

FORMULATION
&
PRE-FORMULATION
TESTING

Pharmaceutical Product formulation

The process in which different chemical substances, drug(s) and excipients, are combined to fabricate a final medicinal product of a desired **dosage form** i.e. syrup, tablet, capsule, injectable liquid or powder etc.

A **dosage form** is the physical form of a dose of a drug intended for administration or consumption.

Pill, tablet, or capsule, liquid, aerosol or inhaler, liquid injection, pure powder or solid crystal etc.

The route of administration for drug delivery is dependent on the dosage form of the substance in question.

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

- therapeutic matters as the nature of the illness,
- the manner in which it is treated (locally or through systemic action),
- Age
- anticipated condition of the patient.

For example;

- **Persistent nausea and emesis or vomiting may make it difficult to use an oral dosage form, and in such a case, it may be necessary to utilize an alternate route such as inhalational, buccal, sublingual, nasal, suppository, or parenteral instead.**
- **Additionally, a specific dosage form may be a requirement for certain kinds of drugs, as there may be issues with various factors like chemical stability or pharmacokinetics.**

For example, insulin cannot be given orally because being protein in nature it is extensively metabolized in the GIT before reaching the blood stream and is thus incapable of sufficiently reaching its therapeutic target destinations.

NEED FOR DOSAGE FORMS

- Safe and convenient delivery of accurate dosage
- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampoules).
- To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric-coated tablets).
- To conceal the bitter, salty, or offensive taste or odor of a drug substance (capsules, coated tablets, flavored syrups).
- To provide liquid preparations of substances which are either insoluble or unstable in the desired vehicle (suspensions).
- To provide clear liquid dosage forms of substances (syrups, solutions).

NEED FOR DOSAGE FORMS

- To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions).
- To provide optimal drug action from topical administration sites (ointments, creams, transdermal patches, and ophthalmic, ear, and nasal preparations)
- To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories).
- To provide for placement of drugs directly in the bloodstream or body tissues (injections).
- To provide for optimal drug action through inhalation therapy (inhalants and inhalation aerosols).

Preformulation study is the first step in the rational development of dosage forms of a drug substance.

- *It can be defined as an investigation of physical and chemical properties of a drug substance - **alone** and when **combined** with excipients.*
- *The overall objective of **preformulation testing** is to generate information useful to the formulator in developing **stable** and **bioavailable** dosage forms which can be **mass-produced**.*

Data collected at the time of isolation / synthesis of drug molecule **includes such information as;**

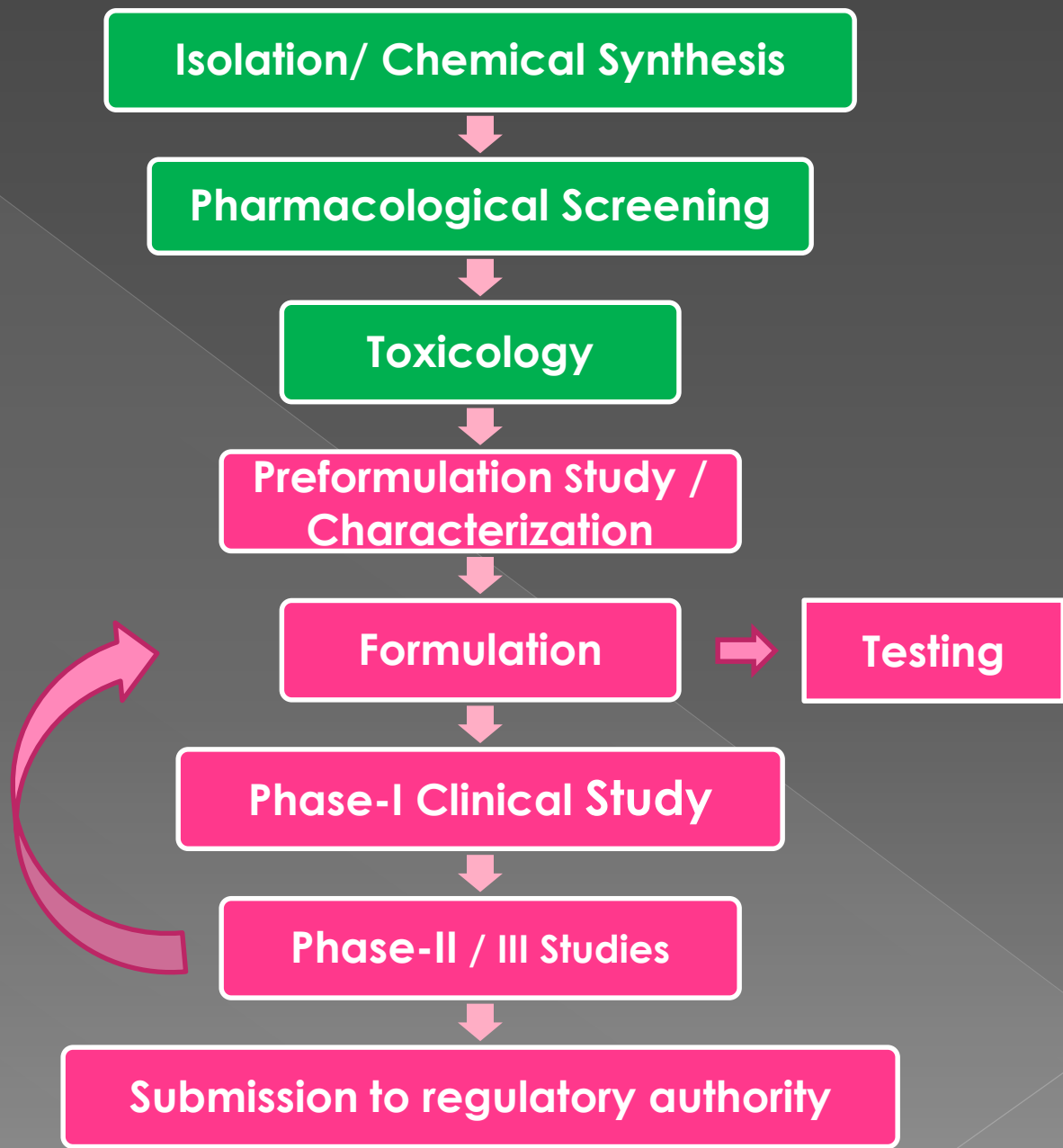
- **gross particle size,**
- **melting point,**
- **infrared analysis,**
- **thin-layer chromatographic purity,**
- **and other such characterizations of different laboratory-scale batches.**

These data are useful in guiding, and becoming part of, the main body of preformulation work.

The formal preformulation study should start at the point after **biological screening**, when a decision is made for further development of the compound in **clinical trials**.

Before embarking upon a formal program, the preformulation scientist must consider the following:

1. **The available physicochemical data (including chemical structure, different salts available)**
2. **The therapeutic class of the compound and anticipated dose**
3. **The supply situation and the development schedule (i.e., the time available)**
4. **The availability of a stability-indicating assay**
5. **The nature of the information the formulator should have or would like to have**



Isolation/ Chemical Synthesis

Pharmacological Screening

Toxicology

Preformulation Study /
Characterization

Formulation

Testing

Phase-I Clinical Study

Phase-II / III Studies

Submission to regulatory authority

Characterization of drug molecule

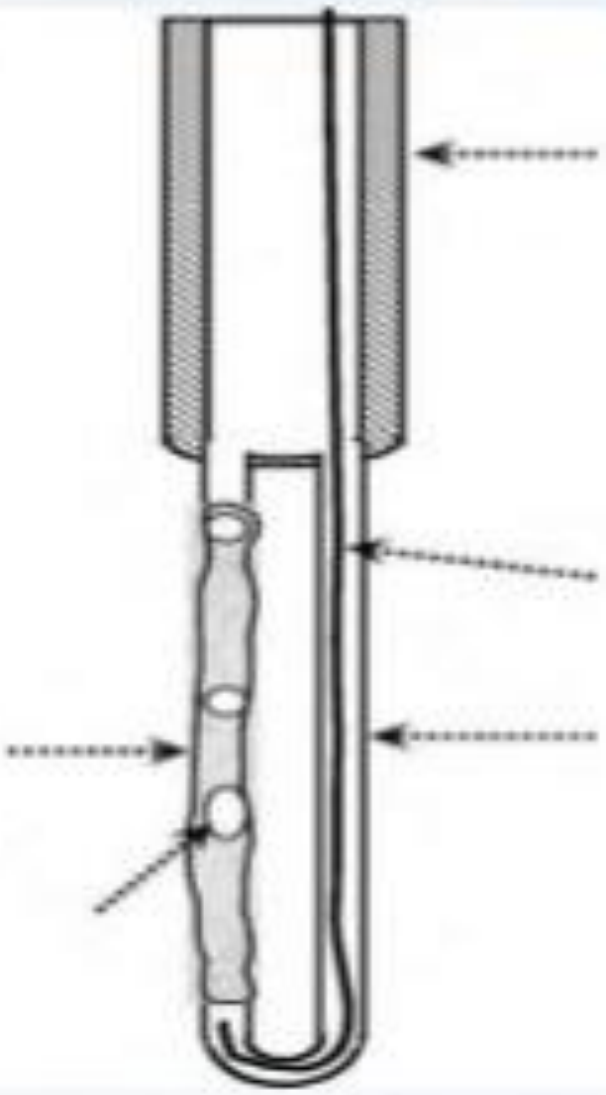
Characterization of drug molecule is a very important step at the preformulation phase of product development.

