PRE - FORMULATION

Challenges in Drug discovery and development

→ slow: taking a compound or molecule from early research to approved product takes over 10 years.

→ inflexible: Drug development process is also very rigid and highly regulated by FDA, EMA etc

→ Linear: Drug R and D is conducted in a stepwise manner

→ Expensive: companies spend well over ~~$$~~ $1 billion dollars to bring an approved drug to market

→ Siloed: R and D process is highly fragmented

What is formulation

↳ a mixture containing a therapeutic compound that can be safely and reproducibly administered to humans or animals

- includes the therapeutic compound in a specific form (e.g. crystalline form or salt) - drug substance API
- contains excipients (e.g. binders or solutions)
- drug substance + excipients = drug product ☆
- Must be safely, consistenly and reproducibly delivered to humans.

☆ Examples of Formulations ☆

Pills | Inhalers | Injectable | lotions

and etc!

Pre formulation Activities

(Must address needs for Preclinical & Phase I clinical trials)

Lead optimisation ⇒ **Pre clinical Studies** ⇒ **Phase I**

Lead characterisation from a formulation and/or manufacturing view and align with patient needs

defines best possible formulation to support pre-clinical studies

define best possible formulation to support clinical testing & establish safety and efficacy

Physicochemical properties?

- They are Physical and chemical properties of a substance

→ molecular weight, melting point, density, solubility, lipophilicity and ionisation

Solubility

↳ amount of drug dissolved in a vol of fluid
↳ measured in various media
↳ can affect absorption, purification etc.

lipophilicity – molecules tendency to dissolve in fats

Lipophilic molecules have poor aqueous solubility

- quantified as log P (higher log P = high lipophilicity)

Ionisation - describes a degree to which a drug is charged or neutral

basic drugs charged in a medium with low PH	neutral drugs charged in a high PH

acidic drugs opposite of basic drugs

Routes of administration - the manner in which a drug is administered to a patient

The route is selected primarily due to 4 factors:

→ physicochemical properties
→ drug's site of action in the body
→ rate and extent of absorption of the drug by the route
→ patient adherence and acceptance

Common routes of administration

Oral | Inhalation | local | Nasal | ocular

Pre-formulation & route of administration

→ The physicochemical properties must align with the selected route of administration
→ Drug absorption by the route of administration must achieve efficacy
→ Drug formulation must be stable
→ Formulation must be acceptable to the patient

Drug product: Delivery of medicine

~~Inject~~

Injection | topical application | Surgical implantation | Ingestion

steps of drug product development

1. Define the drug
2. Understand the target and target location
3. Establish dosing levels for efficacy and safety studies
4. Define the physicochemical properties
5. Design a pre-formulation strategy
6. Develop a formulation with excipients
7. Manufacture the formulation (scaling up production etc)

Types of Drug Product

~~Pre-formulation testing~~

Pre-formulation testing (animals)

Suspension (salts, free form)
Solution ~~(~~ (aqueous, organic)
Creams
~~Creams~~

Pre-formulation testing (humans)

solids (tablets, capsules, Lipids etc)
Solution (ocular)
Suspension (Pediatrics)

Biopharmaceutics Classification System (BCS)

→ class 1 : high solubility & permeability

→ class 2 : low solubility , high permeability

→ class 3 : high solubility , low permeability

→ class 4 : low solubility & permeability

Dissolution and the BCS

- Drug dissolution is the rate at which drug formulation dissolves in aqueous media at
  - → PH 1, stomach that is fasted
  - → PH 4.7, stomach that is fed
  - → PH 6.8, intestine

Extra

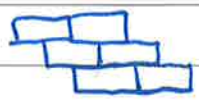
Additional classification systems

1) BCS , 2) DCS , 3) ECCS , 4) BDDCS

Crystals: Neutral drugs and drug salts

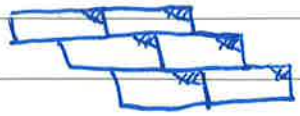
crystalline form may affect properties ranging from solubility to hydroscopicity and ease of physical handling.

Crystals: solvates and Cocrystals



crystal lattice

~~Crystal~~ lattice with gaps



lattice with filled gaps

= solvent / other molecule (cocrystal)

Different patterns of ~~eg~~ crystal lattice ~~are~~ are called Polymorphs (may not be stable)

stability of drug substance
- ↳ within the human body
- ↳ during storage & testing

~~stability~~

Stability in the Human body

hydrolysis | pH | enzymes | light | temperature

More drug substance stability factors

- light
- temperature
- surface pH
- air (humidity & oxygen)
- stereochemistry

Stability of the drug product

- Production · packaging and storage · transport

Production, packaging and storage

↳ excipient interactions (hydrolysis ...)

↳ manufacturing process and packaging (mixing, mechanical agitation etc)

↳ storage (light, heat, humidity)

Stability during Transit

- chemical drugs
  - generally more stable
  - tablets, cream, drops etc
- biological drugs
  - limited shelf-life
  - peptides, ~~anti~~ antibodies etc
  - transported via "cold-chain"

Drug impurity - Any component of a drug substance that is not the chemical entity defined

- Any component of a drug product that ~~do~~ is not in the formulation ingredient
- Organic or inorganic, volatile or non-volatile, identified or not identified

Accounting for impurities

reported if ≥ 0.05%.

identified if ≥ 0.10% (requires structural determination)

qualified if ≥ 0.15% (requires safety testing of impurity)

Aspects Phase I clinical trials

- Drug safety
- & usually in healthy volunteers
- evaluate drug at a range of doses
- Possibly efficacy info (& for oncology trials)

Goals of clinical formulation

→ To understand disease and patient population GI.R.A.S
→ To identify ideal route of administration
→ To determine amount of drug required
→ To design a formulation with consistent drug exposure

Risks of Phase I study

- drug - food interaction
- palatability
- drug loading
- dosing frequency
- cost
- stability

Small molecule drugs vs biologics

Small molecule drugs → polymorphism, physical form

biologics → stability, excipient compatibility, drug loading, sterilisation

Sterility : A key challenge for biologics per pre-formulation

↳ Manufacture of the biologic
↳ formulation of the biologic
↳ packaging of the biologic

Common effects of excipients

- enhance stability
- improve solubility
- reduce aggregation
- control formulation pH
- act as preservations
- prevent microbial growth