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Formulation Development

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Abstract: *From a patient compliance perspective, solid oral dosages have a clear and acceptable precedence and, therefore, term and to be the favored route of administration. Tablets and capsules are widely manufactured and prescribed and provide several advantages over other dosage forms such as ease of storage, portability, straight, composite, administration, and accuracy in dosing. Multiple aspects (such as the selecting the same type of dosage form, excipients, compatibility of the drug with the excipient. Composition, manufacture ability, impact on bio availability, etc.) need to be considered while developing the drug product's formulation. Relatively simply, formulation development can be considered an amalgamation and incorporation of core concepts in chemistry, pharmacokinetics, engineering technologies, and manufacturing practices to produce a product that is bio available, stable, manufacturable, and economically feasible.*

Keywords: Formulation Development

I. INTRODUCTION

From a patient compliance viewpoint, solid oral dosages have a clear and sufficient importance and thus, tends to be the favored route of administration. Tablets and capsules are widely manufactured and prescribed and provide several advantages over other dosage forms such as ease of storage. Portability, straightforward administration, and accuracy in dosing. Multiple aspects (such as the selecting the right type of dosage form, excipients, compatibility of the drug with the excipient. Composition, manufacture ability, impact on bio availability, etc.) need to be considered while developing the drug product's formulation. Quite simply, formulation development can be considered an amalgamation and incorporation of core concepts in chemistry, pharmacokinetics, engineering technologies, and manufacturing practices to produce a product that is bioavailable, stable. Manufacturable, and economically conceivable.

Pharmaceutical formulation development links the discovery of a new drug substance to the successful development of a commercial drug product. 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.

This is a tough challenge. Only 10% of new drug products in preclinical formulation development successfully reach the market. With the costs of pharmaceutical development rising, and pressure to release drug pipelines value also boosting, developer drug development companies are applying considerable endeavor to determining how to speed adequate formulation choice.

Similar challenges exist for generic pharmaceutical companies, where successful development of complex drug formulations stay tricky. There is a significant untapped market for new complex generics.

Guided by global regulators, it is now realized that described physicochemical understanding of the microstructure of complex dosage forms can allow successful product development.

1.1 Concept of cGMP

Definition: The cGMP is defined as the regulations executed by the FDA that provides for systems will be to assure proper design, monitoring, and control of manufacturing processes and facilities.

The first WHO draft text on GMP was adopted in 1968.

GMP in India is prescribed under Schedule M in June 1988.

In India Joint Commissioner (HQ) is authorized by Commissioner of State FDA, to sign and issue the certificate under the WHO GMP certification.

Certification and Membership Fees is Rs 25,000/- for Indian nationals.

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1.2 Concepts

Currently, the FDA is the sole national authority required and charged with the responsibility to issue policies on cGMPs. As a rule of thumb, a drug is considered contaminated if the facilities used to manufacture it and the packaging, and processing do not fit to cGMPs.

FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its Current Good Manufacturing Practice (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the components and stability it declares to have.

The acceptance process for new and generic drug marketing applications includes a review of the manufacturer's compliance with the CGMPs. FDA assessors and investigators determine whether the company has the necessary facilities, equipment, and ability to manufacture the drug it intends to market.

Code of Federal Regulations (CFR). FDA's portion of the CFR is in Title 21, which analyzes the Federal Food, Drug and Cosmetic Act and related laws, including the Public Health Service Act. The pharmaceutical or drug quality-related regulations appear in several parts of Title 21, including sections in parts 1-99, 200-299, 300499, 600-799, and 800-1299.

The regulations enable the common understanding of the regulatory process by characterizing the requirements to be followed by drug manufacturers, applicants, and FDA.

- 21 CFR Part 314 For FDA approval to market a new drug.
- 21 CFR Part 210. Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.
- 21 CFR Part 211. Current Good Manufacturing Practice for Finished Pharmaceuticals.
- 21 CFR Part 212. Current Good Manufacturing Practice for Positron Emission Tomography Drugs.
- 21 CFR Part 600. Biological Products: General

The Outline of GMP: GMP constitutes the license to operate in pharmaceutical manufacturing. GMP guidelines are a series of general principles that must be applied during manufacturing.

