Unit I Controlled Drug Delivery Systems

Subject: Novel Drug Delivery Systems

Mahesh P. More

Assistant Professor

Dr. Rajendra Gode College of Pharmacy, Malkapur, Dist – Buldhana, (M.S.) India

Course Objectives

COS	Course Objectives
CO1	To understand Controlled Drug Delivery Systems and formulation design
CO2	To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems
CO3	To understand various approaches for development of novel drug delivery systems
CO4	To understand NDDS formulation and evaluation
CO5	To understand Various Targeted Drug Delivery Approaches
CO6	To understand organ targeted drug delivery systems

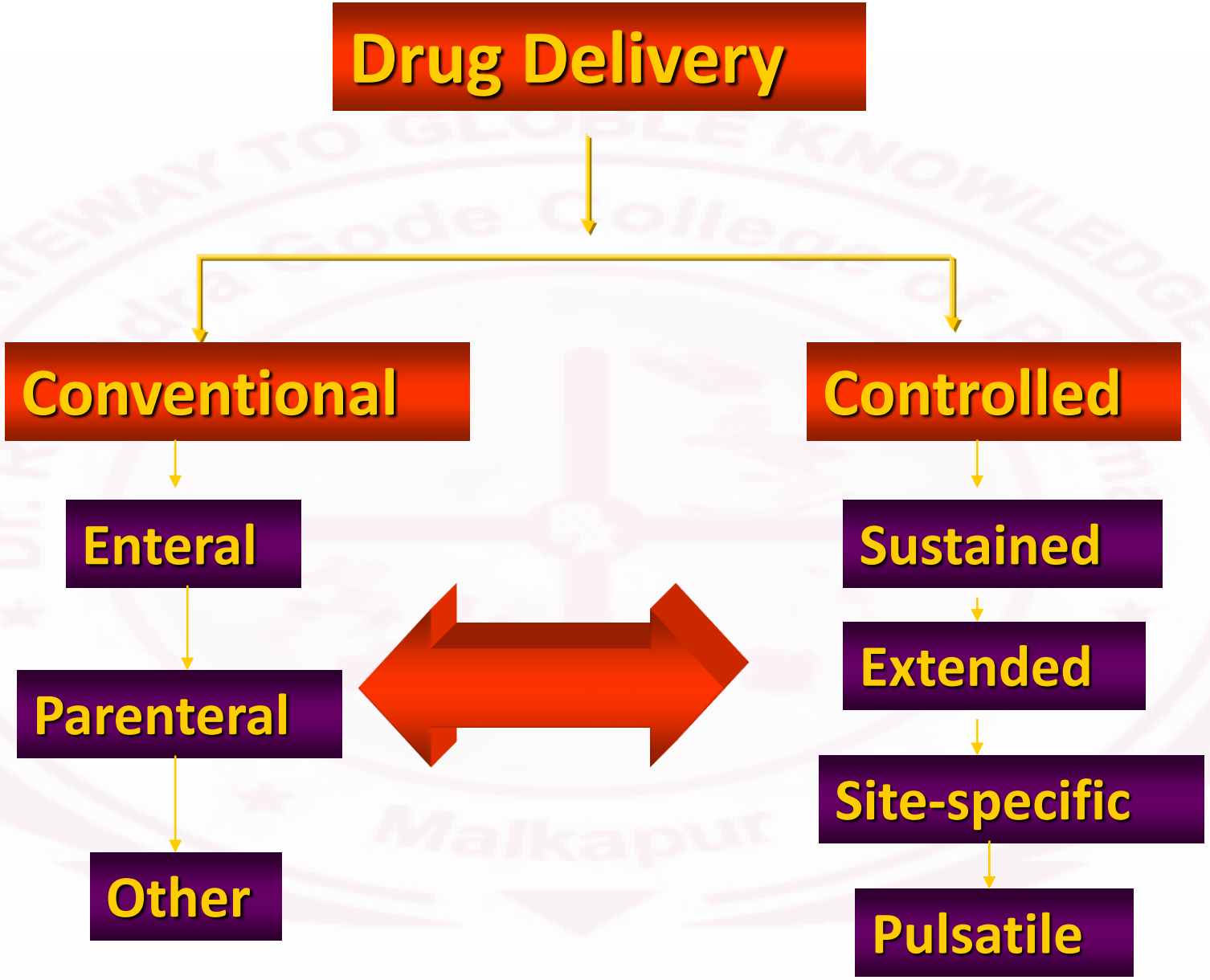
Contents

- Introduction, terminology/definitions and rationale,
- Advantages, disadvantages, selection of drug candidates.
- Approaches to design controlled release formulations based on diffusion, dissolution and ion exchange principles.
- Physicochemical and biological properties of drugs relevant to controlled release formulations
- Polymers: Introduction, classification, properties, advantages
- Polymers: Application of polymers in formulation of controlled release drug delivery systems

Drug Delivery

- **Definition**
  - **The appropriate administration of drugs through various routes in the body for the purpose of improving health**
  - **It is highly interdisciplinary**
  - **It is not a young field**
  - **It has recently evolved to take into consideration**
    - **Drug physico-chemical properties**
    - **Body effects and interactions**
    - **Improvement of drug effect**
    - **Patient comfort and well being**

