Biopharmaceutics Considerations in Drug Product Design

Introduction

- The active drug should be adequately delivered at proper rate to the targeted receptor site in order to achieve the desired therapeutic effect.
  - The drug must traverse the required biological membrane barriers, escape widespread distribution to unwanted areas, endure metabolic attack, and cause an alteration of cellular function.

- Finished dosage form should show the highest bioavailability with minor or no adverse effects.

BIOPHARMACEUTICS CONSIDERATIONS IN DRUG PRODUCT DESIGN

1. **Pharmacodynamics consideration**
    - Therapeutic objective
    - Toxic effects
    - Adverse effect
2. **Drug considerations**
    - Particle size
    - pKa & pH profile
    - Polymorphism
    - Hygroscopicity
    - Partition coefficient
    - Excipient interaction
    - pH stability profile
    - Solubility

BIOPHARMACEUTICS CONSIDERATIONS IN DRUG PRODUCT DESIGN

3. **Drug product considerations**
   - Pharmacokinetics of drug
   - Bioavailability consideration
   - Route of administration
   - Desired dose of drug
   - Dosing frequency
4. **Patient considerations**
   - Acceptability & Compliance of drug product
   - Cost
5. **Manufacturing considerations**
   - Cost
   - Availability of raw materials
   - Stability
   - QC

PHARMACODYNAMIC CONSIDERATIONS

- Evaluation of **the drug effect in the body** and its **mechanism of action**

- **Therapeutic considerations** include **desired pharmacodynamics** and **pharmacologic properties of the drug**, including the desired therapeutic response and the type and frequency of adverse reactions to the drug.

- **Therapeutic objective** influences the design of the drug product, route of drug administration, dose, dosage regimen, and manufacturing process.

- Eg:
  - An oral drug used in the treatment of an acute condition is generally formulated in order to achieve rapid release of the drug and to show rapid onset of action. If more rapid drug absorption is desired, then an injectable drug formulation might be formulated.

PHARMACODYNAMIC CONSIDERATIONS

- E.g.
  - In the case of nitroglycerin, which is highly metabolized if swallowed, a sublingual tablet formulation allows for rapid absorption of the drug from the buccal area of the mouth for the treatment of angina pectoris.

- In order to reduce unwanted systemic side effects, locally drugs such as inhaled drugs have been developed.

- **Advantage**
  - Possible to deliver the drug directly into the lungs,
  - Reducing the amount needed to reach a therapeutic effect at the locality of action
  - Reducing systemic adverse effects resulting in an improved risk of unwanted secondary effects.

PHARMACODYNAMIC CONSIDERATIONS

- Certain diseases such as hypertension, chronic pain, etc are preferably treated by a sustained- or extended-release dosage form.

- The extended-release dosage form releases the drug slowly, thereby controlling the rate of drug absorption and allowing for more constant plasma drug concentrations.

- The main advantage of extended release dosage form is that it releases the drug in a controlled fashion which eventually controls the rate of drug absorption and thus exhibits very uniform plasma drug concentration.

- However, in some situations, both immediate- and extended-release dosage form are required where both rapid onset of action followed with a sustained release of the drug could achieve.
  - E.g. zolpidem tartrate extended-release tablets.