There are many ways to comply GMP while setting up of pharmaceutical quality system, manufacturing processes and control in an institution. The responsibility to define the most useful and efficient quality of process rests with organization. Following few basic principles are basis of GMP guidelines.

1. The production and distribution of the drugs must minimize any risk to their quality.
2. Manufacturing facilities must maintain a clean and hygienic manufacturing area, including laboratories and storage.
3. Manufacturing facility design, operating principles and environmental conditions must be controlled.
4. Manufacturing process must be clearly defined, validated, and controlled to ensure consistency and compliance with specifications
5. Any changes to the process must be evaluated, qualified, or validated as necessary.
6. Instructions and procedures must be written in clear and unmistakable language.
7. Operators should be trained to carry out the production and control of products as per approved procedures.
8. Records should be made during manufacture and quality control. Any deviations are examined documented.
9. The process should remain in a state of control throughout the product life cycle and in must be made when needed.

1.3 Identification and Characterization of Drug

Diclofenac Sodium

Characterization: Painkiller

Excipients in diclofenac

The inactive ingredients in Diclofenac Sodium Delayed-release Tablets include lactose (monohydrate), microcrystalline cellulose, croscarmellose sodium, povidone, tale, magnesium stearate, methacrylic acid copolymer, polyethylene glycol, Opadry brown Titanium dioxide, Hypromellose, polyethylene glycol, iron oxide red.

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Formulation Development of Diclofenac

Diclofenac sodium (DC) is a non-steroidal anti-inflammatory drug used for treatment of inflammatory diseases. DC has a short half-life of 1-2h and should be administered frequently at a high dose, which leads to severe unwanted effects and rises the possibility for missing a dose (Arias et al, 2009). The development of sustained dosage release forms was required to avoid

Formulation Optimization

The study was undertaken with an aim to examine the capacity of native sugars (e.g., glucose, fructose, and sucrose) to induce crosslinking of gelatin for the preparation of modified release microspheres of diclofenac sodium. The microspheres were set by emulsion crosslinking method, and they were evaluated for drug content, in vitro drug release and size analysis. The results of preliminary trials revealed that the parameters such as drug to gelatin ratio, volume of light liquid paraffin and stirring rate were found to affect the morphology and in vitro drug release, of microspheres. The microspheres cross linked with glucose showed highest drug content, good yield, and lowest burst effect. The evidence of glucose mediated crosslinking of gelatin was confirmed by DSC. A 32 full factorial design was adopted to investigate the joint influence of two variables. Amount of glucose (X1: 1.1.5 or 2 g) and concentration of gelatin (X2: 10,15 or 20% w/v) on the percentage drug released in 60 min (Y60) and the time required for 80% drug dissolution (180) while keeping the other variables constant. The results of multiple linear degeneration analysis revealed] that for obtaining modified drug release up to 12 h, the microspheres should be prepared using higher level of glucose and middle level of gelatin. Response surface plots are presented to show the effects of X1 and X2 on Y60 and 180. The drug release pattern fitted well to Kors Meyer und Pappas model indicating anomalous diffusion. An equation was generated by adopting multiple linear regression analysis, for predicting the drug dissolution profile for a check point. Good agreement was observed between the predicted and observed drug dissolution profiles. The results suggest that native glucose could be an interesting agent to crosslink gelatin for obtaining modified release of diclofenac sodium from the microspheres

Stability Study

Stability tests were conducted for the Diclofenac sodium in suppositories containing only 12% AS and 12% DOSS. Suppositories were kept in a desiccator where the relative humidity (RH) was retained at 76% using saturated NaCl solution for a period of four months. The samples were withdrawn after one-month intervals and the drug was extracted with methanol. To verify the stability of compounds, present in the methanol extract, ascending one dimensional TLC technique was adopted. In this method the sample drug in methanolic solution was spotted on a silica coated TLC plate against the standard drug solution in methanol and was allowed to run with a mobile phase which was a mixture of toluene/formic acid/n-hexane (10:1.5:1). After development of the chromatogram, the plate was taken out of the tank, dried, observed under UV light and sprayed with a mixture of chromate/sulphuric acidreagent which was prepared by dissolving 0.5 gm of potassium dichromate in 80 ml of water and slowly adding 20 ml of concentrated sulfuric acid, then degradation products of DS as secondary spots were studied. The physical formation of the suppositories was also checked up for four months.

