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A SYSTEMATIC REVIEW ON FORMULATION AND DEVELOPMENT

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Abstract:

The formulation development is important part of pharmaceutical development and essential for therapeutic and commercial success of product by providing quality, safety and efficiency. Formulation can determine patentability, lifecycle the success of a pharmaceutical product. Pharmaceutical formulation development links the discovery of a new drug substance to the successful development of a commercial drug product. Formulation development is a stage of the pharmaceutical product development during which the physicochemical properties of the drug of drug substance are characterized and established the psychochemical and biopharmaceutical properties gives appropriate formulation and delivery methods. Apart from helping formulation development, Preformulation studies also help in lead identification during drug discovery phase.

Key words: *Stability, dissolution, compatibility studies, Preformulation*

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INTRODUCTION

Drug development is a high trend in the pharmaceutical and Biotechnology industries. With growing responsibilities to study drugs candidates from discovery to human Clinical Trials as soon as possible, most pharmaceutical and biotech companies are providing a portion of the development of their potential new drugs. Outsourcing decreases the timeline of product development and a cost-effective alternative. Changing needs of the people can be consider and fast solution can be provided to the company and people is necessary outsourcing gives a multiple cost structure, increasing resources and spending and decreasing when demand subsides. Formulation can determine patentability, lifecycle the success of a pharmaceutical product. Companies use this formulation development rules and regulations and personnel into their product development to grow better. In large pharmaceutical companies, specific departments may exist as the physical Characterization of drug substances and formulation issues. In many cases, various department are work at deferent places so there handling is very much important by single authority so that the development get speed up and the formulation development timeline decreases. the concept of pre- formulation was known to us around 1950 as result of focus industrial pharmaceutical product development. It is stage of the pharmaceutical product development during which the physicochemical properties of the drug of drug substance are characterized and established the psychochemical and biopharmaceutical properties gives appropriate formulation and delivery methods[1]

DEFINITION

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.[1]

STEPS IN FORMULATION DEVELOPMENT

1. Identification and characterization of drug: The identification of characterization of drug is so much important because it very much affect the final product and also the effect of various characters make drug more potent or toxic.

2. Excipients Compatibility Study: More the excipient compatible with drug more the chances of drug formulation success and effect of drug also increase

3. Formulation development: The next stage deals with the formulation development so that witch chemicals go with which and witch excipients is suitable for drugs.

4. Formulation Optimization: In this stage formulation like vaccine are produces this type of formulation have lots of studies than normal formulation and large amount of the knowledge needed.

5. Formulation Evaluation: The evaluation studies help to improve the already, made formulation by changing the part of formulation like the vehicle types 6. Stability Studies: It deals with the stability of the formulation by doing various tests so that the stability of formulation increase it also helps to improve.

6. Stability Studies: It deals with the stability of the formulation by doing various tests so that the stability of formulation increase it also helps to improves the shelf life of formulation [1]

GOOD MANUFACTURING PRACTICES

The good manufacturing practices helps in following the guidelines given to maintain standard of the product to increase production to maintain safety when one follows rules and regulation given by the G. M. P. the growth of the company is eminent in that cases and due to maintaining the given standard the companies images also developed and it is helpful in product sales also by maintaining quality and improving the product the customer satisfaction index rises by applying good manufacturing practices many problems arises at time of formulation development is decrease and the process fast forwarded due to the less time consumption in the process the new product comes in market as soon as possible [1]

Various equipment and instruments handling

Fludizedbeddryer: Fluidized bed dryer (also known as fluid bed dryers) are commonly used in the pharmaceutical industry to reduce the moisture content of pharmaceutical particles and granules.

Principal: Fluidized bed dryer are hot air is passed though taper for made bottom container containing granules to bed dryer. The granules are suspended by their stream raise from the bottom this condition is called fluidized state. Hot air surrounds each granule to bed dryer completely. Therefore, the material and granules are dried uniformly.[2]

Construction: The fluidized bed dryer consist of all steel shell of cylindrical or rectangular cross section. A detachable bowl which has performed bottom is placed on the bottom is dryer. It is used to load and unload the material. The bowl is used to place the material to be dried. A fan is mounted on the to circulate hot air. The fresh air inlet, the prefilter and heat exchanger reconnect in series to be heat the air to the required temperature. The temperature of the hot air and the exhaust air are monitored. The bag filter are placed on the top of the drying container for the recovery for the fines. The air to flow is adjusted by means of the recirculation control The fabric bag are provided to be prevent the passage of the fine particles[2].

