Formulations and Formulation Development

Pre-Formulation Studies

Incompatibilities encountered in drug multi-component combinations and /or Drugexcipient Compatibility.

Pharmaceutical Formulation Additives, Containers and Closures.

Manufacturing and Quality control of Solid Dosage forms, Semi-Solid Dosage forms, Liquid Dosage forms, Sterile Dosage forms, Metered Dosage forms (Aerosols)

Study of principles, Production techniques, Pilot batch studies, Scale-up Studies, Transfer of technology to commercial scale batches, stability conditions.

Storage and handling of In-Process and finished dosage forms, principles of stability studies as per ICH Guidelines.

PREFORMULATION STUDIES

INTRODUCTION:

All the medicinal products or dosage forms will contain the drug plus a variety of additives or excipients whose role is to enhance the product performance without altering the stability and pharmacology of the drug. It is therefore, a general rule that patients are never administered a drug but rather a medicinal product that contains the drug.

Pharmaceutical development of a medicinal product must retain the drugs promising *in-vitro* pharmacological activity and provide a predictable *in-vivo* response. The marketed product must be stable, correctly packaged, labeled and easily administered, preferably by self administration. The development of pharmaceutical product involves multiple skills, processes and stages and is, therefore, a large undertaking requiring extensive resources.

The development of medicinal product consists of several stages such as

Preformulation

The study involves Characterization of physicochemical properties and includes extensive study of

Physiochemical characteristics of the drug
Solubility characteristics of the drug
Drug-Excipient Compatibility
Analytical method developments
Stability studies

Formulation development

Formulation development is a continuing process which is attempted by the manufacturer after NDA consideration of Application for the medicinal product. The dose of the drug and the route of administration are important in determining the required modifications and involves development of

Injectable drug product
Topical drug product
Oral drug product
Vaginal drug products
Nasal drug products
Pulmonary drug products

Final drug product

Considerations in the development of final dosage form include the following

Color, shape, size, taste, viscosity, sensitivity, skin feel, and physical appearance of the dosage form
Size and shape of package or container
Production equipment
Production site
Country of origin in which the drug is to be manufactured
Country in which the medicine will be marketed.

Definition

Preformulation studies are defined as the application of biopharmaceutical principles to the physicochemical parameters of drug substance that are characterized with the goal of designing optimum drug delivery system.

Preformulation is the characterization of the physical and chemical properties of the active drug substances and dosage forms. The therapeutic indication of the drug and the route of administration dictate the type of drug product or drug delivery system that needs to be developed. The characterization of drug and its excipient compatibility information decides many of the subsequent events and approaches in formulation development**.**

Preformulation activities are usually performed during the preclinical stage. However these activities may continue in to phase I and phase II studies. During

preformulation studies the following information is obtained by the preformulation scientist.

I) Physiochemical characteristics of the drug

II) Solubility characteristics of the drug

IV) Drug-Excipient Compatibility

V) Analytical method developments

VI) Stability studies

I) PHYSIOCHEMICAL CHARACTERISTICS OF THE DRUG:

The physical characterization of the drug involves characterization of various physical properties and involves

Particle Size, Shape, and surface area
Powder flow properties
Crystalline properties and Polymorphism
Saturation Hygroscopicity
Melting point
pKa

1) PARTICLE SIZE, SHAPE, AND SURFACE AREA

In general, each new drug candidate should be tested during Preformulation with the smallest particle size as is practical to facilitate preparation of homogeneous samples and maximize the drug' s surface area for interactions. Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. It is generally recognized that poorly soluble drugs showing a dissolution- rate limiting step in the absorption process will be more readily bio available when administered in a finely subdivided state rather than as a coarse material.

In case of tablets, size and shape influence the flow and the mixing efficiency of powders and granules. Size can also be a factor in stability: fine materials are relatively more open to attack from atmospheric oxygen, the humidity, and interacting excipient than the coarse materials.

- Determination of particle size

-Determination of surface area

Particle size Determination:-

Though microscopy is the simplest technique of estimating size ranges and shapes, it is to slow for quantitative determination the material is best observed as a suspension in non dissolving fluid. Saving is less useful technique at preformulation storage due to lack of bulk material. Andreason pipette is based on the rate difference of sedimentation of different particles, but techniques like this are seldom used due to their tedious nature instruments based on light scattering, (Royco), light blockage (HIAC) and blockage of electrical conductivity path (coulter counter) are used.

Surface Area Determination:-

Surface area is most commonly determined based on brunaver emette teller (BET) theory of adsorption. Most substances adsorb a mono molecular layer of gas under certain conditions of partial pressure of gas and temperature. Knowing the monolayer capacity of adsorbent and the area of absorbable molecule, the surface area can be calculated. the adsorption process is carried out with nitrogen at-195 degree Celsius at a partial pressure attainable when nitrogen is in a 30% temperature with an inert gas (helium). The adsorption takes place by virtue of Vander wall's forces.

2) POWDER FLOW PROPERTIES:

When limited amounts of drugs are available Powder flow properties can be evaluated by measurements of bulk density, Carr's index Hausner ratio and angle of repose. Changes in particles size and shape are generally very important an increase in crystal size or a more uniform shape will lead to a small angle of repose and a smaller Carr's index.

Bulk Density:-

Knowledge of absolute and bulk density of the drug substance is Very useful in Having some idea as to the size of final dosage form the density of solids also of affects their flow Properties Carr's compressibility index can be used to predict the flow properties based on density measurement.

Bulk density = Mass of the powder / Bulk volume

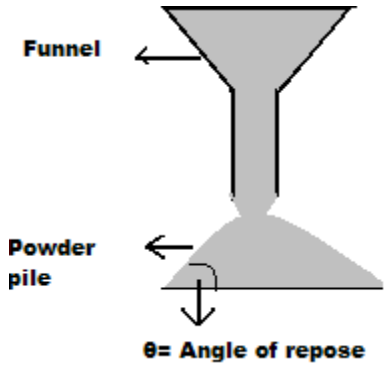
$$\textit{Carr's index (\%)} = \frac{\textit{Tapped density} - \textit{Pored density} * 100}{\textit{Tapped density}}$$

A similar index has been defined by Hausner:

$$\textit{Hausner ratio} = \frac{\textit{Tapped density}}{\textit{Pored density}}$$

Angle of repose:-

The maximum angle which is formed between the surface of a pile of powder and horizontal surface is called the angle of repose. It is represented as ' θ'



Schematic representation of Angle of repose

Where

$Tan\ \theta = h/r$

$\theta = Tan^{-1} h/r$

h= Height of the pile

r=Radius of the pile

Relationship between flow, angle of repose, Carr's index fee power flow

Flow	Angle of repose	Carr's index (%)
Excellent	**<25**	**5-15**
Good	**25-30**	**12-16**
Fair to passable	**30-40**	**18-21**
Poor	**> 40**	**23-35**
Very Poor		**33-38**
Extremely Poor		**>40**

Crystal Properties and Polymorphism:-

Many drug substances can exit in more than one crystalline from with different shape and lattice arrangements. This property is known as polymorphism. Polymorphs generally have different melting points, x-ray diffraction patterns and solubility even though they are chemically identical. Differences in the dissolution rates and solubility's of different polymorphic forms of a given drug are very commonly observed. When the absorption of a drug is dissolution rate limited, a more soluble and faster-dissolving from may be utilized to improve the rate and extent of bioavailability. For drugs prone to degradation in the solid state, physical form of the drug influences degradation. Selection of a polymorph that is chemically more stable is the solution in many cases. Different polymorph also leads to different morphology, tensile strength and density of powder bed which all contribute to compression characteristics of materials. Some investigation of polymorphism and crystal habit of a drug substance as it relates to pharmaceutical processing is desirable during its Preformulation evaluation especially when the active ingredient is expected to constitute the bulk of the tablet mass. Although a drug substance may exist in two or more polymorphic forms, only one form is thermodynamically stable at a given temperature and pressure. The other forms would convert to the stable form with time. In general, the stable polymorph exhibits the highest melting point, the lowest solubility, and the maximum chemical stability. Various techniques are available for the investigation of the solid state. These include microscopy (including hot stage microcopy), infrared spectrophotometer, single-crystal x-ray and x-ray powder diffraction, and thermal analysis.

Saturation Hygroscopicity:

It is one of the important powder parameter that defines the stability of the material and it can be defined as the maximum moisture absorbance capacity of a drug powder from the atmosphere or the surroundings. The method helps in determining moisture sensitivity of the drugs, Equilibrium Moisture Content (EMC) and also aids in selection of packing material for a finished dosage form.

The experimental study is carried out by taking a known quantity of drug material in open trays and placed in desiccators, the samples are collected at regular intervals and moisture content or water content is analyzed by Karl-Fischer titration method.

Melting Point:

The melting point of a drug can be measured using three techniques :-

1) Capillary Melting

2) Hot Stage Microcopy

3) Differential scanning calorimeter or thermal Analysis.

Capillary Melting:

Capillary melting gives information about the melting range but it is different to assign an accurate melting point.

Hot Stage Microcopy:

This the issued observation of melting under a microscope equipped with a heated and lagged sample stage. The heating rate is controllable and up to three transitions can be registered.

Differential Scanning Calorimetry and thermal analysis:

Differential thermal analysis (DTA) measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant

rate. Differential Scanning Calorimetry (DSC) is similar to DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference i.e. it measures the enthalpy of transition.

pKa Determination:-

Determination of the dissociation constant for a drug capable of ionization within a pH rang of 1 to 10 is important since solubility and consequently absorption, can be altered by orders of magnitude with changing pH. The Henderson – Hasseslebach equation provides an estimate of the ionized and unionized drug concentration at a particular pH.

For acidic compounds

pH = pKa + log (un-ionized drug]) / [ionized drug])

II) SOLUABILITY CHARACTERISTICS OF THE DRUG:

The solubility of a drug may be expressed in a number of ways. The *U.S. Pharmacopia and national formulary* lists the solubility of drugs as the number of milliliters of solvent in which 1gm of solute will dissolve. Solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into dissolution medium and consequently, the therapeutic efficiency of the pharmaceutical product. The solubility of the molecules in various solvents is determined as a first step. This information is valuable in developing a formulation. Solubility is usually determined in variety of commonly used solvents and some oils if the molecules are lipophilic.

The solubility of material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged time until equilibrium is achieved :-

Common solvents used for solubility determination are:-

·Water ,

Polyethylene,Propylene Glycol

·Glycerin ,Sorbitol

·Ethyl, Benzyle , Isopropyl Alcohol

·Methanol

·Tweens

·Polysorbates

·Castor, Peanut, Sesame Oil

·Buffer at various pH

Aqueous Solubility:

The availability of a drug is always limited and the preformulation scientist may only have few quantities of drug material to analyze its characteristics, a very few quantity of drug is used to determine aqueous solubility, by dissolving known parts of drug in different parts of water. The Aqueous Solubility of drugs is characterized as follows

Characterization of aqueous solubility of drugs

S.no	Parts of drug	Parts of water	Terms of solubility
1	1	Less than 1	Very soluble
2	1	1-10	Freely soluble
3	1	10-30	Soluble
4	1	30-100	Sparingly soluble
5	1	100-1000	Slightly soluble
6	1	1000-10000	Very slightly soluble
7	1	More than 10000	Practically insoluble

Intrinsic Solubility (Co) :-

An increase in solubility in acid compared to aqueous solubility suggests a weak base and an increase in solubility in alkali suggests a weak acid. An increase in acidic and alkaline solubility suggests zwitter ion behavior. In this case there will be two pKa's, one acidic & one basic. When the parity of the drug sample can be assured the solubility obtained in acid for a weak acid or alkali for a weak base can be assured to be the intrinsic solubility

(Co.) i.e. the fundamental solubility when completely unionized. The solubility should ideally be measured at two temperatures.

1) $4^{O}C$ to ensure physical stability and the minimum density of water occurs at $4^{O}C$. This leads to a minimum aqueous solubility.

2)$37^{O}C$ to support biopharmaceutical evaluation.

Partion coefficient:

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/ hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/ hydrophilic nature of the drug.

Since biological membranes are lipoidal in nature. The rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water.

Drugs having values if P much greater than 1 are classified as lipophilic, whereas those with partition coefficient much less than 1 are indicative of a hydrophilic drug.

Although it appears that the partition coefficient may be the best predictor of absorption rate, dissolution rate.

Dissolution:

The dissolution rate of the drug is only important when it is the rate limiting step in the absorption process. The rate of dissolution is directly proportional to solubility of the drug

Intrinsic Dissolution Rate:

When dissolution is controlled solely by diffusion the rate of diffusion is directly proportional to the saturated concentration of the drug in solution under these conditions the rate constant K_1 is defined by

$K_1 = 0.62\ D^{2/3}\ v^{1/6}\ w^{1/2}$

Where, V is the kinematic viscosity

W is the angular velocity of a rotating disc of drug.

Common Ion Effect:

According to Le Chatelier principle presence of a common ion will shift the equilibrium from right to left and significantly reduces the solubility of a slightly soluble substances and any addition of solvent shift the equilibrium left to right and significantly increses the soluability..

Ex: $AgCl\ (s) \leftrightarrow Ag^{+}(aq) + Cl^{-}$

The 'salting out' results from the removal of water molecules as solvent owing to the competing hydration of other ions. The reverse process 'salting in' arise with large anions e.g. benzoate, which open the water structure. These hydro topics increase the solubility of poorly water soluble compounds such as diazepam.

IV) DRUG-EXCIPIENT COMPATIBILITY

The success of formulating a dosage form depends upon careful selection of excipients that do not interact with drug or with each other this phenomenon can be investigated before the commencement of formulation by studying drug and various excipient mixtures. The knowledge of drug excipients interaction is useful for the formulation to select appropriate excipients. The described preformulation screening of drug excipients interaction involves Geometric dilution of 5mg of drug in a 50% mixture with the excipients to maximize the likelihood of obscuring an interaction. Mixtures should be examined under nitrogen to ultimate oxidation and paralytic effect at a standard heating

rate on Differential Scanning Calorimeter (DSC), over a temperature range, which will encompass any thermal changes due to both the drug and appearance or disappearance of one or more peaks in thermograms of drug excipient mixtures are considered as an indication of interaction.

Preformulation testing provides a basic dossier on the compound and plays a significant role in identifying possible problems and suitable approaches to formulation. Such dossiers already exist for the common excipients.