II. MODULE 2

SOP Handling

Standard Operating Procedures (SOPs) define the essential steps, their sequence, and the precautions essential to formally repeat a quality performance.

Pharmaceutical Standard Operating Procedure (SOP) is a tested, verified, approved, and documented way of executing operations that form the pharmaceutical industry's basis. It provides step-by-step guidance for the personnel to perform a specific process.

Instruments

1. Standard operating procedure for autoclave operation
2. Standard operating procedure for cleaning, operation & calibration of autoclave

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3. Standard operating procedure for validation of autoclave
4. Sop for usage and calibration of weighing balance
5. Sop for cleaning, operation & calibration of weighing balance
6. Sop for laminar airflow
7. Sop for mantra image system
8. Standard operating procedure for microwave oven
9. Standard operating procedure for operation of fire hydrant pumping system
10. Standard operating procedure for operation of ice maker
11. Standard operating procedure for operation of orbital shaker equipment.
12. Sop for hot air oven | cleaning, operation & calibration of hot air oven
13. Sop for operating procedure for digital tele-thermometer
14. Sop for hot plate apparatus
15. Standard operating procedure for ultrasonic probe sonicator
16. Sop for cleaning, operation, and calibration of magnetic stirrer.

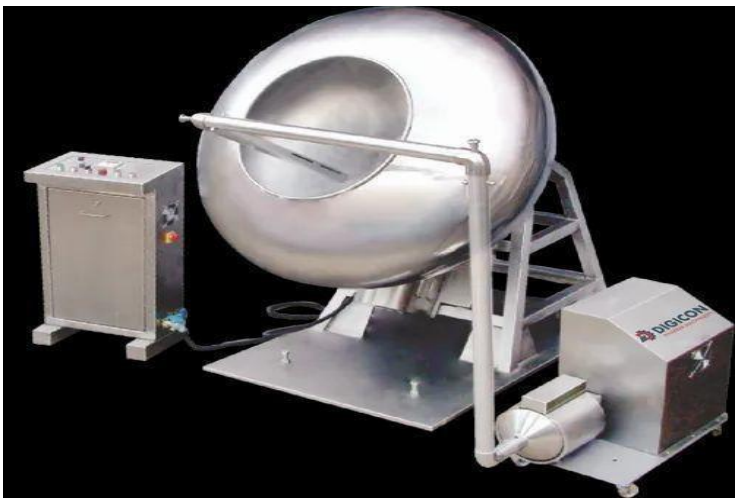
Various Equipment and Instrument Handling

Tablet Compression Machine

A tablet press is an automatic device that compresses powder into tablets of uniform size and weight. A tablet press can be used to manufacture tablets of a wide variety of materials, containing pharmaceuticals, nutraceutical, cleaning products, industrial pellets, and cosmetics.

Tablet Coater

Tablet coating is the outer coating of a tablet with a layer/substance. The coats used range from the traditional sugar coating to the present polymer and polysaccharides-based coats. The types of coats depending on the specific functionality of the tablet as well as the target customer of the tablet.



Capsule Filling Machine

A Hand Operated Capsule filler can produce about 800 capsules in one pressing. These capsule filling machines have loading trays that hold a volume of 300 holes. A powder tray is also connected to the machine itself. The pin plate works as a filter of the machine and a sealing plate that seals the cap of capsules.

