looking at powders, crystal granules, and foils that contain liquids and solids. It offers a fast, reliable approach with minimal sample requirements. [41]

Fourier Transform Infrared (FT-IR) Spectroscopy: Fourier Transform Infrared (FT-IR) Spectroscopy was employed to assess drug-polymer interactions using the KBr pellet method. This involved comparing the individual infrared spectra of Tramadol HCl and various polymers with the spectra of their formulation combinations. [42]

Application of preformulation in dosage form design:

1. The physical properties of the studied API impact its physical and chemical stability.
2. They also affect the route of administration, delivery system, and drug activity.
3. Additionally, the drug's chemical stability is influenced by these physical properties.
4. Commonly studied factors include crystal morphology, polymorphism, amorphous forms, and hygroscopicity.
5. Certain properties are evaluated during the preformulation stage of solid dosage forms. [43][57]

2. Formulation of conventional or novel drug delivery systems

a. Formulation of conventional drug delivery system:

The drug in dosage forms like tablets, capsules, oral liquids, semisolids, ointments, creams, lotions, and parenteral. Conventional methods are commonly used for quick absorption. [44]

1) Tablet:

They are compressed solid dosage forms that contain medicaments with or without excipients used to diagnose or cure the diseases.

Ex. compressed tablets, multiple compressed repeat action delayed release, sugar coated film coated buccal, sublingual troches dental.

2) Capsule:

Capsules are pharmaceutical dosage forms in which the drug or a mixture of drugs is enclosed in a gelatine shell or any other suitable material to form various shapes.

- Type-hard gelation, soft gelatine, enteric coating, sustains release of rectal vaginal
- Methods of formulations punch methods, volume fill, tamping, wax fill.

3) Oral liquids:

Liquid orals are the homogeneous liquid preparations containing one or more active ingredients with or without additives dissolved in a suitable vehicle, meant for oral administration.

- Type: syrups, elixirs, linctus's, mixtures, oral solutions, oral suspensions, emulations, drops

4) Parentals:

Parentals parenteral dosage is a sterile drug product that is presented in the form of solution, suspension, emulsion, or reconstituted lyophilized powder, suitable for administration by injection.

Type: liquid, powder, emulsion, suspension, oily, infusion for injection. [44]

b. Formulation of Novel Drug Delivery System:

1. Controlled Drug Delivery System:

A controlled drug delivery system is aimed at releasing the correct dose of a therapeutic directly in the desired zone and during the required period of time.

2. Nano Carriers:

Nano carriers are useful in the drug delivery process because they can deliver drugs to site-specific targets, allowing drugs to be delivered in certain organs or cells but not in others.

TYPE: liposomes, phytosomes, nanoparticles, microsphere,

3. Vesicular Drug Delivery System:

A vesicular drug delivery system is one of the systems that can improve the bioavailability of the drug and the reduction in toxicity by targeting the targeting the drug to a specific site.

4. Gastro Retentive Drug Delivery System:

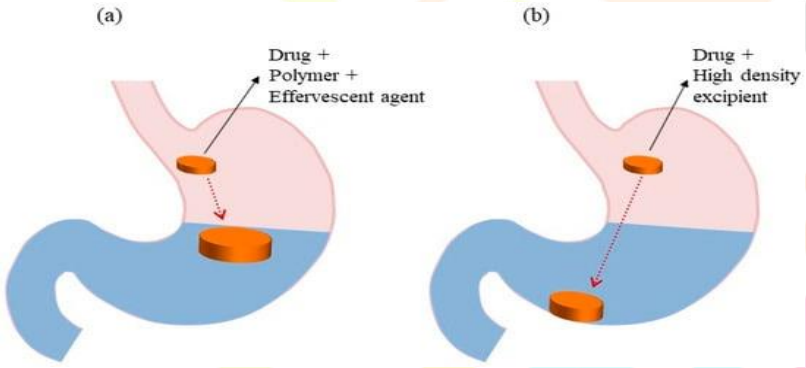

Fig 7: GRDDS based on (a) low density system and (b) high density system

Gastro retentive delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients, thereby enabling sustained and prolonged input of the drug to the upper part of the gastrointestinal.

5. Nose Brain Drug Delivery System:

The o.s.e. to brain drug delivery system is a method for directly delivering drugs to the brain, avoiding first-pass metabolism, and achieving high drug concentrations at a low dose. [45]

3. Evaluation Test:

A continuous review is crucial to identifying and resolving drug-related problems.

1. Solid Dosage Form: The solid dosage needs various tests of evaluation so that it will improve the properties of the drug.

Dissolution Test:

Fig 8:-Dissolution Test Apparatus

The assembly includes a glass-covered vessel, a motor, a drive shaft, and a cylindrical basket for testing. The vessel is partially immersed in a water bath or heated to maintain a temperature of 370.5°C.