Characterization and its impact

| Determination | Impacts on |
|---|---|
| Melting Point or boiling point | Purity determination, dosage form design, stability tests |
| UV absorption spectrum | Assay development |
| IR absorption spectrum | Quantitative & qualitative tests |
| Assay development | All qualitative & quantitative tests |
| Solubility | Assay development, dosage form design, stability, bioavailability |
| pKa (if an acid or base) and pH solubility profiling | Salt selection, dosage form design, stability, bioavailability |
| Partition coefficient | Dosage form design, stability, bioavailability |
| Polymorphism | Processing, stability, solubility, bioavailability |
| Microscopic appearance, Particle Size, Shape & Surface area | Dissolution rate, stability tests |
| Interaction with excipients | Processing, dosage form design, stability, bioavailability |
| Chemical Stability Profile | Pharmacological activity and toxicology |
| Flowability | Formulation Development |
| Hygroscopicity | Stability |




Steps in Preformulation Process Pharmaceutical Research

| | |
|---|--|
| 1. Stability | (2) pH-Solubility Profile |
| a. Solid State | (3) Salt Forms |
| (1) Temperature | (4) Co-solvents |
| (2) Light | (5) Complexation |
| (3) Humidity | (6) Prodrug |
| b. Solution | j. Effect of pH on UV Spectra |
| (1) Solvent | k. Ionization Constant |
| (2) pH | l. Volatility |
| (3) Light | m. Optical Activity |
| 2. Solid State Compatibility | n. Polymorphism Potential |
| a. TLC Analysis | o. Solvate Formation |
| b. DRS Analysis (Dielectric Relaxation Spectroscopy) | 4. Physico-mechanical Properties |
| 3. Physico-chemical Properties | a. Bulk and Tapped Density |
| a. Molecular Structure and Weight | b. Compressibility |
| b. Color | c. Photomicrograph |
| c. Odor | 5. In Vitro Availability Properties |
| d. Particle size, Shape, and Crystallinity | a. Dissolution of Drug Crystal |
| e. Melting Point | b. Dissolution of Pure Drug Pellet |
| f. Thermal Analysis Profile | c. Dissolution Analysis of Pure Drug |
| g. Hygroscopicity Potential | d. Rat Everted Gut Technique |
| h. Absorbance Spectra | 6. Other Studies |
| (1) UV | a. Plasma Protein Binding |
| (2) IR | b. Effect of Compatible Excipients on Dissolution |
| i. Solubility | c. Kinetic Studies of Solution Degradation |
| (1) Water and Other Solvents | d. Use of Radio-labeled Drug |



ORGANOLEPTIC PROPERTIES

Color

| | | |
|--|--|--|
| Unappealing to the eye or variable from batch to batch |  | Instrumental methods |
| Record of early batches is very useful for later production |  | establishing “specs” |
| Undesirable or variable color |  | incorporation of a dye in the body or coating |

Odor and Taste

| | |
|--|--|
| Unpalatable | use of less soluble chemical form (bioavailability not compromised!) suppressed by: -Flavors -Excipients -Coating |
| Drug substances irritating to skin or Sternutatory (sneezing) | handling precautions |
| Flavors, dyes, excipients used | Stability / bioavailability |

Organoleptic Properties of Pharmaceutical Powders

| Color | Odor | Taste |
|--------------|-----------|-----------|
| Off-white | Pungent | Acidic |
| Cream yellow | Sulfurous | Bitter |
| Tan | Fruity | Bland |
| Shiny | Aromatic | Intense |
| | Odorless | Sweet |
| | | Tasteless |

Crystal Properties and Polymorphism:

More than one crystalline form with different space lattice arrangements is called polymorphism. Polymorphs generally have different melting points, x-ray diffraction patterns, and solubilities, even though they are chemically identical.

- Differences in the dissolution rates and solubilities 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 form may be utilized to improve bioavailability.
- For drugs prone to degradation in the solid state, the physical form of the drug influences degradation. Selection of a polymorph that is chemically more stable is a solution is to selected.
- Different polymorphs also lead to different morphology, tensile strength and density of powder bed which all contribute to compression characteristics of materials.

Polymorphism also influences biopharmaceutical behavior of the drug, A pure, more soluble A form of Chloramphenicol palmitate is more bioavailable after oral administration as compared less soluble pure A form and their mixtures.

Various techniques are available for the investigation of the solid state. These include microscopy, infrared spectrometry, single-crystal X-ray and X-ray powder diffraction, thermal analysis.

e.g; sulphathiazole can be composed of crystalline rods (I), plates (II) or prisms (III).

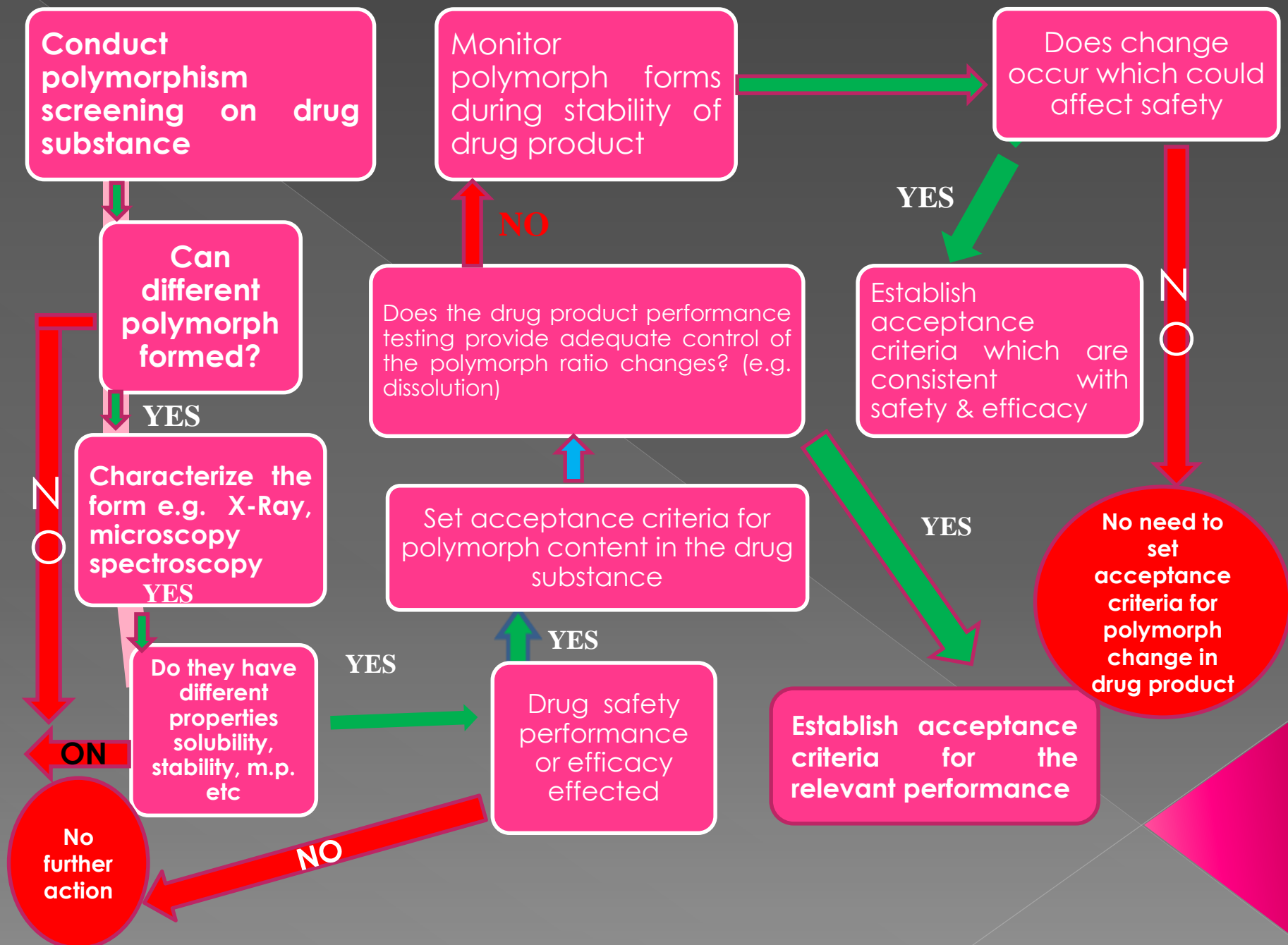
During the pre-formulation phase, the following should be investigated:

- 1. How many polymorphs exist?**
- 2. What is the stability of each form?**
- 3. What is the solubility of each form?**
- 4. Decide which polymorphic form of the drug will be best suited to processing into the desirable dosage form.**
- 5. Prevent transitions to the unwanted polymorph(s).**

Polymorphic transitions can have a profound effect on granule processing, possibly influencing tablet hardness & dissolution rates.

