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MODIFIED/TARGETED DRUG DELIVERY SYSTEM

Dr. Muhammad Asadullah Madni

PhD (Pharmaceutics, IUB-Pakistan)

Post -Doctoral Fellow (Pharm. Nanotechnology University of Auckland, New Zealand)

Associate Professor

Department of Pharmacy,

Faculty of Pharmacy & Alternative Medicines

The Islamia University of Bahawalpur

asadullah.madni@iub.edu.pk

MODIFIED OR TARGETED DRUG DELIVERY SYSTEM

Targeted Drug Delivery System:

Targeted drug delivery is an advanced method of delivering drugs to the patients in such a targeted sequence that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells), which in turn improves efficacy of treatment by reducing side effects of drug administration.

Characteristics of TDDS:

1. Increase the bioavailability of drugs
2. Transport the drugs to the site of action avoiding non diseased tissues
3. Cost effective
4. Easy to administer, safe and reliable
5. Provide control delivery of drug.

Why we prefer TDDS?

1. It assists the drug molecule to reach preferably to the desired site (Localized drug delivery).
2. For the administration of required drug with its reduced dose and reduced its side effect.
3. To improve patient compliance.

Sustained release dosage forms (SRDF'S)

INTRODUCTION

- **Sustained release** describes the release of drug substance from a dosage form or delivery system over an extended period of time.
- Also referred to as prolonged-release (PR), slow release (SR), sustained action (SA), prolonged action (PA) or extended-release (ER).

COMPARISION OF DRUG RELEASE PROFILES

Differences between sustained and controlled drug delivery system

Sustained release dosage form	Controlled release dosage form
• Constitutes dosage form that provides medication over extended period of time	• Constitutes dosage form that maintains constant drug levels in blood or tissue
• SRDF generally do not attain zero order release kinetics	• Maintains constant drug levels in the blood target tissue usually by releasing the drug in a zero-order pattern.
• Usually do not contain mechanisms to promote localization of the drug at active site.	• Controlled dosage forms contain methods to promote localization of the drug at active site.

Merits of SRDF

1. Reduction in blood level fluctuations of drug, thus better management of the disease.
2. Reduction in dosing frequency.
3. Enhanced patient convenience and compliance.
4. Reduction in adverse effects (both systemic and local), esp. of potent drugs, in sensitive patients.
5. Reduction in health care costs.
6. Improved efficiency of treatment.
7. Reduces nursing and hospitalizing time.
8. Maximum bioavailability with a minimum dose.
9. Minimize drug accumulation with chronic dosing.
10. Cure or control condition more promptly.
11. Make use of special effects, e.g. Treatment of Arthritis.

12. Constant blood levels achieve desired effect and this effect is maintained for an intended period of time.
13. Drug susceptible to enzymatic inactivation or by bacterial decomposition can be protected by encapsulation in polymer system suitable for SR.

Limits of SRDF

- Administration of sustained release medication does not permit prompt termination of therapy. Immediate changes in the drug if needed during therapy when significant adverse effects are noted cannot be accommodated.
- The physician has less flexibility in adjusting dosage regimen, as it is fixed by dosage form design.
- Sustained release dosage forms are designed for normal population i.e. on basis of average biologic half-life.

Consequently, disease states that alter drug disposition, significant patient variation, and so forth are not accommodated.

- More costly process and equipment are involved in manufacturing many sustained release dosage forms.

Dose dumping

- Unpredictable and poor in vitro and in vivo relationship.
- Effective drug release time period is influenced and limited by GI residence time.
- Need additional patient education (such as not to chew or crush the dosage form before swallowing)
- Drugs having very short half life or very long half life are poor candidates for sustained release dosage forms. For Ex: diazepam.
- Delayed onset of action, hence sometimes not useful in acute conditions

Characteristics of Drugs Unsuitable for Peroral SRDF

I. Those which are absorbed and excreted rapidly; short biological half-life (<1 hr). Ex- Penicillin G, Furosemide.

II. Those with long biologic half-life (>12 hrs). Ex- Diazepam, Phenytoin.

III. For those which require large doses (>1 gm) Ex- Sulfonamides.

IV. Extensive binding of drugs to plasma proteins will have long elimination half-life and such drugs generally do not require to be formulated to SRDF.

V. Those with cumulative action and undesirable side effects. Ex- Phenobarbital

VI. Those with low therapeutic indices. ex- Digitoxin.

VII. Those requiring precise dosage titration for every individual. Ex- Warfarin, Digitoxin.

VIII. In general, a very highly soluble drug or a highly insoluble drug are undesirable for formulation into SRDF product.