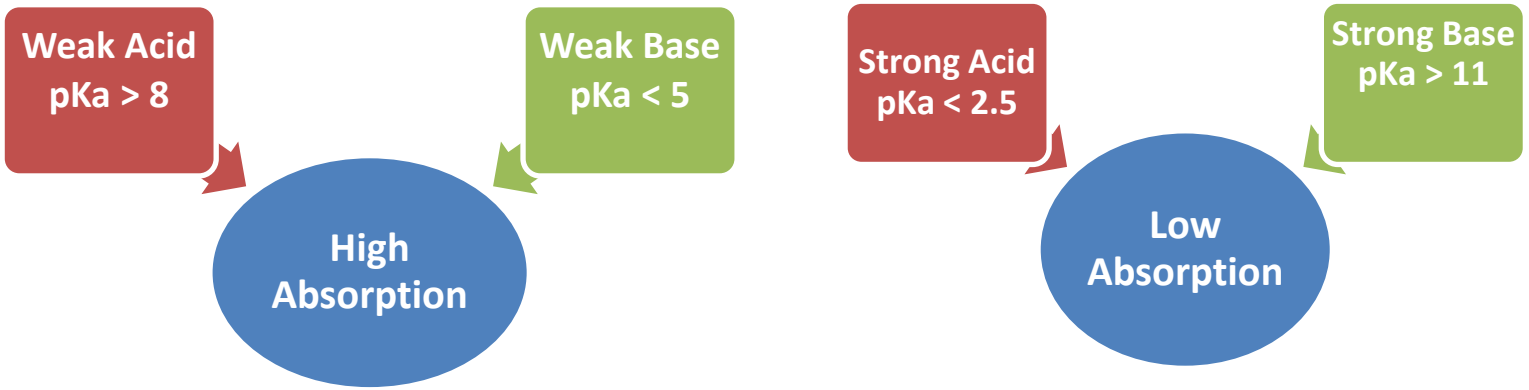
Drug Consideration

Table 1: Physicochemical properties of drug that considered in drug product design

pK_a and pH profile	Necessary for optimum stability and solubility of the final product.
Particle size	May affect the solubility of the drug and therefore the dissolution rate of the product.
Polymorphism	The ability of a drug to exist in various crystal forms may change the solubility of the drug. Also, the stability of each form is important, because polymorphs may convert from one form to another.
Hygroscopicity	Moisture absorption may affect the physical structure as well as stability of the product.
Partition coefficient	May give some indication of the relative affinity of the drug for oil and water. A drug that has high affinity for oil may have poor release and dissolution from the drug product.
Excipient interaction	The compatibility of the excipients with the drug and sometimes trace elements in excipients may affect the stability of the product. It is important to have specifications of all raw materials.
pH stability profile	The stability of solutions is often affected by the pH of the vehicle; furthermore, because the pH in the stomach and gut is different, knowledge of the stability profile would help to avoid or prevent degradation of the product

Drug Consideration

- **pKa & pH profile**



❖ **EXCIPIENT INTERACTIONS**

✓ Should be pharmacodynamically inert

✓ However, it may change the stability of drug substance and BA of drug from the dosage form

✓ Affect the dissolution kinetics of the drug, either by altering the medium in which the drug is dissolving or by reacting with the drug itself

✓ Chemical instability / chemical interactions with certain excipients will also affect the type of drug product and its method of fabrication.

Drug Consideration

❖ POLYMORPHISM

- ✓ Polymorph - lower aqueous solubility than the amorphous forms, cause product - incompletely absorbed.
- ✓ Amorphous drug (non-crystalline form) - dissolves more rapidly/highest apparent solubility or dissolution rate - high free energy compared to the crystalline
- ✓ Amorphous solid dispersion (ASD) - technologies for improving BA of poorly water soluble compounds.
- ✓ Change in crystal form - cause problems in manufacturing the product.

E.g. change in the crystal structure of the drug - cause cracking in a tablet, problem in tablet compression

The order for dissolution of different solid dosage forms drugs;

Amorphous > Meta-stable > stable

Drug Consideration

❖ SOLUBILITY-PH PROFILE

- ✓ Gives rough estimation of the completeness of dissolution for a dose of a drug in stomach /small intestine
- ✓ Basic drug is more soluble in an acidic medium, forming a soluble salt.
- ✓ Acid drug is more soluble in the intestine, forming a soluble salt at the more alkaline pH.
- ✓ Acidic and alkaline pH influence the rate of decomposition of most drugs.
- ✓ Solubility may be improved with the addition of an acidic or basic excipient.

❖ STABILITY-PH PROFILE

- ✓ Many drugs are stable between pH 4 and 8
- ✓ Some drug - has pH-dependent stability profile

e.g. In acidic medium, erythromycin decomposition occurs rapidly, whereas in neutral/alkaline, the drug is relatively stable.

