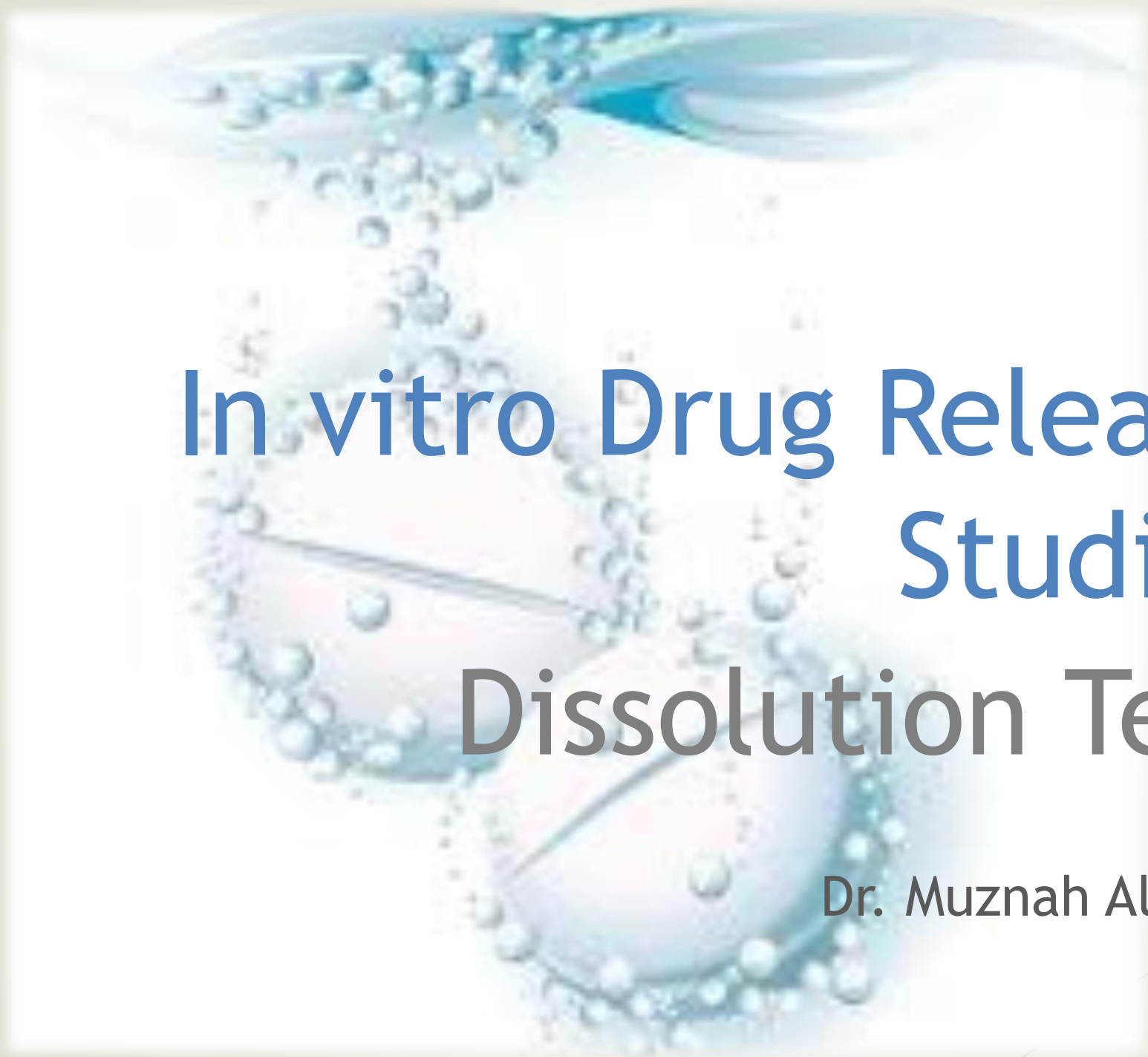

In vitro Drug Release Studies

Dissolution Test

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Pharmaceutic Factors Affecting Drug Bioavailability

- Disintegration
- Dissolution and Solubility

Rate-Limiting Steps in Drug Absorption

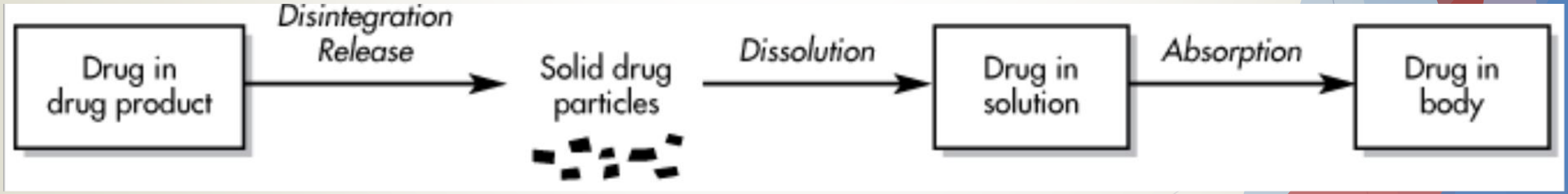
- Systemic drug absorption from a drug product consists of a succession of rate processes
- Include:

(1) disintegration of the drug product and subsequent release of the drug

(2) dissolution of the drug in an aqueous environment

(3) absorption across cell membranes into the systemic circulation.