Materials Used in Coating of Sustained Release Dosage Forms (Encapsulation)

1. Mixtures of waxes [bees wax, carnauba wax, etc.] with glyceryl monostearate, stearic acid, glyceryl mono palmitate and acetyl alcohol. These provide coatings that are dissolved slowly or broken down in the GIT.
2. Shellac and zein – polymers that remain intact until the PH of the GI contents become less acidic
3. Ethyl cellulose, which provides a membrane around the dosage form and remains intact throughout the GIT. However, it does permit water to permeate the film, dissolve the drug, and diffuse out again.
4. Acrylic resins, which behave similarly to ethyl cellulose as a diffusion-controlled drug release coating material.
5. Cellulose acetate [di acetate and tri acetate] Silicone elastomers.

Polymers for Micro-encapsulation

1. Water-soluble resins
2. Water-insoluble resins
3. Waxes and
4. lipids

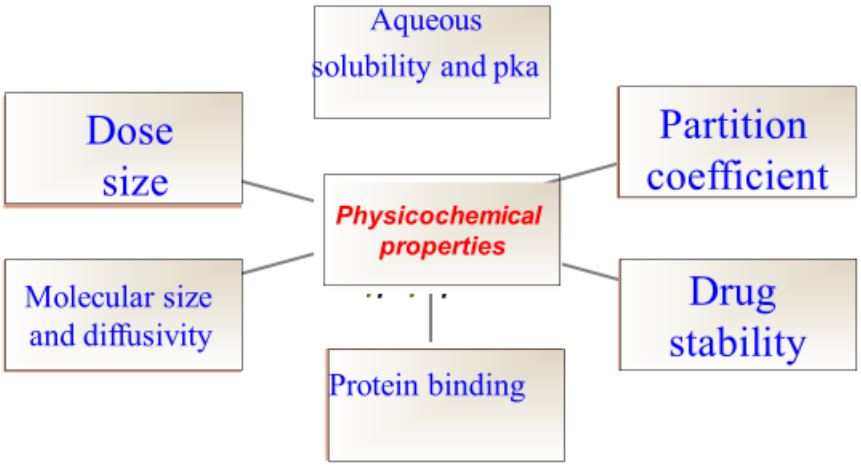
1. Water-soluble resins

- Gelatin
- Povidone (PVP)
- CMC
- HEC
- MC

- PVA

2. **Water-insoluble resins**
   - Ethyl cellulose
   - Polyamide (Nylon)
   - Polyethylene
   - Cellulose nitrate
3. **Waxes and lipids**
   - Paraffin
   - Carnauba
   - Beeswax
   - Stearic acid
   - Stearyl alcohol

Physicochemical Properties of Drug Candidate



Physicochemical <u>properties:</u>

1. <u>Aqueous solubility</u>
2. <u>PKa</u>

1. <u>Aqueous solubility:</u>

A drug with good aqueous solubility, especially if pH independent, serves as a good candidate

Drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into absorbing membrane.

<u>Noyes Whitney Equation</u>

$$\frac{dc}{dt} = K_D A C_s$$

Where

dc/dt= dissolution rate.

KD = Dissolution rate constant

A= total surface area of drug

Cs= aqueous saturation solubility

A. **Drugs with low aqueous solubility have low dissolution rate and have oral bioavailability problems**.
   E.g. Tetracycline.
B. **Drugs with high aqueous solubility are undesirable to formulate SRDF's.**
   E.g. Paracetamol

2. <u>PKa:</u>

The aqueous solubility of weak acids & weak bases is governed by the pKa of the compound and pH of the medium.

FOR WEAK ACID

$$St = So\ (1+Ka/\ [H] = So(1+10pH-pKa)$$

where,

St – Total solubility of the weak acid
So – Solubility of the un-ionized form
Ka – Acid dissociation constant
H - Hydrogen ion concentration

Weakly acidic drug exist as unionized form in the stomach absorption is favored by acidic medium.

FOR WEAK BASES

$$S_t = S_o\ (1+\ [H]\ \backslash Ka) = S_o(1+pKa-pH)$$

Where,

St – Total solubility of both conjugate and free base form of weak base.
S_o– Solubility of the free base.

Weakly basic drug exists as ionized form in the stomach hence absorption of this type is poor in this medium.

2. Partition coefficient:

- Between the time a drug is administered and is eliminated from the body, it must diffuse through a variety of biological membranes.
- Oil/Water partition coefficient plays a major role in evaluating the drug penetration.