Examples include:

- 1) The transitions between different polymorphic forms of carbamazepine cause a reduction in granule yield, in turn affecting tablet hardness & tablet dissolution.**
- 2) Different etoposide polymorphs exhibit differing dissolution rates.**
- 3) Different polymorphic forms of chloramphenicol hydrate show different bioavailabilities.**



Conduct polymorph screening on drug substance

Monitor polymorph forms during stability of drug product

Does change occur which could affect safety

Can different polymorph formed?

Does the drug product performance testing provide adequate control of the polymorph ratio changes? (e.g. dissolution)

Establish acceptance criteria which are consistent with safety & efficacy

Characterize the form e.g. X-Ray, microscopy spectroscopy

Set acceptance criteria for polymorph content in the drug substance

No need to set acceptance criteria for polymorph change in drug product

Do they have different properties solubility, stability, m.p. etc

Drug safety performance or efficacy effected

Establish acceptance criteria for the relevant performance

No further action

PURITY

Control parameter for comparison with subsequent batches

More direct concerns - impurity can affect:

- **Stability: metal contamination in ppm**

- **Appearance: off-color** → **re-crystallized** → **white**

- **Toxic: aromatic amine (p-amino phenol)** → **carcinogenic**

Often remedial action → simple recrystallization

Techniques used for characterizing purity are the same as used in preformulation study :

- Thin layer chromatography (TLC)
- High-pressure liquid chromatography (HPLC)
- Gas chromatography (GC)
- **Impurity index (II)** defined as the ratio of all responses (peak areas) due to components other than the main one to the total area response.
- **Homogeneity index (HI)** defined as the ratio of the response (peak area) due to the main component to the total response.

- USP Impurity Index defined as a ratio of responses due to impurities to that response due to a defined concentration of a standard of the main component. (using TLC)
- General limit 2 % impurities
- All **II**, **HI**, USP II are not absolute measures of impurity since the specific response (molecular absorbance or extinction coefficient) due to each impurity is assumed to be the same as that of the main component.

More accurate analysis - identification of each individual impurity followed by preparation of standards for each one of them.

Other useful tools in assessment of impurity:

- **Differential Thermal Analysis (DTA)**
- **Thermogravimetric Analysis (TGA)**
- **Differential Scanning Calorimetry (DSC)**
- **Powder X-Ray Diffraction (PXRD)**

PARTICLE SIZE, SHAPE, AND SURFACE AREA

Effects of particle size distribution and shape on:

- Chemical and physical properties of drug substances.
- Bioavailability of drug substances (griseofulvin, chlorpropamide).
- Flow and mixing efficiency of powders and granules in making tablets.
- Fine materials tend to require more amount of granulating liquid (cimetidine).
- Stability, fine materials relatively more open to attack from atmospheric O_2 , heat, light, humidity, and interacting excipients than coarse materials.

Table 2. Influence of Particle Size on Reaction of Sulfacetamide with Phthalic anhydride in 1:2 Molar Compacts after 3 hr at 95 °C

| Particle size of sulfacetamide (μm) | % Conversion ± SD |
|--|--------------------------|
| 128 | 21.54 ± 2.74 |
| 164 | 19.43 ± 3.25 |
| 214 | 17.25 ± 2.88 |
| 302 | 15.69 ± 7.90 |
| 387 | 9.34 ± 4.41 |

Weng and Parrott

- Very fine materials are difficult to handle, overcome by creating solid solution in a carrier (water-soluble polymer).
- Important to decide, maintain, and control a desired size range.
- Safest - grind most new drugs with particle diameter $> 100 \mu\text{m}$ (~ 140 mesh) down to $\sim 10 - 40 \mu\text{m}$ (~ 325 mesh).
- Particles with diameter $\leq 30 \mu\text{m}$ (~ 400 mesh), grinding is unnecessary except needle-like \Rightarrow improve flow.
- Drawbacks to grinding:
 - material losses
 - static charge build-up
 - aggregation \Rightarrow increase hydrophobicity
 \Rightarrow lowering dissolution rate
 - polymorphic or chemical transformations

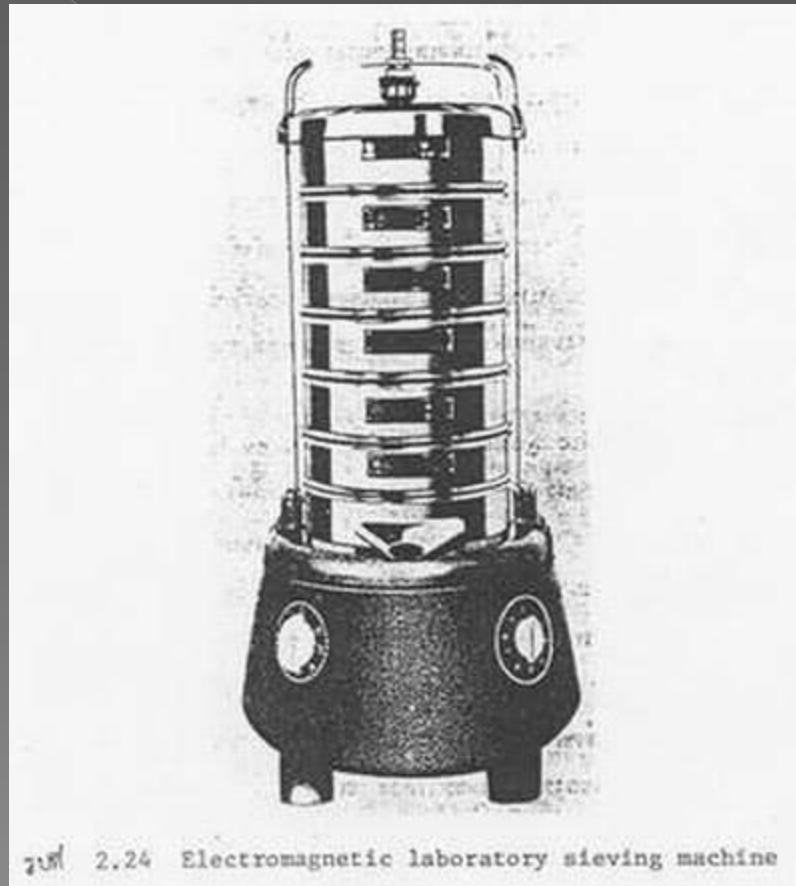
General Techniques For Determining Particle Size

Microscopy

- ✓ Most rapid technique.
- ✓ But for quantitative size determination requires counting large number of particles.
- ✓ For size $\sim 1 \mu\text{m}$ upward (magnification $\times 400$).
- ✓ Suspending material in non-dissolving fluid (water or mineral oil)
- ✓ Polarizing lens to observe birefringence => change in amorphous state after grinding?

Sieving

- Quantitative particle size distribution analysis.
- For size $> 50 \mu\text{m}$ upward.
- Shape has strong influence on results.



2.24 Electromagnetic laboratory sieving machine

Electronic means

- To encompass most pharmaceutical powders ranging in size 1 - 120 μm :
- **Blockage of electrical conductivity path (Coulter)**
 - **Light blockage (HIAC) [adopted by USP]**
 - **Light scattering (Royco)**
 - **Laser scattering (Malvern)**

Other techniques

- **Centrifugation**
- **Air suspension**
- **Sedimentation** (Adreassen pipet, recording balance)

Disfavor now because of their tedious nature.

Common Techniques for Measuring Fine Particles of Various Sizes

Technique

Particle size (μm)

Microscopic

1 - 100

Sieve

> 50

Sedimentation

> 1

Elutriation

1 - 50

Centrifugal

< 50

Permeability

> 1

Light scattering

0.5 - 50

(Parrott)

Determination of Surface Area

- **Surface areas of powders**

=> increasing attention in recent years: reflect the particle size

- **Grinding operation:**

↓ particle size => ↑ surface area.