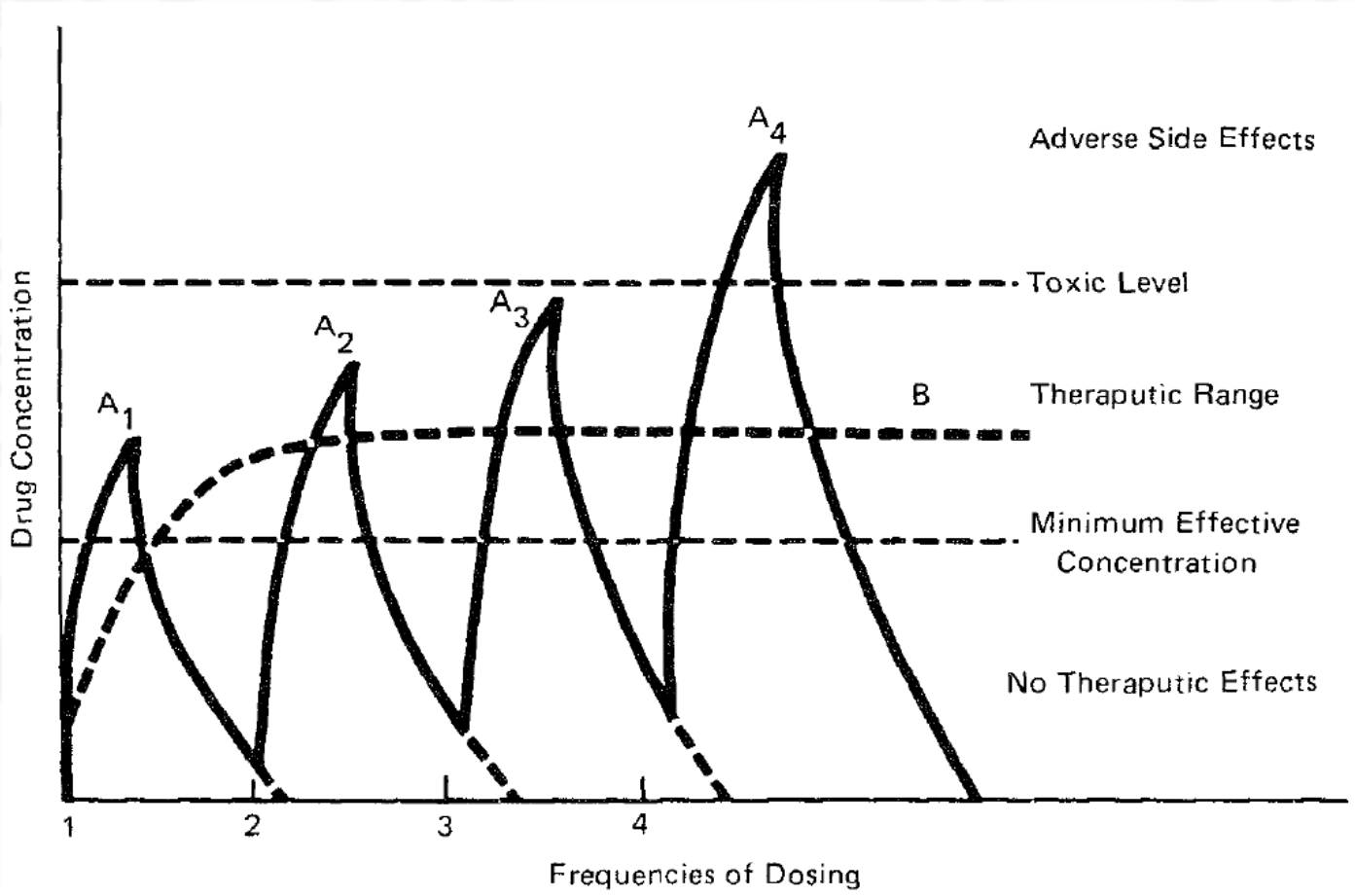
Controlled Drug Delivery


Drug Delivery
Conventional
Controlled
Enteral
Parenteral
Other
Sustained
Extended
Site-specific
Pulsatile

Introduction

- For the treatment of acute to chronic illness
- We have used multiple drug carriers like tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectable, etc.
- Conventional dosage forms seen on prescription and over the counter medicine
- Conventional dosage forms provide prompt release of drug
- To maintain drug concentration for the treatment we need to take several times a day, results in significant fluctuation in drug levels

Introduction



Introduction

- Recent developments leads to controlling the release of drug
- Targeting to tissues, organs, enzymes, etc.
- The terminology controlled and sustained release use interchangeably
- Sustained release term was used over the decades represents retard the release of drug over period of time
- Appearance in systemic circulation was delayed and its plasma profile is sustained in duration
- Pharmacological action is delayed and duration of therapeutic action is sustained
- Controlled release term on the other hand goes beyond the scope of sustained release
- Predictability and reproducibility in the drug release kinetics

Introduction

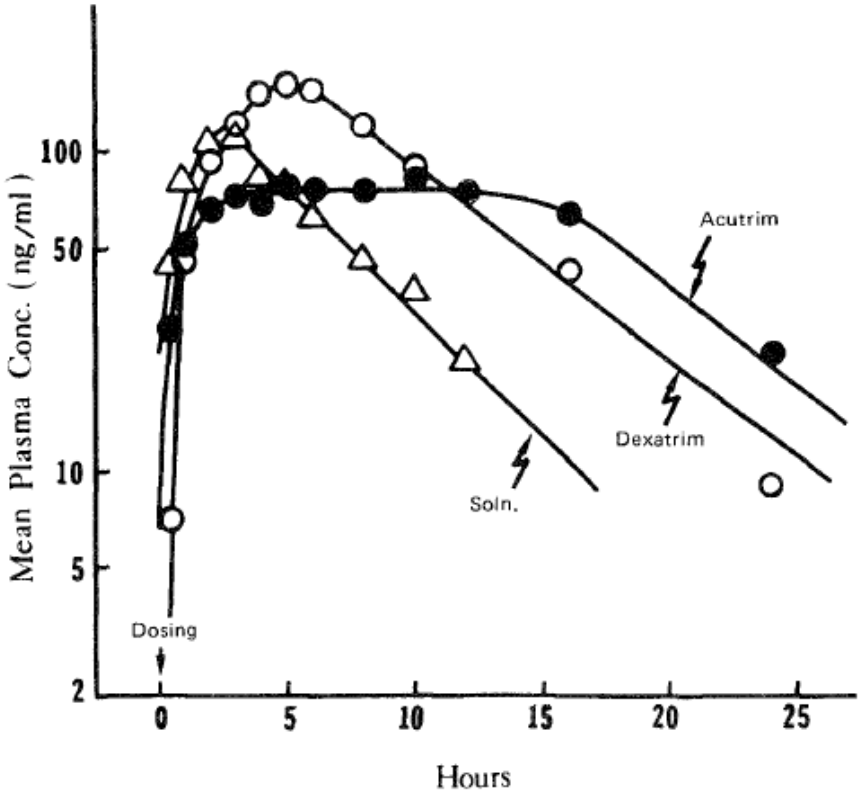


Figure 2 Comparative plasma profiles of phenylpropranolamine (PPA) in 18 healthy human volunteers resulted from oral administration of PPA in solution formulation and delivery by sustained-release Dexatrim or controlled-release Acutrim.