Fig.1 Fluidized bed dryer

Working: The wet granulation to be dried are placed in detachable bowl. The bowl is inserted in the dyer. Fresh air an pass through the prefilter, which is then heated and passing through a heat exchanger. The hot air flows the bottom of the bowl. At the same time, the stared to rotate The air speed increase gradually. When the velocity of the air is greater then the sedimentation rate of the granules, the granules remain partially suspended in the gas stream. After the specific times, a pressure point is reached in which the fraction drug on the partials is equal to the force of gravity. The granules rise in the container due to the high gas velocity of 1.5-7.5 M/min and then flow back. The condition is said to be fluidized state. The gas surround to each granule to dry then completely. The air come out of the dryer passing through the filter in the bag. The entrained particles remain adhered to be interior of the surface of the bags. Periodically, bag are shaken to move entrained particles. The residence time of the drying is approximately 40 minutes. The material are sometimes left in the dyer to reach room temperature. The bowl is removed from unloading. The final product is free flowing.[2]

Preformulation studies and preparation of Preformulation data sheets

Introduction:

Preformulation studies were evolved in 1950 & early 1960.Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. [3].

Objectives

- To develop the elegant dosage forms (stable, effective & safe)
- It is important to have an understanding of the physical description of a drug substance before dos
- It is 1st step in rational development of a dosage form of a drug subt before dosage form development.

Goals

- To establish the physico-chemical parameters of new drug substance.
- To establish the physical characterist
- To establish the kinetic rate profile.
- To establish the compatibility with the common excipient.
- To choose the correct form of a drug substance.

Physiochemical characteristics

1) Organoleptic properties
2) Bulk characteristics
   a) Solid state characteristic
   b) Flow properties
   c) densities
   d) compressibility
   e) crystalline
   f) polymorphism
   g) hygroscopicity
3) Solubility analysis
   a) Ionization constant(Pka)
   b) Partition co-efficient
   c) Solubilization
   d) Thermal effect
   e) Common ion effect(Ksp)
   f) Dissolution
4) Stability analysis
   a) Solution-state stability
   b) Solid-state stability
   c) Drug-excipients compatibility [3]

FORMULATIONOFCONVENTIONALANDNOVELDRUG DELIVERYSYSTEMS

DRUG DELIVERY SYSTEM: - Drug delivery is the method of administering pharmaceutical compound to achieve a therapeutic effect in humans and animals. Most common method of drug delivery includes the oral (through the mouth), topical (skin), trans-mucosal (nasal, buccal, sublingual, vaginal, ocular and rectal), parenteral (injection into systemic circulation) and inhalation routes.[4]

The drug delivery system can further be divided into two main types:

1. Conventional drug delivery system
2. Novel drug delivery system

CONVENTIONAL DRUG DELIVERY SYSTEM: -Conventional drug delivery system is the classical methods for the delivery of drug into the body.[4]

NOVEL DRUG DELIVERY SYSTEM: It is a combination of advanced technique and new dosage forms which are far better than conventional dosage forms and involves medicinal devices. It improves the drug potency, control drug release to give a sustained therapeutic effect, provide greater safety and target a drug specifically to a desired tissue.[4]

FORMULATION OF CONVENTIONAL DRUG DELIVERY SYSTEMS

TABLETS FORMULATIONS

In addition to the active drug, called DS or active pharmaceutical ingredient (API), tablets may contain one or more of functional ingredients such as diluents (also known as Fillers), binders, disintegrants, glidants, lubricants, coating materials, coloring agents, stabilizer(s), sweeteners, and Flavoring agents. These ingredients are called excipients [4].

