UNIT

IV

FACTORS INFLUENCING DRUG ABSORPTION

Dr. Mohini Kalra, Dr. Mukesh Kumar Kumawat

Ch.Id:-ASU/NSP/EB/BAP/2022/Ch-04

DOI: https://doi.org/10.52458/9789391842451.nsp2022.eb.asu.ch-04

INTRODUCTION

There is a great deal of information available on the relationship between drug absorption and physicochemical properties, and there is widespread agreement that passive diffusion absorption is largely governed by factors such as molecular size and shape, degree of ionisation, and solubility. It follows, then, that changes in a given agent's physicochemical state are more likely to affect its absorption if absorption is primarily a passive process. Only when a drug is administered as a solid and has a rate of dissolution slower than its rate of absorption can changes in the physicochemical state of an agent affect its absorption independent of the transport mode employed. Although modifications in drug properties have been the most effective and exploitable means of influencing drug absorption, only a few of the these changes have an effect on an agent's absorption once it is in solution. Pharmaceutical chemists have altered absorption in a variety of ways by altering the chemical form or formulation of a drug.

The percentage of the drug liberated from the dosage form administered that becomes available in the body for biological effect is known as bioavailability, or biological availability. Bioavailability can differ significantly across different formulations of the same drug, and variation might even occur between batches due to variations in manufacturing procedures. The onset, intensity, and duration of pharmacological response, the incidence and severity of side effects, and the stability of active substances can all be significantly influenced by the procedures used to formulate drugs into various dosage forms. Official pharmacopoeias and other compendia have yet to implement tests that ensure optimal physiological availability of a drug from its pharmaceutical formulations.

FACTORS INFLUENCING DRUG ABSORPTION FROM DOSAGE FORM

Pharmaceutical Factors

Pharmaceutical considerations include dosage form parameters and pharmaceutical components, as well as physicochemical properties of the drug.

ISBN- 978-93-91842-45-1

a) Drug Substance Physicochemical Properties

1. Drug solubility and rate of dissolution
2. Effective surface area and particle size
3. Amorphism and polymorphism
4. Hydrates/solvates pseudo polymorphism
5. The drug's salt form
6. The drug's lipophilicity
7. The drug's pKa and the pH of the gastrointestinal tract
8. Stability of drugs
9. The drug's stereo chemical nature

b) Pharmaceutical Ingredients and Dosage Form Characteristics (Pharmaco-technical Factors)

1. Tablet/capsule disintegration time
2. Manufacturing factors
3. Dissolution time
4. Ingredients in pharmaceuticals (excipients/adjuvants)
5. Dosage form kind and nature
6. Product age and conditions of storage

Physicochemical Properties of Drug Substances

i. Drug solubility and dissolution rate

Following the breakdown and deaggregation of a dosage form, the absorption of orally administered medications is determined by two essential slower rate-determining processes:

- **Dissolution rate-** Limited absorption is typically used to describe the absorption of hydrophobic, poorly water soluble medicines such griseofulvin and spironolactone.

- In the case of hydrophilic drugs like cromolyn sodium or neomycin, the rate of drug absorption across the biomembrane. In other words, such medications' absorption is constrained by **permeation rate**.
- **Effective surface area and particle size-** These characteristics are inversely proportional, i.e., the smaller the drug particle, the larger the surface area. There are two types of surface areas of interest: i. Absolute surface area is the total area of a particle's solid surface, and ii. Effective surface area is the area of a particle's solid surface exposed to the dissolving medium, and it is related to the dissolution rate.

ii. Amorphism and Polymorphism

Depending on its internal structure, a solid might have a crystalline or amorphous shape. The many crystalline forms of a substance are known as polymorphs, and the phenomenon is known as polymorphism.

The metastable forms are preferred in formulations because they have higher aqueous solubility and bioavailability than the STABLE forms—for example, of the three polymorphic forms of chloramphenicol palmitate (A, B, and C), the B form has the best availability and the A form is biologically inactive.

The crystalline form of novobiocin is 10 times more water soluble than the amorphous form. The order in which different solid forms of medicines dissolve is —

Amorphous > Metastable > Stable

iii. Hydrates/Solvates (Pseudopolymorphism)

A medication's anhydrous form is usually more water soluble than its hydrates form. The anhydrous forms of theophylline and ampicillin have higher water solubilities, dissolve faster, and have better bioavailability than their monohydrate and trihydrate counterparts.

Organic (nonaqueous) solvates, on the other hand, are more water-soluble than non-solvates—for example, griseofulvin's chloroform solvate is more water-soluble than its non-solvated forms.