V) ANALYTICAL METHOD DEVELOPMENTS

Analytical method development is one of the initial priorities in preformulation studies for detection of drug (main component), Intermediate compounds carried from synthesis and degradation products from chemical breakdown or instability. Paradoxically, these latter contaminants are of greater importance because there quantification, identification and control affect the quality of drug batches. In addition chemical instability is more easily detected through an increased concentration of degradants than through decreased concentration of the main component. Methods are also required for quantification of other impurities such as residual solvents, catalyst residues and heavy metals and microbial contamination. Further analytical tests will also be specified such as general characteristics, colour, melting point, loss on drying and basic identification method

Drug Assays are usually conducted using various analytical methods such as Spectrophotometers such as UV spectrophotometry or specific chromatography such as High Performance Liquid Chromatography (HPLC) or capillary electrophoresis. These techniques ensure that the drug is separated from impurities and breakdown products, all of which can then be quantified.

Development of these methods allows specifications to be set for the required percentage of main component usually 98-101% by weight and limits for the tolerated levels of impurities. If required identification of impurities will also be conducted. A reference sample will be retained and used as a standard for subsequent analysis.

VI) STABILITY STUDIES

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include both solution and solid state experiments under condition typical for the handling, formulation, storage, and administration of a drug candidate as well as stability in presence of other recipients.

Factor effecting chemical stability critical in rational dosage form design include temperature, pH and dosage form diluents. The method of sterilization of potential product will be largely dependent on the temperature stability of the drug. Drugs having decreased stability at elevated temperatures cannot be sterilized by autoclaving but must be sterilized by another means, e.g., filtration. The effect of pH on drug stability is important in the development of both oral and parental dosage forms. Oral administration must be protected from the highly acidic environment of the stomach. Buffer selection for potential dosage forms will be largely based on the stability characteristic of the drug such as

- Solid state stability

- Solution phase stability

- Compatibility studies: stability in the Presence of excipients

- Typical stability protocol for anew Chemical Entity

Solid state stability:-

Chemical instability normally results from either of the following reaction: - hydrolysis, oxidation, and photolysis. Esters and lactase and to lesser extent, amides are prone to solvolysis . Instauration or electron rich centre in the structure make the molecule vulnerable for free radical mediated or photo-catalyzed oxidation. Amorphous materials are less stable than their crystalline forms. Denser materials are more stable to ambient stress.

Elevated temperature studies:-

The elevated temperatures commonly used are 40, 50, and 60 degree centigrade with ambient humidity. The samples stored at highest temperature are observed weekly for physical and chemical changes and compared to an appropriate control. If a substantial change is seen, samples stored at lower temperature are examined. If no change is seen after 30 days at 60 degree centigrade, the stability prognosis is excellent.

Stability under high humidity conditions:-

Solid drug samples can be exposed to different relative humidity conditions by keeping them in laboratory desiccators containing saturated solutions of various salts. The closed desiccators in turn are kept in oven to provide constant temperature. The preformulation data of this nature are useful in determining if the material should be protected and stored in controlled low humidity environment or if non aqueous solvent be used during formulation.

Photolytic stability:-

Many drugs fade on exposure light. Though the extent of degradations small and limited to the exposed surface area, it presents an aesthetic problem. Exposure of drug to a 400 and 900 foot-candles of illumination for 4 and 2 week periods respectively is adequate to provide some idea of photosensitivity. Resulting data may be useful in determining if an amber colored container is required or if color masking bye should be used in the formulation.

Stability to Oxidation:-

Drug's sensitivity to oxidation can be examined by exposing it to atmosphere of high oxygen tension. Usually a 40% oxygen atmosphere allows for rapid evaluation. A shallow layer of drug exposed to a sufficient headspace volume ensures that the system is not oxygen limited. Samples are kept in desiccators equipped with three-way stop cocks, which are alternatively evacuated and flooded with desired atmosphere. The process is repeated 3 or 4 times to ensure 100% desired atmosphere. Results may be useful in predicting if an antioxidant is required in the formulation or if the final product should be packaged under inert atmospheric conditions.

After completion of individual characteristics study the preformulation scientist By comparing the physicochemical properties of each drug candidate with in a therapeutic group, can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

After completion of the studies it is the responsibility of formulation scientist to develop a formulation by considering the required parameters.

DRUG INCOMPATIBILITIES

Incompatibilities in pharmaceutical products are undesired physical, chemical or biopharmaceutical processes which take place during preparation, storage or administration resulting in decomposition of drugs and a failure to improve the patient's condition.

Incompatibilities may take place in a manner of drug-drug interactions or drug-additive and additive-additive interactions. Physicochemical conditions are the common factor causing incompatibilities.
The most common physicochemical factors involving incompatibilities were reviewed as following:

1. Acid-Base Character
2. pH
3. Concentration
4. Oxidation
5. Hydrolysis or Solvolysis
6. Temperature
7. Photolysis

All incompatibilities may take place in a visual or hidden manner. Visual or visible incompatibilities usually result from inadequate solubility, viscosity changes, color change, turbidity, etc. The hidden incompatibilities which are not visible apparent may be difficult in detection. Pharmacists may encounter these incompatibilities, an understanding of physicochemical principles is useful for solving these problems.

DRUG INTERACTIONS

Drug Interaction: Involves one drug which precipitates the change in the effect of other drug.

Drug which precipitates the interaction - Precipitant

Drug whose action is affected is called - Object Drug

Diff. Causes:

- Administration of two or more drugs simultaneously
- Patients may visit many doctors
- Concurrent use of prescribed & non – prescribed drugs
- Patient non-compliance

Types of Drug Interactions:

Beneficial Drug Interactions:

Ex: Improved Compliance- Anti TB agents, Ferrous Sulphate & Folic Acid

Ease of administration- Triple Vaccine (Diphtheria, Pertusis, Tetanus)

Synergistic effect - Trimethorphan + Sulfamethoxazole
Aspirin + Codeine

Decreased adverse effects - Levodopa + Carbidopa

Adverse Drug Interactions: Undesirable / Unintentional

Hetergic (Antagonism) - When two drugs produce diff. effects

Homergic (Synergistic) - when two drugs produce similar effects

Mechanisms:

- § Pharmaceutical
- § Pharmacokinetic
- § Pharmacodynamic

1) Pharmaceutical: Even before administration

Ex: Noradrenaline, tetracyclines, corticosteroids - Electrolytes

2) Pharmacokinetic Drug Interactions:

Interference with absorption

Changes in protein Binding

Modification of drug metabolism

Interference with renal excretion

3) Pharmacodynamic Interactions.

Modification of drug at receptor sites.

Disturbance of water & electrolyte balance.

PHARMACEUTICAL FORMULATION ADDITIVES

Formulation
Bulk Drugs

Active
In active (Excepients)

Active Ingredients

Soluble Drugs – Systemic Effect
Insoluble Drugs – local effect

Any formulation or design may be described as the process whereby the formulator insures that the correct amount of drug in the right form is delivered at or over proper time at the proper rate and in the desired location, while having its chemical integrity protected to that point.

Excepients:

- to produce satisfactory drug release
- to active acceptable physical & mechanical properties
- to facilitate the manufacture

Cubic: If the drug contains proper Crystalline Structure

Non cubic: Direct compression

Cubic Structure:

Structure is same along each axis, so no alignment is necessary between individual particles. Ex: NaCl

Non Cubic:

Some realignment is necessary which results in a reduced probability of bonding. So addition of Excepients, Compaction of crystals depends on Particle size distribution, crystal shape, bulk density & moisture content.

Compression: Crystals are fractured & the fragments form a close – packed arrangement, which readily consolidates on compression.

Formulation Development:

Bioavailability Consideration:

Availability of Drug in different formulations: - Solution
- Suspension
- Micronised drug in capsule form
- uncoated tablets
- Coated Tablets

Non Active Ingredients: They fall under 6 categories:

- Diluents
- Binders
- Lubricants
- Disintegrants
- Colors
- Sweeteners (flavors)

By Function: 2 categories

Those effects compress ional characteristics.

Viz., Diluents, Binders & Adhesives, Lubricants, Anti adherents, Glidants

Those which effect biopharmaceutics, Chemical & Physical stability and Marketing Considerations. Viz., Disintegrants, colors, Flavors & Sweeteners and other miscellaneous components like Buffers, Adsorbents etc.

Diluents: (Fillers)

- Small Dosage formulations.

Bound Ex: $CaSO_4 . 2H_2O$

- Moisture 12% moisture, hygroscopic

Unbound

For Chewable Tablets – taste & mouth Feel Diluents

Ex: Lactose, Starch, MCC etc.

Lactose: Has good drug release rates.

Disadvantages: it may discolor in the presence of amine drug Bases or Salts & alkaline Lubricants.

Starch: (Corn, Wheat / Potatoes)

Moisture: 11-14%

Dried Starch: 2 – 4 %

It serves as local desiccant by localizing the moisture in moisture sensitivity drugs.

Directly Compressible Starch: (Physically Corn Starch)

Diluent, Binder, Disintegrant agent.

Mannitol: For Chewable tablets,

Mouth Feel is due to negative heat of solution & its slow solubility with cool sensation during dissolution of sugar. 72% as sweet as sucrose

Non Hygroscopic – Best diluent in Vitamin Preparations

MCC: Hardness, Friability and Disintegrant.

Binders & Adhesives:

Water Soluble / Dispersible Binders

Water Insoluble Binders - PVP, MC, Na CMC, HPMC

- To add cohesiveness to powders
- Granules tend to entrap less air than powders when compressed.

Criterion to choose a binder is

- Its compactability

- It must impart sufficient cohesion to powders, to allow normal processing; (Sizing, Lubrication, Compression & Packaging) yet allow tablet to disintegrate & the drug to dissolve.

Ex: Acacia, Tragacanth, Sucrose, Gelatin, Starch, Cellulose – MC. Na CMC. Etc.,

Disintegrants: they facilitate the Break-up

- Can be added during granulation (Intragranulation) / In Lubrication (extra Granulation)

If Intragranular – they cause much finer dispersion

Disadvantage : they impede tablet wetting, disintegration & Dissolution.

- The effectiveness of many Disintegrants is affected by their position with in the tablet
- Some possess binder / adhesive properties.

Adding Lubricants and Disintegrants at Blending Stage is termed as

- RUNNING POWDER Ex: Starch, Celluloses, MCC

MCC: (as low as)10% - good disintegrant.

- allows the water to enter the tablet matrix by means of capillary pores, which breaks the hydrogen bonding b/n adjacent bundles of cellulose micro crystals

Disadvantage:

- Excessive levels – sticking to tongue, due to rapid capillary absorption, dehydrating the moist surface & causing adhesion.

Lubricants, Anti adherents & Glidants:

Lubricant: reduce friction b/n the granulation & die wall during compression & ejection.
Anti Adherent: prevent sticking to the punch & to a lesser extent, the die wall.

Glidant: improve flow characteristics of the granulation.

Lubricants: Classified as

Water soluble – effervescent (Boric acid, Na Benzoate, NaCl, SLS)

Water insoluble – more effective & useful at lower concentrations.

Function by two mechanisms:

Fluid (or hydrodynamic) lubrication
Boundary Lubrication

Fluid Lubrication:

The two moving surfaces are viewed as being separated by a finite & continuous layer of fluid lubricant. Ex: Mineral oils.

Boundary Lubrication:

Adherence of polar portions of molecules with long carbon chains to the metal surfaces of the die wall

The adherence is more than fluid type. Ex: Mg. Stearate

Different aspects of Lubricants :

1. Lubricants tend to equalize the pressure distribution in a compressed tablet.
2. They increase the density of the particle bed prior to compression.
3. If lubricants are added to granulation, they form a coat around the individual particles which remain more or less intact during compression. This effect may extend to tablet surface.
4. Best lubricants are **HYDROPHOBIC**, they effect the disintegration time. (So add a less hydrophobic ingredient along with the Lubricant.) The mixture of Lubricant and a hydrophilic agent (Disintegrant) is called as RUNNING POWDER.

Ex: Starch / Lubricant – 1:1, 1:4.

1. As the particle size decreases, formula requires more quantity of lubricant. (NMT 1% is best conc.)
2. Lubricants should be of fine size as they tend to function by coating so they are effected by their surface area & extent of particle size reduction.
3. Length of mixing with lubricant also effects disintegration – dissolution.

Lubricants should not be added in granulation because they are expected to exert action **on** granules. If used they decrease the binding efficiency.

Problems due to lack of proper Lubrication:

- Lack of adequate lubrication leads to Binding machine strain
- Excessive binding leads to cracked & fragmented tabs at ejection.
- Damage to lower Punch heads.

Sticking: Dull tab faces

Early stages of sticking

Filming to punch faces

(This occurs when punches are improperly cleaned or polished / when tabs are compressed in a high humidity / when lubrication is inadequate.)

Advanced state of sticking is Picking

(When portions of the tablet faces are lifted or picked out & adhere to punch faces.)

Reasons for Sticking

- Results from improperly dried granulation, from punches with incorrectly designed logos
- From inadequate glidant use

Capping & Laminating: associated with proper bonding or with over lubrication.

Antiadherants: Used mainly in formulas which have a tendency to pick moisture like Multivitamins. Ex: Colloidal silica.

Glidants:

- Can improve the flow of granulation
- They also act to minimize the tendency of a granulation to separate or segregate due to excessive vibration.
- Glidants are poor lubricants

- But good lubricants are better glidants / Antiadherants.

Glidants act by:

- Dispersion of electrostatic charges on the surface of granules.
- Minimizing of vanderwaal forces by separating the granules.
    - Reduction of friction occurs between particles & surface roughness by the glidant adhering to the surface of the granulation.

Colorants:

Mainly added to the formula:

· For identifying similar looking products from different manufacturers.

· Minimize the possibility of mix-ups during manufacture

· To improve aesthetic value

Dyes

Colorants

Lakes

(are formed by the absorption of a water soluble dye on a hydrous oxide (AlOH))

Method of incorporation

Flavors

Sweeteners:

Adsorbents:

CONTAINERS AND CLOSURES

- Container is that which holds the article and is or may be in direct contact with the article.

- Closure is part of container and is most vulnerable and critical component of container. It must be effective in preventing any escape from the container and allow no substance to enter the container.

Main Requirement

Should not interact physically or chemically with the article placed in it, so as to alter the strength, quality or purity of the article beyond the official requirements.

Types of Containers:

Tamper Resistant Packaging:
for ophthalmic/otic use.

It shall be so sealed that the contents cannot be used with out obvious distruction of seal.

Light Resistant Container:
Protects contents from effects of light.

Well closed container:
Protects contents from extraneous solids & from loss of article under ordinary/ customary conditions of handling, shipment, storage & distribution.

Tight Container:
Protects contents from contamination by extraneous liquids, solids / vapours and also protects from loss of article from efflorescence or evaporation.

Hermetic containers:
Impervious to air / any other gas.

Single unit container:
It holds a quantity of drug product for administration as a single dose or a single finished device intended for use promptly after the container is opened.