Tablet Ingredients/Excipients: -In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:

1. Diluent / Filler
2. Binder and adhesive
3. Disintegrants
4. Lubricants and glidants
5. Coloring agents.
6. Flavoring agents
7. Sweetening agents[5]

1.Diluents: -Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. A diluent should have following properties:

- ✓ They must be non-toxic and low cost.
- ✓ Mannitol and Sorbitol
- ✓ They must be commercially available in acceptable grade
- ✓ They must be physiologically inert, physically & chemically stable by themselves & in combination with the drugs.
- ✓ They must be free from all microbial contamination.
- ✓ They do not alter the bioavailability of drug.
- ✓ They must be color compatible [5].

Commonly used tablet diluents

- ✓ Lactose-anhydrous and spray dried lactose
- ✓ Directly compressed starch-Sta Rx 1500
- ✓ Hydrolyzed starch-Emdex and Celutab
- ✓ Microcrystalline cellulose-Avicel (PH 101and PH 102)
- ✓ Dibasic calcium phosphate dehydrate
- ✓ Calcium sulphate dihydrate
- ✓ Sucrose- Sugartab, DiPac, Nutab
- ✓ Dextrose Lactose [5]

2.Bindersand Adhesives: - These materials are added either dry or in wet- form to form granules or to form cohesive compacts for directly compressed tablet. Example: Acacia, tragacanth-Solution for 10-25% Conc. Cellulose Derivatives-Methyl cellulose, Hydroxy propyl methyl cellulose, Hydroxy propyl cellulose Gelatin- 10-20% solution, Glucose-50% solution, Polyvinylpyrrolidone (PVP)-2% conc. Sorbitol Starchpaste-10-20%solution, Sodium alginate.[5]

3.Disintegrants: - A disintegrant is a substance to a mixture of substances, added to tablet to facilitate its breakup or disintegration after in the GIT[5]. Disintegrants can be classified chemically as: Starches, clays, celluloses, alginates, gums and cross-linked polymers.

Super disintegrants: Super disintegrants like Croscarmellose - cross linked cellulose, Crospovidone - cross linked polyvinyl pyrrolidone and Sodium starch glycolate- cross linked starch[5].

4.Lubricant and Glidants:- Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

Example: Stearic acid, Stearic acid salt - Stearic acid, Magnesium stearate, Talc, PEG(Polyethylene glycols), Surfactants[5]

Glidants are intended to promote flow of granules or powder material by reducing the friction

between the particles.

Example: Corn Starch – 5-10% conc., Talc-5% conc., Silica derivative - Colloidal silicates such

as Cab-O- Sil, Syloid, Aerosil in 0.25-3% conc4.

5.Colouring agents: All coloring agents must be approved and certified by FDA. Two forms of colors are used in tablet preparation FD & C and & C dyes. These dyes are applied as solution in the granulating agent or Lake form of these dyes. Lakes are dyes absorbed on hydrousoxideand employed as dry powder coloring [6].

6.Flavours and Sweeteners: Flavors are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other adsorbents or are emulsified in aqueous granulating agents (i.e. binder).

The use of sweeteners is primarily limited to chewable tablets. E.g. Sugar

- Mannitol– 72% as sweet as sugar, cooling & mouth filling effect
- Saccharin– Artificial sweetener, 500 times sweeter than sucrose
- Cyclamate– either alone or with saccharin– it is banned
- Aspartame (Searle) – widely replacing saccharin [6]

Tablet Manufacturing Techniques

1. Direct compression: The direct compression method is by far the most effective technique of tablet manufacturing. This technique is least tedious and hence is preferred over the other techniques. Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques such as wet granulation and roller compaction[6]

Fig.2 Direct Compression

2.Wet granulation: Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid required to be properly adjusted, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.[6]

Fig.3 Wet granulation

3.Dry granulation: Dry granulation requires drugs or excipients with cohesive properties. Dry granulation is simpler than wet granulation, therefore the cost is reduced. This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet.[6]

Fig.4 Dry granulation

NOVEL DRUG DELIVERY SYSTEM (NDDS):-

CONTROL DRUG DELIVERY SYSTEM:-

FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS

(1) Physiological properties

(i) Aqueous Solubility's: Most of the active pharmaceutical moiety (API) are weakly acidic or basic in nature that affect the water solubility of API. Weak water soluble drugs are difficult to design the controlled release formulations. High aqueous solubility drug show burst release followed by a rapid increment in plasma drug concentration. These types of drugs are a good candidate for CRDDS [7] .