Disintegration Test:

Fig 9: Disintegration test apparatus

A disintegration test for tablets involves placing a basket of 1-6 tablets in a beaker of water, simulated stomach conditions at 3737 ± 0.5 °C, and placing perforated plastic disks to maintain stability.[46]

Disintegration time:

Six solid dosage forms should be placed in each tube for coated, uncoated, plain, capsules, and vice versa. If disintegrated, repeat with 12 tubes. [46]

Weight variation test:

The uniformity of weight was determined by comparing average and individual weights of 20 tablets, with results showing 30-N F 25 limits for weight variations.

Formula= W average-W initial/W average 8*100

Drug uniformity test:

Fig 10: Content uniformity test apparatus

10 tablets powdered and 100 mg equivalence powder dissolve in a suitable solvent, make a 100-ml solution, and dilute it. 100 time calculations are carried out.

Result: Pass the test when not less than 85% and not more than 115%. [46]

2. Liquid dosage form:

The liquid dosage needs various tests of evaluation so that it shows the popper properties of drugs.

Leakage test:

10 containers filled with liquid dosage form and inverted for 24 hours; also check for leakage in case of rubber closure.

Dye bath test:

To check the ability of an empty container or container with product, the container is deep in a dye bath and pressure and vacuum applied to it, and then after an estimated time, check for the dye marks.

Direct transfer method:

Non-feasible product test by this method test sample 10% - culture medium. 9-ml tubes to 75-ml bottles-direct inoculum incubate 14 days - M. growth.

Membrane filtration method:

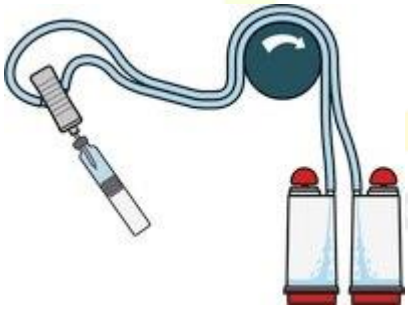

Fig 12: Membrane filtration method

The sample was filtered through a 47-mm-diameter filter, cut into two halves, and then cultured in a 100-ml medium at different temperatures for 7 days.

Pyrogen test:

Pyrogens are metabolic products of the microbes that produce fever with body cach.

Lal test:

Limulus Amoebocyte Lysate (L.AL.) of limulat polymethyls gel is und 0.1 ml sample with the lal reagem incubation for 1 hr. at 37 °C clot it analyzed due to properties of hors. shoe crab get. [47]

3. Semisolid dosage form:

The liquid dosage sends various tests of evaluation so that it shows proper properties of drugs.

- **PH. Measurement:** The ph. is determined by means of the various methods, like the use of a PH meter electrode that measures the ph.
- **Viscosity Measurement:** It is measured by instruments called a viscometer and rheometer.

4. Labelling and packaging:

a. Types of packaging:

Packaging for drugs includes primary, secondary, and tertiary types, such as ampoules, syringes, sachets, and containers, which are crucial for handling and transportation. [48]

b. Packaging material:

a. Glass: They are most commonly used for storing pharmaceutical products due to their superior protection quality.

- **Borosilicate glass type:** 80% silica 10% boric acid small amount of sodium oxide
- **Soda lime glass:** Sulfide treatment has more resistance than type 3.
- **Regular soda lime glass:** 75% silica 15% sodium oxide 10% CALCIUM OXIDE

b. Plastic polymers: polypropylene, polyvinyl chloride, polyethene, polystyrene, polycarbonate, etc.

c. Metals: Metals such as aluminum and tin, along with products like tablets, blisters, collapsible tubes, cans, sachets, pouches, membranes, and more.

d. Paper and paperboard: These are traditional materials that have been used for ages, including for items like boxes and sachets.

Rubber: Rubber is utilized for closures, stoppers, cap liners, and bulbs. [49]

c. Evaluation Test For Packaging Materials:

Identification: The appearance of the packaging material, both alone and in combination with the product content, is checked.

Physical Test: Evaluations include appearance, light absorption, pH, non-volatile matter, residue on ignition, heavy metals, buffering capacity, and oxidizable substances.

Chemical Test: Tests include pH levels, chloride and sulfate content, analysis of paper or board, glass alkalinity, and compatibility tests for contaminants.

Mechanical Test: To check working and strength. [50][51]

MODULE 4: HANDS ON ACTIVITIES

1. Identification and characterization of drug by melting point, solubility study, UV spectroscopy, etc.

Melting point:

The melting point is the temperature at which a pure solid transforms into a liquid, indicating its purity. It helps clarify the power of the material's properties.