- In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence. The slowest step in a series of kinetic processes is called the *rate-limiting step.*



- Except for controlled-release products, disintegration of a solid oral drug product is usually more rapid than drug dissolution and drug absorption.
- For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (*dissolution*) is often the slowest step and therefore exerts a rate-limiting effect on drug bioavailability.

Dissolution and Solubility

Dissolution is the process by which a solid drug substance becomes dissolved in a solvent.

Solubility is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature (eg, 1 g of NaCl dissolves in 2.786 mL of water at 25°C).

- Solubility is a static property; whereas dissolution is a dynamic property.
- dissolution tests may be used to predict bioavailability and may be used to discriminate formulation factors that affect drug bioavailability
- is required for all U.S. Food and Drug Administration (FDA)-approved solid oral drug products.

Noyes–Whitney equation

$$\frac{dC}{dt} = \frac{DA}{h}(C_S - C)$$

dC/dt = rate of drug dissolution at time t

D = diffusion rate constant

A = surface area of the particle

C_S = concentration of drug (equal to solubility of drug) in the stagnant layer

C = concentration of drug in the bulk solvent

h = thickness of the stagnant layer.

The rate of dissolution, dC/dt, is the rate of drug dissolved per time expressed as concentration change in the dissolution fluid.

Factors that affect drug dissolution of a solid oral dosage form

(1) Physical and chemical nature of the active drug substance

(2) Nature of the excipients

(3) Method of manufacture.

Formulation Factors Affecting Drug Dissolution

Excipients are added to a formulation to provide certain functional properties to the drug and dosage form.

are used to:

- improve the compressibility of the active drug
- improve stabilize the drug against degradation
- decrease gastric irritation
- control the rate of drug absorption from the absorption site
- increase drug bioavailability

etc..

Dissolution and Drug Release Testing

- dissolution test is an important quality control procedure for the drug product and is often linked to product performance *in vivo*.
- *In-vitro* drug dissolution studies are most often used for monitoring drug product stability and manufacturing process control.

- The USP-NF (United States Pharmacopeia) sets standards for dissolution and drug release tests of most drug products.
- Ideally, the dissolution method used for a particular drug product *in vitro* relates to the bioavailability of the drug *in vivo*: *(in-vitro–in-vivo* correlation*)*

- In addition, the dissolution method should be able to discriminate changes in formulation of the drug product.
- Furthermore, dissolution and drug release tests are important quality control components for the manufacture of the drug product.

Dissolution and Drug Release Testing

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As a quality control test, dissolution and drug release testing may be used for:

- Batch-to-batch drug release uniformity
- Stability
- Scale-up and postapproval changes (SUPAC)
- Predicting in-vivo performance
- Often, the dissolution test is a valuable tool in formulation development

- A suitable dissolution method may uncover a formulation problem with the drug product that could result in a bioavailability problem.
- Each dissolution method is specific for the drug product and its formulation.

- The dissolution test should be able to distinguish between acceptable and unacceptable drug formulations as observed by different drug dissolution rates under the same experimental conditions.
- A suitable dissolution test should be able to reflect changes in the formulation, manufacturing process, and physical and chemical characteristics of the drug, such as particle size, polymorphs, and surface area

- The dissolution test is a major requirement for scale-up and post approval changes, SUPAC

- After a change is made in a formulation, the manufacturer should assess the potential effect of the change on bioequivalence, which usually includes multipoint and/or multimedia dissolution profiling and, if necessary, an *in-vivo* bioequivalence study.

Dissolution Conditions

The development of an appropriate dissolution test requires to try:

- different agitation rates
- different media (including volume and pH of medium)
- different kinds of dissolution apparatus

The current USP-NF (United States Pharmacopeia) lists officially recognized dissolution apparatus.

Dissolution Criteria

- Are developed for the drug product and its formulation.
- These criteria or dissolution specifications (eg, percent of drug dissolved in 30 minutes) are used to investigate formulation problems.
- For example, devised a method using pH 6.6 phosphate buffer as the dissolution medium instead of 0.1 N HCL to avoid instability of the antibiotic drug erythromycin. Using the USP paddle method at 50 rpm and a temperature of 22°C,

- The dissolution of the various erythromycin tablets was shown to vary with the source of the bulk active drug