Factors Influencing the Selection of the Delivery Route

- Drug physico-chemical properties
  - **Drug molecular size (molecular weight)**
  - **Half-life**
  - **Chemical stability**
  - **Loss of biological activity in aqueous solution**
    - **Proteins**
      - **Denaturation, degradation**

Factors Influencing the Selection of the Delivery Route

- **Solubility in aqueous solution (hydrophobicity/hydrophilicity)**
  - **pH**
  - **pKa - ionization**
  - **Temperature**
  - **Concentration**
  - **Crystalinity**
  - **Particle size**
  - **State of hydration**

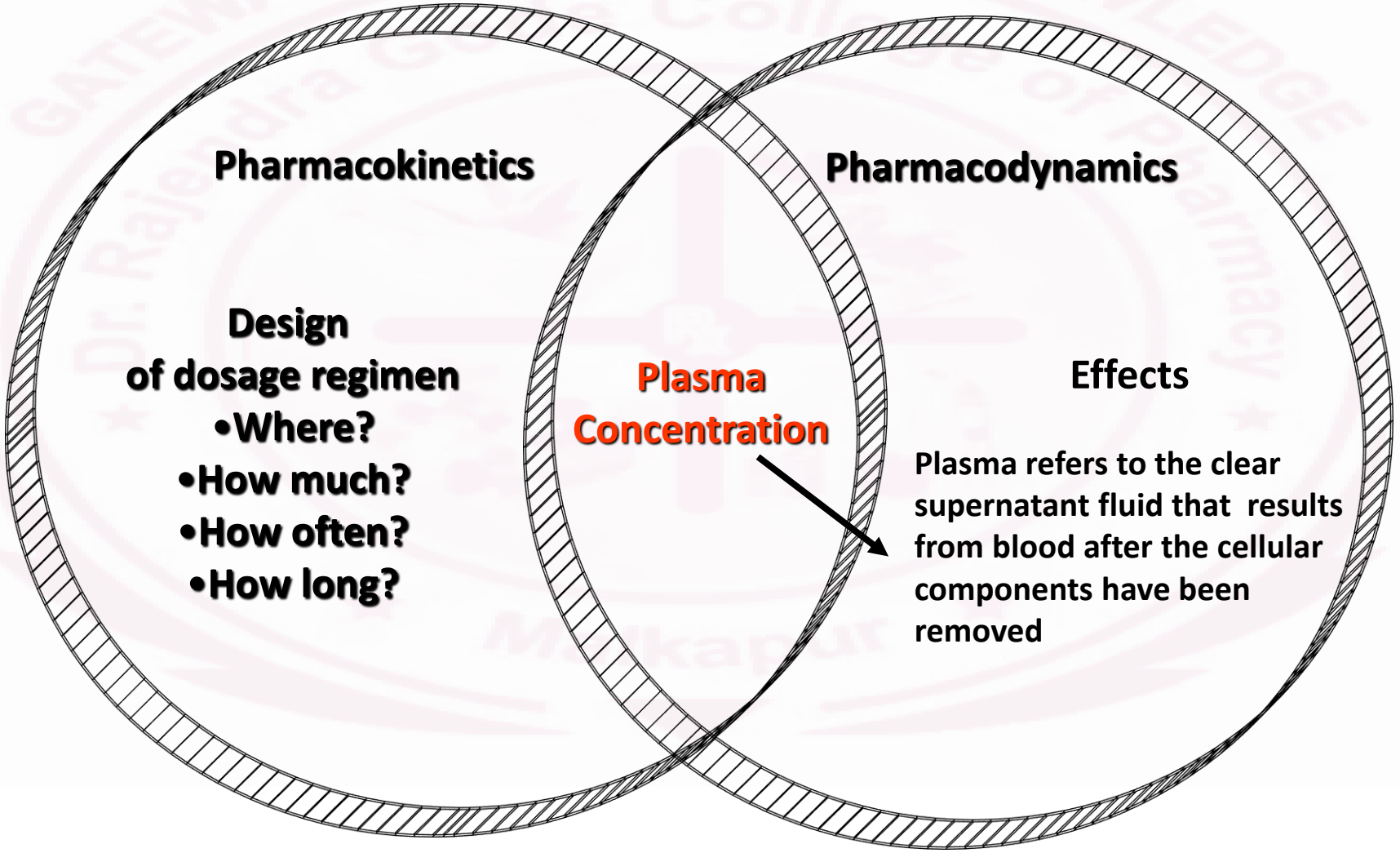
Factors Influencing the Selection of the Delivery Route

- Drug biological interactions
  - **Sensitive to FPM**
  - **Low membrane permeabiltiy**
    - **Efflux pumps (MRP, MDR) – cancer drugs**
    - **Hydrophilicity**
    - **High-density charge**
  - **Enzymatic degradation**
  - **Bacterial degradation**
  - **Half-life**
  - **Side effects**
    - **Irritation**