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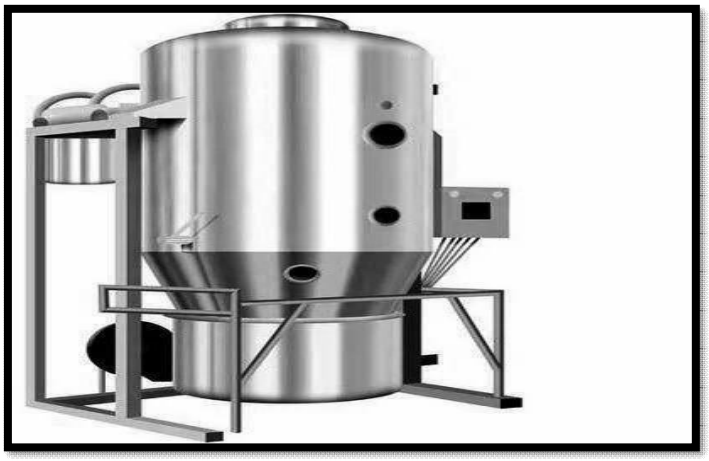
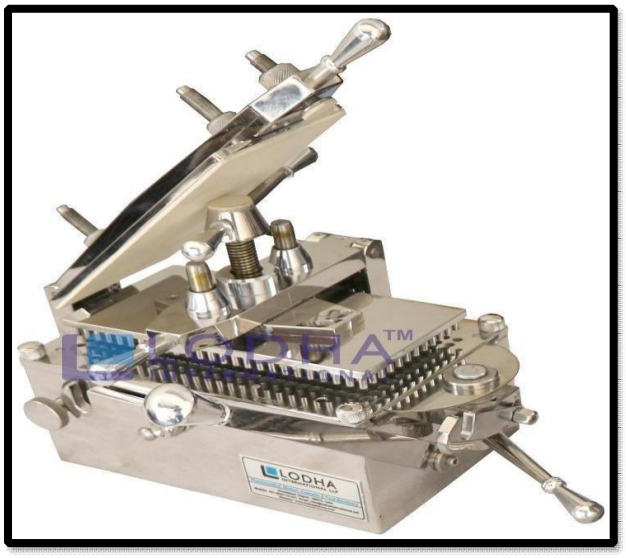


Fluidized Bed Dryer

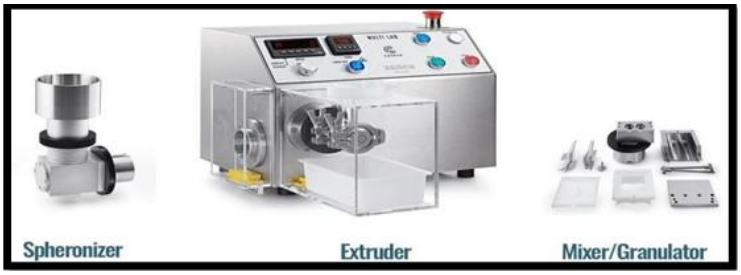
A continuous fluid-bed system is a machine in which a continuous flow of "wet" powder, granular or flakes material is conveyed over a perforated bed. Hot drying air is blown through the holes of a perforated plate. The wet solids are lifted from the bottom and causes the solids to behave as a fluid



Extruder & Spheronizer

Extrusion is a process in which pharmaceutical material or other material is forced through a sequence of dies to create preferred shapes.

Spheronization or maramuerization, is a quick and adjustable process where pharmaceutical products are made into small spheres, or spheroids of diameter ranging from about 0.5mm to 10mm



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III. MODULE 3

Preformulations Studies and Preparation of Preformulation Data Sheet

Introduction

Starting the preformulation studies, we should know the properties of the drug, strength comparative to the competitive products and the dosage form, literature search providing strength and erosion data, the proposed route of drug administration, publications search regarding the formulation strategies, bioavailability, and pharmacokinetics of chemically associated drugs.

Once a pharmacologically active compounds has been determined, a project team consisting of ambassadors from the disciplines has duty for ensuring that the compound enters the development process in its optimum molecular form. When the first quality sample of new drug comes to be available, studying experiments should be conducted to define the magnitude of each doubted problem area. If a defect is detected the project team should define on the molecular modifications that would most likely improves the drug properties.