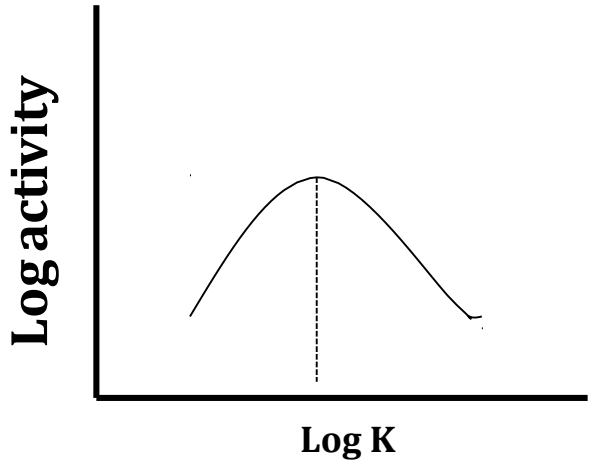
K=Co/Cs

where,

Co= Equilibrium concentration in organic phase.

Cs= Equilibrium concentration in aqueous phase.

According to 'Hanch correlation' a parabolic relationship between the log of its partition coefficient has with that of the log of its activity or ability to be absorbed.



- Drugs with extremely high partition coefficient are very oil soluble and penetrates in to various membranes very easily
- There is an optimum partition coefficient for a drug in which it permeates membrane effectively and shows greater activity.
- Partition coefficient with higher or lower than the optimum are poorer candidates for the formulation
- Values of partition coefficient below optimum result in the decreased lipid solubility and remain localized in the first aqueous phase it contacts.
- Values larger than the optimum, result in poor aqueous solubility but enhanced lipid solubility and the drug will not partition out of the lipid membrane once it gets in.

3. Drug stability:

- Solid state undergoes degradation at much slower rate than in the suspension or solution etc.
- Drugs stable in stomach gets released in stomach and which are unstable gets released in intestine.
- Drugs with stability problems in any particular area of G.I.T are less suitable for the formulation.
- Drugs may be protected from enzymatic degradation by incorporation in to a polymeric matrix.

4. Protein binding:

- Drug binding to plasma proteins (albumins) & resulting retention of the drug in the vascular space.
- Drug -protein complex can serve as a reservoir in vascular space.
- Main forces for binding are Vander Waal forces, hydrogen bonding, electrostatic forces.
- Charged compounds has greater tendency to bind proteins than uncharged ones.
- Extensive binding of plasma proteins results in longer half-life of elimination for the drug.
- E.x..95% binding in Amitriptyline, diazepam, diazepoxide.

5) Molecular size & diffusivity:

The ability of a drug to diffuse through membranes is called diffusivity which is a function of molecular weight.

In most polymers it is possible to relate log D to some function of molecular size as,

$$\text{Log } D = - Sv \log v + Kv = - S_M \log M + Km$$

where,

V – Molecular volume.

M – Molecular weight.

Sv, Sm, Kv & Km are constants

The value of D is related to the size and shape of the cavities, as well as the drugs.

The drugs with high molecular weight show very slow kinetics.

6. Dose size:

- For those drugs requiring large conventional doses, the volume of sustained dose may be too large to be practical.
- The compounds that require large dose are given in multiple amounts or formulated into liquid systems.
- The greater the dose size, greater the fluctuation.
- So, the dose should have proper size.

MARKETED FORMULATIONS:

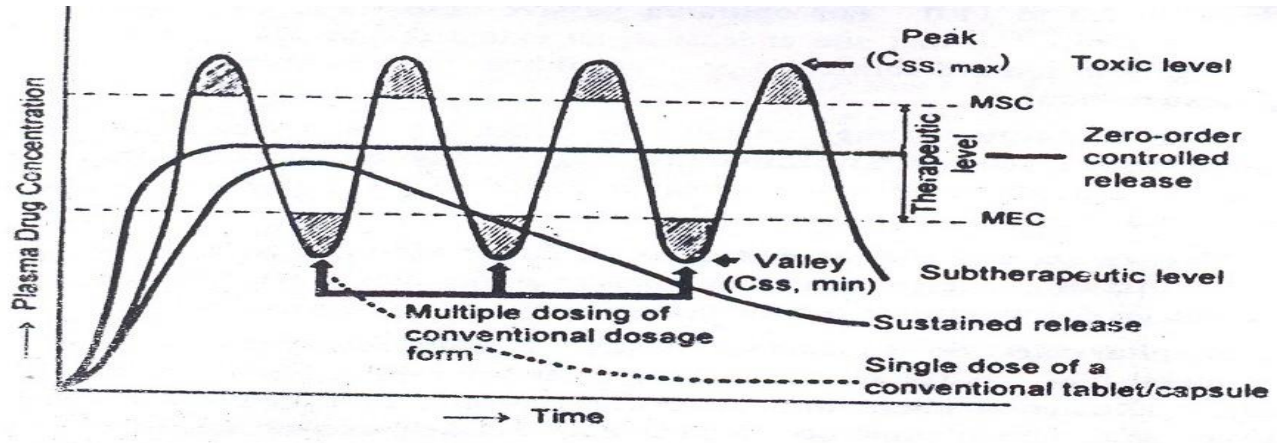
Name	Marketer	Dosage form	Indication
Carbotrol	Shri Us	Oral capsule	Epilepsy
Glucotrol Xl	Pfizer	Oral Tablet	Hyperglycemia
Adderall XR	Shri US	Oral Capsule	ADHD
Procardia Xl	Pfizer	Oral Tablet	Angina/Hypertension
Ortho Evra	Ortho– Mcneil	Trans Dermal Patch	Contraceptive
Dura gesic	Janssen	Trans Dermal Patch	Chronic pain

Controlled Release Oral Drug Delivery System

Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time.