(ii) Partition coefficient (P-value): P-value denotes the fraction of the drug into oil & aqueous phase that is a significant factor that affects the passive diffusion of the drug across the biological membrane [8].

(iii) Drug pKa:pKa is the factor that determined the ionization of drug at physiological pH in GIT. Generally, the high ionized drugs are poor candidates for CRDDS. The pKa range for an acidic drug that ionization depends on the pH is 3.0 to 7.5 and for a basic drug it lay between 7 and 11[9].

(iv) Drug stability: Drugs that are stable in acid/base, enzymatic degradation, and other gastric fluids are good candidates for CRDDS. If drug degraded in the stomach and small intestine, it not suitable for controlled release formulations because it will decrease in bioavailability of concern drug[10].

(v) Molecular size & molecular weight: The molecular size & molecular weight are two important factors which affect the molecular infusibility across a biological membrane [11].

(vi) Protein binding: The drug-protein complex act as a reservoir in plasma for the drug. Drug showing high plasma protein binding are not a good candidate for CRDDS because the protein binding increases the biological half-life[12].

(2) Biological factors

(i) Absorption: The absorption rate should rapid then release rate to prevent the dose dumping. The various factors like aqueous solubility, log P, acid hydrolysis, which affect the absorption of drugs[13].

(ii) Biological half-life (t1/2): Ideally, the drugs having t1/2 2-3 hrs are a suitable candidate for CRDDS. Drugs have t1/2 more than 7-8 hrs not used for controlled release system[13-14].

(iii) Dose size: The CRDDS formulated to eliminate the repetitive dosing, so it must contain the large dose than conventional dosage form. But the dose used in conventional dosage form give an indication of the dose to be used in CRDDS. The volume of sustained dose should be as large as it comes under acceptance criteria[15].

(iv) Therapeutic window: The drugs with narrow therapeutic index are not suitable for CRDDS. If the delivery system failed to control release, it would cause dose dumping and ultimate toxicity[16].

(v) Absorption window: The drugs which show absorption from the specific segment in GIT, are a poor candidate for CRDDS. Drugs which absorbed throughout the GIT are good candidates for controlled release[17].

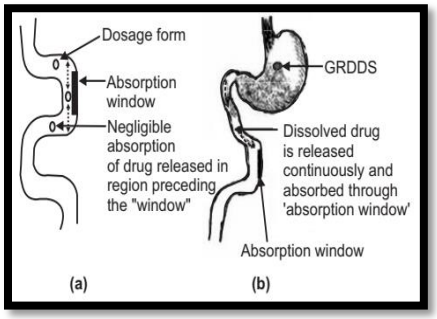

Fig.5 Absorption window

(vi) Patient physiology: The Physiological condition of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly [18].

Approaches to design-controlled release formulations

1. Dissolution controlled release
   - Encapsulation Dissolution control
   - Seed or granule coated
   - Micro encapsulation
   - Matrix Dissolution control
2. Diffusion controlled release
   - Reservoir type devices
   - Matrix type devices
3. Diffusion and Dissolution controlled systems

4. Ion exchange resins
5. Osmotically controlled release[19]

EVALUATION TEST

Medication evaluation is a continuous activity. The review begins before a drug is dispensed, and continues during and after dispensing. A continuous review is crucial to identifying and resolving drug-related problems [20].

1. SOLID DOSAGE FORM: The solid dosage for needs various test of evaluation so that it shows popper properties of drugs.

i. DISSOLUTION TEST: The assembly consists of the following: vessel, which may be covered, made of glass or other inert, transparent material, which should not sorb, react or interfere with the preparation to be tested; a motor; a drive shaft; and a cylindrical basket (stirring element). The vessel is partially immersed in a suitable water-bath of any convenient size or heated by a suitable device such as a heating jacket. The water-bath or heating device permits maintaining the temperature inside the vessel at 37 ± 0.5 ºC during the test.