Single dose container:
Intended for parenteral administration in general

Multiple unit container:
Without changing the strength, quality or purity of remaining portions.

Multiple dose container: for parenterals.

Different Storage Temperatures:

Freezing:
Maintained thermostatically between
- 250 to –10 0C (-130 to 14 0F)

Cold:
Between 20 to 8 0C (360 to 46 0F)

Cool:
Between 80 to 15 0C (460 to 59 0F)

Room Temperatures:
Temperature prevailing in working area 200 to 25 0C (680 to 77 0F)

Controlled room temperature:
150 to 30 0C (590 to 86 0F) (Label: "Controlled room temperature" / " Upto 25 0C")

Warm:
Temperature between 300 to 40 0C (860 to 104 0F)

Excessive heat:
Temperature above 40 0C (104 0F)

Storage under non specific conditions:
Conditions include protection from moisture, freezing and excessive heat.

Different types of Containers:

- GLASS
- PLASTIC

Composition of Glass:
- Sand — Pure silica
- Soda ash — Sodium carbonate
- Lime stone — Calcium Carbonate
- Cullet — broken glass acts as fusion agent

Common Cations found in pharmaceutical glass ware are Si, Al, Bo, Na, K, Ca, Mg, Zn, Ba.

Main Anion is Oxygen

Uses of Cations:

Sodium	– Chemically Resistant
Boron Oxide	- aids in melting process to reduce temp.
Lead	- gives clarity and brilliance
Alluminium oxide	- increases hardness & Durability and also Resistance to chemical action.

Different grades of Glass

Type	Description	Test	LIMITS		Used in
			Size (ml)	ml of 0.02N acid	
I	Highly resistant borosilicate glass	Powdered glass	All	1.0	parenterals
II	Treated soda lime Glass	Water attack	100 or less Above 100	0.7 0.2	
III	Soda Lime Glass	Powdered glass	all	8.5	With exception
NP	GP Sodalime Glass	Powdered glass	all	15.0	Oral & topical

PLASTIC CONTAINERS

- Polyethylene
- Poly propylene
- Poly vinyl chloride
- Polystyrene

Containers are usually made from one or more polymers with additives viz., Antioxid, Antistatic agents, Colors, Impact modifiers, Lubricants, Plasticizers, Stabilizers

Problems encountered with Drug-Plastic containers:

Permeation, Leaching, Sorption, Chemical reaction, Modification

TESTS:

- LIGHT TRANSMISSION TEST: Containers intended to provide protection from light.
- CHEMICAL RESISTANCE: Containers composed of glass.
  - Powdered glass test
  - Water attack at 121 0C
  - Arsenic test.
- Containers composed of plastic & intended for packaging parenteral products
  - BIOLOGICAL TESTS
  - PHYSICO CHEMICAL TESTS

Light Transmission Test:
Measure light transmittance with reference to air 290 to 450nm

Chemical Resistance:
Measure of resistance to water attack i.e., the amount of alkali released from the glass under the influence of the attacking medium.
More resistant Glass – Less release of Alkali

Powdered Glass Test:
Crushed material retained on 50 mesh, take 10g in 250ml conical flask, Add 50ml of HPW. Place in autoclave, Heat till steam releases & hold for 10 min, Set temp. at 121 0C (± 0.2 0C) for 30 min, Cool at once in running water. Decant and wash the portions with water and collect. Take 15ml in a conial flask + 5 drops methyl red sol. Titrate with 0.02 N H2SO4

Water attack Test:
3 or more containers, Fill 90% with HPW, (Continue as in Powdered glass test), Holding Time is 60 min.Take 100ml of solution for testing, (Continue as in Powdered glass test),

Permeation:
12 containers, fill with dessicant, record weights, Store at RH 75 ± 3%, Temp 20 0C (± 2 0C) 14 days, record weights every day

Moisture permeation:
5 containers, fill with water, record weights, transfer water contents & measure volume

Limits: 10 – NMT 2000mg/ day weight gain, Should not exceed 3000mg /day are considered as Well closed containers

Tests on Plastics:

1) Biological Tests: Where extractions obtained from samples are injected to test animals for possible reaction.

In Vitro:
Agar Diffusion Test, Direct Contact Test, Elution Test (Mammalian Cell Culture)

In Vivo:
Systemic injection Test, Implantation Test, Intracutaneous Test, Eye Irritation Test
Safety Tests – for unacceptable, unexpected, biological reactivities.
2) Physico chemical Tests:

With Extracted Solution:	Non Volatile Residue
	Residue on Ignition
	Heavy Metals
	Buffering Capacity

CLOSURES

Different Types of closures : 5 designs

- Screw on, threaded or Log
- Crimp on (Crowns)
- Press on (Snap)
- Roll on
- Friction

In variation to the basic types :

- Vacuum
- Tamper PRoff
- Safety
- Child Resistant
- Linerless types
- Dispenser Applications

THREADED SCREW CAPS:
The threads engage with the corresponding threads molded on the neck of the bottle. Liner of the cap, gets pressed against the opening of the container, seals the product in the container.

LUG CAPS:
Same principle as above, but a simply interrupted thread on the glass finish. It requires a quarter turn to close or open.

CROWN CAPS: Crimped closure for beverage bottles.

ROLL ON CLOSURES:
Straight sided, thread less which forms the threads on the packaging line, can be securely sealed and opened and resealed again.

Other types include:

- Resealable / Reusable Closures
- Pilfer Proof Closures:

Similar to roll on closures but with greater skirt length.

Additional length extends below the threaded portion to form a bank, which is fastened to the basic cap by series of narrow metal “Bridges”.

- Non Resealable / Non Reusable Closures:
  They require unthreaded glass finishes.

The skirts of these closures are rolled under retaining rings on the glass container and maintain liner compression. They have tear off tabs that make them tamper proof and Pilfer proof.

Closure Liners:
Any material that is inserted in a cap to effect a seal b/n closure and container. It is glued into the cap / the cap is made with an under cut to facilitate the liner and so easily rotates.

- Made of resilient backing and a facing material.
- The backing material should be soft and elastic enough.

Factors in selecting a liner:
Chemically inert.

Types of liners:
Homogenous Liner:

- One piece liners available either as disk or ring of rubber or plastic.
- Properties are uniform and can withstand high temperature sterilization.
- Widely used in pharmaceuticals.
- More expensive and more complicated to apply.

Heterogenous or Composite Liners:
Composed of 2 layers 1. Facing – with the product
2. Backing – for cushion with cap

TORQUE TESTING:
Owens – Illinois Torque Tester.
Controlling Cap Tightness
With Torque Tester.
Prevents evaporation or leakage of material

Rubber Stoppers:
Primarily used for multiple dose vial, Disposable syringes.
Different Rubber Polymers used are:

Natural Neoprene Butyl rubber

Different ingredients in rubber closures are:
Rubber, Vulcanizing agent, Accelerator / activator
Extended filler, Reinforced filler, Softener / Plasticizer
Antioxidant, Pigment, Special Components - Waxes

Plastic Closures: Two Types: Thermosetting Resins.
Thermoplastic Resins

Thermosetting Closures:
Widely used, made of Thermosetting phenolic and urea plastic resins.
Usually fabricated by compression molding.
Plastic first softens under heat and then cures and hardens to a final state.

Thermoplastic Closures: Polysterene , Polyethylene , Polypropylene,

STABILITY STUDIES

WHY STABILITY

- The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with the time under the influence of variety of environmental factors such as temperature, humidity and light.
- Stability testing permits the establishment of recommended pack, storage condition, retest periods and shelf life.
- Development of the product.
- Registration of application.

ICH Guidelines

For stability :

Q1 (i.e.) Q1A to Q1 F

Q1 Stability

Q1A : Stability Testing of New Drug Substances & Products.

Q1B : Stability Testing : Photostability testing of New Drug Substances & Products.

Q1C : Stability Testing for New Dosage Forms.

Q1D : Bracketing & Matrixing Designs for Stability Testing of Drug Substances & Products.

Q1E : Evaluation of Stability Data.

Q1F : Stability Data Package for Registration Applications in Climatic Zones III & IV.

Q1 – Stability Guidance Document

No.	Year of Publication
Q1A	1993
Q1A(R)	Nov. 2000
Q1A(R2)	Feb. 2003

PROGRESSIVE CHANGES IN ICH GUIDELINE

	Q1A	Q1A(R)	Q1A(R2)
Testing Frequency Long Term ⇨⇨	0, 3, 6, 9, 12,18, 24, … .months	0, 3, 6, 9, 12,18, 24, … .months	0, 3, 6, 9, 12,18, 24, … .months
Intermediate ⇨⇨	0, 3, 6, 9 & 12 months	0, 3, 6, 9 & 12 months	0, 3, 6, 9 & 12 months
Accelerated ⇨⇨	0, 1, 2, 3 & 6 months	0, 1, 2, 3 & 6 months	0, 3 & 6 Months ⇨

⇖⇳⇗

PROGRESSIVE CHANGES IN ICH GUIDELINE

	Q1A	**Q1A(R)**	**Q1A(R2)**
Stability Storage Condition Long Term ⇨⇨	25 ± 20C / 60 ± 5% RH	25 ± 20C / 60 ± 5% RH ↘ ↗	25 ± 20C/ 60 ± 5% RH or 30 ± 20C/65 ± 5% RH (Decision is left to the applicant)
Intermediate ⇨⇨	30 ± 20C / 60 ± 5% RH	30 ± 20C / 60 ± 5% RH ↘↗	30 ± 20C / 65 ± 5% RH
Accelerated ⇨⇨	40 ± 20C / 75 ± 5% RH	40 ± 20C / 75 ± 5% RH	40 ± 20C / 75 ± 5% RH

Zones specification As per ICH

Mean kinetic temperature (MKT)

- It is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradation that would occur at various temperature

ZONE	MKT	Yearly average RH(%)
1. MODERATE	**21**	**45**
2.MEDITERRANEAN	**25**	**60**
3. HOT & DRY	**30**	**35**
4. HOT & HUMID	**30**	**70**

Global Climatic Zones

Distribution of nations into deifferent climatic zones

REGION	ZONES I &II	ZONES III&IV
EUROPEAN	ALL COUNTRIES	
AMERICAN	CHILE, CANADA,US	BRAZIL, JAMICA, VENEZUELA
ASIAN	CHINA, JAPAN, TURKEY	INDIA, PHILIPPINES, SRILANKA
AFRICAN	SOUTH AFRICA, ZAMBIA, ZIMBABWE	BOTSWANA, GHANA, UGANA
AUSTRALIAN / OCEANIC	AUSTRALIA, NEW ZEALAND	FIJI, PAPUA – NEW GUINEA

Stress Testing – Drug Substance

Stress testing is to be carried out on a single batch of the drug substance.

- The testing should include the effect of temperature 50/60 oC (i.e. 10 oC increment) above that of an accelerated testing, humidity (e.g.: 75% RH or reater) where appropriate oxidation & photolysis on the drug substance has to be performed.
- Photo stability Testing should be an integral part of stress testing.
- Stress testing can help identify the likely degradation products which can help to establish:
  i. The degradation pathways.
  ii. The intrinsic stability of the molecule.
  iii. Validate the stability indicating power of the analytical procedures used.

Selection of Batches

- Data from 3 primary batches required.
- Primary batches could be from pilot / plant scale.
- Plant / pilot batches should be Apple to Apple (process, equipment, route should be similar).

Container Closure System :

- Stability study should be conducted on the drug substance / product packed in a container closure system same as that proposed for storage & distribution. Incase of drug product it should be performed for individual strength & pack.

Testing Frequency :

- **Long Term :** **First year :** Every 3 months.
  Second year : Every 6 months.
  Thereafter : Annually.

- Intermediate : 0, 3, 6, 9, 12 months

- Accelerated: 0, 3, 6 months.

Storage Condition :

General case:

Study	Storage condition	Minimum time period covered by data at submission
Long Term	25 ± 20C / 60 ± 5% RH	12 months
Intermediate	30 ± 20C / 65 ± 5% RH	6 months
Accelerated	40 ± 20C / 75 ± 5% RH	6 months

Any "significant change" occurs during 6 month accelerated study, additional testing at intermediate storage should be conducted. The initial application should include a minimum of 6 months data from 12 month study of intermediate storage condition.

Drug Substance / Drug Product intended for storage in refrigerator :

Study	Storage condition	Minimum time period covered by data at submission
Long Term	5 ± 30C	12 months
Accelerated	25 ± 20C / 60 ± 5% RH	6 months

ii. Drug Substance / Drug Product intended for storage in FREEZER :

Long term -20 ± 50C 12 months

If “significant change” occurs between 3 & 6 months of accelerated study, data on long term study should be submitted.

If “significant change” occurs within 3 months of accelerated study, it is unnecessary to continue further testing.

SIGNIFICANT CHANGE

What does significant change means

For Drug Substance :

- Failing to meet its specification.
- For Drug Products :
- 5% assay variation from its initial value.
- Any degradation products exceeding acceptance criteria.
- Failure to meet acceptance criteria with respect to :
    - Appearance, Color, Hardness, pH, Dissolution on 12 units

- Some acceptable factors such as softening of suppositories & melting of creams may be accepted at accelerated conditions.

Expiry date

- Determination of expiry date from long-term data.
- Accelerated data considered only supportive.

If the expiry date of raw material is 5 years and it is used in the last month before expiry for manufacturing the product, what should be the expiry of finished product ?

If the drug product is going to be domestic market expiry date will be the RM expiry date.

If it is in International market the expiry date can be vary based on the stability data.

Photo stability

- Two light options

  Option 1: Artificial Daylight, Xenon or Halide Lamp
  (with filter for radiation below 320 nm)

  Option 2: Combination of Cool White Fluorescent Lamp and a Near UV Lamp (spectral distribution from 320-400 nm, maximum energy emission between 350 and 370 nm)

  Minimum light exposure
  Visible: 1.2 million lux hour
  UV: 200 Wh/m2

Bracketing

- Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

CONCLUSION

- Re-test period for the drug substance & expiration of drug product should be derived from stability information & should be displayed on the container label as appropriate.
- In future, there may be only accelerated & long term study since storage condition for both long term & intermediate will remain same.