Continuous oral delivery of drugs at predictable & reproducible kinetics for predetermined period throughout the course of GIT.

Plasma concentration time profile



Challenges in Oral Drug Delivery

1. **Development of drug delivery system**

Delivering a drug at therapeutically effective rate to desirable site.

2. **Modulation of GI transit time**

Transportation of drug to target site.

3. **Minimization of first pass elimination**

Mechanism aspects of Oral drug delivery formulation

1. **Dissolution :**
   I. Matrix
   II. Encapsulation
2. **Diffusion :**
   I. Matrix
   II. Reservoir
3. Combination of both dissolution & diffusion
4. Osmotic pressure controlled system

Advantages

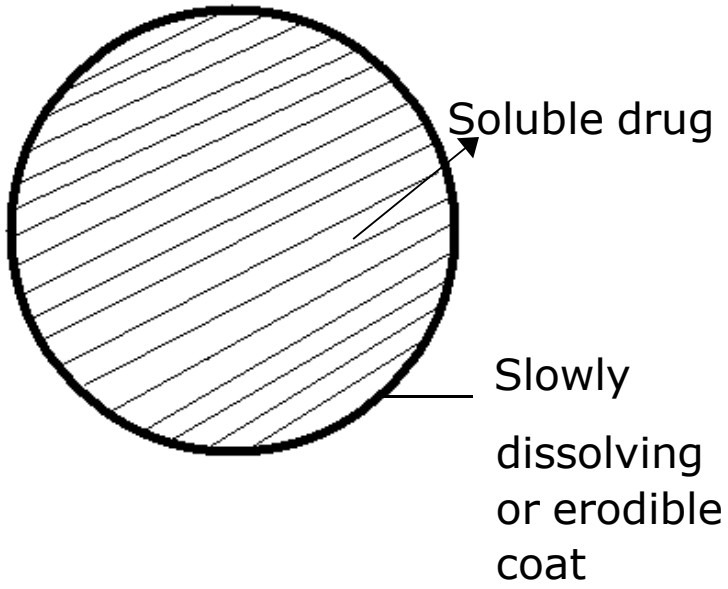
1. Total dose is low.
2. Reduced GI side effects.
3. Reduced dosing frequency.
4. Better patient acceptance and compliance.
5. Less fluctuation at plasma drug levels.
6. More uniform drug effect
7. Improved efficacy/safety ratio.

Disadvantages

1. Dose dumping.
2. Reduced potential for accurate dose adjustment.
3. Need of additional patient education.
4. Stability problem.

Encapsulation

- Called as Coating dissolution controlled system.
- Dissolution rate of coat depends upon stability & thickness of coating.
- Masks colour,odour,taste,minimising GI irritation.
- One of the microencapsulation method is used.
- Examples:
- Ornade spansules,
- Chlortrimeton Repetabs



Diffusion

- Major process for absorption.
- No energy required.
- Drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attainded.
- Directly proportional to the concentration gradient across the membrane.

MATRIX DIFFUSION TYPES

1. **Rigid Matrix Diffusion**

Materials used are insoluble plastics such as PVP & fatty acids.

2. **Swellable Matrix Diffusion**

- Also called as Glassy hydrogels. Popular for sustaining the release of highly water soluble drugs.

- Materials used are hydrophilic gums.

Examples :

1. Natural- Guar gum, Tragacanth.
2. Semisynthetic -HPMC, CMC, Xanthum gum.
3. Synthetic -Polyacrilamides.
   Examples: Glucotrol XL, Procardia XL

Higuchi Equation

$$Q = DE/T \quad (2A.E\ Cs)Cs.t)^{1/2}$$

Where ,

Q=amt of drug release per unit surface area at time t. D=diffusion coefficient of drug in the release medium. E=porosity of matrix.

Cs=solubility of drug in release medium. T=tortuosity of matrix.

A=concentration of drug present in matrix per unit volume.

DISSOLUTION

Definition:

- Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.
- Dissolution is the rate determining step for hydrophobic, poorly aqueous soluble drugs.

E.g. Griseofulvin, spironolactone

Noyes Whitney Equation

$$dc/dt = k\ D.A\ (Cs - C)\quad dc/dt = D/h\ A.\ (Cs - C)$$

dc/dt = Dissolution rate.

k= Dissolution rate constant (1^{st} order).