- **Brunauer-Emmett-Teller (BET) theory of adsorption**

Most substances will adsorb a monomolecular layer of a gas under certain conditions of partial pressure (of the gas) and temperature.

Knowing the monolayer capacity of an adsorbent (i.e., the quantity of adsorbate that can be accommodated as a monolayer on the surface of a solid, the adsorbent) and the area of the adsorbate molecule, the surface area can, in principle be calculated.

Most commonly, nitrogen is used as the adsorbate at a specific partial pressure established by mixing it with an inert gas, typically helium. The adsorption process is carried out at liquid nitrogen temperature (-195 °C).

It has been demonstrated that, at a partial pressure of nitrogen attainable when it is in a 30 % mixture with an inert gas and at -195 °C, a monolayer is adsorbed onto most solids.

Apparently, under these conditions the polarity of nitrogen is sufficient for van de Waals forces of attraction between the adsorbate and the adsorbents to be manifest.

The kinetic energy present under these conditions overwhelms the intermolecular attraction between nitrogen atoms. However, it is not sufficient to break the bonding between the nitrogen and dissimilar atoms. The latter are most often more polar and prone to van de Waals forces of attraction.

The nitrogen molecule does not readily enter into chemical combinations, and thus its binding is of a nonspecific nature (i.e., it enters into a physical adsorption); consequently, the nitrogen molecule is well suited for this role.

Brunauer-Emmett-Teller (BET) adsorption isotherm

$$\frac{1}{\lambda(P_o/P - 1)} = \frac{C - 1}{\lambda_m C} \frac{P}{P_o} + \frac{1}{\lambda_m C}$$

λ = g of adsorbate per g of adsorbent

λ_m = maximum value of that λ ratio for a monolayer

P = partial pressure of the adsorbate gas

P_o = vapor pressure of the pure adsorbate gas

C = constant

P , P_o , and C are temperature-dependent

- The values of λ (g of adsorbate/g of adsorbent) at various P values (partial pressure of the adsorbate gas) could be obtained from the experiment through instrument.
- P_0 (vapor pressure of the pure adsorbate gas) can be obtained from the literature.
- Plotting the term $1/[\lambda(P_0/P - 1)]$ against P/P_0 will obtain a straight line with
 - slope = $(C - 1)/\lambda_m C$
 - intercept = $1/\lambda_m C$
- The term C and λ_m can readily be obtained

Dynamic Method of Gas Adsorption

- Accurately weighing the sample into an appropriate container
- Immersing the container in liquid nitrogen
- Passing the gas over the sample
- Removing the liquid nitrogen when the adsorption is complete (as signaled by the instrument)
- Warming the sample to about the room temperature
- Measuring (via the instrument) the adsorbed gas released
- Performing the calibration by injecting known amounts of adsorbed gas into the proper instrument port
- P is the product of the fraction of N_2 in the gas mixture and the ambient pressure

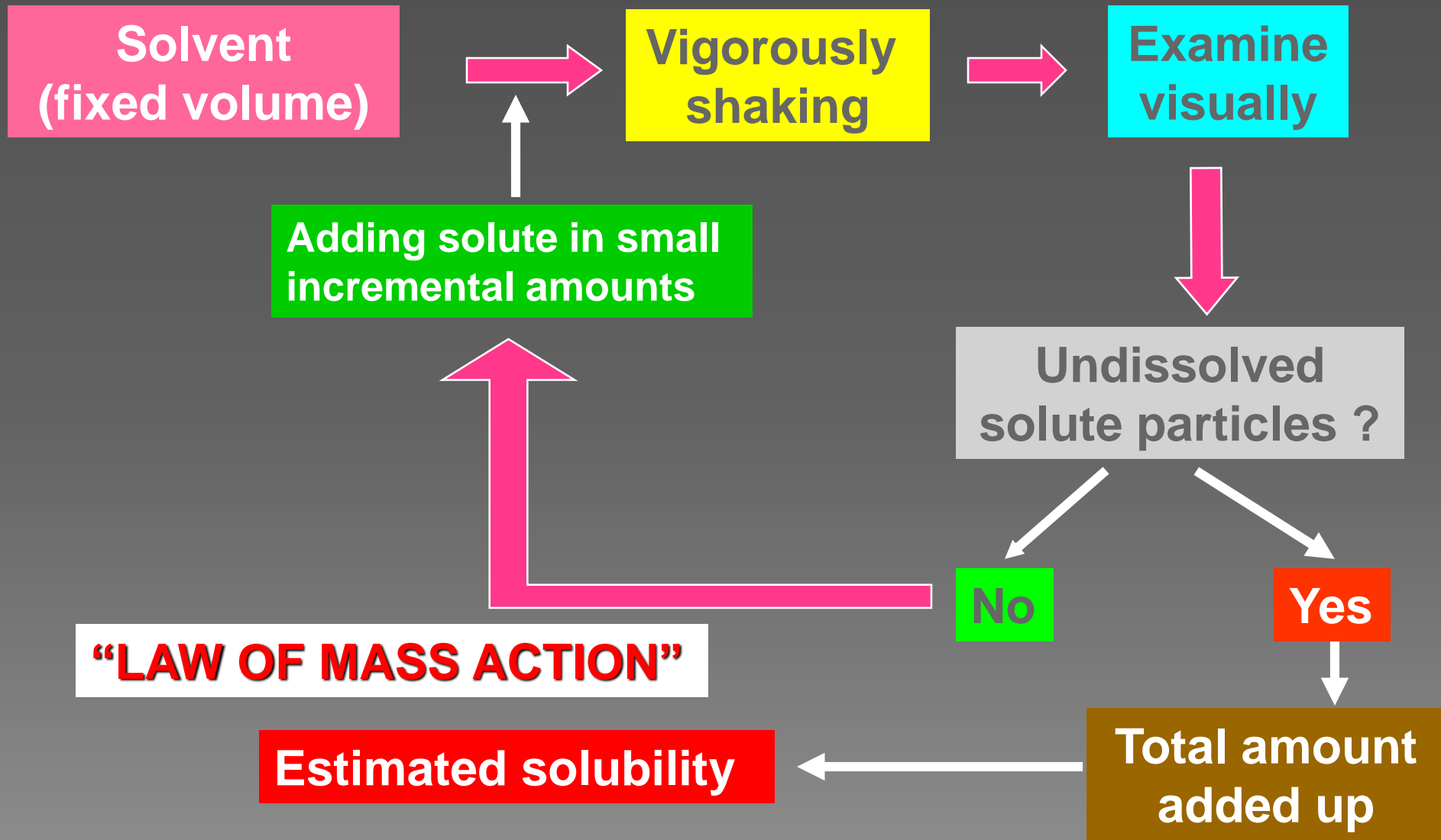
- At relatively large diameters, the specific surface area is insensitive to an increase in diameter
- At very small diameters the surface area is comparatively very sensitive.
- Relatively high surface area most often reflects a relatively small particle size, except porous or strongly agglomerated mass
- Small particles (thus of high surface area) agglomerate more readily, and often to render the inner pores and surfaces inaccessible to dissolution medium