ISBN- 978-93-91842-45-1

iv. Salt Form of the Drug

Weak acids or bases make up the bulk of pharmaceuticals. One of the simplest ways to improve the solubility and dissolving rate of such drugs is to convert them to salt forms. Weakly acidic drugs are frequently used to make a strong base salt, such as the sodium and potassium salts of barbiturates and sulphonamides. In the case of weakly basic medicines, a strong acid salt is formed, similar to the hydrochloride or sulphate salts of certain alkaloidal pharmaceuticals.

v. Drug pKa and Lipophilicity and GI pH—pH Partition Hypothesis

According to the theory, the process of absorption for drug compounds with molecular weights larger than 100 that are largely transported across the biomembrane via passive diffusion is determined by:

- The drug's dissociation constant (pKa).
- The unionised medication's lipid solubility (a function of drug Ko/w).
- The pH of the absorption area.
- Stability of the drug

A medicine for oral administration may cause instability in the GIT or near the end of its shelf life. Two significant stability issues in the GIT that result in low bioavailability are:

1. Drug degradation into inactive form, and
2. Interaction with one or more other component(s) from the dosage form or from the GIT to form a complex that is poorly soluble or unabsorbable.

vi. Drug's Stereochemical Nature

The majority of medications are available in chiral form and are sold as a racemic combination. Despite large variances in spatial layout, enantiomers have similar physical and chemical properties. Biological mechanisms such as protein binding, on the other hand, can be stereoselective and affect drug absorption.

DOSAGE FORM CHARACTERISTICS AND PHARMACEUTICAL INGREDIENTS

1. Disintegration Time

Disintegration time (DT) is particularly significant for solid dosage forms like tablets and capsules. The therapeutic effectiveness of a solid dose form is thus dependent on rapid breakdown. The DT of a tablet is directly proportional to the amount of binder present and the compression force (hardness) of the tablet. Using disintegrants in the right amounts throughout the formulation process can help speed up the disintegration process.

2. Dissolution Time

Because fine particles dissolve faster than granules, after a solid dosage form is disintegrated into granules, the granules must deaggregate into fine particles.

3. Manufacturing/Processing Variables

Drug dispersion from solid dosage forms is influenced by the following production processes:

a) Method of granulation

b) Compression force

c) Intensity of Packing of Capsule Contents

d) Pharmaceutical Ingredients/Excipients (Formulation factors)

Excipients are non-drug substances in a formulation. Excipients are employed in drugs to provide acceptability, physicochemical stability over time, composition and dosage homogeneity, and optimal bioavailability and functionality.

a) Vehicle

b) Diluting agents (Fillers)

c) Granulating and binding agents

d) Disintegrants

ISBN- 978-93-91842-45-1

e) Antifrictional/lubricant agents

f) Coatings

g) Suspending/Viscosity Imparting Agents

h) Surfactants

i) Buffers

j) Dosage Form Nature and Type

The correct dose type is also important for enhanced absorption and bioavailability. The oral bioavailability of a medicine might vary by 2 to 5 times or more depending on the nature and kind of dose form. Such a discrepancy is caused by the relative rate at which a certain dose form releases the drug into the biological fluids. The more rate-limiting phases there are in a dosage form, the higher the likelihood of bioavailability difficulties.

PATIENT RELATED FACTORS AFFECTING DRUG ABSORPTION

The anatomical, physiological, and pathological aspects of the patient are among these factors:

1. Age
2. Gastric emptying time
3. Intestinal transit time
4. Disease states
5. Gastrointestinal pH
6. Blood Flow in the Gastrointestinal Tract
7. GI contents, including other medicines, food, water, and other regular GI contents
8. Luminal enzymes, Gut wall enzymes, Bacterial enzymes, and Hepatic enzymes contribute in pre-systemic metabolism.

1. Age

Newborns have a high stomach pH, as well as a low intestinal surface and blood flow to the GIT, resulting in an abnormal absorption

pattern. Medication absorption is reduced in the elderly due to changes in stomach emptying, lower intestinal surface area and GI blood flow, and a higher incidence of achlorhydria.

2. Gastric Emptying

The process of food/drug content travelling from the stomach to the small intestine is known as gastric emptying. The volume, composition, physical state, viscosity, and temperature of the meal; gastrointestinal pH; body posture; emotional state; activity; disease state, and so on, all influence gastric emptying.

