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# Dosage Form Design

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## Preformulation studies

- Preformulation is branch of Pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance.
- A phase in drug development in which a number of fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined.
- provide the type of information needed to define the nature of the drug substance.
- This information dictates many of the subsequent events and approaches in formulation development.

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## Introduction

- Investigation of physico-chemical properties of the new drug compound that could affect drug performance and development of an efficacious dosage form
- Preformulation commences when a newly synthesized drug shows a sufficient pharmacologic promise in animal model to warrant evaluation in man.
- The preformulation is the first step in the rational development of a dosage form of a drug substance alone and when combined with excipients.

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## Goals of Preformulation

- To establish the necessary physicochemical parameters of new drug substances.
- To determine kinetic rate profile.
- To establish compatibility with common excipients.
- To generate useful information to the formulator to design an optimum drug delivery system.

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# Pre-formulation studies

- Physical description
- Microscopic examination
- Heat of Vaporization
- Melting point depression
- The phase rule
- Particle size
- Polymorphism
- Solubility
- Dissolution
- Membrane permeability
- Partition coefficient
- Pka/dissociation constants

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**Table 1.3** Molecular sample properties and the assays used to determine them.

| Property | Assay | Requirement of sample |
|---|---|---|
| Solubility[a]<br>• Aqueous<br>• Nonaqueous | UV | Chromophore |
| p$K_a$ | UV or potentiometric titration | Acid or basic group |
| $P_{o,w}$/log $P$ | UV<br>TLC<br>HPLC | Chromophore |
| Hygroscopicity | DVS<br>TGA | No particular requirement |
| Stability<br>• Hydrolysis<br>• Photolysis<br>• Oxidation | HPLC, plus suitable storage conditions | No particular requirement |

[a]Solubility will depend on physical form.

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**Table 1.4** Macroscopic (bulk) sample properties and the techniques used to determine them.

| Derived property | Technique |
|---|---|
| Melting point | DSC or melting point apparatus |
| Enthalpy of fusion (and so ideal solubility) | DSC |
| Physical forms (polymorphs, pseudopolymorphs or amorphous) | DSC, XRPD, microscopy |
| Particle shape<br>• Size distribution<br>• Morphology<br>• Rugosity<br>• Habit | Microscopy<br>Particle sizing<br>BET (surface area) |
| Density<br>• Bulk<br>• Tapped<br>• True | Tapping densitometer |
| Flow | Angle of repose |
| Compressibility | Carr's index<br>Hausner ratio |
| Excipient compatibility | HPLC, DSC |

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# Physical description

- Most drug substances in use today are solid materials, pure chemical compounds of either crystalline or amorphous constitution.

- Drugs mainly used as solids, less frequently liquids, and rarely used as gases.

*Problems with liquid drugs*

***Volatile liquids***

- must be physically sealed from the atmosphere to prevent evaporation loss.

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# Physical description

- Amyl nitrite inhalant drug used for:
  - Heart diseases such as angina.
  - Euphoric effect for depression.
  - Cyanide antidote

- Amyl nitrite
  - Clear yellowish liquid
  - Volatile even at low temperatures
  - Highly flammable.


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# Physical description

- It is kept for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material.

- For administration, glass is broken between the fingertips, and the liquid wets the gauze, producing vapors that are inhaled by the patient.


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# Physical description

- Propylhexedrine: Volatile liquid
  - is a stimulant drug used mainly to provide temporary symptomatic relief of nasal congestion due to colds, allergies and allergic rhinitis.
  - A cylindrical roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in plastic, sealed nasal inhaler.


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# Physical description

*The other problem is:*

*Liquids – Oral administration as solids*

- Can not be formulated as tablets

- Exception: Nitroglycerine
  - Sublingual tablets
  - Volatile, should be tightly sealed.

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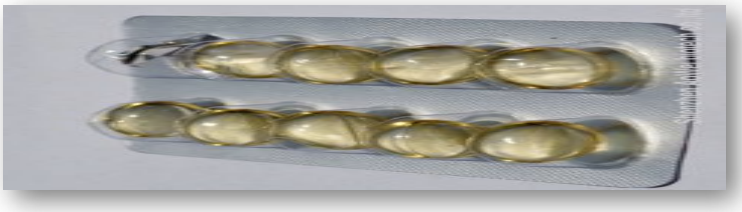
# Physical description

- Examples on drugs formulated as soft gelatin capsules:
  - Vitamins A, D, and E, cyclosporin (Neoral, Sandimmune).



- Liquid drug may be developed into a solid ester or salt form that will be suitable for tablets or drug capsules.
  - Examples: Scopolamine hydrobromide is a solid salt of the liquid drug scopolamine and is easily pressed into tablets.

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# Physical description

- Another approach is:
  - mixing the drug with a solid or melted semisolid material, such as a high–molecular-weight polyethylene glycol.
  - The melted mixture is poured into hard gelatine capsules to harden and the capsules sealed.
- Liquid drugs taken in large doses are better to be used as liquids
  - 15-mL doses of mineral oil may be administered conveniently as such.
  - For **topical** use, liquid drugs may be favored on solids.

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# Physical description

- Many new drugs reach the market as solids rather than liquids
  - Formulation and **stability difficulties** arise less frequently with solid dosage forms than with liquid preparations.
  - Drs and patients alike **prefer** small, tasteless, accurately dosed tablets or capsules to the analogous liquid forms.
  - Therefore, **marketing** a drug in solid form first is more practical for the manufacturer and suits most patients.
  - It is estimated that tablets and capsules constitute the dosage form dispensed **70%** of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

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## ORGANOLEPTIC PROPERTIES

| COLOR | ODOUR | TASTE |
|---|---|---|
| OFF-WHITE | PUNGENT | ACIDIC, sour |
| CREAM-YELLOW | SULFUROUS | BITTER |
| SHINY | FRUITY | SWEET or Salt |
| | AROMATIC | Ummami. |
| | ODOURLESS | TASTELESS |