Dissolution Time: 6 solid dosage form in each tube for coated 15 min uncoated 30 min plain 60 min for capsules 30 min and vice versa if not disintegrate do again with 12 ,16

Fig. 6 Dissolution Test

ii. DISINTEGRATION TEST: To carry out a disintegration test for tablets, we use a basket which holds 1 to 6 tablets. This is then raised and lowered into a beaker of water, which is used to simulate conditions in the stomach at 3737 ± 0.5 ºC. If the tablets or capsules float, perforated plastic disks are placed on the top of the tablets to keep them under the water level. The tablet disintegration time is taken when no residue is left in the mesh. Disintegration Time: 6 solid dosage form in each tube for coated 60 min uncoated 45 min plain 60 min for capsules 30 min and vice versa if not disintegrate do again with 12.

Fig.7 Disintegration Test

iii. WEIGHT VARIATION TEST: To find out the uniformity in the weight ,20 tablets average weight bis calculated individual weight calculated, comparison is done Result's 30-N F 25 LIMITS FOR WEIGHT VARIATIONS CASE OF TABLET WEIGHING UP TO 130±10% ,130/324±7.5%, 324 mg ±5%

formula= W average – W initial/W average 8*1000

Fig.8 Weight variation Test

iv. Drug uniformity test:10 tablets powdered and 100 mg equivalence powder dissolve in suitable solvent make 100 ml solution and dilute it 100 time calculations are carried out.

Result: Pass test when not less than 85 % and not more than 115%.

Fig.9 Drug uniformity test

2. LIQUIDE DOSAGE FORM: The liquid dosage for needs various test of evaluation so that it shows popper properties of drugs.

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

Fig.10 Dye Bath Test

ii. CLARITY TEST: Dilute the preparations and check for cloudiness with control that is clean water In this test transparent particles or white particles observed against the black background and the black or dark particles observed against the white background.

Fig.11 Clarity Test

iii. STERILITY TEST: It is done for detecting the presence of viable forms of bacteria, fungi and yeast in parenteral products he test for Sterility must be carried out under strict aseptic conditions in order to avoid accidental contamination of the product during test. Two main types

Direct transfer method:

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

Fig.12 Sterility Test

Membrane filtration method: Sample →0.22 to 0.4 um pore size 47 mm diameter filter→ membrane cut into 2 halves → 100 ml culture medium →incubated 30 to 35 ºC 7 days →anther halve 20 to 25 ºC for 7 days

iv. PYROGEN TESTING: Pyrogens are metabolic product of the microbes produces fever with body each.

Fig.13 Pyrogen Testing

SHAM TEST: 3 rabbits→ 1 to 3 days observation →temp check 30 to 40 min prior → sample solution administration (37 ºC prior to injection) →thermometer in rectal cavity up to 7.5 cm →initial and second reading temp 0.2 c →1 hr temp determine →do not vary from 1 ºC →rabbit shows 0.5 ºC rise test pass otherwise 5 additional rabbits are used.

LAL TEST: Limulus Amoebocyte Lysate (LAL) of limulus polymethyls gel is used 0.1 ml sample with the lal reagent incubation for 1 hr at 37 ºC clot is analysed due to properties of hors shoe crab gel.

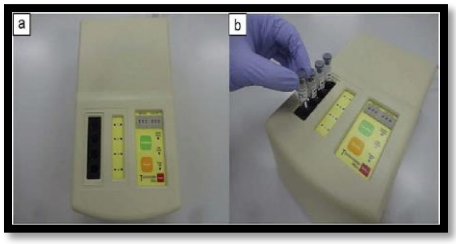

Fig.14 LAL Test

3. Semisolid dosage form:
The liquid dosage for needs various test of evaluation so that it shows proper properties of drugs

PH MEASUREMENT: The ph. is determine by means of the various methods like used of ph.meter electrode measures the ph.

VISCOSITY MEASUREMENT: It measured by Instruments called "rheometers" and viscometer.