SCALE-UP AND TECHNOLOGY TRANSFER

Scale-up: Theoretical and practical aspects

- Scale-up of a manufacturing process, involves the transformation of a small-scale process occurring in the laboratory or in a pilot to a large-scale process occurring in a production plant.
- Proper design and development of the scale-up process reduces the time to market and allows for more rapid commercialization of a product.
- There is no scale-up algorithm that permits us to rigorously predict the behavior of a large-scale process based on the behavior of a small-scale process.
- Each unit operation per se may be scalable, in accordance with a specific ratio, but the composite manufacturing process may not be, as the effective scale-up ratios may be different from one unit operation to another.
- Commercial production introduces problems that are not a major issue on a small (e.g., storage and materials handling, heat generation)
- The operational scale-up ratio is defined as:

  Scale-up ratio = large-scale production rate / small-scale production rate
- Disperse system scale-up ratios vary from 10 to 100 for lab to pilot-plant process translation and 10 to 200 fro scaling from pilot-plant to commercial production.
- The concept of scale-up has taken on a substantive regulatory aspect in more recent years with the issuance of Guidance 22-90 by the FDA's Office of Generic Drugs in September 1990 and the establishment of the Scale-Up and Post Approval Changes (SUPAC) Task Force by the FDA's Center for Drug Evaluation and Research (CDER).
- In 1993, the American Association of Pharmaceutical Scientists, the FDA and USP cosponsored a workshop on the scale-up liquid and semisolid disperse systems.
- The consensus of the workshop committee was that four criteria be used to evaluate sameness: 1) adherence to raw material controls and specifications 2) adherence to in-process controls 3) adherence to finished product specifications and 4) bioequivalence to previous lots.

How to achieve scale-up-Principles of similarity

Four types of similarity in effective process translation are

1. Geometric similarity(e.g., two mixing tanks – a 1000-fold difference in volume corresponds to a 10-fold difference on a linear scale, in tank and impeller diameters) .
2. Mechanical similarity[(static – relates deformation under constant stress exists when geometric similarity; kinematic- at a constant time scale ratio; and dynamic- involves pressure, gravitational, centrifugal forces that accelerate or retard moving masses) .

3. Thermal similarity (i.e., Constant thermal ratio of heat flow by radiation, conduction, convection or bulk transfer).
4. Chemical similarity (i.e., existence of comparable concentration gradient -concerned with variation in chemical composition from point to point as a function of time.

How to achieve scale-up- Interrelationships Among Surface Area and Volume upon Scale-Up

- As the scale of processing increases, volume effects become increasingly more important while area effects become increasingly less important.

- The surface area to volume ratio is much greater on the small scale than on the large scale. Surface area effects are more important on small scale than on large one.

- Conversely, volume to surface area ratio is much greater on the large scale than on the small scale. Volumetric effects are more important on a large scale than on a small scale

Volume-dependent processes are more difficult to scale up than surface-dependent processes- Examples

1) Exothermic processes may generate more heat than can be tolerated by a formulation, leading to undesirable phase changes or product degradation unless cooling coils, or other means of intensifying heat transfer are added.

2) A 10-fold increase in tank volume from 400 to 4000L, and an increase in surface area from 2 to 10 sq.m. The surface area to volume ratios are 1/200 and 1/400 respectively. In spite of the 10-fold increase in tank volume, the increase in surface area is only five fold, necessitating the provision of additional heating or cooling capacity to allow for an additional 10 sq.m surface area for heat exchange.

How to achieve scale-up-dimensional analysis

- Dimensional analysis is an algebraic treatment of the variables affecting a process and allows experimental data to be fitted to an empirical process equation that results in scale-up being achieved more readily.

- Application: Successful establishment of scale-up requirements for microspheres produced by an emulsification process in continuously stirred tank reactors.

Scale-up paradigm

At the outset, as part of process analysis, the formulator must know and understand the physical and physico-chemical principles that are relevant to the unit operations that to be scaled up.

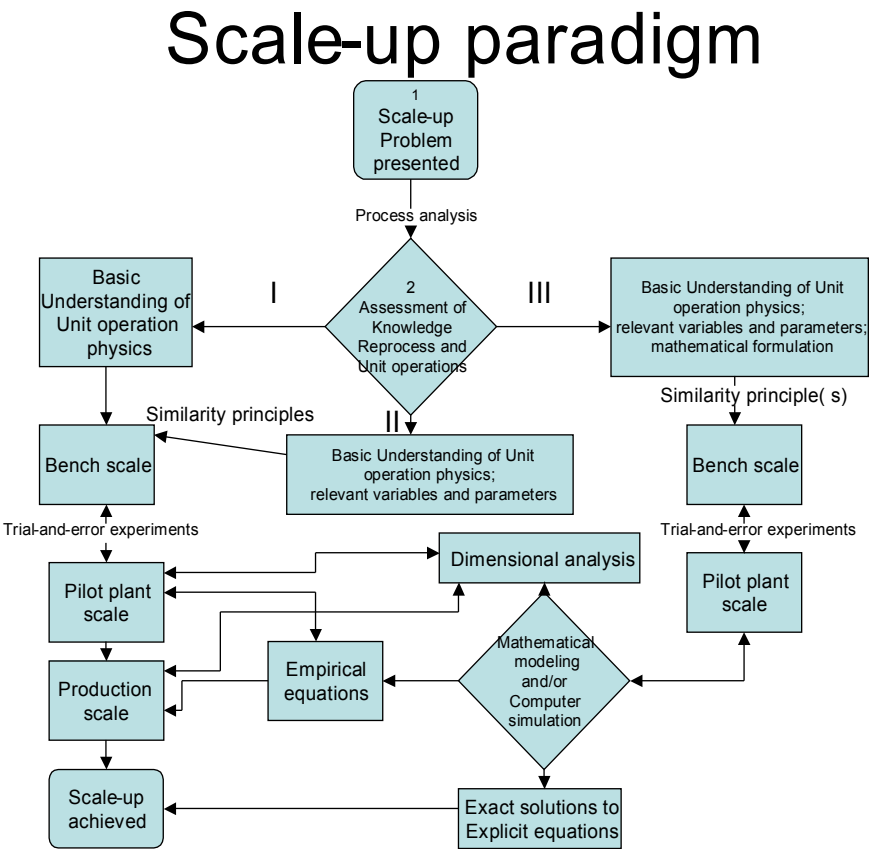
Path1: If the relevant operation variables and parameters are inadequately known or characterized.

Scale- up is accomplished through empirical experiments conducted in a trial-and-error manner all scales (bench, pilot, and production), with little more than similarity principles to guide the technologist.

Path 2: If the relevant operation principles and parameters are known or characterized, and similarity principles used, scale-up is still accomplished through empirical experiments conducted in a trial-and-error manner at all scales (bench, pilot and production) although the path length is likely to be shorter.

Path 3: Involves mathematical modeling and/or computer simulation and still requires experimentation to eliminate inconsequential variables or functions from equations – shortest path length.

No matter what path is followed: Commit your blunders on a small scale and make your profits on a large scale.



TECHNOLOGY TRANSFER AND SCALE-UP

- The goal of technology transfer and scale-up is to show, through process control, that any modifications made from conception to implementation have been appropriately evaluated and documented, and that the product is safe, pure, and effective.
- The Food and Drug Administration pre-approval and post-approval inspections focus on the review of data generated from the development plan used to define the manufacture and evaluation of the proposed drug product or device.
- Changes in project personnel, corporate leadership/ownership, material traceability, equipment modification/identification, site-to-site transfers etc., compound the difficulty, of the task.
- A series of reports issued at each transfer point and audited for 100% data integrity.
- Each report would contain a summary of factual data, supplemented with scientific judgment defining the meaning of the data, and a set of conclusions or recommendations for process controls based on the facts.
- The overall collection of the completed and approved reports would represent the documentation trail of the technology transfer process.

The change control cycle

TEC

The technology transfer master plan can be broken into three elements that are applicable to all drug dosage forms and medical devices.

Element 1: Documentation Practices
Element 2: Technical Writing styles
Element 3: Illustration of Equivalence

Element 1: Documentation Practices

- Primary documentation includes all original batch records, raw testing data, raw material testing records, packaging component testing records, and all developmental, validation and clinical data reports.
- The FDA will focus on primary documentation to evaluate the product under review for safety, purity, and efficacy.
- Developmental, validation, and clinical data reports are summaries of the activities and data generated during selected phases of product/process development.
- The FDA will review these records to evaluate the safety, purity, and efficacy of the proposed drug product.
- Support documentation includes all purchase orders, inventory records,distribution reports and major handling systems(water, air, lighting, power and security).
- These systems have tremendous impact on how well a process is controlled.
- The FDA will focus on support documentation to evaluate the current Good Manufacturing Procedures compliance status of the facilities in which the primary documentation was generated.
- By reviewing these types of documents the agency can establish that you have engaged in interstate commerce by accepting and paying for materials from other states and countries.
- The FDA can also use these documents to verify the authenticity of the actual shipment of raw materials or components.
- A review of these records will help in an FDA inspector evaluate the effectivity of change control procedures.
- Effective change control procedures gives a reviewer confidence that cGMP compliance will be maintained on an on-going basis.
- An evaluation of the process capability of the laboratory environment and the potential manufacturing site is an important piece of the technology transfer process.
- If sites A and B are not environmentally equivalent or do not have similar system capacities, then questions could be raised on how the differences between the two facilities can affect the safety, efficacy, and purity of the drug product.
- Additionally, if change control procedures are not equivalent, the FDA will have limited assurance that cGMP compliance will be met on an on-going basis.

Documentation Nomenclature

- A well-planned technology transfer process will have a clear set of legends defined for the process, including part numbers, product name, equipment identifications, day and date of work performed, location of work performed, and signatures of persons performing and/or witnessing the work performed.

Part Numbers: As a reviewer moves through the body of work associated with a particular product/process, a change in numbering may be confusing.

- It may be advisable to supply the reviewer with a cross-reference to aid in the review process.

Product Name: are the most modified piece of documentation within the body of documentation work.

- Changes in nomenclature may confuse to a reviewer.
- It is advisable to supply the reviewer with a cross-reference to aid in the review process.

Equipment Identifications: A record of identification numbers may be appropriate to assure that similar pieces of equipment do no receive the same identification number.

- It is important that a unified system be in place plant wide to identify pilot plant equipment and production equipment.

Day and Date of work performed: The use of military time such as 14 hours for 2:00PM may be preferential in environments where product and process are on a well-defined time continuum.

- The laboratory environments may work best in a month-day-year scenario.

Location of work performed: Multiple sites within a division or corporation may carry the corporate distinction. A reviewer may not be able to distinguish data from individual sites if a secondary designation is not incorporated into the data-gathering process.

Signature Lines: It is advisable to have a signature log in place for areas with the highest product impact, including laboratory, manufacturing, and filling environment.

- The signature log should include a place for full signature, initials and a printed version of the person's legal name.
- The FDA is charged is charged in their Inspection Guideline to verify the authenticity of the raw data that support the application

Recording of Data

Bound Versus Unbound Laboratory Note Books: Offer a security advantage because pages cannot be removed without damaging the integrity of the volume.

Electronic Data:

Offer the optimum in record-retention capacity
More data can be stored in less space.
Environmentally friendly by reducing the tonnage of paper.

Data are more portable and may be changeable depending on the security level attached to individual users.

Individual Batch Records and stability data: The advantage to store individual batch record and stability data for a single batch of product as one unit is the ease of reviewbility and the ability to retrieve everything with one request**.**

Destruction of Data: It is especially important to assure that Biobatches(batches of product used to support regulatory submissions and/or bioequivalency studies) are archived in a fashion that prevents their destruction for as long as the product in the market place.

Transferring Data Between Locations: Centralization of data is optimal because it reduces secondary sites' exposure to additional FDA inspection and facilitates the review process
A well organized plan of record retention/retrieval that anticipates these types of issues is an invaluable tool in preserving the audit trail of the technology transfer process.

Element 2: Effective Technical writing styles

They accurately communicate the facts: Tables, charts, graphs, and spreadsheets must be used to present facts by including appropriate legends to minimize misunderstandings.

They keep the audience in mind: The lack of traceability may cast doubt onto the validity of the data generated. The FDA is instructed in their inspectional guideline to assure the accuracy of the data that is included in regulatory submissions. It would not be in the company's best interest to receive a "no-go" from the FDA.

They can be assembled with other reports and form an organized and consistent overview of the product/process: (pyramid fig)

They do not use supposing statements: The use of personification should be discouraged (e.g.,The batch record indicates that we should have used 100 liters of D water in Step 3). Step three requires 100 liters of D water. The volume was recorded on page five of the batch record.)

The pyramid effect of documentation

TECH

Element three – Illustration of Equivalence

- Equivalence, Equivalence, Equivalence is the key to technology transfer and scale-up.
- As project progresses from conception to the bench, through the pilot plant, and eventually to production and commercial distribution, a series of technical modifications are performed.
- The easier it is for a reviewer to see the equivalence modifications made to the product/process, the easier it will be for the reviewer to evaluate the change in regard to the safety, purity and efficacy of the drug product.
- Side-by-Side/Ste-by-Step Comparisons allow the reviewer to trace the steps horizontally as the batch is scaled up. (fig)
- Flow diagrams that illustrate process modifications (one diagram for each pivotal batch) and can be shown for comparison (fig).
- Critical Step Definitions are narrative comparisons of steps with the highest impact on the product/process that outline the operating parameters directly related to process control.
- Physical space comparisons of tank, building, and filling equipment drawings are helpful when trying to illustrate environmental equivalence between different manufacturing facilities.
- Terminology equivalence is best achieved by the use of a glossary of standard terms. These can be agreed upon and modified as required during the course of product development.

TEC

F

TEC

E

Identifying the critical elements of a technology transfer operation

- The operation of technology transfer plays an increasingly important role in drug development.
- Each transfer includes key elements specific to the type of transfer being conducted.
- Successful and timely technology transfer will occur only when these critical elements are given full consideration.
- The success of both the large and the small pharmaceutical companies depends on successful product transfers whether they are internal (domestic or international), external, or total third party.

CRITICAL ELEMENTS OF A TECHNOLOGY TRANSFER OPERATION –

THE TEAM

- Project team:
- Formulations
- Process Development
- Product Development
- Analytical Development
- Clinical Trial Materials Manufacturing
- Regulatory Affairs
- Clinical Research

Outside contract facility:

- Joint Team
- Assigned leader
- Project Management Model
- Accountability
- Focus for Communication
- Regular Team meetings
- Face- to- Face meetings
- Telephone Conferences
- Good pre-transfer planning
- Coordination
- Execution of technical transfer
- Clear Objectives
- Agendas
- Follow-up notes.
- Define activities
- Establish a time line
- Evaluation of risks
- Evaluation of benefits
- Establish communications

THE PLAN

- Availability of equipment for CTM mfg should be determined.
- Requirements for sourcing of excipients and packaging components should be specified
- Definition of the analytical methods that must be developed and justified must be discussed by the team as part of preplanning
- Determination of appropriate tests to be performed on the API and drug product.
- Plan to manufacture a trial batch at the site of the transfer prior to producing the actual CTM batch reduces the risk of a failed CTM batch in the event that difficulties are incurred.
- The team must consider an adequate time for each activity in the transfer process.
- One month of stability data on the CTM batch(recommended)
- Lead times for sourcing of materials
- Time for review and approval of package labels
- Time for review and approval of release documentation
- Time for preparation of regulatory submission (IND)
- The required 30-day hold period that occurs after the filing of an IND before an acceptable start date for the clinic.
- Each activity should be discussed in detail to ensure that all parties understand their responsibilities for that activity.