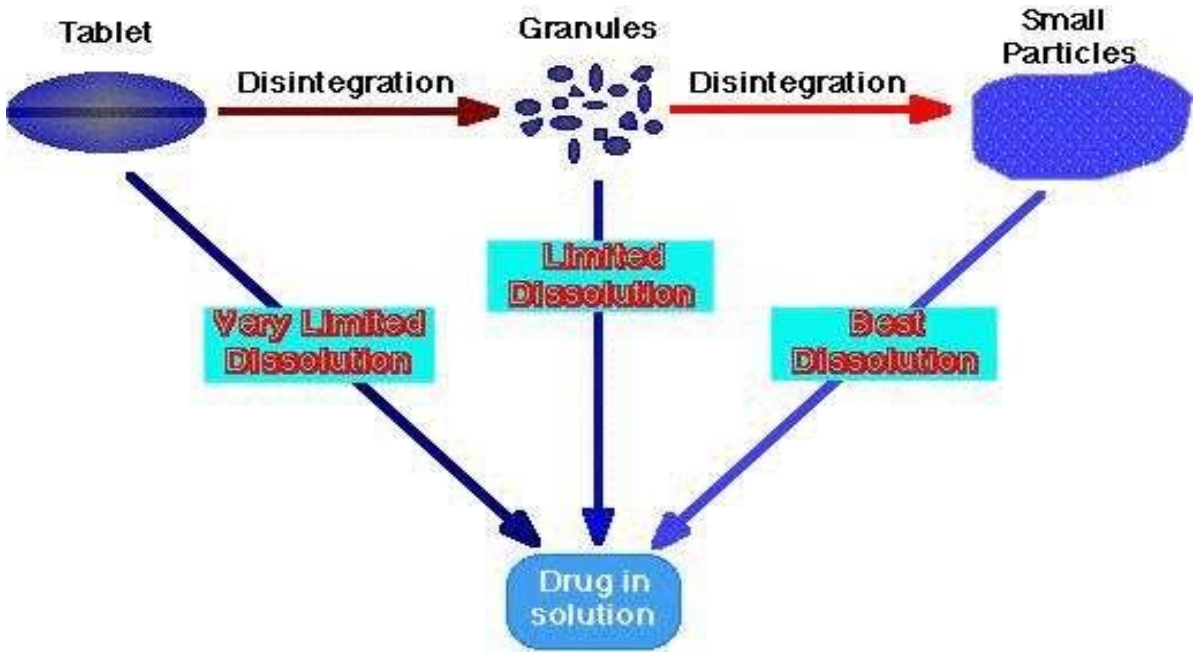
D = Diffusion coefficient/diffusivity

Cs = Saturation/ maximum drug solubility.

C = Con. Of drug in bulk solution.

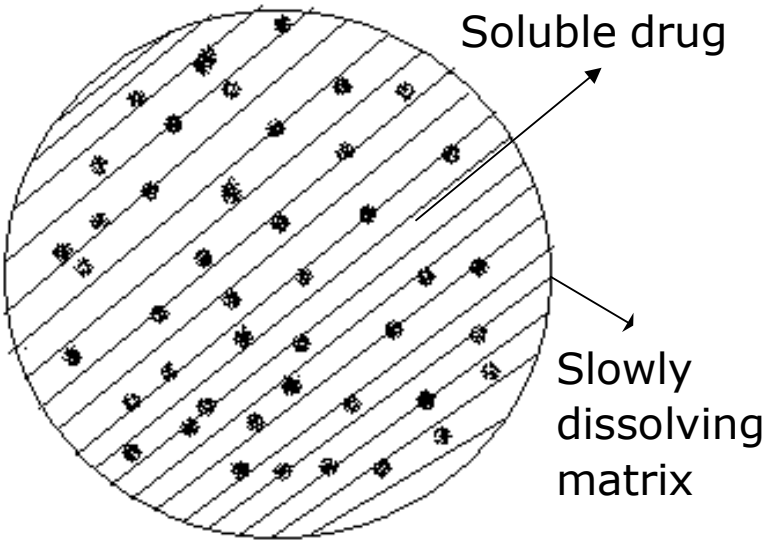
Cs-C=concentration gradient.

h =Thickness of diffusion layer.



Matrix Type

- Also called as Monolith dissolution controlled system.
- Controlled dissolution by:
  1. Altering porosity of tablet.
  2. Decreasing its wettebility.
  3. Dissolving at slower rate.
- First order drug release.
- Drug release determined by dissolution rate of polymer.
- Examples: Dimetane extencaps, Dimetapp extentabs.



Why dissolution studies?