Drug Consideration

❖ PARTICLE SIZE

✓ Reduction in the particle size results in a number of advantages:

a) Enhance the surface area effectively.
b) Increase in the total surface area of the particles
c) Once the surface area of the particle enhances, it increases the penetration of water into the particles and eventually increases drug dissolution rate.

SMALLER PARTICLE SIZE -- GREATER SURFACE AREA -- HIGHER DISSOLUTION RATE – BETTER ABSORPTION

❖Pharmacokinetics of Drug

Table 2: Pharmacokinetics of drug and its factors which considered in drug product design

Process	Definition	Factors
Absorption	Transfer drug from its site of administration to the bloodstream. The rate and extent of absorption mainly depends on administration route, the formulation of the drug and chemical entity of the drug.	1. Patient-specific factors 2. Contact time with epithelial lining of the GI tract
Distribution	The absorbed drug get dispersed or distributed into the systemic circulation throughout the body. However, this is a reversible process which depicted that some drug entity binds to the receptors, while others get released from the receptor and taken up back again by the blood stream.	1. Affinity of drugs 2. Body composition; cardiac decompensation 3. Age 4. Volume of distribution- to determine appropriate dose of drug
Metabolism	The distributed drug are then undergo few biochemical changes before excretion. This changes takes place in the liver or other tissues to allow excretion.	1. Group population; generic 2. Age 3. Drug interactions 4. Diet
Excretion	Complete removal of drug from the body is a very crucial part which generally occur through the kidneys. The main and important passage of drug removal is through urination.	1. Condition of liver and kidney functions 2. Drug interactions; multiple drugs competition for metabolic process reduces drug removal

Drug Products Consideration

❖ Bioavailability consideration

- ✓ Rate: The amount or rate of drug absorption from the given dosage form.
- ✓ Duration: how long does the drug present into the blood stream
- ✓ Due to poor bioavailability of some drugs, alternative route of drug administration or higher dose may be needed.

❖ Desired dose of drug

- ✓ Optimal dosage that gives desired effect with minimum side effects
- ✓ The potency of the drug, determines the plasma concentration of the drug required for the desired therapeutic effect
- ✓ The desired final drug size manufactured is determined by main two factors: the dose of the drug and the excipients.

Drug Products Consideration

- **Dosing frequency**
- ✓ Empirical approach - involves certain quantity of drug and therapeutic response
- ✓ Kinetic approach - therapeutic & toxic effects on drug related to amount of drug in body / plasma concentration of drug at the receptor site
- ✓ Drug clearance and drug concentration of plasma.
- ✓ Pharmacokinetic evaluation - determine the levels of drug attained from multiple dosing estimation
- ✓ If the drug has a short half-life which means high clearance from the body, then the duration of action of the drug will become shorter and hence the frequency of drug administration must be increased.

- ✓ Factors
  - Inherent activity-toxicity
  - Pharmacokinetic of drug
  - Clinical factors: patient s' condition and management of therapy
  - Tolerance-dependence
  - Pharmacogenetics-idiosyncrasy
  - Drug interactions

Drug Products Consideration

❖Route of administration

- ✓ Bioavailability of drug: Route of drug administration greatly effect the bioavailability of the drug which eventually can affects the duration of the pharmacologic effect
- ✓ Design: the design of a drug must taken into careful consideration to achieve intended pharmacologic effect
- ✓ Types: Systemic or local effects.
- ✓ Local effects – application of the drug directly on the site of action (e.g. eyes, nose, or skin)
- ✓ Systemic effects – administration of the drug into the systemic circulation and its subsequent action on the specific desired site (oral, rectal, parenteral, topical), implant, transdermal patch)

Drug Products Consideration

Table 3: Variation in time of onset action differs for each dosage forms. (Ch. Taraka ramarao et al, 2016)

Dosage forms	Onset actions
I.V injections	Seconds
I.M and S.C injections, Buccal, Aerosols	Minutes
Solutions, suspensions, powders, capsules, granules, tablets, modified release	Minutes-hours
Enteric coated formulations	Several hours
Depot injections, implants	Days to weeks
Topical preparations	Varies