Questions during technical transfer process

- **General:**
- Is there any possible negative or positive impact on subject/patient safety?
- Is there a regulatory risk? If so, is it enough to cause a clinical hold?
- How much will it cost or save in time and/or dollars?
- Is it value-added?
- Is there a regulatory or technical benefit? Is that benefit significant enough to justify the cost of time or dollars associated with it?
- Is there any possible negative or positive impact on CTM batch quality?

Specific issues:
Equipment:

- Is it of similar design and operating principles?
- Is there a capacity issue, or can batch size remain unaffected?

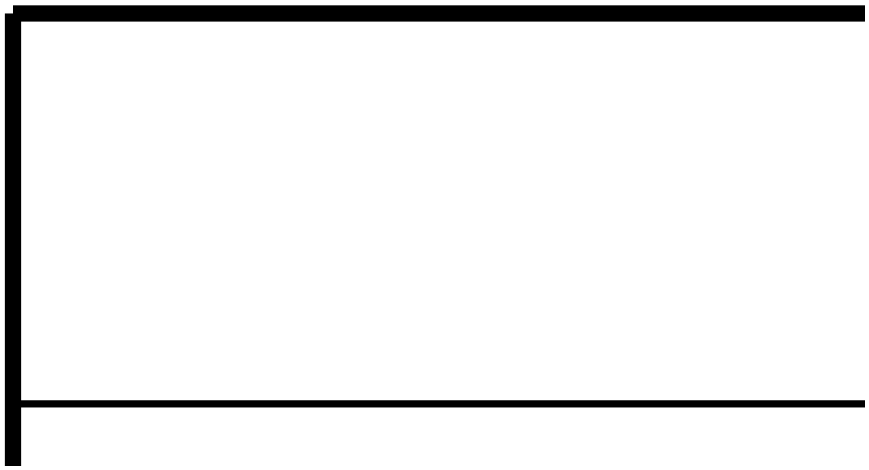
Facilities:

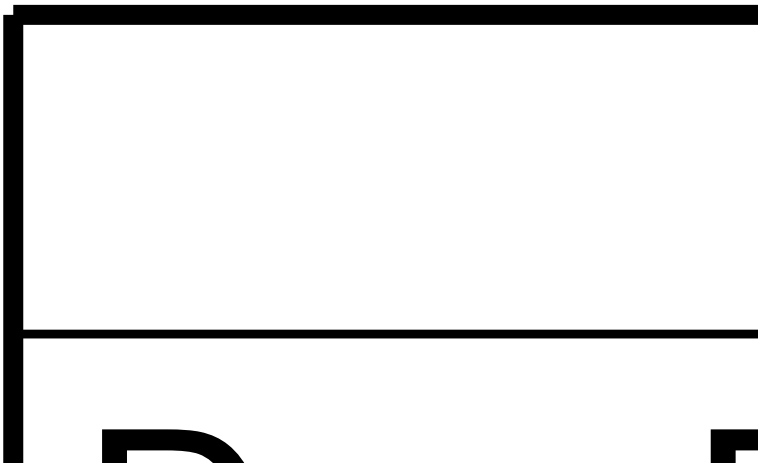
- Do they have the same equipment?
- What were the results of the last GMP inspection?
- Have they been inspected by internal QA?

Contract house:
Is the level of personnel experience or expertise appropriate?
Is there an advantage or disadvantage with regard to time or cost?
Do they have the capability to do the job?

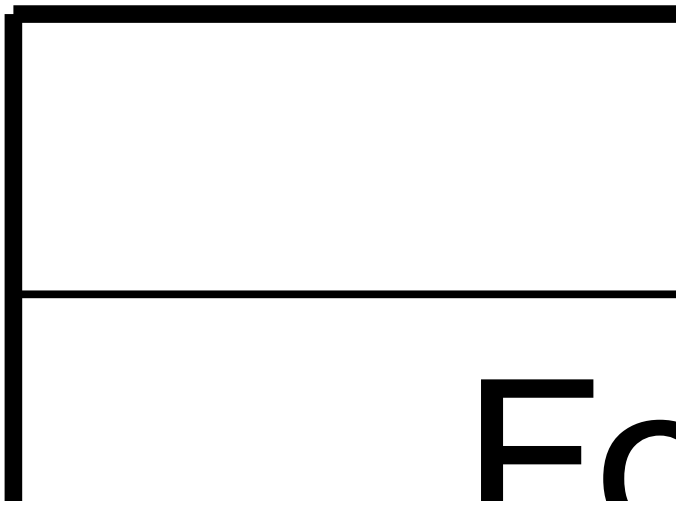
Are there equipment or facility issues related to the contract house?

Time line for technology transfer activities





Ti



CRITICAL ELEMENTS OF A TECHNOLOGY TRANSFER OPERATION –

FORMULATION CONSIDERATIONS

- Identification of the site for CTM manufacture at the initiation of the formulation work may decrease project costs as well as the time.
- If an excipient is non-compendial and not listed in FDA's Inactive Ingredient Guide, then additional information should be requested from the vendor on the safety of the material for use in human drug products.
- When transferring to a contract manufacturing site, it may save time and be more cost-effective to provide materials to the contract site than to have the contractor source the material(especially for critical specifications e.g., Starch USP is not specific description)
- The differences in particle size of API is just enough to raise concerns that segregation could occur in the blend during shipping.

API CONSIDERATIONS

- The transfer and scale-up of the API often results in changes to purity, polymorphic, and particle-size characteristics of the API
- The analytical methods for fully characterizing the API are not necessarily completely evolved at this stage.
- It is often difficult to assess the impact of the change on the API material and ultimately, its effect on the drug product manufactured with that material.

Equipment considerations

- If possible formulation development work should take into account the equipment available for manufacturing at the selected CTM manufacturing site.
- Changes in milling or granulation equipment may significantly affect the final drug product.
- Change from one brand of tablet press to another may have little effect on the final drug product.
- Changes in granulation or coating equipment for modified-release products can provide significant technical challenges during the transfer process because many parameters must be adjusted to mimic the characteristics obtained during formulation development studies.

Analytical considerations

- By the time the drug product is to be tested for release into the clinic, there should be enough data to justify that the analytical methods used for testing of both the API and the drug product provide meaningful results.
- The timing of the method justification process is important since many projects have been delayed because of unexpected findings or difficulties during the method justification studies.

Person in plant

- The use of the person-in-plant is especially critical when a contract house is used to perform any or all parts of the transfer process.
- The on-site formulation expert can assist with recommendations for adjustment to parameters, should they be necessary, based on data generated and observations made during the formulation development studies.

Timing considerations

- If difficulties are encountered in getting API for use by the formulations lab to conduct developmental studies, the risk from having only one month of data instead of three to ensure formulation stability is deemed acceptable.
- If difficulties occur during manufacturing or if manufacturing is delayed because of difficulties with analytical methods, the risk from filing the IND with stability data on the formulations batches and release data only on the CTM batch is deemed acceptable.
- Another example of time line compression may be the decision to manufacture CTM batches before completion of testing on the raw materials to be used in that batch. These decisions may acceptable, however, they must also be recognized as risks, not as guarantees to save the time line.

SUI

S

SUPA

SU

SUP

SUP

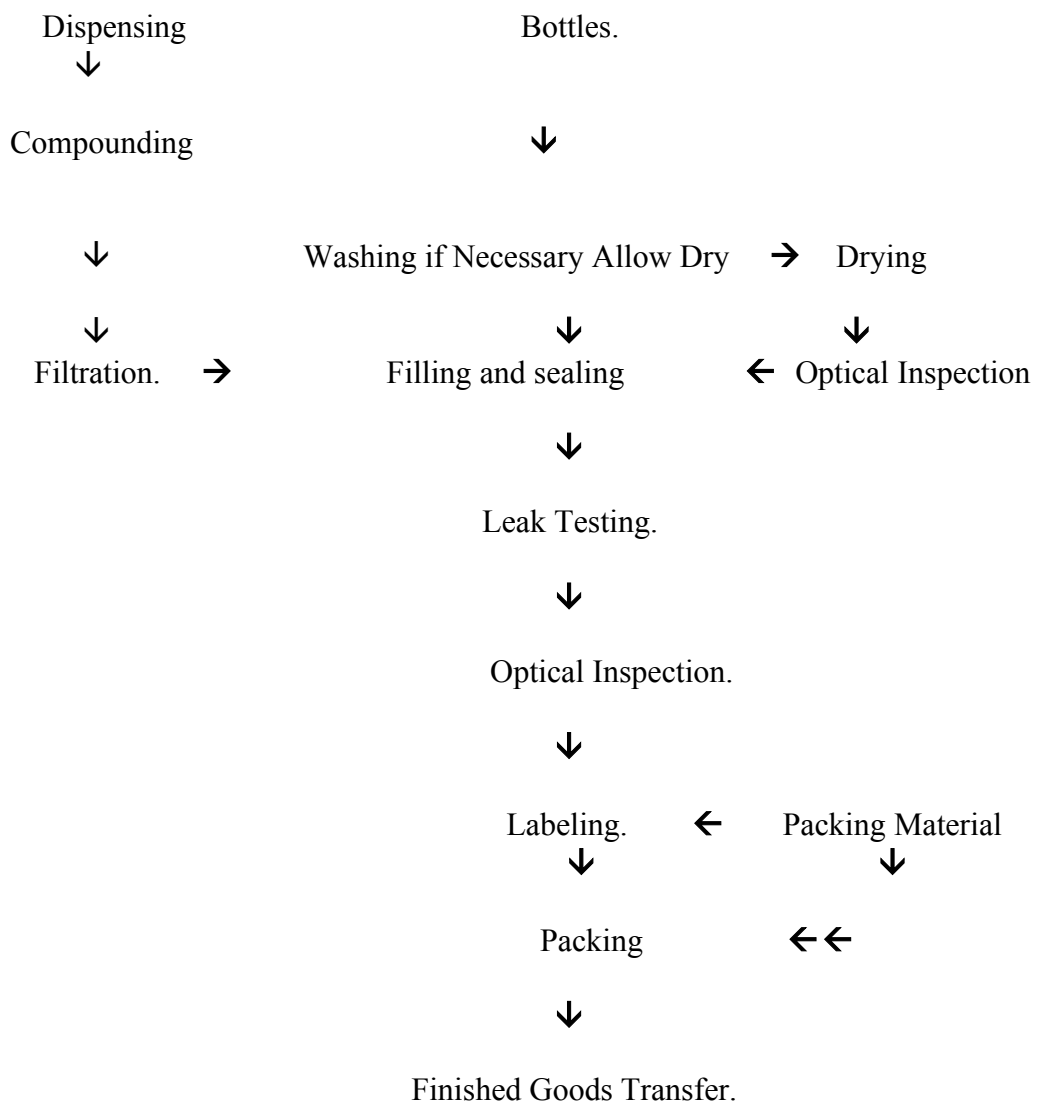
Forr

References

- Identifying the critical elements of a technology transfer operation (Pharmaceutical technology November 1997)
- Scale-up of Disperse Systems – (Pharmaceutical Dosage Forms-Disperse Systems by Lieberman, Martin and Banker)
- Preparation for FDA- Pre-Approval Inspections(by James Swarbrick)
- SUPAC-Immediate Release Solid Dosage Forms – Attachment #3)

LIQUID ORAL FORMULATIONS MANUFACTURING

Liquid Oral Process Flow



Syrups are aqueous pharmaceutical solutions containing sugar.
These may contain Sorbitol solution 70%, Glycerin etc.

Preservatives used are

1. Sodium Benzoate ----0.4% --effective at pH about 5, Antifungal and bacteriostatic
2. Mehtyl Para Ben Sodium ----0.16% -- effective at pH below 8, antifungal
3. Propyl Para Ben Sodium -----0.04% -- effective at pH below 8, anti fungal
4. Benzoic Acid ------ 0.1% to 0.2% ----effective at ph above 6.5, anti fungal
5. Bronidiol ----------0.001% to 0.05% -- effective at pH 4.0 to 6.0, anti fungal

We use organoleptic additives such as coloring agents and flavoring agents

We use antioxidants, surfactants in suspensions, emulsions and in multivitamin preparations.

Citric acid, Hydrochloric acid, as well as orthophosphoric acid, Lactic acid are also used to decrease the pH of the solutions.

Nitrogen gas is used as air displacement agent to enhance product stability, specially in Multivitamin preparations.

Ammonia solution, Sodium Borage, Sodium Carbonate, Sodium Hydroxide, Potassium Hydroxide or Ammonium Carbonate are used to make the solutions alkaline.

pH of all liquid oral preparations should be determined as routine to all the liquid oral preparations.

Propyl Gallate, Sodium Bisulphite, Sodium Metabisulphite or Monothioglycerol are used as antioxidants.

Buffering agents like calcium chloride, sodium citrate are used to prevent drastic changes in pH.

Dilute solutions of sugar are prone to contaminations

High concentrated sugar solutions are prone for crystallization and to prevent this we add Sorbitol 70%

Only demineralised water to be used in the preparations passed through uv lamps

Hyflo super cell may be used as media for filtration

Cellulose products like Carboxy methyl cellulose, are used to build up the viscosity in the suspensions

Guar Gum, Veegum, Xanthane Gum may be used to build up the viscosity in the suspensions.

Cetostearyl alcohol and waxes are used in the preparations of emulsions for external use and for example Gamma Benzene Hexachloride emulsion

Some active ingredients like Ascorbic acid are being converted to its respective salts for the stability reasons and incorporated.

ThioUrea is used as .001% as stabilizing agent for Vitamin B12.

In general in syrups Vitamin B1—70%, Vitamin B2—30%, Vitamin B6 --- 30%, Niacinamide 20%---Vitamin B12 – 200%, d-Panthenol – 20%, Folic Acid – 100% overages added to compensate loss on storage.
Enzymes used in the pharmaceutical preparations are Papain, Pepsin (1:3000), Diastase (1:2000),

Papain is stable at pH 4 to 6 and is soluble with the help of Sorbitol solution 70%

Pepsin (1:3000) is stable at pH less than 3 and is soluble in acidified water pH less than 3

Diastase is stable at pH 5.0 and soluble in water

Combination of Diastase and Pepsin is not advisable in any liquid preparation since they are stable at different pH.

Combination of Pepsin and Papain can be achieved, and combination of Papain and Diastase can be achieved.