1. To show that the release of drug from the tablet is close to 100%.
2. To show that the rate of drug release is uniform batch to batch.
3. And to show that release is equivalent to those batches proven to be bioavailable and clinically effective.

Fick's law:

$$\frac{dC}{dt} \alpha \Delta C$$

OR

$$\frac{dC}{dt} = k\Delta C$$

where k = rate constant

Mechanism of Dissolution

1. Diffusion layer model
2. Danckwert's model
3. Interfacial barrier model

1. **Diffusion Layer Model**
   - Also called 'film theory'.
   - Formation of a thin film at the interface, called as stagnant layer.
   - 2 steps are involved:
     1) Interaction of solvent with drug surface to form a saturated drug layer , called stagnant layer.
     2) Diffusion of drug molecules from stagnant layer into bulk of the system.

Dissolution mechanisms

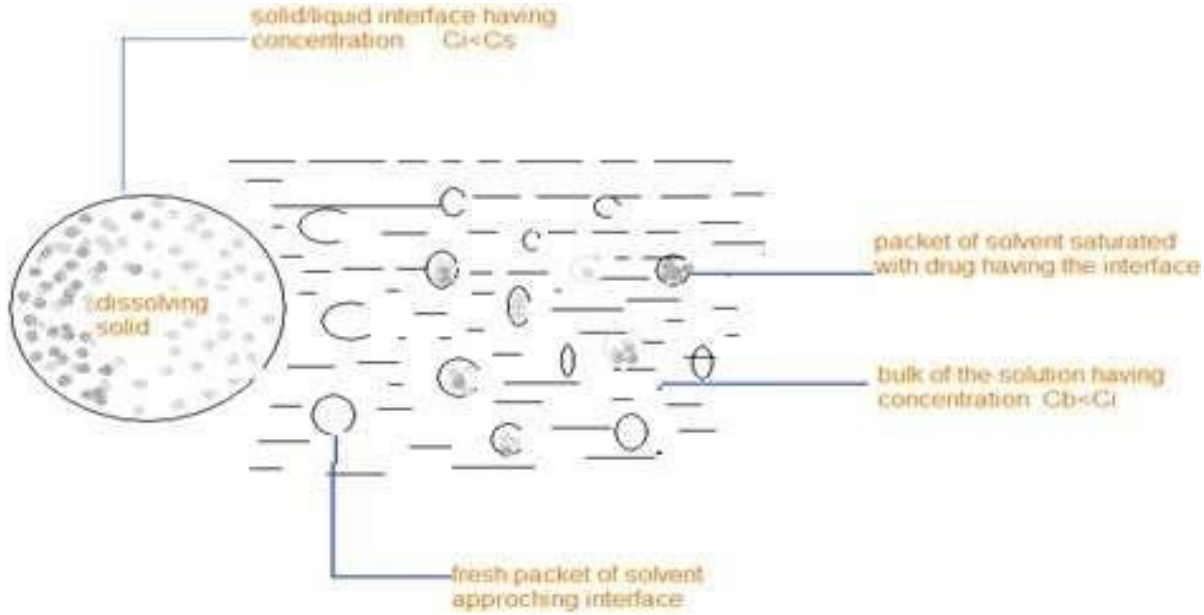
2 steps:

1. Interfacial reaction à cause liberation of solid particles into boundary layer (C_s).
2. Migration of solute from boundary layer into bulk of solution (C) by diffusion & convection.

- Overall rate of dissolution depends on the slowest step.
- Usually Step (2) is the RDS.

2. Danckwert's Model

Also called "Penetration or Surface Renewal Theory".



$$V\frac{dC}{dt} = \frac{dm}{dt} = A(C_s - C_b) * \sqrt{\gamma D}$$

- m = mass of solid dissolved, and
- γ = rate of surface renewal (or the interfacial tension)

3. Interfacial Barrier Model

- Drug dissolution is a function of solubility rather than diffusion.
- Intermediate concentration exist at the interface as a result of solvation.
- Dissolution rate per unit area, G is given by,

$$G = K_i(C_s - C_b)$$

where Ki = effective interfacial transport constant.

POWDER DISSOLUTION:

The Hixson-Crowell Cube Root Law

- Applicable for drug powders of uniform size.