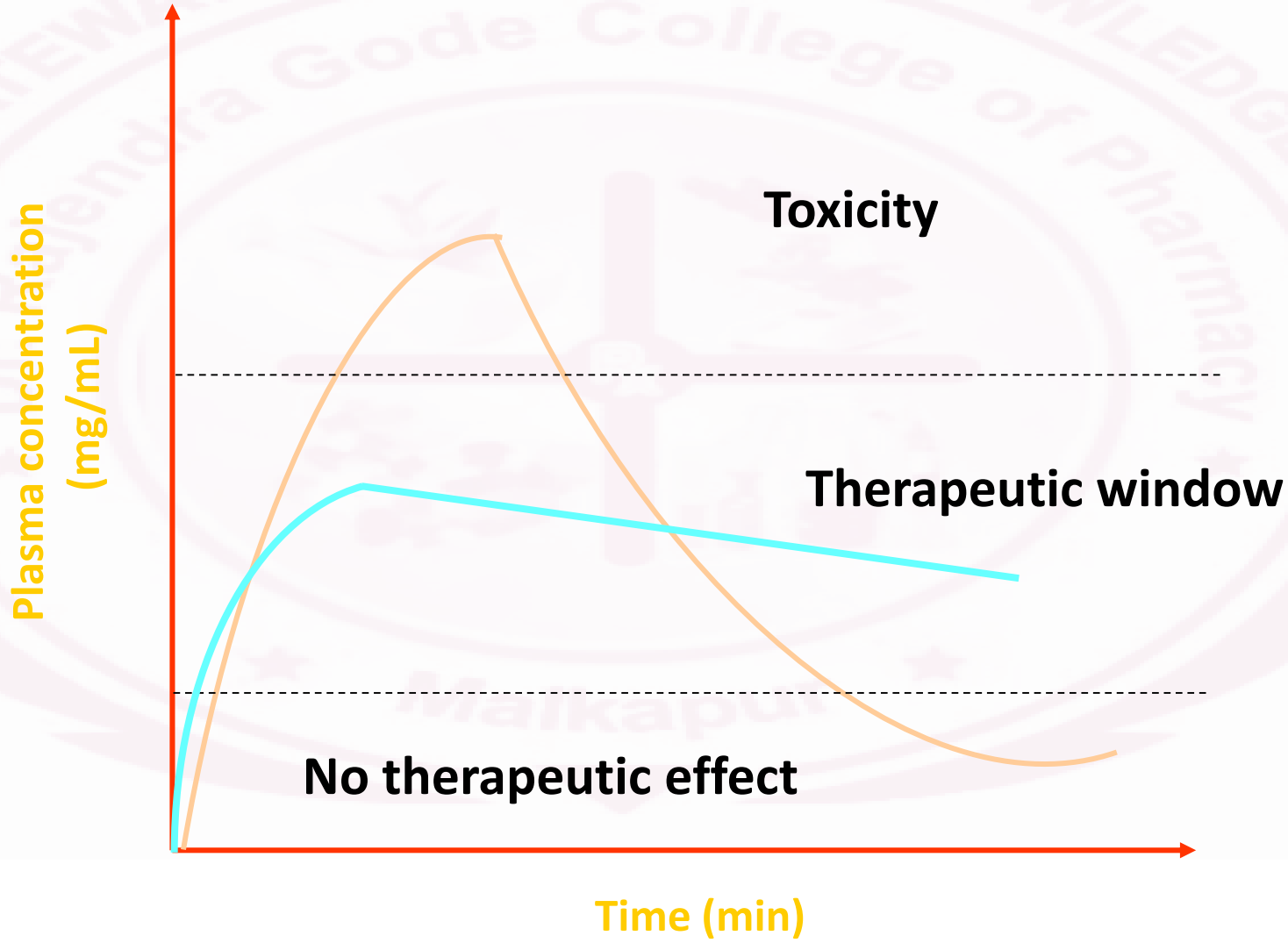
Factors Influencing the Selection of the Delivery Route

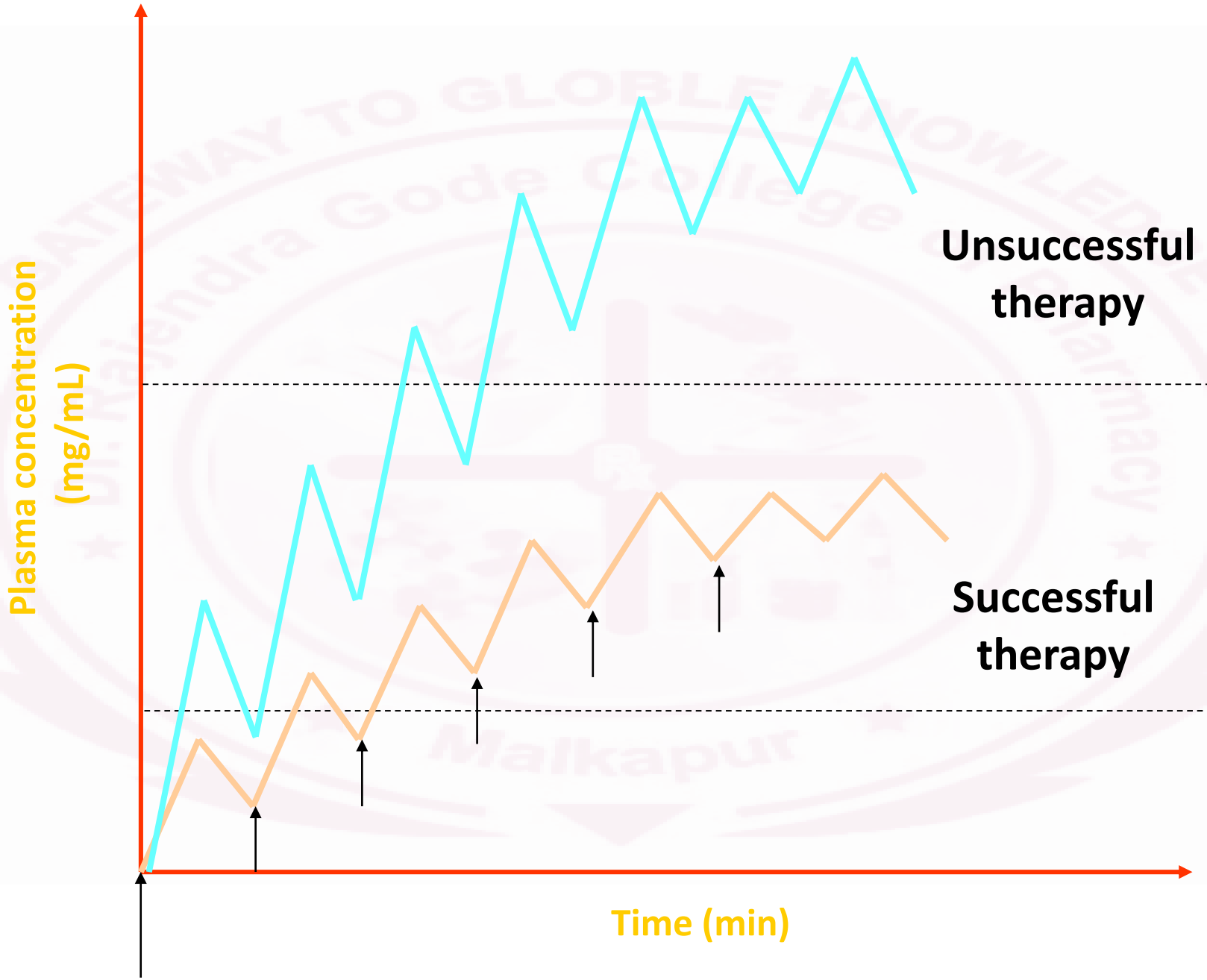
- Desired pharmacological effect
  - **Local**
    - **topical, vaginal**
  - **Systemic**
    - **oral, buccal, IV, SC, IM, rectal, nasal**
  - **Immediate response**
    - **IV, SC, IM, nasal**
  - **Dose size**
  - **Drug molecular size**