Diastase is given in sachets as powder form or in tablet form and can be incorporated into the bottle before commencing the use.

Papain – 50%, Pepsin – 100%, Diastase –100% overages are added to compensate loss on storage.

Generally used iron salt in liquid orals is Ferric Ammonium Citrate since it is palatable

Generally used calcium salts are calcium lactate, calcium gluconate, calcium hypophosphite.

Flavors used for iron—combination of orange oil and orange sweet, enzymes – cardamom or pine apple, calcium –Mixed Fruit, for bitter taste masking, liquorice is used in combination with cardamom, for cough syrups – Raspberry or Strawberry.

Polysorbate 80 or Polysorbate 20 are used as surfactants in suspensions or emulsions.

Benzoic acid is the preservative of choice for antacid formulations.

Saccharin Sodium may be used as a sweetening agent except in the pediatric formulations

Caramel(burnt sugar), Ponceau 4R, Brilliant Blue FCF, Erythrosine, Sunset Yellow, Tartrazine are some of the general coloring agents used in the liquid oral formulations.

Syrup whether cold process, or hot process is decided depending upon the concentration of the syrup

Water is the best solvent for many of the ingredients, propylene glycol, sorbitol 70% solution, Glycerin are also used as solvents.

EDTA Disodium salt is used as chelating agent for the metals present in the sugar.

Pharma Grade sugar is available in the market.

Riboflavine is dissolved with the help of Niacinamide , the ration is 1: 16minimum ie. If 50gms. of vitamin b2 is there then min. 800gms. of Niacinamide should be there to get b2 dissolved. Niacinamide to be dissolved in water, heat it and add and dissolve b2 in it.

COUGH SYRUP
Each 5ml. Contains:

Bromhexine Hydrochloride	4mg.
Pseudoephedrine Hydrochloride	30mg.
Chlorpheniramine Maleate	2mg.

Batch Size 1000 lit.

1. Bromhexine Hydrochloride	0.88Kg.	10% overage
2. Pseudoephedrine Hydrochloride	6.0Kg.	
3. Chlorpheniramine Maleate	0.44Kg.	10% overage
4. sugar	500Kg.	
5. Sorbitol Solution	100Kg.	
6. Citric Acid	2.50Kg.	(sufficient for the pH adjustment)
7. Sodium Benzoate	5.0Kg.	
8. EDTA Disodium salt	1.00Kg.	
9. Methyl Para Ben Sodium	0.80Kg.	
10. Propyl Para Ben Sodium	0.20Kg.	

11. Propylene Glycol	50Kg.
12. Menthol	0.3Kg.
13. Sunset Yellow Color	50gms.
14. Raspberry flavor	1.00Lit.
15. D.M.Water to make	1000Lit.

Charge 250 Lit.s of water to a mixing tank and heat to boil, add and dissolve Sodium Benzoate, parabens, EDTA to it. Add and dissolve sugar. Add and mix Sorbitol solution
Cool to room temp and pass the syrup through muslin cloth.
Add and dissolve chlorpheniramine maleate and pseudo ephedrine hydrochloride in 50 lit.s of d.m. water and add to the bulk and mix well.
Dissolve citric acid in 10 lit.s of water and add to the bulk and adjust the pH to 3.0 +/- 0.2
Load propylene glycol into a steam jacketed vessel and heat to 70dec. C and add and dissolve Bromhexine hydrochloride to it and mix well.
Dissolve menthol in .5 lit. of chloroform and add to the bulk
Dissolve sunset yellow color in 5 lit.s of water and add to the bulk.
Add flavor to the bulk and make up the batch.
Mix for 20min.s and give advice to the concerned department for sampling

The above is a typical cough syrup.
Other general ingredients used in the cough syrups are Ammonium Chloride, Sodium Citrate, DiphenHydramine Hydrochloride, Terpin Hydrate, Pheylephrine hydrochloride, Dextromethorphan hydrobromide, Guaiphenisen, Phenyl Propanolamine Hydrochloride, Terbutaline Sulphate, salbutamol Sulphate etc. depending upon the combination we have to proceed for the batch.

SUSPENSION

S.NO.	NAME OF THE MATERIAL		LABEL CLAIM PER 5ml.	QUANTITY REQUIRED PER 500LIT.	QUANTITY USED PER 500 LIT.	% OVER-AGES ADDED
1	TRIMETHOPRIM	I.P.	40mg.	4.00Kg.	4.00Kg.	Nil
2	SULPHAMETHOXAZOLE	I.P.	200mg.	20.0Kg.	20.0Kg.	Nil
3	ERYTHROSINE		Nil	Nil	20gms.	Nil
4	CARBOXY METHYL CELLULOSE	I.P.	NIL	NIL	5 Kg.	NIL
5	SORBITOL SOLUTION 70%	I.P.	NIL	NIL	100Kg.	NIL
6	SODIUM BENZOATE	I.P.	NIL	NIL	2.00Kg.	NIL
7	E.D.T.A. DISODIUM	I.P.	NIL	NIL	500gms.	NIL
8	METHYL PARABEN SODIUM	I.P.	NIL	NIL	800gms.	NIL
9	PROPYL PARABEN SODIUM	I.P.	NIL	NIL	200gms.	NIL
10	CITRIC ACID	I.P.	NIL	NIL	500gms.	NIL
11	POLYSORBATE - 80	I.P.	NIL	NIL	1.00Kg.	NIL

12	OIL ORANGE FLAVOR	NIL	NIL	200ml.	NIL
13	SWEET ORANGE FLAVOR	NIL	NIL	1.00lit.	NIL
14	SUGAR	NIL	NIL	150Kg.	NIL

MACHINERY AND EQUIPMENT USED

1.stainless steel tanks 500 lit.s -- 2 numbers
2.stainless steel tanks 250 lit.s -- 2 numbers
3.stainless steel tank 100 lit. heater fitted.
4. Plastic tub 30 lit. capacity
5.stainless steel vessels 15 lit. 10 lit. 5 lit. one each
6.stainless steel spoons,, scoops etc.
7.filter press horizantal type 6 plates
8. Stirrer cum homogeser 3.0 hp
9. Small portable stirrer 0.25 h.p.
10. Filling machine volumetric two head
11. Cap sealing machine manual type and three head
12. D.m. water plant
13. Stainers

DESCRIPTION : IT IS A PINK COLORED LIQUID WITH

ORANGE FLAVOR FILLED IN AMBER COLORED BOTTLES WITH A PILFER PROOF CAP

PROCESS INSTRUCTIONS :

1. Heat about 200 lit.'s of Demineralised water with the help of the electrical heater
2. Load hot water into 500 lit.of stainless steel tank which is cleaned and checked by the competant person for any traces of previous batch
3.Add and dissolve Sodium Benzoate ,Methyl Paraben Sodium, Propyl Paraben Sodium, EDTA Disodium, in 15 lit.'s of hot water and add to the 500 lit.'s tank and add and dissolve sugar in it.
4.Add Carboxy methyl Cellulose to step 3 in the hot water and soak over night.
5. Ensure that the preservatives and complexing agents are dissolved completely and now add and dissolve citric acid in about 10 lit.'s of water and add to step 3.
6. Take sorbitol in 100 Lit.S.S.Tank and add tween 80 to it and add Sulphamethoxazole and trimethoprim to it slowly under stirring and keep it overnight..

7. Add sulphamethoxazole and trimethoprim in sorbitol slowly to step 3 under stirring.

8. Add and dissolve oil orange in 500ml. Of Chloroform and to step 3

9. Stir continuously for about 3 hours and add sweet orange flavor to step 3

10.Make the volume to about 475 lit.'s with water and check the P.H. and adjust to5.0-5.5 if necessary with citric acid or sodium Hydroxide and make up the volume to. 500 Lit.
11. Get the sample picked up by the quality control people and after getting the inprocess approval filter the batch into two 250lit.'s tanks proviousl cleaned and checked by the competent person.

12.Fill the liquid into the cleaned containers passed through the screening lamp to the required volume with the help of the filling machine .

13. Seal the bottle with the help of the pilfer proof cap previously washed with Sodium Hypochlorite solution.

14. Check the filled volume for every half an hour and record it.

15. Label the bottles with labels printed with batch No. Mfg. Date. Exp.Date. And M.R.P. on them. Carton them with the cartons printed with Batch No. Mfg.Date. Exp.Date and M.R.P. on them.

RELEASE THE BATCH AFTER GETTING APPROVAL FROM THE QUALITY CONTROL DEPARTMENT.

PRECAUTIONS TO BE TAKEN WHILE PROCESSING THE BATCH.

1.Ensure that all the machinery and equipment is clean and free from traces of previous batch.

2. Check water PH and hardness before taking for the batch.

3. Ensure that the TMP and SMX is completely dispersed in sorbitol before charging .

4. Ph of the liquid to be filled should be in between 5.0-5.50.

5. Ensure that the sealing is done neatly and there are no leakages after sealing.

6. Ensure that all the labels and cartons are with batch No.,Mfg.Date,Exp.Date.and M.R.P.

7. Batch Volume upto the mark is made only after getting the p.h.checked and batch filtered only after getting inprocess approval from the quality control.

EXAMPLE FOR

ORAL LIQUID Finished Product Testing

Written by: Date:	PRODUCT: Acetaminophen oral solution 80 mg/ 5ml	BATCH NO:
		QUANTITY:
Approved by: Date:	FORMULA NO: XXXX	STANDARD: USP
	SPEC NO: XXXX	DIN: XXXXX

TEST	METHOD	SPECIFICATION	RESULTS
Description	**Visual**	A Clear yellow liquid with banana odour	
Identity	**USP**	A. The RT of the major peak in the chromatogram of the assay preparation corresponds to that of the standard preparation. B. The TLC major spot from the test corresponds to that of the standard.	
SPECIFIC GRAVITY (20C)	**In House**		
PH (25C)	USP	3.8 – 6.1	
ASSAY	USP	72 – 88 mg / 5 ml	
MICROBIAL LIMITS	USP	TAMC : NMT 10 org / ml	
STORAGE		Store in tight containers	
Analyst: Date:	Q.C. Review & Approval: Date:	Final Review: Date:	Analyst: Date:

Tablets & Capsules Manufacturing Process

- These are the most popular dosage forms
- They are unit dosage forms in solid form
- Very convenient dosage forms when compared to liquid oral dosage forms
- No measurements of medicaments, no problem in carrying.
- Stability is of very high order
- Safe because of no high peak blood levels and toxic effects.
- No incompatibilities of medicaments and their deterioration due to environmental factors

Each individual unit can be identified
Strip packing >> identification>> protection fom moisture, light, etc

Classes of Tablets:

1. Oral tablets: for swallowing intact, disintegration in the stomach, get dissolved in gastric fluids
2. Chewable tablets : may be for children or to the persons having difficulty for swallowing
3. Buccal/Sublingual tablets: kept in the buccal cavity(cheek), drug dissolved through oral mucosa,

   Metabolism by liver enzymes is minimized, under the tongue called sublingual, small and flat, drugs like steroids, hormones etc, are carried by these type of tablets, formulate that they do not disintegrate with in 30 minutes or so.
4. Lozenge tablets: action on throat tissues, for smoothening the strained throat, slow dissolution in the oral cavity, prolonged local action, they contain naturally no disintegrants, more binding agent.
5. Dental cones: for placements in the empty sockets after tooth extraction. Antimicrobial drugs – meant to dissolve in 20-40 minutes.
6. solution tablets: meant to dissolve completely in specified liquids to produce solutions of definite concentrations, mouth washes, gargles, skin lotions, buffer tablets of pH 4,7,9.2 etc.
7. Vaginal tablets: substitutes for the traditional pessaries , meant to dissolve slowly in the vaginal cavity.generally they are pear shaped for ease of insertion. Antimicrobial products, steroids
8. Implants: inserted under the skin, cylindrical shaped and more than 8mm in length, capable of releasing the drug for more than 3- 6 months,, steroidal hormones,
9. Effervescent tablets: which react in the presence of water, ENO, they dissolve completely in water, Disprin
10. Core tablets: central core , two successive compressions, for separating two incompatible medicaments, sustained release of medicaments
11. Layered tablet: two or more layers, either to separate incompatible ingredients physically ,
12. Enteric tablets: to bypass the stomach and dissolve in the intestines only.
13. Sustained action or timed release or prolonged release tablets: medicament available in controlled way, coating makes this possible, pelletisation etc.

Manufacturing procedures:

1. what type of tablet we want to formulate
2. its physical and per formational characteristics
3. how much tensile strength it should have
4. disintegration characteristics
5. dissolution characteristics

Additives to be used besides the active ingredients:

1. Diluents
2. Adsorbants
3. Binders(granulating agents)
4. Disintegrating agents
5. Organoleptic additives
6. Glidants, anti-adhesives, lubricants

Diluents:

Why should we add any diluents?
Criteria for selecting a diluent
Should be compatible, non reactive, organoleptically acceptable, inert, should have compressibility, no moisture content, bio-availability nor effected (calcium salts with tetracyclines form complexes, delaying the absorption),sodium chloride, sugar (people with hypertension)
Examples: lactose, mannitol, Sorbitol, starch, microcrystalline cellulose celluloses, dicalcium phosphates etc.

Adsorbents:
Materials which can adsorb fluids like essential oils, exaples, silica, magnesium oxide and carbonate, magnefsium aluminium silicate, kaolin tricalcium phosphate etc. simethicone

Binding Agents:
To convert powders into granules for compression we have to add these agents.
Adhesive materials like acacia, gelatin, liquid glucose, sucrose syrup, starch paste etc. are used as binding agents
Starch paste 10% is the order of choice as binding agent since it does not retard the disintegration time.
For water sensitive substances, polyvinyl pyrrolidone, ethylcellulose, hydroxypropyl cellulose etc. in alcohol or some other organic solvents can be used.
Binding agents such as microcrystalline cellulose, clays, acacia etc are used in dry granulation to afford adhesion of components in slugging operations.

Disintegrating agents.

These are the materials included into the tablets so that tablet break up into small fragments in the g.i.t. soon after ingestion. Water is absorbed into the materials and they swell up and make the tablet to become disintegrated.
Microcrystalline cellulose, carboxymethyl cellulose, ets.
The dissolution of binder makes the tablets structure crumble into fragments.
Surfactants such as sodium lauryl Sulphate etc. are also used as wetting of granules.
They are mixed either during granulation and before compression also

Organoleptic additives:
Colors, flavoring agents and sweeteners may be included in the tablet for elegancy, acceptability etc.

Glidants, anti-adhesives, lubricants:
For proper flow of the granules from hopper to the die cavity, to avoid sticking of the material to the punches and die walls, and to release and free movement of the compressed tablets for the die cavity.
Talcum powder is the example as a lubricant.