Procedure:

- Take a fine capillary tube and seal one end. Insert the open end horizontally into the flame of a small burner for a few seconds while rotating the tube.
- Place a small amount of the compound whose melting point you want to determine on a porous plate and grind it into a powder using a spatula.
- Introduce the powdered compound into the capillary tube by inserting the open end into the powder and gently rotating it. Tap the tube against the porous plate so the compound settles at the bottom. Repeat this process three to four times.
- Moisten the bulb of a thermometer with concentrated sulfuric acid or liquid paraffin, then attach the capillary tube to the lower end of the thermometer.
- Position the thermometer with the capillary tube in a melting point apparatus filled with at least two-thirds of its volume with liquid paraffin, ensuring that the closed end of the capillary is submerged below the surface of the liquid.
- Heat the beaker gently and monitor the temperature closely. Note the temperature at which the compound begins to melt and when it has completely melted.
- Repeat the experiment using a new capillary tube and a fresh quantity of the substance.[52]

Result: The melting point of paracetamol powder was found to be 171^0C

Solubility Study: Solubility is quantitatively defined as the concentration of a solute in a saturated solution at a specific temperature. Qualitatively, it refers to the spontaneous interaction of two or more substances that results in the formation of a homogeneous molecular mixture.

Procedure:

- Clean all necessary glassware thoroughly with acid, then rinse twice with fresh distilled water.
- Measure approximately 60 ml of distilled water into a flask.
- Add an excess amount of paracetamol to the flask containing distilled water while stirring continuously.
- After saturation, place the flask in a rotating chamber at 37°C and set it to 60 rpm for overnight mixing.
- Prepare a standard solution of paracetamol in distilled water.
- Measure the absorption using a UV-visible spectrophotometer.
- Determine the solubility of paracetamol using the standard calibration curve.[53]

Result: The solubility of paracetamol in distilled water was found to be 16 (mg/ml).

2. To study the dissolution of given solid dosage form

Dissolution test: The dissolution test evaluates the time it takes for an oral solid dosage form to dissolve in a solution under defined conditions, with particles needing to pass through a mesh-10 screen.

Procedure:

- Measure 600 cm^3 of deionized water into a 1 dm^3 beaker, add a mechanical stirrer, stir gently, and record the water temperature.
- Select a point about 4 cm below the water surface and 2 cm from the side of the beaker to withdraw samples.
- Place the paracetamol tablet into the water, start the stopwatch, and withdraw a sample to fill a 100 cm^3 volumetric flask with deionized water, labeling it 'zero time.
- Withdraw additional 1 cm^3 samples every minute for 10 minutes, diluting them as described in step 3. Label these samples from '1 min' to '10 min.' For 'zero time' and each of the diluted samples.
- Add 5 cm^3 of the solution to a 100 cm^3 volumetric flask, then include 2 cm^3 of iron chloride solution and 4 cm^3 of potassium hexacyanoferrate solution. Let this mixture sit for 10 minutes.
- Afterward, add 1 cm^3 of 5 mol/dm^3 hydrochloric acid and bring the volume up to the mark with deionized water.
- After 20 minutes, measure the absorbance and use this measurement to calculate the concentration of paracetamol.
- Finally, calculate the concentration of paracetamol in the sampled solution.[54]

Result: The Dissolution Test of Paracetamol Tablet was found to be 18 min.

3. Study of disintegration time of different marketed tablets

Procedure: According to the US pharmacopeia, the following procedures were done during the experiment.

- Six paracetamol tablets were weighed on an analytical balance, and their weights were recorded along with the mean weight (M).
- 900 mL of pH 5.5 phosphate buffer was added to each of the six vessels.

- Proper dilution was performed using 0.1 M NaOH until a final volume of 100 cm3 was reached.
- The absorbance of these sample solutions was measured using a UV spectrophotometer.
- The total amount of paracetamol in each sample was calculated using Beer's Law and the dilution equation.
- Finally, the mean concentration of dissolved substances was compared to 0.00075% w/v to determine the percentage of paracetamol that had dissolved.[55]

4. Determination of different bulk characteristics like bulk density, tapped density

Measurement of Bulk density

Procedure:

- Pass a quantity of the powder sample through a sieve with apertures of 1.0 mm or larger, if needed, to break up any agglomerates that may have formed during storage.
- Gently introduce 100 g of the test sample (m) into a dry 250 mL graduated cylinder (with a readability of 2 mL), taking care not to compact it.
- Calculate the bulk density in g/mL using the formula: bulk density = m / V_0.
- Typically, it is advisable to perform replicate measurements for determining this property.

Result: The disintegration time of Paracetamol Tablet was found to be 11 min.