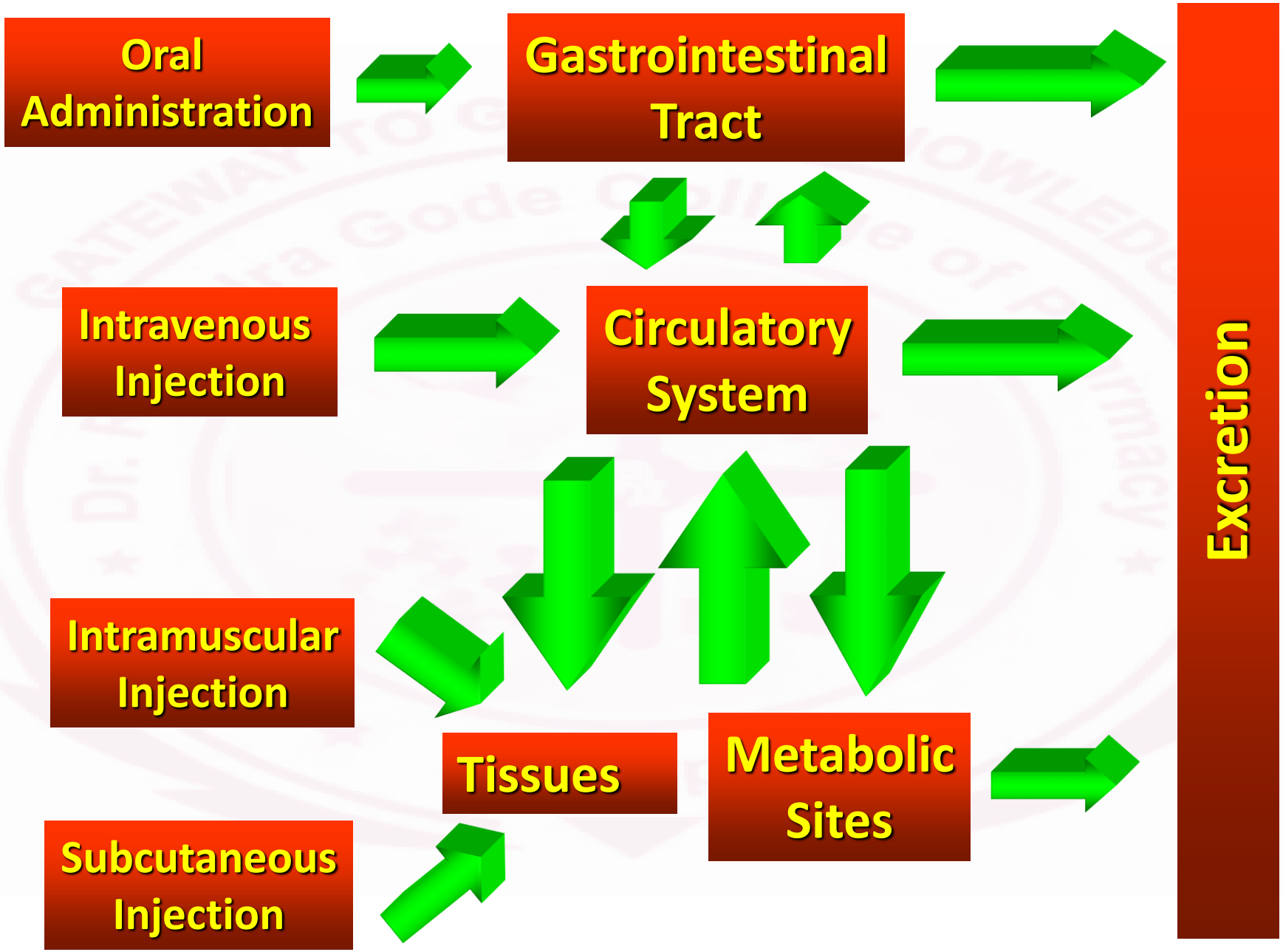
Pharmacokinetics and Pharmacodynamics



Plasma Concentration




Plasma concentration (mg/mL)
Unsuccessful therapy
Successful therapy
Time (min)