Granulation Processes
Why granulation at all?
To increase the compressibility, uniformity, flow, durability, to sustain the stress etc.
Pulverization and mixing
Granulation

1. **Wet Granulation:**

   Most widely used and general method of granulation technique
   It meets many of the requirements for the compression of good tablets.
   Steps required are
   1. Weighing
   2. Mixing
   3. Granulation
   4. screening the damp mass
   5. Drying
   6. Dry Screening
   7. Lubrication
   8. Compression

Granulation:
Addition of solution of Binding agent >> the powder mass is wetted with binding solution until the mass has the consistency of wet dough.>> if granulation is over wetted, the granulation will be hard requiring considerable pressure to form the tablet and the resultant tablets may have a mottled appearance. If the powder mass is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.
Example: Paracetamol tablets

2. Dry Granulation:

When ingredients are sensitive to moisture
When they are unable to withstand elevated temperatures during drying
When the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules.
Example: Phenobarbitone Sodium tablets

3. Direct Compression Process:

When materials possess cohesive and flow properties
Example: Aspirin tablets

1. **Binding solutions** :

5-10% Gelatin solution, Poly Vinyl Pyrolidone (PVP K-30)

2. Colorless Denatured spirit is used along with PVP as binding agent when water cannot be used as a binding agent.
3. Dry Starch is included in the lubrication to improve the disintegration time.
4. Stearic Acid may be used as lubricant for embossed tablets
5. less than 3% moisture content is desirable in the granules for compression
6. fines to the extent of more than 30% causes problem

General Problems

Weight Fluctuations
Unsuitable granule size: small granules for small tablets
Shape of the granules, if they are round the air spaces in between will be less and uniformity achieved.
Fines should not be more than 20%
Flow control ie which depends on lubrication should be uniform
Humidity >> if the moisture content is more then the flow of the granules is effected.

Capping:

Less moisture content: you may spray with water or water glycerin mixture.
Excessive moisture: Dry the granules again
Binding not sufficient: Re granulate
Excess powder content: Sifting or re granulate
Excessive pressure: Reduce the pressure

Cracking:

Excess moisture in granules
Lubrication
Sticking
Excess moisture in granules
Low melting of the ingredients
Excess fines
Insufficient lubrication
Dies and punches dull

Lubricants
Boric Acid-----1%
Sodium Benzoate---5%
Sodium Acetate—5%
Sodium Oleate—5%
PEG --- 4000 ---1-4%
PEG---- 6000 --- 1-4%

Tablets (Conventional)

Process Flow

Dispensing

↓

Sifting

↓

Dry Mixing

↓

Granulation (Binding Agent)

↓

Drying

↓

DRY Screening

↓

Blending (Lubricants)

↓

Compression

↓

Coating

↓

Tablet Packaging

Example for Tablets Finished Product Testing
SPECIFICATION CARD

Acetyl Salicylic Acid Tablets 325 mg (Plain)

MANUFACTURER NAME:	**DIN :**	**CARD :**	**SPEC #**
QUANTITY:	**FORMULA / CODE #**	**STANDARD: USP**	
DATE MANUFACTURED:	**RECEIVING / LOT #**		

TEST	METHOD	SPECIFICATION	RESULTS
DESCRIPTION	**VISUAL**	White, round, biconvex C.T.	
IDENTIFICATION	**USP <197K>**	(a) A violet-red colour is produced. (b) I.R. spectrum matches that of USP Reference standard.	
THICKNESS (Avg.)	**In House**		
DIAMETER (Avg.)	**In House**		
AVERAGE WEIGHT	**In House**		
HARDNESS (Avg.)	**In House**		
FRIABILITY	**USP**	N.M.T. 1.0%	
FREE SALICYLIC ACID	**USP <1216>**	N.M.T. 0.3%	
DISSOLUTION	**USP**	N.L.T. 80% (Q) in minutes.	
UNIFORMITY OF DOSAGE UNITS	**USP <905>**	Potency of each of 10 tablets determined by weight variation and assay lies within 85 – 115% of label claim:RSD≤ 6.0% see USP criteria. Meets USP requirements.	
POTENCY / TABLETS (ASSAY)	**USP**	292.5 – 357.5 mg Acetylsalicylic Acid	
STORAGE	**USP**	Preserve in tight containers**.**	

Specification Approved by: QA Manager Date:	Specification Written by: Date:	Accepted: Rejected:	Expiry Dt: By: Date:	Control sample:
Analyst: Date:	Q.C. Review & Approval: Date:	Final Review: Q.A. Manager Date:		

Capsules Process Flow (Conventional)

Dispensing

↓

Sifting

↓

Dry Mixing

↓

Granulation

↓

Drying

↓

Dry Screening

↓

Blending

↓

Capsule Filling

↓

Capsule Packaging

Example for Capsule Finished Product Testing
SPECIFICATION CARD

Written by: Date:	PRODUCT: XXXXXX capsules (Vegetable Capsule)			BATCH NO:
Approved by: Date:	FORMULA NO: 901		STANDARD: D.C.	QUANTITY:
	SPEC NO: 3610	DIN: N/A	EXPIRY Dt:	RESULTS

TEST	METHOD	SPECIFICATION	RESULTS
DESCRIPTION	**VISUAL**	Clear, Hard Vegetable Capsule (Size # 0) containing brown powder.	
AV. WEIGHT (GROSS)	**In House**		
AV. WEIGHT (NET)	**InHouse**		
WT. VARIATION OF CAPSULE (GROSS)	**USP**	NMT 2 TABS IS ≥= 10% NONE 20%	
DISINTEGRATION	**USP**	NMT 30 MINUTES	
Dissolution			
ASSAY			
MICROBIAL LIMIT	**USP**	TAMC: NMT 100/G E.coli, P. aeruginosa – Absent Salmonela, S.aureus – Absent Yeast and Molds – NMT 100/G	

Analyst: Date:	Q.C. Review & Approval: Date:	Final Review: Date:

PARENTERALS

These are sterile dosage forms, which are free from pyrogens, foreign organic matter and micro- organisms.

Advantages:

1. Rapid onset of action
2. Predictable effect
3. Predictable and complete bio-availability
4. Avoidance of GIT due to - Problem of variable absorption
   - Drug inactivation
   - GI distress

Dis advantages:

1. Frequent pain and discomfort of injections with psychological fears associated with needle.
2. In correct drug or dose is often harder or impossible to counteract when given parenterally than orally.

Parenteral I.V:

1. New and better approach
2. It helps in nutritional therapy through I.V lipids, amino acids, and trace metals
3. Multiple drug administration is also possible in hospitalized patients including Generic and pediatric patients
4. In patient residence also possible to continue the therapy
5. Now, it is increasing number of drugs through the I.V infusion.

Routes of Administration:

Primary routes:

Intra muscular - Directly into the body of relaxed muscle
Intravenous - Injections or infections directly into vein
Sub-cutaneous -Injection into loose connective tissue and adipose tissue beneath the skin

Secondary routes:

Hypo dermoclysis: Large volume infusion into sub- cutaneous tissue
Intra abdominal/ Intraperitoneal: Injection or infusion directly into peritoneal cavity through needle or indwelling catheter or directly into abdominal region such as kidney, liver or bladder.
Intra – arterial:- Infusion or injections into artery which leads directly into organ**.**
Intra- articular: Injections or infusion into synovial sacs to various accessible joints.

Intra- Cardia: Injections directly into chambers of the heart
Intra- cisternal: Injections directly into cisternal space surroundings the base of the brain.
Intra lesional: Injections directly into or around a lesion, present on the skin or soft tissues.
Intra dermal: Injections into the dermis, present beneath the epidermis.
Intra ocular: There are four types of Intra ocular

a) **Anterior chamber:** Injection or irrigation into anterior chamber of the eye
b) **Intra – vitreal:** Injection into vitreous cavity
c) **Retrobulbar:** Injection around posterior segment of globule
d) **Sub- Conjuctival:** Injection beneath the conjuctiva.

Intrapleural: Injection into pleural cavity
Intrathecal: Injection directly into the lumbar sac at the end of the spinal cord.
Intraventricular: Injection or infusion directly into lateral ventricles of the brain.

Characteristics of Parenteral Drugs:

These are having the following properties:

1) Sterile
2) Free from Pyrogens
3) Free from visible particulate matter
4) Isotonic – I.V infusions, body injections, ophthalmic preparations, Cerebrospinal fluid etc
5) It should be sterile
6) It should be compatible with other diluents, excipients, polymers, and other co- administered drugs.

Formulations: These are formulated as solutions, suspensions, emulsions, liposomes, micro spheres, nano particles and powders.

VEHICLES:

Water: It is prepared through distillation or reverse osmosis. These can separate liquid, gas and solid pollutants from the water.
Water- miscible vehicles: Some of the solvents are to solubilize the drug to reduce hydrolysis

Eg: Ethyl alcohol – cardiac glycosides
Liquid polyethylene glycol and propylene glycol
Glycols: Barbiturates, alkaloids, antibiotics

Added substances:

These are substances-

1) Increase and maintain drug solubility
   Eg: Complexing agents - cyclodextrins, Captisol
   Surface-active agents- polyoxyethyelene sorbition monolaurate
   - Polyoxyethyelene sorbitions mooleate

2) It should be comfortable, by making isotonic.
   Tonicityadjustmentagents
   Ex: Sodium chloride, Dextrose, Glycerin
3) Chemical stability enhances: antioxidants, Inert gases, Chelating gases, buffers etc
4) Physical and chemical stability of freeze dried product by adding cryoprotectants and lyoprotectants.
5) Minimizing self-aggregation through the use of surface-active agents enhances physical stability of proteins.
6) Minimize protein interaction with inert substances such as glass and rubber and plastic.
7) Preservatives are used to prevent the growth of microorganisms.

Non- aqueous vehicles:-

Fixed oil from vegetable origin – Corn oil, cottonseed oil, peanut oil and sesame oil.

It is used for the harmones – Progesterone
Testosterone
Deoxycortiosterone
and vitamins – Vitamin –K
Vitamin –E

Label must be state the name of the vehicle, to avoid the sensitivity reactions in the individuals

GMP:

They have to adopt GMP procedure to prevent cross contamination care must be taken while selecting the ingredients

They have to adopt the following precautions.

1) Dedicated equipment or properly validated for cleaning to prevent cross contamination.
2) Rinse with WIF during cleaning the equipment
3) Closed system under aseptic conditions for bulk manufacturing process.
4) End toxin and other specified limit test we have to follow.

Added Substances:

Class	Added Substances	Concentration (%)
Anti- Microbial	Benzalkonium Chloride	0. 01
	Benzyl alcohol	1- 2
	Chlorobutanol	0.25- 0.5
	Metacresol	0.1-0.3
	Butyl p-hydroxybenzoate	0.015
	Methyl p – hydroxybenzoate	0.1 – 0.2
	Propyl- P hydroxybenzoate	0.25-0.5
	Phenol	0.25 – 0.5
	Thimersol	0.01
Anti – oxidants	Ascorbic aid	0.01- 0.5
	Cysteine	0.1 – 0.5
	Monothioglycerol	0.1 -1.0
	Sodium bisulphate	0.1 – 1.0
	Sodium meta bisulphate	0.1 – 1.0
	Tocopherols	0.05-0.5
Buffers	Acetates	1-2
	Citrates	1-5
	Phosphates	0.8-2.0
Bulking agents	Lactose	1 – 8
	Mannitol	1 – 10
	Sorbitol	1 – 10
Chelating agents	salts of Ethylene diaminetetra acetic acid	0.01 - 0.05
Solubilizing agents	Ethyl alcohol	1 – 50
	Glycerine	1 – 50
	Poly ethylene glycol	1 – 50
	Lecithin	0.5 –2.0
Surfactants	Poly oxyethylene Sorbitan Mono oleate	0.1 – 0.5
	Sorbitan Mono oleate	0.05 –0.25
Tonicity – adjusting agents	Dextrose	4 –5
	Sodium chloride	0.5 –0.9
	Potassium chloride	

Large Volume Parenterals Preparations

The IV infusion of large volume of fluids (100 to 1000 ml) has become increasingly popular. This technique is called venoclysis. Utilizes products known as large – volume parenterals (LVPS).

It is used to supply – electrolytes & nutrient, to restore blood volume, to prevent tissue dehydration and to dilute toxic materials already present in body fluids.

Various parenteral drug solutions may be added to the LVP products, to provide continuous & prolonged drug therapy.

Containing parenteral dosage forms of administration, as a unit product is known as IV admixtures.

Pharmacists need sound knowledge about IV additive to avoid physical & chemical in compatibility.

Creation of any therapeutic incompatibility with other drug given parenterally.

These consist of single-dose injections having a volume of 100 ml (or) more and containing having a capacity: 100 to 1000 ml.

Mini type infusion containers of 250mll capacity are available with 50 and 100 ml partial fills for solution of rings used in the piggyl techniques.

All precautions must be taken during the preparation of I.V fluids. They are free from foreign particle and microorganism. They should be isotonic with body fluids.

No bacteriostatic agent should be added.

Vehicle:

The vehicle of greatest importance for parenteral products in water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by – distillation (or) by reverse osmosis to meat USP specifications for water for injection (WFI).

Only this method is it possible to separately adequate, gas and solid contaminating substance from water. Only aqueous vehicles are used.

Preparation of water for injection (WFI):

The degree of contamination will vary with source. The source of water may be contaminated with natural suspended mineral & organic substances, dissolved mineral bottles, colloidal silica industrial & agricultural chemicals.

It may be pretreated by one (or) combination of the following treatments. Chemical softening, filtration, deionization, carbon adsorb (or) reverse osmosis.

Here, two methods are discussed as follows.

a) Compression distillation: <vapor compressor >

1) It is used to produce more distillate with low energy.

2) The feed water is heated from external source to boiling.

3) The vapor produced is separated from entrained distillated in the separator & sent to compressor that compresses at 107° temperature & sent to steam chest, from this condense & distillate is available.

Reverse Osmosis: (RO)

The selective permeation of molecules through a semi permeable membrane separating two aqueous solutions of different concentrating is reversed. Pressure at 200 & 400 psig is applied to over come osmosis & force pure water to permeate through the membrane.

Risk of failure – Pyrogens & bacteria.

Pyrogens:

Pyrogens are products of metabolism of microorganism. Potent Pyrogenic substances (endotoxins) are from cell wall of Gram – ve bacteria (20, 000 daltons high Molecular weight – endotoxin).

When injected, it cause fever, chills, pain in back & legs & malaise

Control of Pyrogens:

Pyrogens destroyed by heating at high temperature. A dry heat temperature of

250° for 45 min,

650° for 1 min (or)

180° for 4 hr to destroy pyrogens.