- Rate of dissolution based on cube root of wt. of particles.

$$\sqrt[3]{M_0} - \sqrt[3]{M} = kt$$

M_0 = initial mass of powder

M = mass of powder dissolved in time, t

k = cube root dissolution rate constant

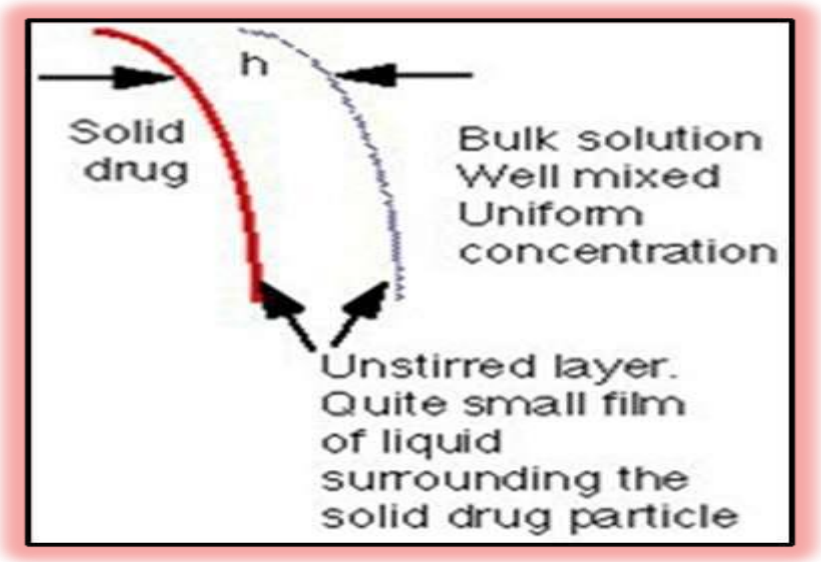


Diagram Representing Diffusion through the Stagnant Layer

Noyes- Whitney's equation:

$$\frac{dC}{dt} = k(C_s - C_b)$$

dC/dt = dissolution rate of the drug,

k = dissolution rate constant,

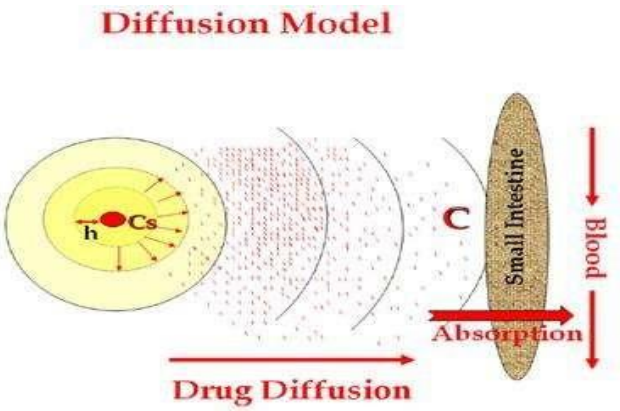
C_s = concentration of drug in the stagnant layer, and

C_b = concentration of drug in the bulk of the solution at time t

Modified Noyes-Whitney's equation:

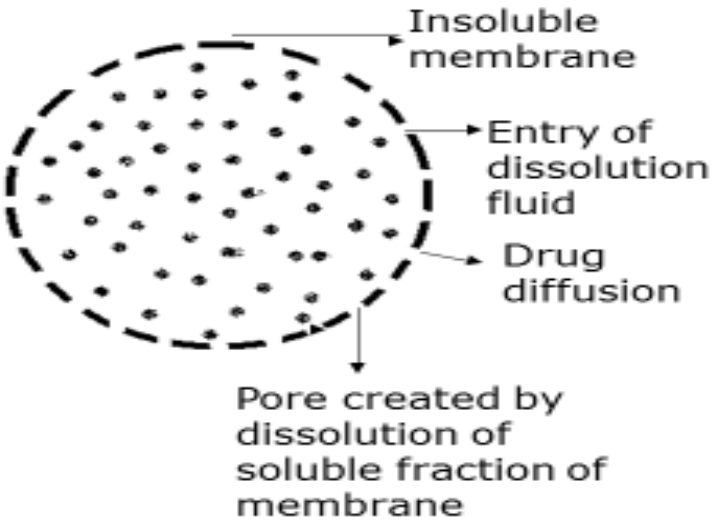
$$\frac{dC}{dt} = \frac{DAK_{w/o}(C_s - C_b)}{Vh}$$

- Where,
- D = diffusion coefficient (*diffusivity*) of the drug
- A = surface area of the dissolving solid
- $K_{w/o}$ = water/oil partition coefficient of the drug.
- V = volume of dissolution medium
- h = thickness of the stagnant layer
- $(C_s - C_b)$= concentration gradient for diffusion of drug.



Dissolution & Diffusion Controlled Release system

- Drug encased in a partially soluble membrane.
- Pores are created due to dissolution of parts of membrane.
- It permits entry of aqueous medium into core & drug dissolution.
- Diffusion of dissolved drug out of system.
- Ex- Ethyl cellulose & PVP mixture dissolves in water & create pores of insoluble ethyl cellulose membrane.