SOLUBILITY

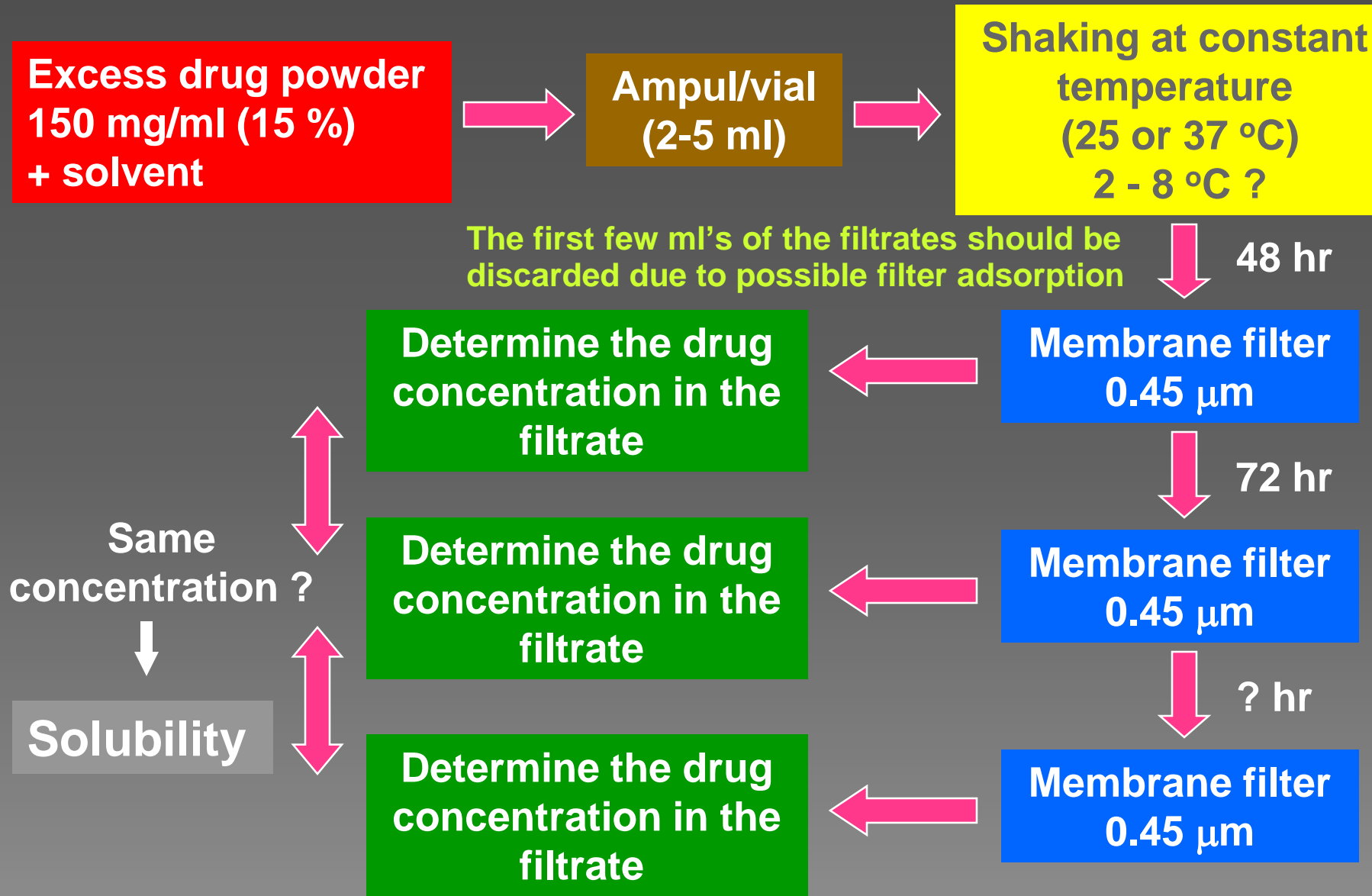
- Solubility $> 1\%$ w/v
=> no dissolution-related absorption problem
- Highly insoluble drug administered in small doses may exhibit good absorption
- Unstable drug in highly acidic environment of stomach, high solubility and consequent rapid dissolution could result in a decreased bioavailability
- The solubility of every new drug must be determined as a function of pH over the physiological pH range of 1 - 8

Determination of Solubility

Semi-quantitative determination:



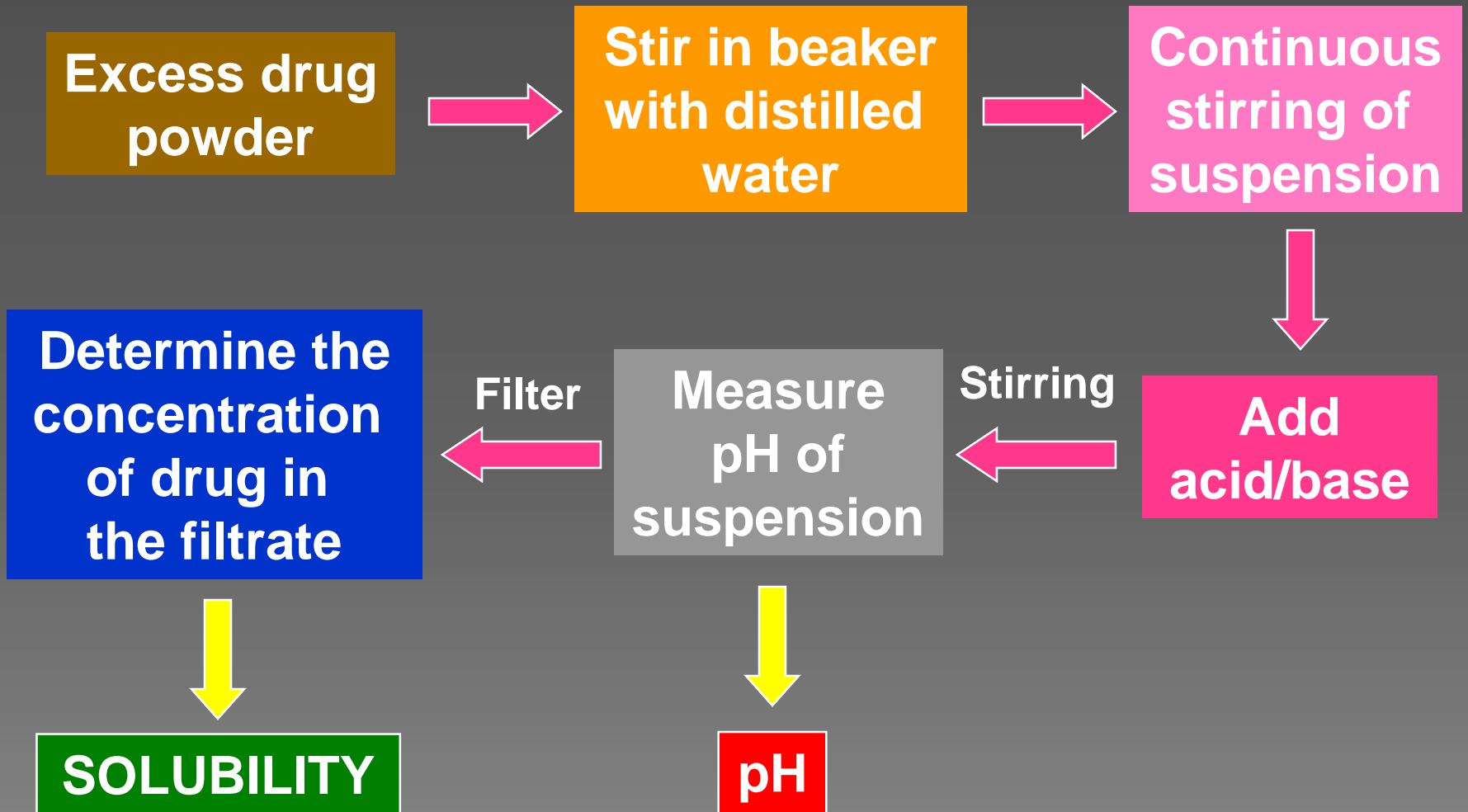
Accurately Quantitative determination:



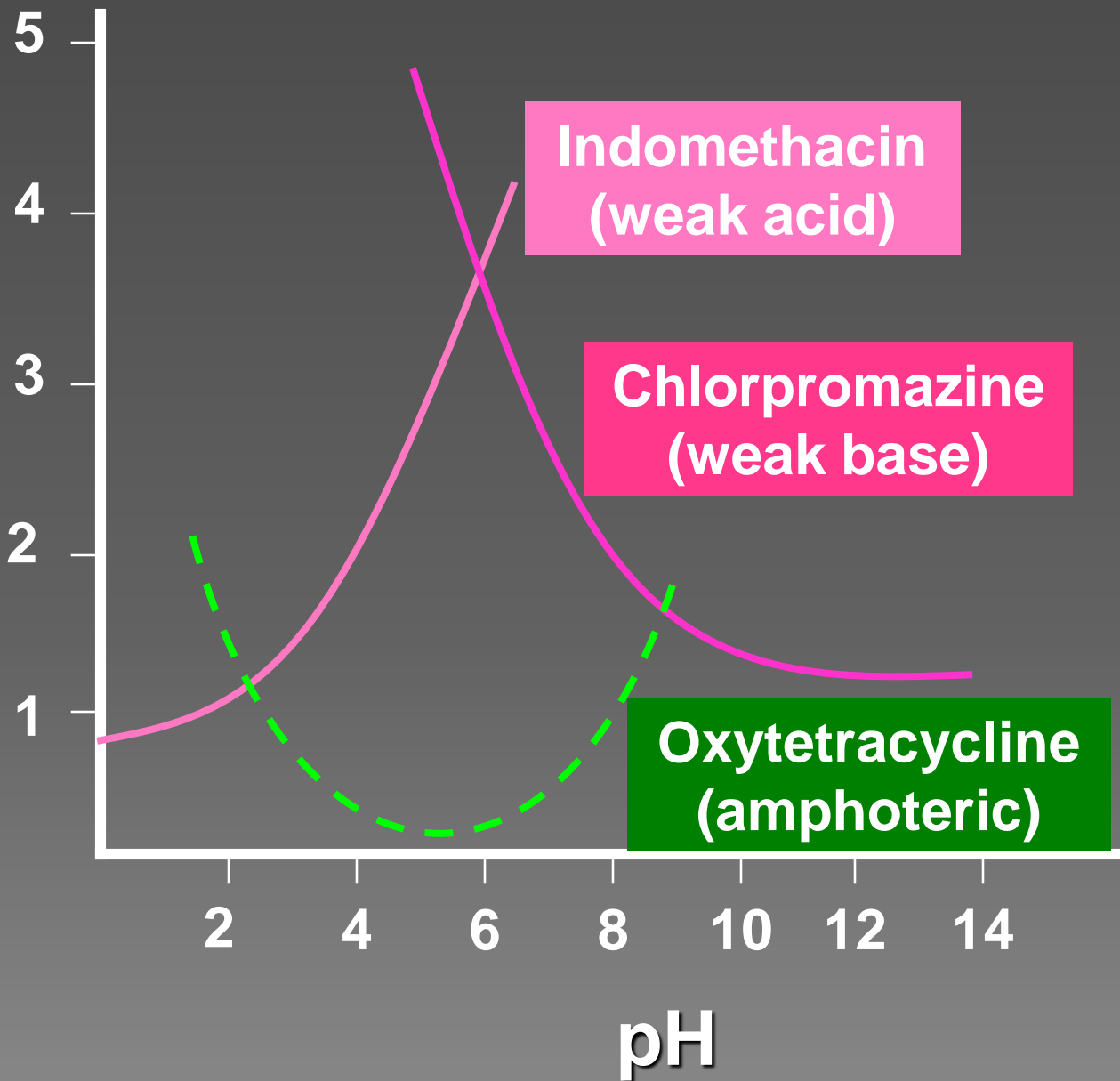
Unique Problems in Solubility Determination of Poorly Soluble Compounds

- Solubility could be overestimated due to the presence of soluble impurities
- Saturation solubility is not reached in a reasonable length of time unless the amount of solid used is greatly in excess of that needed to saturation
- Many compounds in solution degrade, thus making an accurate determination of solubility difficult
- Difficulty is also encountered in the determination of solubility of metastable forms that transform to more stable forms when exposed to solvents

pH-Solubility Profile



Log aqueous solubility (μmol)



**Indomethacin
(weak acid)**

**Chlorpromazine
(weak base)**

**Oxytetracycline
(amphoteric)**

⦿ Poorly-soluble weakly-acidic drugs:

$$\text{pH} = \text{pK}_a + \log [(S_t - S_o)/S_o] \quad (2)$$

⦿ Poorly-soluble weakly-basic drugs:

$$\text{pH} = \text{pK}_a + \log [S_o/(S_t - S_o)] \quad (3)$$

where

S_o = solubility of unionized free acid or base

S_t = total solubility (unionized + ionized)

Salt Forms

NSAID's alclofenac, diclofenac, fenbufen,
ibuprofen, naproxen

Weak acid $pK_a \sim 4$, low solubility

Salt forms sodium

N-(2-hydroxy ethyl) piperazinium
arginium

N-methylglucosammonium

Solubility

diclofenac (free acid) : $0.8 \times 10^{-5} \text{ M}$ (25 °C)

diclofenac sodium : 24.5 mg/ml (37 °C)

Salt Forms (cont.)

Quinolones

enoxacin, norfloxacin,
ciprofloxacin

Salt forms

lactate, acetate, gluconate,
galacturonate, aspartate,
glutamate, etc.

Solubility

Free base :

< 0.1 mg/ml (25 °C)

Salt forms :

> 100 mg/ml (25 °C)

Solubilization

Drug not an acidic or basic, or the acidic or basic character not amendable to the formation of a stable salt

- Use more soluble metastable polymorph
- Use of complexation (eg. Ribloflavin-xanthenes complex)
- Use of high-energy coprecipitates that are mixtures of solid solutions and solid dispersions (eg. Griseofulvin in PEG 4000, 6000, and 20,000)
 - in PEG 4000 and 20,000 -> supersaturated solutions
 - in PEG 6000 -> bioavailability in human twice > micronized drug
- Use of suitable surfactant

Dissolution

$k_d \ll k_a \Rightarrow$ "dissolution rate-limited"

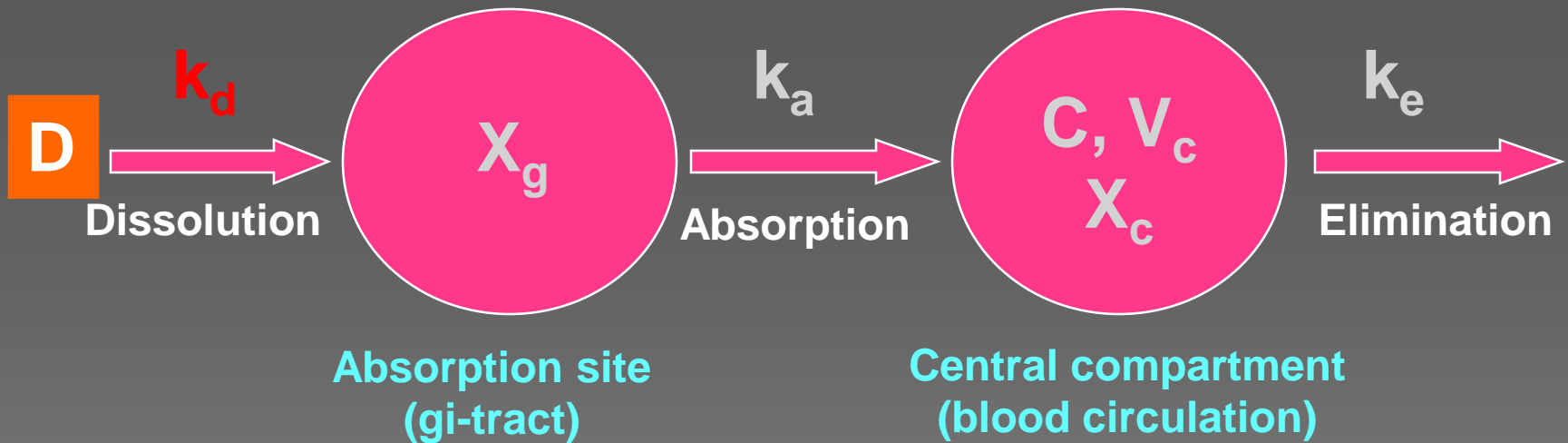


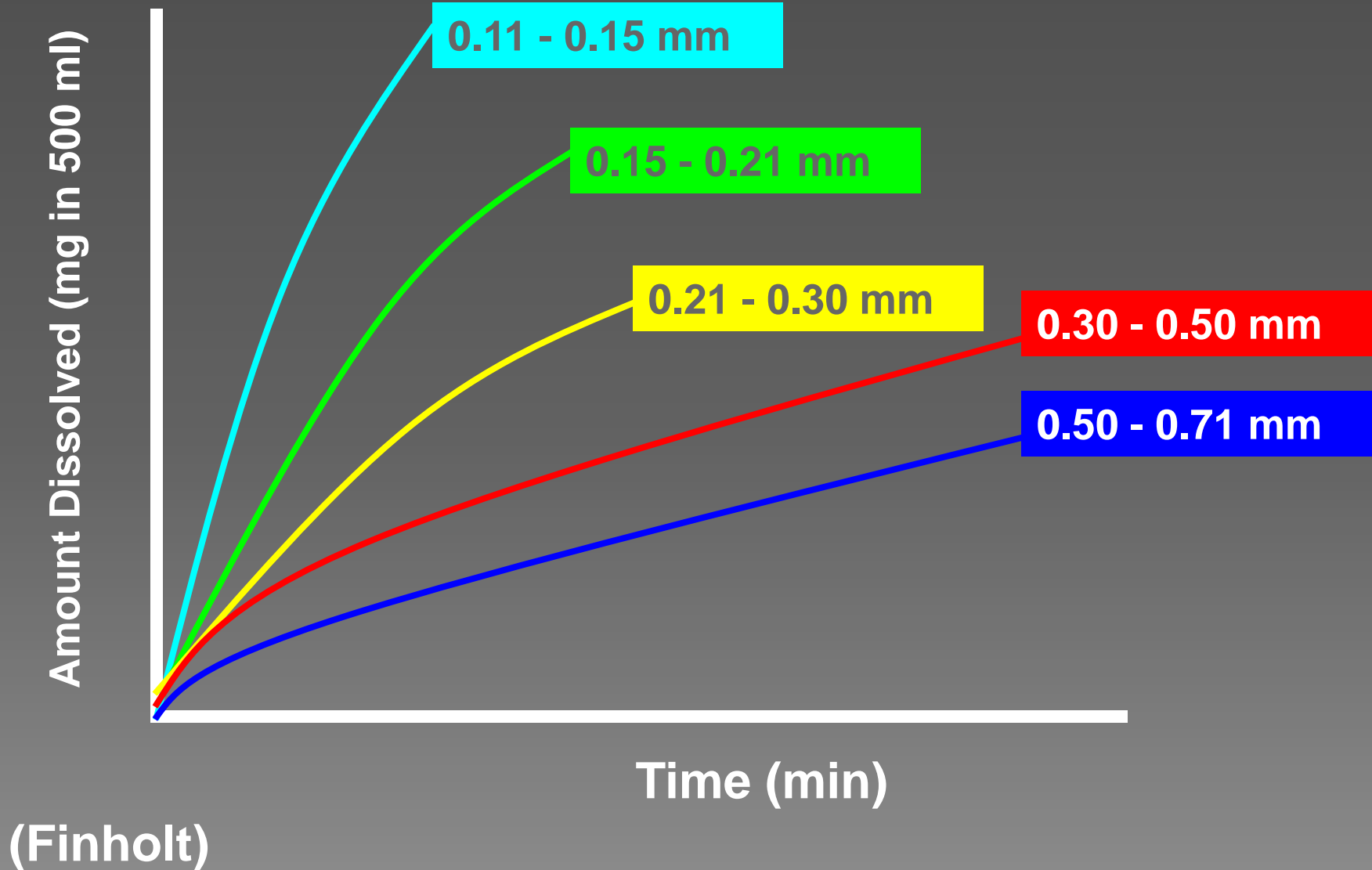
Diagram showing dissolution and absorption of solid dosage form into blood circulation