Goals of preformulation studies

1. To establish the physicochemical parameters of a candidate drug molecule.
2. To determine the kinetic rate profile of drug substances.
3. To establish the compatibility of a candidate drug molecule with common excipients.

Physical Characteristics

1. Organoleptic properties of the candidate drug molecule e.g., color, odor, and taste.
2. Bulk characterization e.g., particle size and surface area, powder flow properties, density, compressibility, crystallinity, polymorphism and hygroscopicity.
3. Solubility analysis e.g., ionization constant/ drug Pka, partition coefficient, solubilization, thermal effect, common ion effect (Ksp) and dissolution.
4. Stability analysis e.g., solution-state stability testing, solid-state stability testing, and drug- excipient compatibility studies.

Formulation of Conventional Drug Delivery System

1. **Tablet**: Tablets may be defined as the solid unit dosage form of medicament ormedicaments with suitable excipients.
2. **Capsules**: solid dosage form in which the drug is enclosed in a hard or soft soluble container, usually of a form of gelatin.
3. **Oral liquids**: Oral liquids are homogeneous liquid preparations, usually consisting of a solution, an emulsion, or a suspension, of one or more active ingredients ina suitableliquid base.
4. **Semisolids:** Semi-solid means one substance which contains both solid and liquid. Semisolid dosage forms are also contained solid and liquid both. These types of dosage forms are viscous in nature. Normally used for topical or external application.
5. **Parenteral**: Parenteral drug administration refers to drugs given by routes other than thedigestive tract. The term parenteral is usually used for drugs given by injection or infusion

Formulation of Novel Drug Delivery System

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

1. **Nano carrier**: Nanocarriers offer multiple benefits over conventional drug delivery systems like increased plasma half-life, improved biodistribution, and targeted delivery of a drug to tumor microenvironment through endothelial layers.
2. **Vesicular drug delivery system:** Novel vesicular drug delivery systems aim to deliver thedrug at a rate directed by need of body during the period of treatment, and channel the active entity to the site of action.
3. **Gastro retentive drug delivery system**: Gastro retentive drug delivery is an approachto prolong gastric residence time**,** thereby. targeting site-specific drug release intheupper

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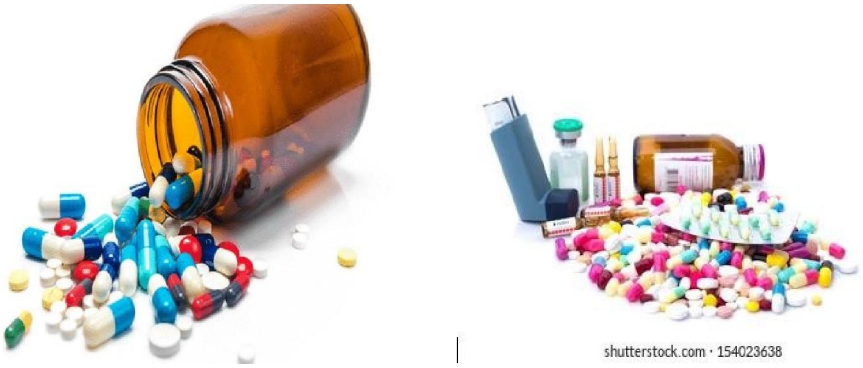
4. **Nose brain drug delivery system**: Nose-to-brain drug delivery allows the direct transport of therapeutic molecules by bypassing the BBB and increases drug concentration in the brain.

Evaluation

Solid Dosage Form

Solid dosage form means capsules or tablets intended for oral use.

Solid dosage forms are the most important dosage forms for pharmaceuticals, which contain a unit dose of one or more drugs. Commonly used solid dosage forms are powder, granules, tablets, capsules. As compared to liquid dosage forms, solid dosage forms are physically and chemically more stable. The solid dosage forms are relatively having less cost and they are easy to take and carry. The pretreatment of the preparation process undergoes the same unit operation to ensure uniform mixing and accurate dosage of the drug, there is a relationship between the dosage forms.