Patient Considerations

- ✓ Must be acceptable to the patient
- ✓ Cost of products
- ✓ Age, urine pH, condition being treated, existence of other disease states, patients' background
- ✓ Poor patient compliance may result from poor product attributes, such as
  - Swallowing difficulty
  - Unacceptable odour
  - Bad medicine taste
  - Dosing frequency /unusual dosage requirements
  - Side effects /allergic reaction

Manufacturing Consideration

- ✓ Product quality and performance
- ✓ Quality control important components for drug product manufacturing – dissolution & drug release tests
- ✓ Stability – long term stability of drug product – critical attribute of overall product quality
- ✓ Lower cost
- ✓ Availability of raw materials

For Read Only

Post Approval Changes

POST-APPROVAL CHANGES

- Post approval changes means **changes required in the drug after it has been approved for marketing** by the **FDA.**
- May impact drug product quality
- The reasons for changes in a marketed drug product:
  - A revised market fore-cast
  - Change in an API source or excipients
  - Manufacturing process optimization
  - to make changes or upgrade in the packaging

- if any change required in the container closure/system (little impact on oral tablet dosage)
- primary packaging component

POST-APPROVAL CHANGES

- Pharmaceutical manufacturer should take a precaution in evaluating drug formulation and should pay attention to the following changes of the approved drug product:
  1. Identity of the drug
  2. Strength of the drug should monitor carefully like content uniformity
  3. Quality of the drug like physical, chemical, and biological properties
  4. Drug should be pure and free from any kind of impurities and degrading components potency (biological activity, bioavailability, bioequivalence)
  5. The potency of the drug in terms of its bioavailability and bioequivalence.

  – Several guidelines has been published by FDA including Changes to an Approved NDA for the pharmaceutical companies.

POST-APPROVAL CHANGES

- Following issues has been addressed by the ANDA guidance:
  1. Components and composition of the drug product
  2. Manufacturing site change
  3. Scale-up of drug product
  4. Manufacturing equipment and process
  5. Packaging
  6. Active pharmaceutical ingredient
- The **levels of change** as described by the FDA :
  - **Level 1**: Changes that are unlikely to have any detectable impact on the formulation quality and performance.
  - **Level 2**: Changes that could have a significant impact on formulation quality and performance
  - **Level 3**: Changes that are likely to have a significant impact on formulation quality and performance.

Assessment of the Effects of the Change

- Should include a determination that the drug substance intermediates, drug substance, in-process materials, and drug product affected by the change follow to the approved specifications.
- The evaluation may include of any changes in the chemical, physical, microbiological, biological, bioavailability, or stability profiles.
- Additional assessment - may involve testing of the post-change drug product or the component directly affected by the change.

Assessment of the Effects of the Change

- **Examples of additional** tests are as follows:
  - Impurity or degradation profile evaluation
  - Tests on toxicology
  - Tablet hardness or friability evaluation
  - Bioequivalence evaluation
  - Moisture permeability evaluation (new container closure system)

Equivalence

- Purity and strength (potency) of the drug can be affected by the manufacturing changes, thereby to check if the test results are equivalent, the final drug product measured by comparing test results from *pre*- and *post-change* materials.

- The final drug product after changes should be equivalent to the product used prior to the change.

- Equivalence does not always mean identical, however, it does basically means to keep the quality and stability characteristics.

CRITICAL MANUFACTURING VARIABLES

- Factors that can affect *in vitro* dissolution are: formulation products, processing, equipment's, materials and methods for the drug product used.

- If there is any relationship between CMV, *in vitro* dissolution, and *in vivo* bioavailability, that should be efficiently determined by the manufacturer.

- To obtain this relationship, bioavailability of the test products should be compared to the bioavailability of the marketed drug product with slowest and fastest dissolution characteristics.

- The establishment of dissolution specifications for the drug product should be made so that the production of the marketed drug product in future do not fall outside the bioequivalence of the marketed drug product.

Adverse Effect

- A change in process may cause a degradation that need to be quantified carefully.

- If any degradation occur during the process, the new degradant should not affect the safety or efficacy of the product and the manufacturer must confirm.

- Qualitative or quantitative changes in the formulation may significantly pose an impact on the quality and performance of the formulation.