- ⊙ ***Intrinsic dissolution rate (mg/cm²/min)*** is characteristics of each solid compound in a given solvent under fixed hydrodynamic conditions
- ⊙ ***Intrinsic dissolution rate*** helps in predicting if absorption would be ***dissolution rate-limited***
- ⊙ **> 1 mg/cm²/min** --> not likely to present dissolution rate-limited absorption problems
- ⊙ **< 0.1 mg/cm²/min** --> usually exhibit dissolution rate-limited absorption problems
- ⊙ **0.1 - 1.0 mg/cm²/min** --> more information is needed before making any prediction

Particulate Dissolution

- Particulate dissolution is used to study the influence on dissolution of particle size, surface area, and mixing with excipients.
- The rate of dissolution normally increased with a decrease in the particle size.
- Occasionally, however, an inverse relationship of particle size to dissolution is encountered.
- This may be explained on the basis of effective or available, rather than absolute, surface area; and it is caused by incomplete wetting of the powder.
- Incorporation of a surfactant in the dissolution medium may provide the expected relationship.

5.2.1 Effect of particle size of phenacetin on dissolution rate of the drug from granules



Means of enhancing the slow dissolution:

In absence of more soluble physical or chemical form of the drug -

- ⊙ **Particle size reduction (most commonly used).**
- ⊙ **Enhanced surface area by adsorbing the drug on an inert excipient with a high surface area, i.e., fumed silicon dioxide.**
- ⊙ **Comelting, coprecipitating, or triturating the drug with some excipients.**
- ⊙ **Incorporation of suitable surfactant.**

Partition coefficient

Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes.

Ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

$$P_{o/w} = (C_{oil}/C_{water})_{\text{equilibrium}}$$

It can provide an empiric handle in screening for some biologic properties.

For drug delivery, the lipophilic / hydrophilic balance is a contributing factor for the rate and extent of drug absorption.

Partition coefficient data alone does not provide understanding of *in vivo* absorption, but it provide a means of characterizing the lipophilic / hydrophilic nature of the drug.

Biological membranes, being 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 of $P \gg 1$ are classified as lipophilic, whereas those with partition coefficients $\ll 1$ are indicative of a hydrophilic drug.

Value of Partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate, pK_a , and solubility on absorption, therefore, must not be neglected.

Comparison Between Colonic Absorption and Lipid/Water Partition of the Un-ionized forms of Barbiturates

| Barbiturate | % Absorbed | Chloroform / water partition coefficient |
|----------------------|------------|--|
| Barbital | 12 \pm 2 | 0.7 |
| Aprobarbital | 17 \pm 2 | 4.0 |
| Phenobarbital | 20 \pm 3 | 4.8 |
| Allylbarbituric acid | 23 \pm 3 | 10.5 |
| Butethal | 24 \pm 3 | 11.7 |
| Cyclobarbital | 24 \pm 3 | 18.0 |
| Pentobarbital | 30 \pm 2 | 23.0 |
| Secobarbital | 40 \pm 3 | 50.7 |
| Hexethal | 44 \pm 3 | > 100.0 |

(Schanker)

Ionization Constant

- **The unionized species are more lipid-soluble and the gastro intestinal absorption of weakly acidic or basic drugs is related to the fraction of unionized drug in solution.**
- **Factors affecting absorption:**
 - **pH at the site of absorption**
 - **ionization constant**
 - **Lipid solubility of unionized species**

Henderson-Hasselbalch equation

For acids:

$$\text{pH} = \text{pK}_a + \log \frac{[\text{ionized form}]}{[\text{unionized form}]}$$

For bases:

$$\text{pH} = \text{pK}_a + \log \frac{[\text{unionized form}]}{[\text{ionized form}]}$$

Determination of Ionization Constant

1. Potentiometric pH-Titration
2. pH-Spectrophotometry Method
3. pH-Solubility Analysis

Chemical stability profile

To study the behaviour, both in solution and solid state under conditions typical for the handling, formulation, storage, and administration of a drug candidate as well as stability in presence of other excipients.

Factors affecting chemical stability critical in rational dosage form design include;

Temperature, pH and dosage form diluents e.g.

The sterilization of parenteral products 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.

Acid labile drugs intended for oral administration must be protected from the highly acidic environment of the stomach. Buffer selection for parenteral dosage forms will be largely based on the stability characteristics of the drug.

Solid State Stability:

To indentify stable storage conditions for drug in the solid state.

To indentify compatible excipients for a formulation.

In general, solid state reactions are much slower and more difficult to interpret than solution state reactions, and it is customary to use stress conditions in the investigation of stability. The data obtained under stress conditions are then extrapolated to make a prediction of stability under appropriate storage conditions.

Elevated Temperature Studies:

The elevated temperatures most commonly used are 40°, 50° and 60°C in conjunction with ambient humidity.

Samples stored at the highest temperature are examined for physical and chemical changes at weekly intervals, and any change, when compared to an appropriate control (usually a sample stored at 5°C), is noted.

Corroborative evidence is to be obtained by monitoring the samples stored at lower temperatures for longer durations. Samples stored at room temperature and at 5°C for at least 6 months.

The data obtained at elevated temperatures is extrapolated using the Arrhenius equation to determine the degradation rate at a lower temperature;

Arrhenius Equation:

$$K = A e^{-E_a/R}$$

E_a : activation energy; R : gas constant

$$\log K = \log A - (E_a/2.303RT)$$

Plotting the rate of reaction (K) against $1/T$ allows the calculation of rate at any temperature and therefore a prediction of shelf-life (t_{90} , time to 90% potency). This forms the basis of many accelerated stability tests.

Not all solid-state reactions are amenable to Arrhenius treatment. Their heterogeneous nature makes elucidation of the kinetic order and prediction difficult. Long-term lower temperature studies are, therefore, an essential part of a good stability program.

High-Humidity Conditions:

In the presence of moisture, many drug substances hydrolyze, react with other excipients, or oxidize. These reactions can be accelerated by exposing the solid drug to different relative-humidity conditions. Controlled humidity environments can be readily obtained using laboratory desiccators containing saturated solutions of various salts.