MEASUREMENT OF DISSOLUTION RATES

APPARATUS CLASSIFICATION IN USP

1. Apparatus 1 (rotating basket)
2. Apparatus 2 (paddle assembly)
3. Apparatus 3 (reciprocating cylinder)
4. Apparatus 4 (flow-through cell)
5. Apparatus 5 (paddle over disk)
6. Apparatus 6 (cylinder)
7. Apparatus 7 (reciprocating holder)

APPARATUS CLASSIFICATION IN USP FOR DIFFERENT DOSAGE FORM

For solid dosage forms	Paddle apparatus Basket apparatus Flow-through apparatus
For transdermal patches	Disk assembly method Cell method Rotating cylinder method
For special dosage forms	Chewing apparatus (medicated Chewing gums) Flow-through apparatus

PROBLEM ASSOCIATED WITH DEVELOPMENT OF DSSOLUTION TESTS

1. Need to have a manageable volume of dissolution medium.
2. Development of less-soluble drugs.

3. Insufficient analytical sensitivity for low-dose drugs.

Factors Affecting Dissolution

Surface area & undissolved solid

- Surface area α dissolution.
- Coherent masses may reduce total surface area available à overcome by using wetting agent.
- Presence of pores.
    - E.g. dissolution of phenacetin (hydrophobic) is enhanced by adding diluent gelatin (hydrophilic) during granulation.
- Addition of Tween 80 to dissolution medium (0.1 N HCl) for phenacetin increased the dissolution rate by increasing effective surface area.

Solubility of solid in dissolution medium

- ✓ Temp. of dissolution medium
- ✓ pH of the medium
- ✓ Solubility of the drug in dissolution medium
- ✓ Presence of cosolvents

Concentration of solute in solution

- Should simulate sink conditions present in GI tract.
- Larger volume of dissolution medium helps to maintain 'C' negligible compared to 'C_s'.
- Removal of dissolved solute from dissolution medium enhances rate of dissolution.
    - Eg. Adsorption onto another substance
    - Partition to another immiscible liquid
    - Removal of solute by dialysis
    - Cont. replacement of dissolution medium

Dissolution rate constant

Depend upon

- Thickness of boundary layer
- Degree of agitation
- Speed of stirring
- Shape, size & position of stirrer
- Vol. of dissolution medium
- Shape & size of container
- Viscosity of dissolution medium

Disintegration & Deaggregation

- Disintegration and subsequent deaggregation may also be RDS for dissolution.

  E.g. coated dosage forms

- After disintegration, larger aggregates need to deaggregate to yield fine particles.

Effect of manufacturing processes

ADDITION OF LUBRICANT

E.g. 325-mg salicylic acid dissolved rapidly in 0.1 N HCl when SLS was added to it.

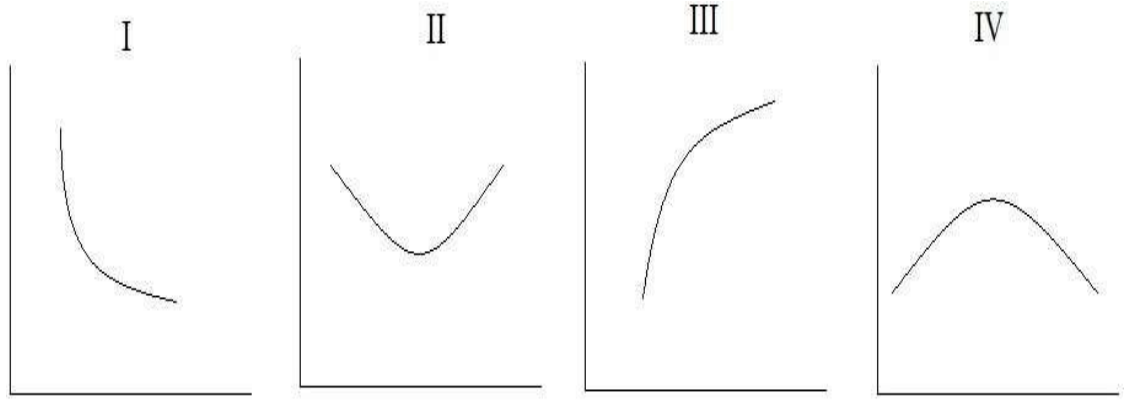
Dissolution rate decreases with addition of hydrophobic lubricants like Mg. stearate.

- Most effective lubricants are hydrophobic à act by particle coating à hence mfg. process is imp.

❖ Addition of disintegrating agents
like starch → swell & enhance dissolution.

❖ Compression force

- Increase in compression force may decrease or increase dissolution rate.



Recent developments in dissolution testing

- Use of more biorelevant media—FaSSIF & FeSSIF media.
- FaSSIF—Fasted State Simulated Intestinal Fluid
- FeSSIF—Fed State Simulated Intestinal

ADVANTAGES:

- Provide physicochemical properties similar to human GIT.

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