- **Meal volume:** The larger the meal, the longer it takes for the stomach to empty.
- **Meal composition:** Gastric emptying rates for various foods are, predictably, in this order: carbohydrates > proteins > lipids.
- **Physical condition and meal viscosity:** Liquid meals empty in within an hour, whereas solid meals might take up to seven hours.
- **Meal temperature:** The stomach emptying rate is slowed when the temperature of the swallowed fluid is either too hot or too cold (in comparison to body temperature).
- **Gastrointestinal pH:** Gastric emptying is slowed at low stomach pH, but it is hastened at higher or alkaline pH.
- **Posture:** Standing and lying on the right side help to empty the stomach.
- **Emotional state:** Stress and concern increase stomach motility, whereas despair decreases it.
- **Exercise:** Vigorous exercise decreases stomach emptying.
- Gastroenteritis, stomach ulcers, pyloric stenosis, diabetes, and hypothyroidism are among diseases that impede gastric emptying.

3. Transit through the Intestine

Because most medications are absorbed primarily through the small intestine, a long intestinal transit time is ideal for full drug

absorption. Delayed intestinal transit is advantageous for the following reasons:

- For long-acting products or when the dose-to-solubility ratio is large, such as chlorothiazide.
- Medications that only breakdown in the gut (enteric-coated formulations).
- Drugs absorbed at specific locations in the gut (several B vitamins, lithium carbonate, etc.).
- When a medicine, such as acyclovir, enters the intestinal mucosa very slowly.
- When the drug's absorption from the colon is low.

4. Disease Conditions

The rate and extent of drug absorption can be influenced by a variety of diseases. The following are the three major disease states that can affect a drug's bioavailability:

- **Gastrointestinal diseases** such as achlorhydria, celiac disease, and Crohn's disease alter stomach emptying, GI permeability, GI microbiota, and GI pH, affecting drug absorption.
- **Cardiovascular diseases,** such as congestive heart failure, influence drug bioavailability by causing gastrointestinal oedema, decreased blood flow to the GIT, and a slower rate of stomach emptying, as well as changes in GI pH, secretions, and microbial flora.
- **Hepatic diseases:** Disorders like hepatic cirrhosis affect the bioavailability of drugs like propranolol, which undergo a lot of first-pass hepatic metabolism.

5. Blood Flow to the Gastrointestinal Tract

GIT blood flow affects medicines with high penetration rates, such as highly lipid soluble pharmaceuticals or drugs absorbed through holes. Blood flow is especially important for actively absorbed drugs since oxygen and energy are required for delivery.

ISBN- 978-93-91842-45-1

6. Gastrointestinal Contents

The rate and extent of drug absorption can be influenced by type of food, fluid volume, etc.

- **Food-drug interactions:** Food can affect drug absorption by delaying (aspirin, paracetamol), reducing (Penicillins, erythromycin), increasing (griseofulvin, water soluble vitamin), or not (methyldopa).
- **Fluid volume:** Administering erythromycin in a big dose results in improved solubility, faster stomach emptying, and increased absorption.
- **Drug interaction with normal GI constituents:** Mucin, a protective mucopolysaccharide that lines the GI mucosa, inhibits the absorption of streptomycin and certain quaternary ammonium compounds. It also works as a medication diffusion barrier.
- **Drug-drug interactions in the gastrointestinal tract:** Drug interactions in the GI tract could be caused by:
  - ✓ Adsorption: Antidiarrhoeal medications, such as adsorbents, slow or inhibit the absorption of promazine and lincomycin.
  - ✓ Antacids containing heavy metals including aluminium, calcium, iron, and magnesium limit tetracycline absorption.
  - ✓ Anticholinergics such as propantheline inhibit GI motility and enhance the absorption of medications such as ranitidine and digoxin, whilst paracetamol and sulpha-methoxazole are delayed.
  - ✓ Improved GI motility and tetracycline, pivampicillin, and levodopa absorption: Metoclopramide improves GI motility and tetracycline, pivampicillin, and levodopa absorption

7. First-Pass Effects/Presystemic Metabolism

The loss of a drug due to biotransformation by the GIT and liver during its transfer to systemic circulation is referred to as first-pass or presystemic metabolism. The following are the basic pathways that affect a drug's presystemic metabolism:

- **Luminal enzymes** include digestive and bacterial (microflora) enzymes. Digestive enzymes include hydrolases, which hydrolyze ester drugs like chloramphenicol, and peptidases, which inactivate protein/polypeptide pharmaceuticals.
- **Mucosal enzymes gut wall enzymes** - In the stomach mucosa, alcohol dehydrogenase (ADH) inactivates ethanol. The intestinal mucosa contains phase I and phase II (predominant) enzymes, such as sulphation of ethinyloestradiol and isoprenaline.

ISBN- 978-93-91842-45-1