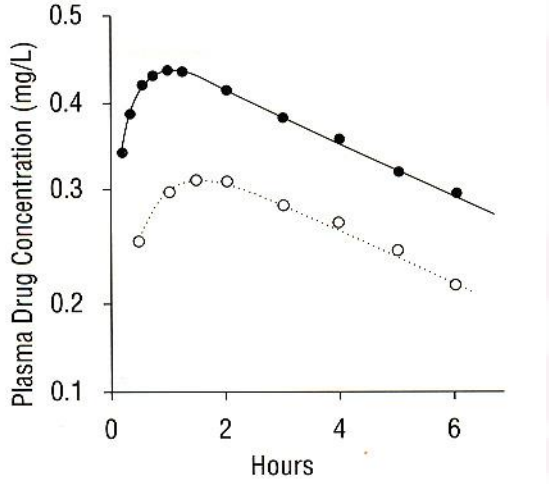

Oral Administration
Gastrointestinal Tract
Intravenous Injection
Circulatory System
Intramuscular Injection
Tissues
Metabolic Sites
Subcutaneous Injection
Excretion

Absorption of drugs could vary within different administration routes

- 500 mg dose given
  - intramuscularly ●
  - orally ○

**to the same subject on separate occasions

- Biological barriers greatly affect the extent of drug absorption



Advantages

- Decreased incidence and intensity of adverse effects and toxicity
- Better drug utilization
- Controlled rate and site of release
- More uniform blood concentration
- Improved patient compliance
- Reduced dosing frequency
- More consistent and prolonged therapeutic effect
- A greater selectivity of pharmacologic activity

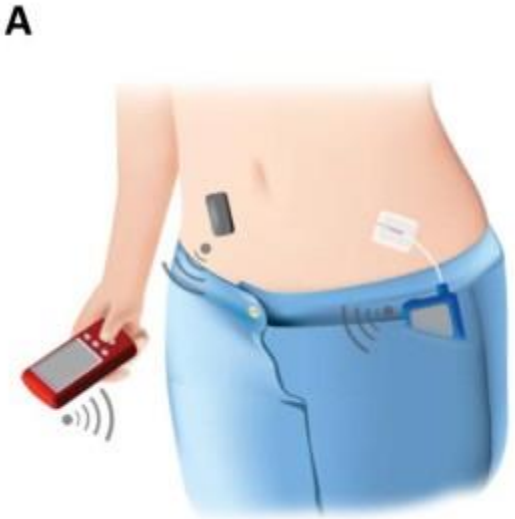
Disadvantages

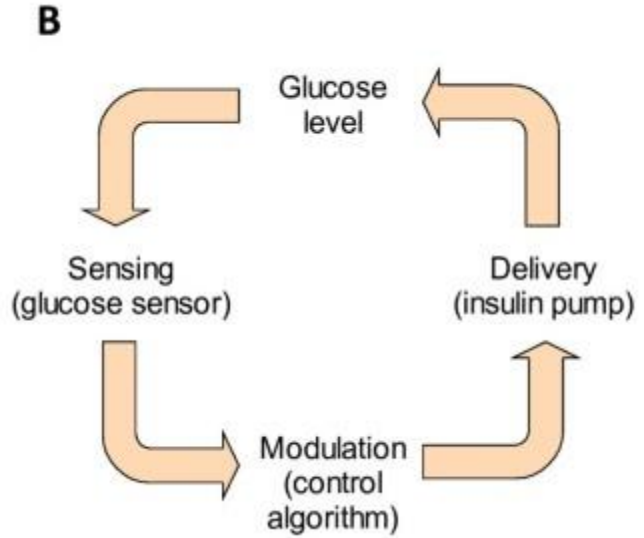
- Increased variability among dosage units
- Stability problems
- Toxicity due to dose dumping
- Increased cost
- More rapid development of tolerance
- Need for additional patient education and counselling

Major Limitations of CDDS

- Delay in onset of action
- The possibility of dose dumping in the case of a poor formulation strategy
- Increased potential for first pass metabolism
- Greater dependence on the gastric residence time of the dosage form
- Possibility of less accurate dose adjustment
- Cost per unit dose is high
- All drug are not suitable for delivery using extended release