Liquid Dosage Forms

Liquid dosage forms are pourable pharmaceutical preparations it is also one of the oldest dosage forms used in the treatment of patients and affords rapid and high absorption of therapeutic products. Liquid dosage form contains a mixture of active pharmaceutical ingredients and non-pharmaceutical ingredients (excipients) dissolved or suspended in a suitable solvent or mixtures of solvents. They are administered by oral and parenteral (injection, inhalation, ophthalmology, ear canal, nasal cavity and topical) routes. Oral liquids are non-sterile, while liquids administered by parenteral routes are available in sterile and non-sterile formulations.

Fig.1 Liquid dosage forms.

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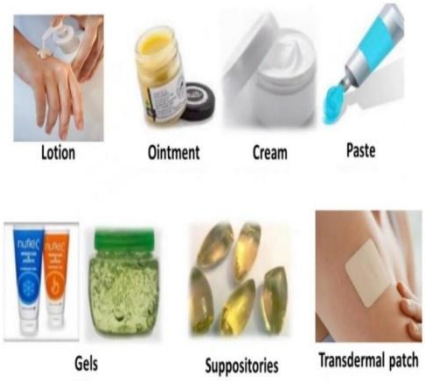
Semisolid Dosage Forms

Semi-solid dosage forms, also known as Quasi-solid, are highly viscous in nature, and are slightly flexible as liquids



Labeling and Packaging

There are several different types of packaging for pharmaceutical products which are categorized as primary, secondary, and tertiary. Primary drug packaging is the material that encircles the pharmaceutical product, while secondary and tertiary packaging provide additional external protection.

The most common types of PRIMARY pharmaceutical packaging types

- Vials.
- Bottles.
- Blister packs.
- Sachets.
- Syringes.

Packaging Materials

The most used materials are glass and plastics. The type of packaging that is assigned for a specific drug will depend on factors such as: The degree of protection that is needed for the product.

Evaluation Test for Packaging Materials

Quality Control of Packing Materials

1. **Leakage Test: -** Fill 10 containers with water, fit with intended closures and keep them inverted at room temperature for 24hr.The test is said to be passed if there is no signs of leakage from any container.
2. **Collapsibility Test: -** This test is applicable to the containers which are to be squeezed for removing the contents. A container by collapsing inward during use, yield at least 90% of its normal contents at the required rate of flow at ambient temperature.

Labeling for Different Dosage Forms

The term labeling designates all labels and other written, printed, or graphic matter on an article's immediate container or on or in any package or wrapper in which it is enclosed, except any outer shipping container. The term label designates that part of the labeling on the immediate container. The label states the following information: name of the preparation in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume in the case of a dry preparation, the amount of active ingredient the route of administration a statement of storage conditions and an expiration date the name and place of business of the manufacturer, packer, or distributor an identifying lot number.

FTIR and DSC

It has been indicated that the interchanges observed at high temperatures during DSC experiments might not be expected of those occurring at normal storage temperatures [17, 18, 39, 40]. The instrument that determines the