Measurement of Tapped density

Procedure:

- Follow the procedure outlined previously to determine the bulk volume (V_0).
- Secure the cylinder in the holder of the bulk density apparatus.
- Tap the powder sample 10, 500, and 1250 times, recording the corresponding volumes to the nearest graduated unit. If the difference is less than or equal to 2 mL, record the tapped volume.
- If the difference between V (500) and V (1250) exceeds 2 ml, continue tapping in increments of 1250 until the difference between consecutive measurements is less than or equal to 2 ml.
- To calculate the tapped density (g/mL), use the formula: tapped density = m / V_1, where V_1 is the final tapped volume. It is generally advisable to conduct replicate measurements for accuracy.[55]

Result: The Bulk Density and Tapped Density of Paracetamol Powder was found to be 0.54 and 0.78 respectively.

Measurement of Bulk density

Procedure:

- Heat approximately 50-100 g of the soil at 110°C to remove the absorbed moisture. Extended heating may be necessary to ensure all moisture is eliminated.
- Clean and dry a 50-mL measuring cylinder, then record its empty weight.
- Pour the air-cooled dry soil into the measuring cylinder.
- Gently tap and vibrate the measuring cylinder to eliminate any air pockets.
- Record the weight of the measuring cylinder with the soil, along with the volume of the soil occupying the cylinder.[56]

Result: The Bulk Density of Paracetamol Powder was found to be 0.45.

References:

1. Azhar Chand Shaikh, Simran Sallubhai Shaikh, Review Formulation Development, IJCRT- Volume 10, Issue 3 march 2022.
2. Stewart KD, Johnston JA, Matza LS, Curtis SE, Havel HA, Sweetana SA, Gelhorn HL. Preference for pharmaceutical formulation and treatment process attributes. Patient Prefer Adherence. 2016;10:1385-99. [PMC free article] [PubMed]
3. Miss. Madhuri Pandurang Shikhare, Miss. Priyanka Ashok Meher, Miss. Priti Sandip Pawar, Miss.Priti Balaso Chopade, Miss.punam Kiran Chavan Institute of pharmaceutical sciences and Research (for girls) (college code- 6914), Pune-Solapur Highway Swami chincholi (Bhigwan), Tal- Daund, Dist-pune 413130.
4. Shaivee Gautam, Abhay Kumar Gupta, Satakshi Katiyar, Satyendra Mishra, Sonia Pandey and Divya Dwivedi Study on Formulation and Development with New Drug Application and Investigational New Drug Application Process. Dec 11,2023
5. Dr.Vikas Kumar Chaudhari, Dr. Vijay Yadav, Department of Pharmacognocy, Kunwar Haribansh Singh College of Pharmacy, Jaunpur, Uttar Pradesh, India Parma Tutor-2014; 2(9) ;8-19.
6. Dr.satish Kumar Gupta, Dr. Tarkeshwar P. Shukla Review formulation development studies Authors. (IJRASET) ISSN: 2321-9653; IC Value: 45.98; PJ Impact Factor: 7.538 Volume 11 Issue I jan 2023.
7. Industrial pharmacy i textbook by nirali by dr.ashok hajare page no.1.1 to 1.40.
8. Preformulation Studies: An Integral Part of Formulation Design By Pinak Patel Submitted: July 16th 2018 Reviewed: December 3rd 2018 Published: June 9th 2019 DOI: 10.5772/intechopen .8 2868
9. Various disintegration test dissolution test usp pharmacopeia stage 4 harmonization official may 1, 2020 (701-1 to 703-25)
10. Escoe, Adrienne. 1997. Nimble Documentation. The Practical Guide for World-Class Organizations. Milwaukee, Wisconsin: American Society for Quality, Quality Press.
11. Federal Emergency Management Agency, 1999. Developing Effective Standard Operating Procedures for Fire and EMS Departments, Federal Emergency Management Agency, Washington DC.
12. Mr. Aditya Bharat Jadhav, 2Mrs. Khamkar S.P. Review on Formulation development Authors. Diclofenac sodium. 2012 Nov; 22(3): 205-208.
13. Shubhangi S. Pawar, Sanjay K. Bais, Fabtech College of Pharmacy, Sangola, Solapur, Maharashtra, India. Review on Preparation of SOPs for Different Instruments or Equipment. 2016, Pages 221-233
14. Anan S More , Review on Preformulation Study of Drug , SJIF (2019): 7.583 Research Gate Impact Factor (2018) : 0.28
15. Adarsh Mishra, Aditya Gupta and DR. Jayant Kumar Maurya, Ashok Singh Pharmacy College, Maharoopur Jaunpur U.P. 222180 A review on standard operating procedure instruments ,Volume 11, Issue 12 December 2023 , ISSN: 2320-2882.