Why controlled drug delivery system necessary

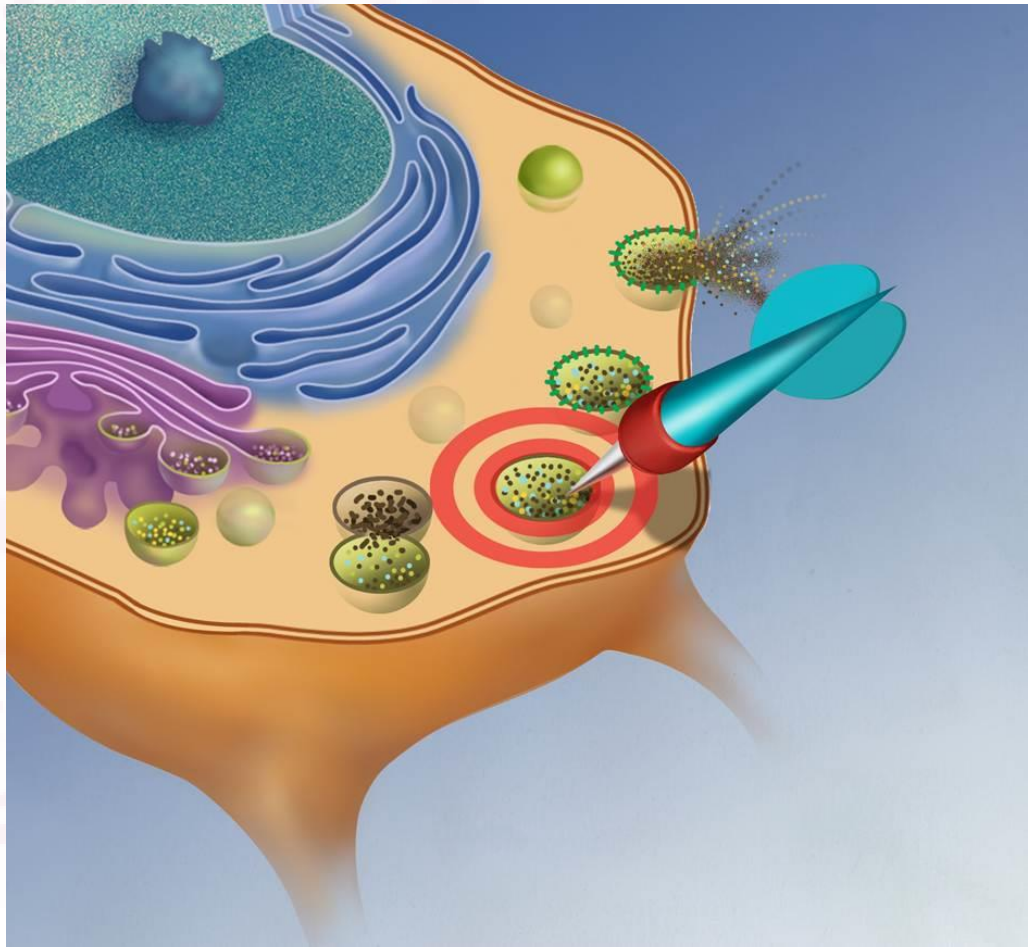




- Recognizing the possibility of repatenting of successful drugs.
- For the delivery of genetically engineered pharmaceuticals i.e. peptides, proteins, enzymes.
- For the delivery of complex biopharmaceuticals i.e. antibodies, nucleic acids, etc – biological inactivation or immunogenicity
- Treating enzyme decifient diseases and cancer therapies
- Reduces size and number of doses
- Deliver the drug at rate dictated by the needs of the body e.g. insulin
- The delivery of drug at constant rate have close relationship with steady state plasma levels and resultant therapeutic response

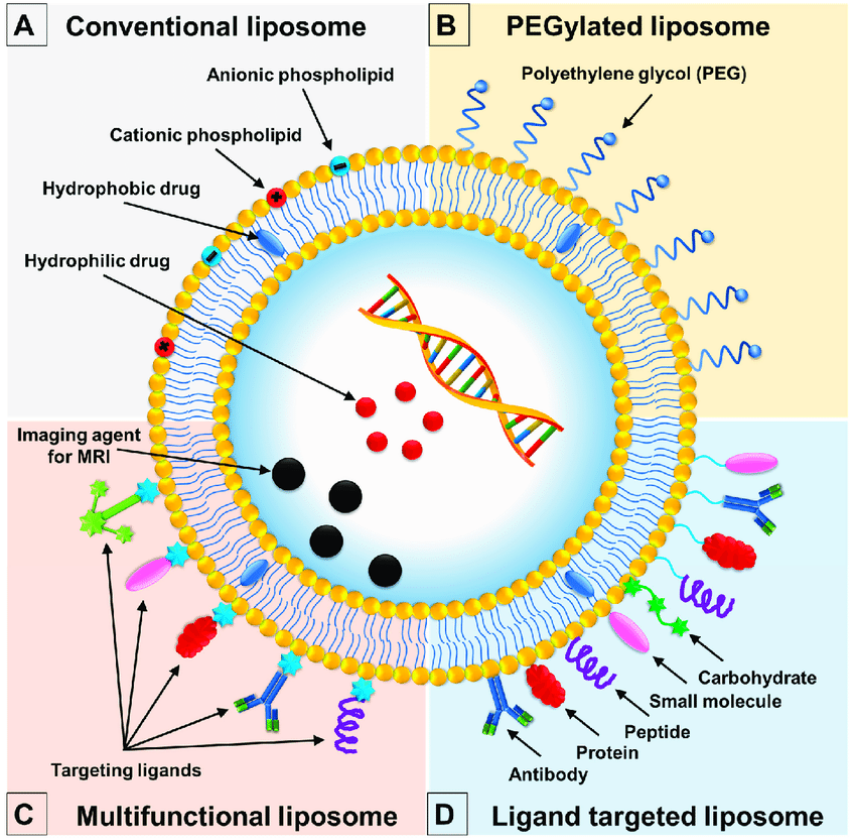
Terminology

- Controlled release system denotes which provide control over release of drug in the body (system attempt to control drug concentration in target tissue or cells)
- Prolonged or sustained release system only prolong the drug concentration in blood or tissue for extended period of time
- Did not have control over release system
- Drug Targeting – it a type of CDDS, exercises spatial control of drug release within body.
- Rate controlled and drug targeting are totally separate approcahes



Terminology

- Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a sawtooth kinetic pattern
- Localize drug action by spatial placement of a controlled release system (usually rate-controlled) adjacent to or in the diseased tissue or organ
- Target drug action by using carriers or chemical derivatization to deliver drugs to a particular "target" cell type