- On the other hand, minor changes will be considered if intended to affect only the colour of a product by the removal or reduction any ingredient, that is unlikely show any harmful affect on the drug safety.

Post Approval Changes of Drug Substance

- *Active pharmaceutical ingredient* (API) changes in the manufacturing may likely to change its quality attributes which includes:

- Chemical purity: it is dependent on the synthetic pathway and purification process.

- Solid-state properties: it includes particle size, polymorphism, and solubility. API bulk density and tablet hardness may get affected by the change in particle size. Whereas, API solubility and stability may affected by different polymorphs.

Practical Focus

- **Quantitative Change in Excipients**

❖ For immediate-release drug products, minor changes in some excipients are allowed by FDA

❖ Less than or equal to the following percent ranges stated are considered Level 1 changes.

❖ The total additive effect of all excipient changes should not be more than 5%.

❖ In an immediate-release drug product, even a small change in the excipients amount will affect the bioavailability of a drug.

- **Changes in Batch Size (Scale-Up/Scale-Down)**

❖ According to FDA, if a change in batch size greater than tenfold is considered as a Level 2 change.

❖ All testing of scale-up/scale-down documentation should be notify to the FDA by the manufacturer before marketing the product.

Excipient	Percent Excipient (W/W) of Total Target Dosage Form Weight
Filler	±5
Disintegrant	±3
Starch	±1
Other	
Binder	±0.5
Lubricant	±0.25
Calcium stearate	±0.25
Magnesium stearate	±1
Other	
Glidant	±1
Talc	±0.1
Other	
Film coat	±1

Table 4: Level 1—Allowable Changes in Excipients
These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency.

Product Quality Problems

❖ Manufacturing of all approved drug products must be done according to current Good Manufacturing Practices (GMP).

❖ Complexity of synthesis and manufacturing generally increases if the quality of drug substances and drug products are of high quality risk.

❖ Examples of drug products with high quality risk:

- ✓ High quality risk of biotechnology-derived drugs is more compared to chemically synthesized small molecules,
- ✓ Extended-release and delayed-release drug products possess greater quality risk than an immediate-release drug product.

❖ Therefore, to maintain the quality of the final product, GMP and critical manufacturing control operations play an important role.

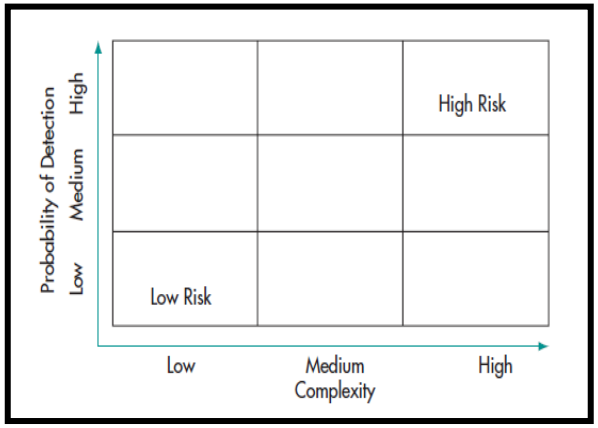


Figure 1: General principles to define low-risk drugs.

Product Quality Problems

- A set of quality attributes and acceptance criteria have been established by FDA and industry for certain less manufacturing risk approved drug substances and products which are given below in the table.

Table 5: Quality Attributes and acceptance criteria for Certain Approved Drug Substances and Products

Drug Substances		Drug Products	
Attribute	**Criteria**	**Attribute**	**Criteria**
Chemical structure	Well characterized	Dosage form	Oral (immediate release), simple solutions, others
Synthetic process	Simple process		
Quality	No toxic impurities; adequate specifications	Manufacturing process Quality	Easy to manufacture (TBD) Adequate specifications
Physical properties	Polymorphic forms, particle size are well controlled	Biopharmaceutic Classification Systems (BCS)	Highly permeable and highly soluble drugs
Stability	Stable drug substance	Stability	Stable drug product (TBD)
Manufacturing history	TBD		
Others	TBD	Manufacturing history	TBD
		Others	TBD

Thank you