Fig.15 PH Measurement

LABELLING AND PACKAGING
DEFINITION: Pharmaceutical packaging (or drug packaging) is the packages and the packaging processes for pharmaceutical preparations. It involves all of the operations from production through drug distribution channels to the end consumer [20].

1. TYPES OF PACKAGING
i. PRIMARY PACKAGING: they have direct contact with drugs ex. cap liner label
ii. SECONDARY PACKAGING: external to the primary packaging add additional physical protection, leaflets cartons etc.
iii. TERRITORY PACKAGING: provides protection handling Wearhouse storage and transportation ex brown cardboard boxes wood pallets etc.
•**Airtight containers.** These containers prevent the contents from dust, moisture, and air. ...
•**Light resistant containers**. Multi-dose containers. Single-dose containers. Well closed containers. Aerosol containers. Childproof containers etc.

2. PACKAGING MATERIAL:
•**GLASS:** They are most commonly used for storing pharma products due to superior protecting quality Borosilicate glass type 1 :80 % silica 10% boric acid small amount of sodium oxide Soda lime glass: suffer treatment more resistance than type 3Regular soda lime glass: 75% silica 15% sodium oxide 10% CALCIUM OXIDE Products: colored glass ampules, bottles etc.

•**PLASTIC:** Materials used: polyethene, polystyrene, polycarbonate, polyvinyl chloride, poly vinyl dine chloride polypropylene etc.

METALS: Metals are more versatile of the all products that used Material used: aluminum, tin, Products tablets, blisters, collapsible tubes cans, sachets, poches, membranes, etc.

PAPER PAPERBOARD: They are traditional material used ever since ex boxes sachets etc.

•**RUBBER:** They are used for closures stoppers and cap liners and bulbs.

TYPE 1: Most preferred strictest requirement type 2 ; mechanical properties Materials: natural, neoprene, nitryl, butyl, Chornobyl , silicon.

Materials: natural, neoprene, nitryl, butyl, Chornobyl , silicon

COTTON: It is used for wadding in solid preparations prevent collisional

FILMS FOILS LAMINATIONS: they used to support barrier heat sealing decoration

ADESSIVE LINKS: they used for labelling adhesion[20].

EVALUATION TEST FOR PACKAGING MATERIALS

•**IDENTIFICATION:** appearance of packaging material alone and combination of the content is checked.

•**PHYSICAL TEST:** appearance light absorption, ph., non-volatile matter, residue on ignition, heavy metals, buffering capacity, oxidizable substances are check

•**CHEMICAL TEST:** test include ph. materials chloride sulphates, paper or board, alkalinity of glass, compatibility test for containers.

•**MECHANICAL TESTs:** to check working and strength

•**BIOLOGICAL TEST:** USP. provides procedure for it implantation test, systemic injection test, intracutaneous test,

•**ENVIRONMENTAL TEST:** materials test in environment

TESTS AS FOLLOWS: Leakage test, collapsibility, clarity, transparency, water vapourpermeability, test for metallic additives, non-volatile residual, metallic additives resistance, hydraulic resistance, etching, light transmission, rather soluble, thermal shock, internal bursting, penetrability test, frag mentation, self-stability, extractive, capability, light absorption.

4. LABELLING OF DIFFERENT DOSAGE FORM

DEFINITION: The term "labelling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. Drug labelling is also refer metallic red to as prescription labelling, is a written, printed or graphic matter upon any drugs or any of its container, or accompanying such a drug. Drug labels seek to identify drug contents and to state specific instructions or warnings for administration, storage and disposal. For labelling of dosage form one should follows all the guidelines given Product Name, Drug Facts, Table, Active Ingredients, Purpose and Use, Warnings, Directions, Allergic Reactions active Ingredients, expiry date, date of manufacturing, various type of drugs properly should be mentioned[20].

CONCLUSION:

The formulation development studies along with the pre-formulation studies various tests and the sop handling are the important aspects of the pharmaceutical industries without this the industries cannot work properly and the quality efficiency and the new solution of the problems occurring during development cannot be solve one can know that the large amount efforts required with knowledge required for formulation development because 'small mistake big consequences.

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