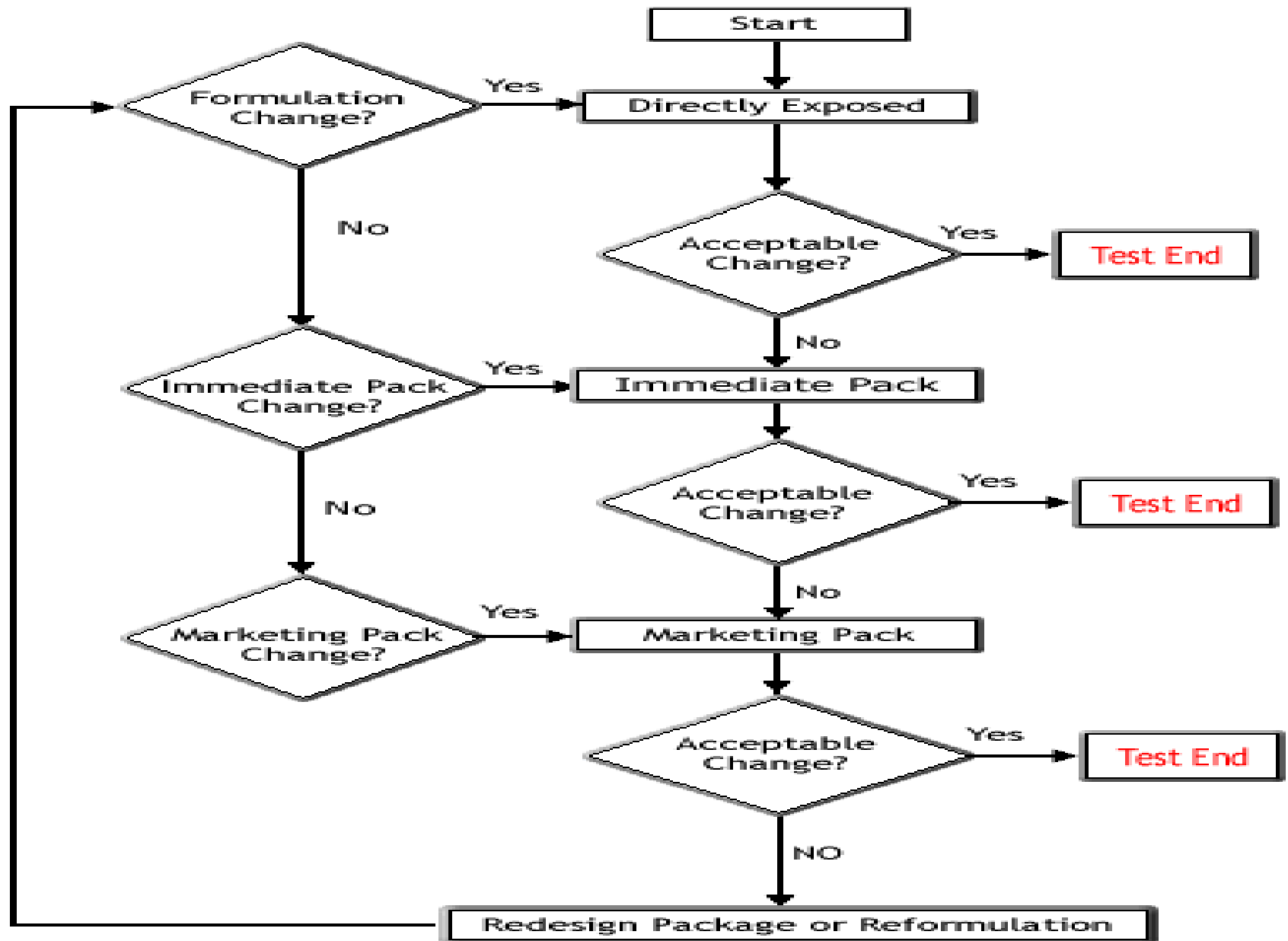
Preformulation data of this nature are useful in determining if the material should be protected and stored in a controlled low-humidity environment, or if the use of an aqueous-based granulation system, in the case of a solid dosage form, should be avoided. They may also caution against the use of excipients that absorb moisture significantly.

Photolytic Stability:

Many drug substances fade or darken on exposure to light. Usually the extent of degradation is small and limited to the exposed surface area. This can be controlled by using amber glass or an opaque container or by incorporating a dye in the product to mask the discoloration (if the only issue is aesthetics).

Exposure of the drug substance to 400 and 900 footcandles of illumination for 4- and 2-week periods, respectively, is adequate to provide some idea of photosensitivity. Over these periods, the samples should be examined frequently for change in appearance and for chemical loss, and they should be compared against samples stored under the same conditions but protected from light.

Photostability Testing Of Drug Products



Solution Phase Stability:

The primary objective of this phase of preformulation research is identification of conditions necessary to form a stable solution. These studies should include the effects of pH, ionic strength, co-solvent, light, temperature and oxygen.

Solution stability investigations usually commence with probing experiments to confirm decay at the extremes of pH and temperature (e.g., 0.1N HCl, water, and 0.1N NaOH all at 90°C). These intentionally degraded samples may be used to confirm assay specificity as well as to provide estimates for maximum rates of degradation. This initial experiment should be followed by the generation of a complete pH-rate profile to identify the pH of maximum stability. Aqueous buffers are used to produce solutions over a wide range of pH values with constant levels of drug, co-solvent and ionic strength.s

Compatibility Studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients.

Example:

A typical tablet contains binders, disintegrants, lubricants, and fillers. Compatibility screening for a new drug must consider two or more excipients from each class. The ratio of drug to excipient used in these tests is very much at the discretion of the preformulation scientist.

The three techniques commonly employed in drug-excipient compatibility screening are:

Thin-layer chromatography

Differential thermal analysis

Diffuse reflectance spectroscopy

Thin-Layer Chromatography:

This method involves storage of drug-excipient mixture both "as is" and granulated with water at elevated temperatures.

The granulation is carried out so that the mixture contains fixed amounts of moisture e.g. 5%.

The mixtures are sealed in ampoules to prevent any escape of moisture at elevated temperatures.

The samples are examined periodically for appearance and analyzed for any decomposition using thin-layer chromatography.

Unstressed samples are used as controls.

Any change in the chromatograph such as the appearance of a new spot or a change in the R_f values of the components is indicative of an interaction.

The technique can be quantitated if deemed necessary. If significant interaction is noticed at elevated temperatures, corroborative evidence must be obtained by examining mixtures stored at lower temperatures for longer durations.

If no interaction is observed at 60 or 70°C, especially in the presence of moisture, none can be expected at lower temperatures.

Among the advantages of thin-layer chromatography in this application are:

- Evidence of degradation is unequivocal.
- The spots corresponding to degradation products can be eluted for possible identification.
- The technique can be quantitated to obtain kinetic data.

Differential Thermal Analysis:

Thermal Analysis is useful in the investigation of solid-state interactions. It is also useful in the detection of eutectics.

Thermograms are generated for pure components and their physical mixtures with other components.

In the absence of any interaction, the thermograms of mixtures show patterns corresponding to those of the individual components.

In the event that interaction occurs, this is indicated in the thermogram of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components.

Diffuse Reflectance Spectroscopy:

Diffuse reflectance spectroscopy is gaining increasing popularity among preformulation scientists as a tool to detect and monitor drug-excipient interactions.

In this technique solid drugs, excipients, and their physical mixtures are exposed to incident radiation. A portion of the incident radiation is partly absorbed and partly reflected in a diffuse manner.

The diffuse reflectance depends on the packing density of the solid, its particle size, and its crystal form, among other factors. When these factors are adequately controlled, diffuse reflectance spectroscopy can be used to investigate physical and chemical changes occurring on solid surfaces. A shift in the diffuse reflectance spectrum of the drug due to the presence of the excipient indicates physical adsorption, whereas the appearance of a new peak indicates chemisorption or formation of a degradation product.

Stability of new drug and product

| General Case of Drug Substances | | |
|---------------------------------|--------------------------|-----------------------------------|
| Study | Storage condition | Minimum time period at submission |
| Long term | 25°C ± 2°C/60% RH ± 5%RH | 12 months |
| Intermediate | 30°C ± 2°C/% 60RH ± 5%RH | 06 months |
| Accelerated | 40°C ± 2°C/% 75RH ± 5%RH | 06 months |

| Drug Substances Intended for Storage in Refrigerator | | |
|--|--------------------------|-----------------------------------|
| Study | Storage condition | Minimum time period at submission |
| Long term | 5°C ± 3°C | 12 months |
| Accelerated | 25°C ± 2°C/60% RH ± 5%RH | 06 months |

Stability of new drug and product

| Drug Substances Intended for Storage in Freezer | | |
|---|-------------------|-------------------------------|
| Study | Storage condition | Min time period at submission |
| Long term | -20°C ± 5°C | 12 months |

| General Case for Drug Product | | |
|-------------------------------|--------------------------|-----------------------------------|
| Study | Storage condition | Minimum time period at submission |
| Long term | 25°C ± 2°C/60% RH ± 5%RH | 12 months |
| Intermediate | 30°C ± 2°C/% 60RH ± 5%RH | 06 months |
| Accelerated | 40°C ± 2°C/% 75RH ± 5%RH | 06 months |