Sources of Pyrogens:

Micro – organisms metabolize, pyrogens will be produced.

Formulation & Manufacturing: Preparation of i.v. fluids

The following are some of the commonly used intravenous fluids:

1) Dextrose injection (I.P): In the concentration of 5, 10, 25 & 50% w/v sol

Use: fluid and nutrient replenishes.

2) Sodium chloride & dextrose injection (I.P): Nacl – 0.11 to 0.9% a dextrose – 2.5 to 25%.

Use: Fluid, nutrient & electrolyte replenisher.

3) Sodium chloride injection (I.P): 0.9% Nacl, Normal sodium solution.

Use: Isotonic vehicle, fluid & electrolyte the replenisher.

4) Sodium lactate injection (I.P): 1.75 to 1.95% w/v of sodium lactate.

Use: Fluid & electrolyte replenisher.

5) Mannitol injection: 5, 10, 15 and 20% mannitol.

Use: Diagnostic aid & renal function determination & diuretic.

6) Mannitol & Nacl injection: 5, 10, 15% mannitol & 0.45% Nacl.

Use: Diuretic.

7) Ringer injection I.P: 0.86% Nacl, 0.03% KCl, & 0.33% Cal

use – Fluid & electrolyte replenisher

8) Ringer Lactate solution for injection I.P: 2 – 7 meq Calcium, 4 meq potassium, 130 meq sodium & 2.45g lactate/litre.

Use: system, alkaliser fluid & electrolyte rephenisher.

Specialized Large Volume Parenteral & sterile solutions:

1) Hyper alimentation solution (Hypertonic): Parenteral hyper alimentation induces administration of large amounts of nutrients through primeval vein. Formulation consists of mixture of dextrose, amino acids & containing added electrolytes, trace metals & vitamins.

2) Cardioplegia solutions:

It is used during breast surgery to prevent ischemia.

Electrolytic solution.

Cold in order to cool myocardium & minimize metabolism.

3) Peritoneal Dialysis solutions:

Infused into abdominal cavity, bathing peritoneum and with toxins continuously.

To remove toxic substance from body or kidneys.

Contain glucose, similar to ECF, metabolites diffuse with circulating dialysis through peritoneum & are remove toxins.

4) Irrigation solutions:

To irrigation, flush, & aid in cleaning body cavities & wounds.

Normal saline, which is sterile, pyrogen free.

Not used for parenterally.

Production facilities:

For parenteral preparations special precautions & facilities are needed. The production area is divided into five sections.

1) Clean – up area – free from microorganism & foreign particles.
2) Preparation area – products mixed & filling operation.
3) Aseptic area – free from, dust fiber 7 M.O's – contains HEPA filter U.V – lamps are used to sterile rooms.
4) Quarantine area – After filling, sealing & sterilization, products.
5) Finishing & packaging area – In this area labeling & packed.

Air cleaning: Air passed through a pre-filter, glass wool, cloth (or) shrple

Electrostatic precipitator: Electric charge on particles removes them by attraction to oppositely charged plates.

HEPA filter – (High efficiency particulate air filters): Have an efficiency atleast 99.97% in removing particles of 0.32 mm & larger based on DOP (di-octylphthalate) test.

Laminar – flow Enclosures:

HEPA filter present one entire side of confined space. If bathes the total space with very clean air; Sweaping away contaminants.

The area inside is clean, class 1000 (or) 10, 000.

In short time it meet class 100 clean room standard.

Production procedure:

1) Cleaning containers & equipment:

Containers & equipment coming in contact with parenteral preparation must be cleaned.

a) Air or liquid treatment, will strike bottom of insides inverted containers, spread in all directions & smoothly flow down.

b) Outside rinse.

c) Cycle of treatment, very hot & cool, final WFI.

d) All metal parts – contact with containers – stainless steel (or) non – corroding & non – continuing material.

Product preparation:

A master formula sheet confirmed for accuracy.

All measurements of quantities should be made accurate checked by second person.

For liquid preparation, prepared by weighing than volume because it comes accurately.

The order of mixing requires considerable mixing time for large volume, to attain homogeneity.

Filtration:

A high degree of clarification is termed polishing a particles down to 2 mm is size is removed.

Bubble point test: The basic test is performed by gradually casing pressure on upstream side of water – wet filter. The pressure at which bubbles first appear down stream is the bubble.

Ex: 0.2 μ m cellulose ester filter will bubble at about 50 psig. If bubble point is lower than the rated pressure, the filters are defective, probably because of a puncture or tear & should be used.

Filling: Filling is under a basket of HEPA – filtered laminar flow air with in aseptic area. For large volume – filled by gravity, pressure pump (or) vacuum pump.

Sealing: An incomplete sealer is called *leaker.* It is done under *HEPA* filtered laminar air flow. Closures are placed to bottles and single layer aluminum caps are crimped.

Sterilization: It is performed in an auto clave.

Labeling & Packaging: Transfusion bottles should be properly labeled packed. The label should state.

1) Name of preparation, Qty of preparation, Mfg lic No., Batch No., Date of manufacture, Date of expiring, Storage conditions, Retail price , Manufactures address.

Quality Control: Under this, the following should be performed.

Discription

Identity

pH

Fill Volume

Assay

Sterility test

Pyrogen test

Leaker test

Particulate evaluator test

Bacterial Endotoxin test

Basic Principles in Making Ointments

This document provides the principles in making ointments from plant derived ingredients in a home setting, it being the instruction sheet used in the segment on making ointments in the Medicinal Herb Seminars held at Pindari .
(170811)

Introduction

Ointments may be used as skin conditioners and as a means of treating skin conditions, they are mostly simple to make with the base ingredients being readily available.

Definitions

- Ointments are fatty preparations of a softer consistency than waxes.
- Compound ointments are a mix of different oils and waxes as the principle ingredients. They are generally much "greasier" than creams and may be used for skin softening, skin protection, as a water repellent and for the application of medications to the skin surface.
- Waxes are generally solidified oils at room temperature.

Ingredients for ointment bases:

- Vegetable oils

As heat is used in the preparation of most ointments it is better to choose more saturated oils that are stable to heat such as Coconut and Olive oil to make the ointment base.

- Beeswax

White beeswax is chemically treated to clean and bleach it. Yellow beeswax is filtered and has had the honey removed by washing in water. Beeswax is added to the vegetable oils to "set" the oil giving the ointment its consistency.

- Lard and other animal fats.

The use of lard (pig fat) and other animal fats has fallen out of fashion, being mostly replaced by the more cosmetically acceptable and readily available vegetable oils.

- Paraffins and other petroleum products.

These also have fallen out of favour but are still used in some commercial creams such as Sorbolene cream.

Medications that may be added.

- Medicated oils - Herbs such as Calendula, Chamomile and St. Johns wort may be infused into oils such as Olive and then used as the base oil or as an additive. Detail of how to infuse oils with herbs is given in another document on this web page.
- Jojoba oil - this is really a wax and may be added at around 5% to give the ointment a "slip" texture that is useful for massage.
- Herbal tinctures - Approximately 5 -10% of the total weight can be successfully added when the ointment is close to setting.
- Fragrant oils - Approximately 0.1 - 1% of the total weight can be added when the ointment is close to setting.
- Antioxidants - These slow the oxidation of oils especially unsaturated oils such as Sunflower, Almond and Safflower. They extend the shelf life of the ointment. Examples of anti-oxidants are:
  - Vitamin E oil (available as either oil capsules or in Wheat germ oil).
  - Rosemary frond extract known commercially in Australia as "Amiox."
- Preservatives - Bacteria and yeasts (moulds) grow mostly in aqueous mediums thus ointments generally do not require preservatives.

Quality and efficacy

The ingredients used in making an ointment directly influences its quality and efficacy.

For optimum quality use:

- Cold pressed and virgin (un-processed) oils and waxes.
- Extracts made from fresh herbs.
- An added anti-oxidant.

Storage

Ointments containing unsaturated oils (omega 6 and especially omega 3) must be kept away from light, air and kept cool. In warm to hot climates they are best kept refrigerated. A batch number and the expiry date should be included on the label.

Manufacturing procedure

General comments:

- Caution: Applying heat to oils and waxes should ONLY be achieved using a water bath. Keep the oil mix away from direct heat especially naked flame. Always have a suitable fire extinguisher and a wet blanket nearby.
- Medications should be added at the lowest possible temperature.
- It is easier to measure ingredients by weight using scales sensitive down to 1gm rather than measuring by volume. This avoids ingredient loss to

the measuring vessels and clean up time. 10mL of a vegetable oil approximates 9gm by weight.

- Suitable mixing vessels are either stainless or enamel, having straight sides and an open pouring spout.

Steps

1. To make the ointment base, weigh out the oil and wax components into a suitable stainless vessel and heat them by placing in a heated water bath. Do this until they have just melted.
2. Remove from the bath and with stirring, allow the mix to cool until just starting to set. This is indicated by thickening and a milky appearance. You can encourage cooling by placing the mixing vessel in or over a cold-water bath but use constant stirring and remove the set ointment from the sides of the vessel, stirring it back into the liquid.
3. Have the other ingredients ready to be added directly by weighing into the vessel or from separate measuring containers.
4. Place the mix back in the un-heated hot water bath to maintain a little heat input and to the non-lumpy liquid ointment slowly and separately add the aqueous/alcohol ingredients with vigorous stirring . Excessive heat will evaporate alcohol leading to insoluble herb deposits in the ointment.
5. Then add the Rosemary antioxidant and infused essential oils slowly with vigorous stirring.
6. Then add the fragrant essential oils with vigorous stirring.
7. Last add the Flax seed oil slowly and stir until the liquid mix is clear of solids.
8. If lumps are still present, with vigorous stirring apply a little heat by placing briefly in a gently heated water bath.
9. Remove the mixing vessel from any heat input and as the liquid ointment starts to set it will increase in viscosity, go milky and start setting on the sides.
10. When the liquid starts to go milky and thickens, wipe the bottom of the vessel and with stirring, pour into ready un-topped jars. Heat the vessel gently in a little hot water bath heat to melt the remaining ointment from the sides, wipe the water off and pour again.
11. When filling the jars, pour to "over fill" to allow for contraction of the ointment as it sets.
12. Clean up is best facilitated by using paper towels to wipe the vessel clean then wash well with very hot soapy water and if possible pour out onto the soil rather tham down the sink when it can set. Rinse the vessels well to remove any soap residues.
13. Keep notes on your process and prepare and apply a label.....and have fun!

~~~~~~~~~~~~~~~~~
~~~~~~~~~~~~~~~~~

Sample formulas:

A cosmetically acceptable, efficacious compound ointment is made with olive oil and beeswax. Both these ingredients are reasonably stable to heat, are inexpensive and readily available. They are easily used at home to make lip salves and herbal ointments, formulas for which are given below. The proportion of the beeswax added gives the ointment its consistency, a "solid" ointment requiring around 20% beeswax and a softer ointment as little as 5%.

Calendula Ointment

Olive oil	30 gm
Infused Calendula flowers (in olive oil)	10 gm
Yellow Beeswax (mp 62C)	10 gm
Fragrance (essential oil)	3 drops

Herbal LIP Balm

Olive oil	35 gm
Yellow Beeswax (mp 62C)	10 gm
Jojoba oil	0.5 mL (25 drops)
Flax seed oil	2mL (100 drops)
Rosemary extract (anti-oxidant)	2 drops
St Johns wort infused oil	1mL (50 drops)
Lavender oil	2 drops
Calendula tincture	2mL (100 drops)
Friars balsam tincture	2mL (100 drops)

USP Guideline for CREAM AND OINTMENT

Identification— {**N**eed at least one ID test for each active ingredient. If more than one ID test is incorporated, tests have to be alphabetized, e.g., **A:**, **B:**, etc., and ordered as follows: IR, UV, TLC, retention times comparison, and other tests. Proceed as directed under the template for Tablets and Capsules in the addendum of the USP *Guideline for Submitting Requests for Revision for USP–NF*.}

Microbial limits <61>—It meets the requirements of the tests for absence of [*Salmonella* species] [*Escherichia coli*] [*Staphylococcus aureus*] [*Pseudomonas aeruginosa*]. [The total aerobic microbial count does not exceed __ per g, and the total combined molds and

yeasts count does not exceed __ per g][the total aerobic microbial count is less than __ per mL.] {If counting colony-forming unit(s), use cfu for singular or plural.}

Sterility <71>—meets the requirements.
{This test applies to Ophthalmic Ointments only.}

Minimum fill <755>—meets the requirements.
{Applies to articles that are packaged in containers in which the labeled content is not more than 150 g or 150 mL.}

pH <791>: between [ ] and [ ], [in a solution (__ in __)].

Water, *Method [I][II]* <921>: not more than [.]%.
{This test applies to Ointments that require a limit on the water content}
Alcohol content[, *Method* [*I*]/[*II*] <611>] [(*if present*)]: [between __% and __% is found] [between __% and __% of the labeled amount of C_2H_5OH is found].

Metal particles—It meets the requirements of the test for *Metal Particles in Ophthalmic Ointments* <751>
{This test is required for Ophthalmic Ointments.}

Residual solvents <467>: meets the requirements.
Impurity—
{Proceed as directed for *Impurity* under the template for Tablets and Capsules in the addendum of the USP *Guideline for Submitting Requests for Revision for USP–NF*.}
[Test solution— Transfer an accurately weighed portion of [Cream][Ointment], equivalent to about ___ mg of [active ingredient], to a ___-mL [volumetric flask][beaker][separator], [ ] {Insert extraction procedure}]
Assay—{Proceed as directed for *Impurity* under the template for Tablets and Capsules.}
NOTE: FOR COMBINATION DRUG PRODUCTS, AN ASSAY TEST FOR EACH ACTIVE IS REQUIRED.
[Assay preparation—Transfer an accurately weighed portion of the [Cream][Lotion], equivalent to about ___ mg of [active ingredient], to a ___-mL [volumetric flask][beaker] [separator], [ ]. {describe the procedure for extraction in detials.}

Microbiological Assay—
{**FOR ANTIBIOTICS** }
{AN HPLC ASSAY PROCEDURE IS PREFERRED OVER A MICROBIAL ASSAY PROCEDURE FOR A *USP–NF* MONOGRAPH. THE MANUFACTURERS ARE URGED TO EXPLORE THE POSSIBILITY OF SUBMITTING AN HPLC PROCEDURE FOR ASSAY FOR ANTIBIOTICS. SEE THE TEMPLATE DESCRIBED UNDER INJECTION AND FOR INJECTION IN THE ADDEDDUM OF THE USP GUIDELINE FOR SUBMITTING A REQUEST FOR REVISION TO THE *USP–NF* FOR DETAILS.}