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absorption spectrum for a compound is called a spectrophotometer. Fourier transform spectrophotometer provides the IR spectrum much more rapidly compared to the traditional spectrophotometer. The IR spectrum obtained from FTIR spectrometer lies in the mid-IR region 2.5-
15 µm between 4000 and 666 cm_1. Transition energies corresponding to changes in vibrational energy state for many functional groups are in the mid-IR region (4000-400 cm_1) and hence the appearance of an absorption band in this region can be used to determine whether specific functional groups exist within the molecule. There are four regions of types of bonds that can be analyzed from the FTIR spectra, single bond (OH, CH, and NH) is detectable in higher wavenumber (2500-4000 cm_1).
The triple bond and double bond are observable in the middle wavenumber region 2000-2500 cm_1 and 15002000 cm_1, respectively. At low wavenumber region 650-1500 cm-1 can be used for the identification of the molecule. FTIR is a simple methodology for the detection of variations within drug-excipient blends. The disappearance of an absorption peak, a reduction of the peak intensity, or the appearance of new peaks are indicative of the existence of interactions between the API and the excipient under study [17, 18, 34, 38]. By DSC, Daniel et al. [41] have reviewed the compatibility of binary mixtures (1:1) of risperidone and pharmaceutical excipients. These binary mixtures were also kept at room temperature and then analyzed by FTIR in combination with principal component analysis (PCA) to evaluate solid-state incompatibilities.
Lima et al. [42] have studied the compatibility of trioxolane with sodium lauryl sulfate by DSC, DTA, and FTIR at 25°C, 240°C (after the fusion event) and 260°C.Figure 1 shows that trioxalen peak of fusion disappear in the mixture (1:1) with sodium lauryl sulphate. The trioxolane bands in the FTIR spectrum of the mixture (1:1) with sodium lauryl sulphate were well retained, indicating no change in the structure of the drug at room temperature (Figure 2). Same results were obtained before the mixture were heated at 240°C and 260°C (data not shown). It was concluded that trioxolane is compatible with sodium lauryl sulphate.

IV. MODULE 4

Activity of Diclofenac Sodium

Min purity space	98%(HPLC)
Physical form (at 20*c)	Solid
Melting point	279-289*c
Long Term Storage	Store long term in cool and dry place

The solubility of diclofenac sodium in purified water at 23 c has been determined to be 14.2 mg/ml and its pka 3.8
The solubility of diclofenac sodium in acetone ethyl acetate and dimethyl sulfoxide in the temperature range from 293 up to 313 kelvin was measured
As predicted solubility of the drug increased with temperature for all solvents but this effect is more pronounced in the case of dimethyl sulfoxide
Disintegration Time
The disintegration test indicates that Brand A and Brand B fall within a 15-minute time interval segment with disintegration time estimated as 6.69 min and 7.02 min for Brands A and B, respectively. Brand B of Diclofenac Sodium has a drug dissolution percentage of 90.7% within a 45-min sampling time interval.

QC Test for Diclofenac

Quality control (QC) testing ensures drug safety, efficacy, and effectiveness. It involves specific instruments to assure the quality of drug testing as per set approaches. Some of the testing procedures are as follows: friability, weight variation test, disintegration test, dissolution test, and drug assay. The equipment used are as follows: friabilator, electronic weighing balance, mixer, ultraviolet (UV)-visible spectrophotometer, digital pH meter, dissolution test apparatus, and disintegration test apparatus.
Friability tests the content uniformity and weight variation. It refers to the tendency of the tablet to fragment, powder, or chip, which could affect the appearance and uniformity of the drug, while weight variation involves drug distribution

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uniformity. The weight variation test is valid when the drug substance is more than 50 mg or 50% by weight of the tablet. The disintegration test involves the time required to break tablet ingredients into particles. It also involves a 10-mesh screen and time is measured while disintegrated particles pass through the mesh screen. The bioavailability of the drug is measured through a dissolution test. It refers to the amount of drug that goes into a solution as per unit time under standardized situations. The drug assay analyzes in vitro quality control testing. It measures and determines the quantity and quality of the specified analyte using the UV-visible spectrophotometer through the amount of radiation absorbed. It also includes the Beer-Lambert law, which relates to the attenuation of light and the properties of the material through which itis

V. CONCLUSION

Formulation development is essential for the success of a drug.

Formulation-related challenges include stability and bioavailability issues, among others.

When defining a drug formulation, it is very important that late-stage development is kept in mind from a very early phase.

Biotech companies must know that deficiencies in formulations can lead to costly failures and extended delays in the overall drug development process.

Outsourcing formulation work provides drug development acceleration and access to specialized knowledge, which are very important advantages biotech companies should benefit from.

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.

The clinical relevance of pharmaceutical formulation is that they have a significant impact on one's quality of life, disease outcomes, and adherence to the treatment protocol

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