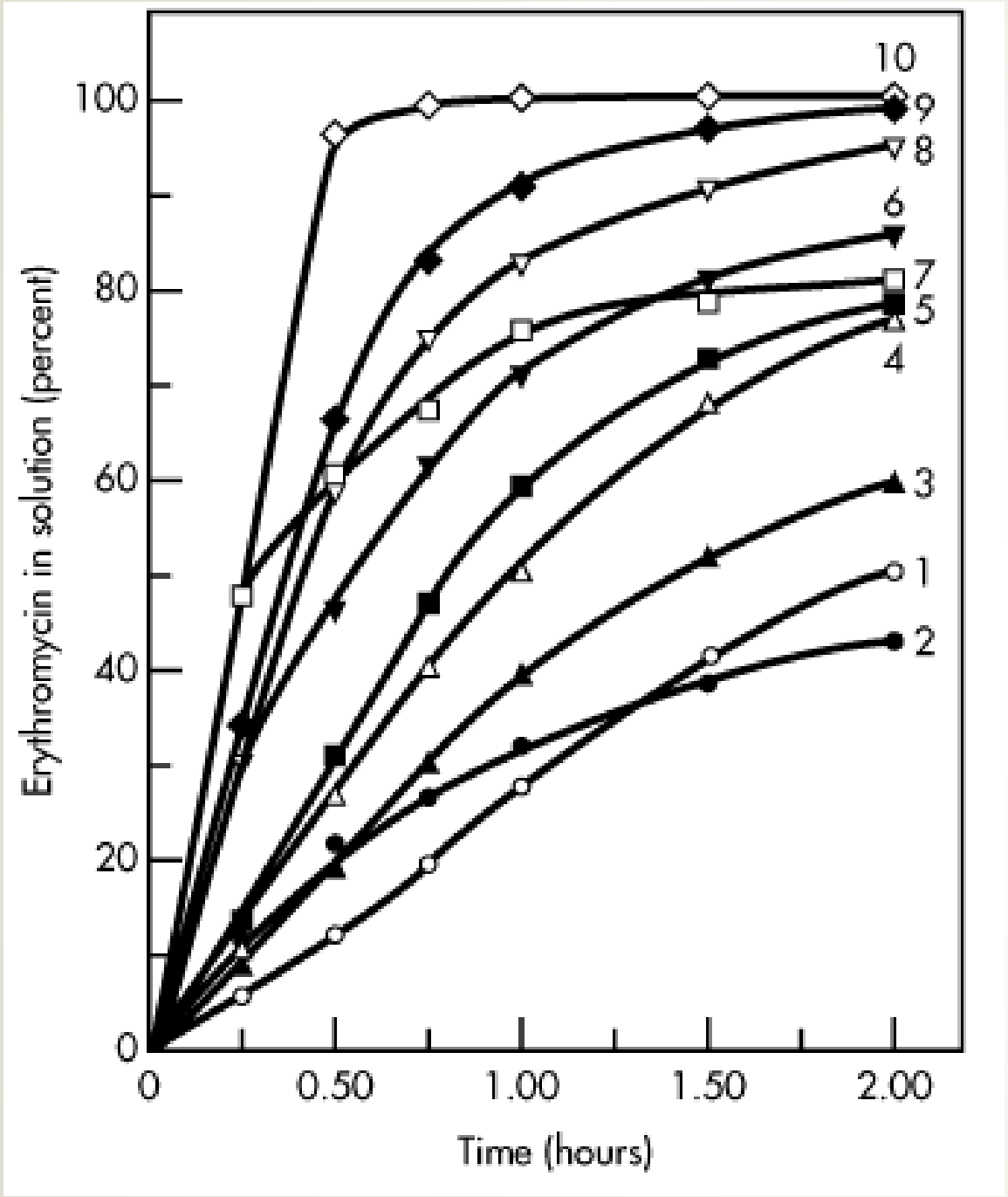
Conditions that May Affect Drug Dissolution and Release

Drug substance
Particle size
Polymorph
Surface area
Chemical stability in dissolution media
Formulation of drug product
Excipients (lubricants, suspending agents, etc)
Medium
Volume
pH

Molarity
Co-solvents, added enzymes/surfactants
Temperature of medium
Apparatus
Hydrodynamics
Agitation rate
Shape of dissolution vessel
Placement of tablet in vessel
Sinkers (for floating products and products that stick to side of vessel)

Dissolution of Erythromycin Stearate Bulk Drug and Corresponding Tablets

	Percent Dissolution After 1.0 hr		
Curve No.	**Bulk Drug**	**500-mg Tablet**	**250-mg Tablet**
4	49	44	
6	72	70	
7	75	70	
—	78	—	80
8	82	75	
9	92	85	



Dissolution profile of various lots of erythromycin stearate as a function of time (0.05 M, pH 6.6 phosphate buffer).

- Visual observations of the dissolution and disintegration behavior of the drug product are important and should be recorded.
- Dissolution and disintegration patterns can indicate manufacturing variables.
- These observations are particularly useful during method development and formulation optimization.

- Usually, the report on the dissolution test will state that a certain percentage of the labeled amount of drug product must dissolve within a specified period of time.