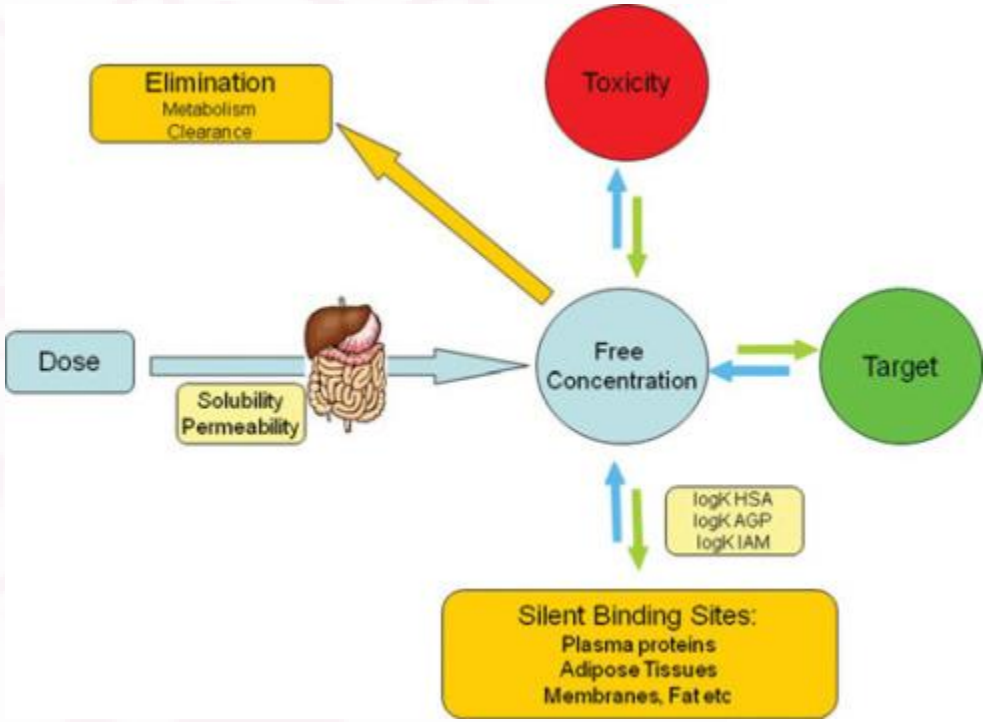


Terminology

- Release system creates constant concertation of drug over the extended period of time.
- It is assume that drug should be placed at the targeted site, leaving rest of the body drug free
- May be it a tissue
- Population of cells or receptors
- It is very difficult to control the delivery due to various biological barriers like blood brain barrier limits delivery of drug to the brain.

Terminology

- It is difficult to control the elimination rate from plasma or target tissue
- Release rate from controlled system should be equal to elimination rate from targeted site
- In conventional approaches, intravenous infusion use to control the blood plasma levels
- Oral route or transdermal route may also use in certain cases as non invasive route of administration

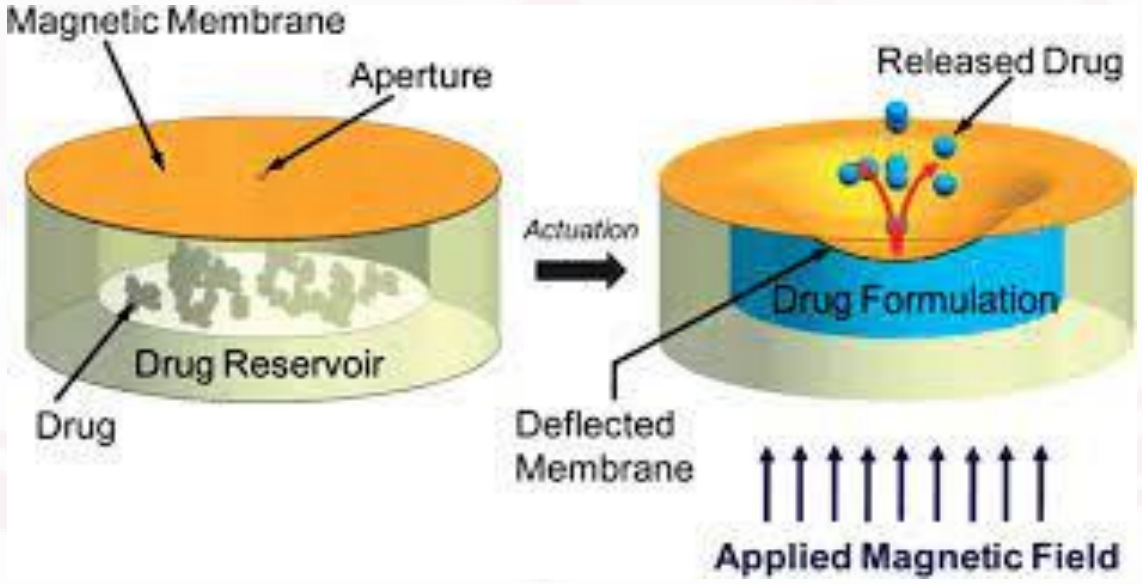


Terminology

- Smart, Targeted, Intelligent, Novel, Therapeutic, etc. interchangeable terms use for controlled release system.
- Advanced engineered system consist of logic element with or without sensor.
- 3 major therapeutic systems were classified
  - Passive Preprogrammed
  - Active Preprogrammed
  - Active Self Programmed
- The rate controlled release system fall under the category of **Passive preprogrammed**

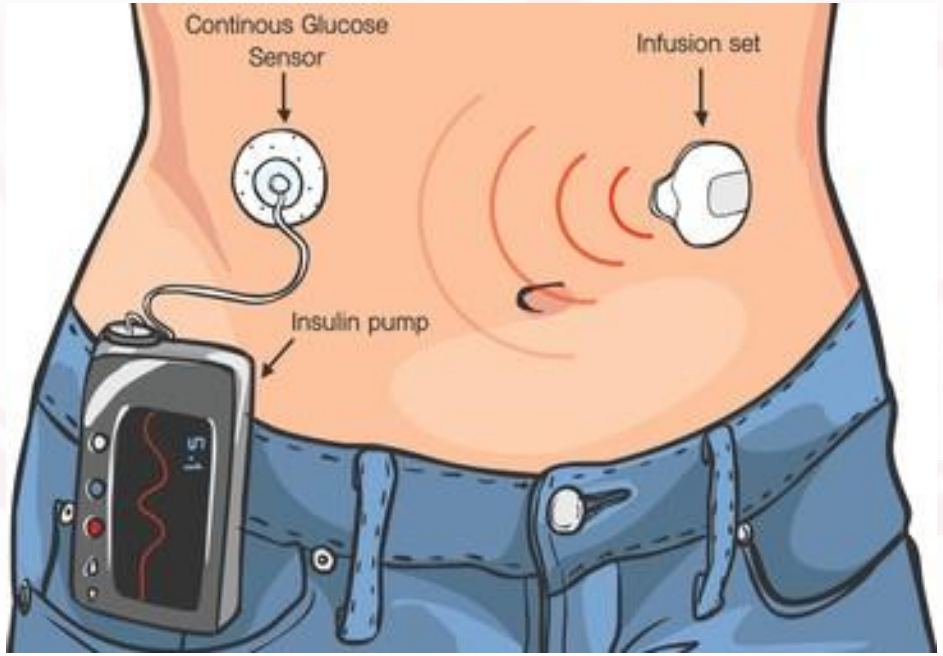
Passive Preprogrammed

- Release rate was predetermined and irresponsive to the external biological environment



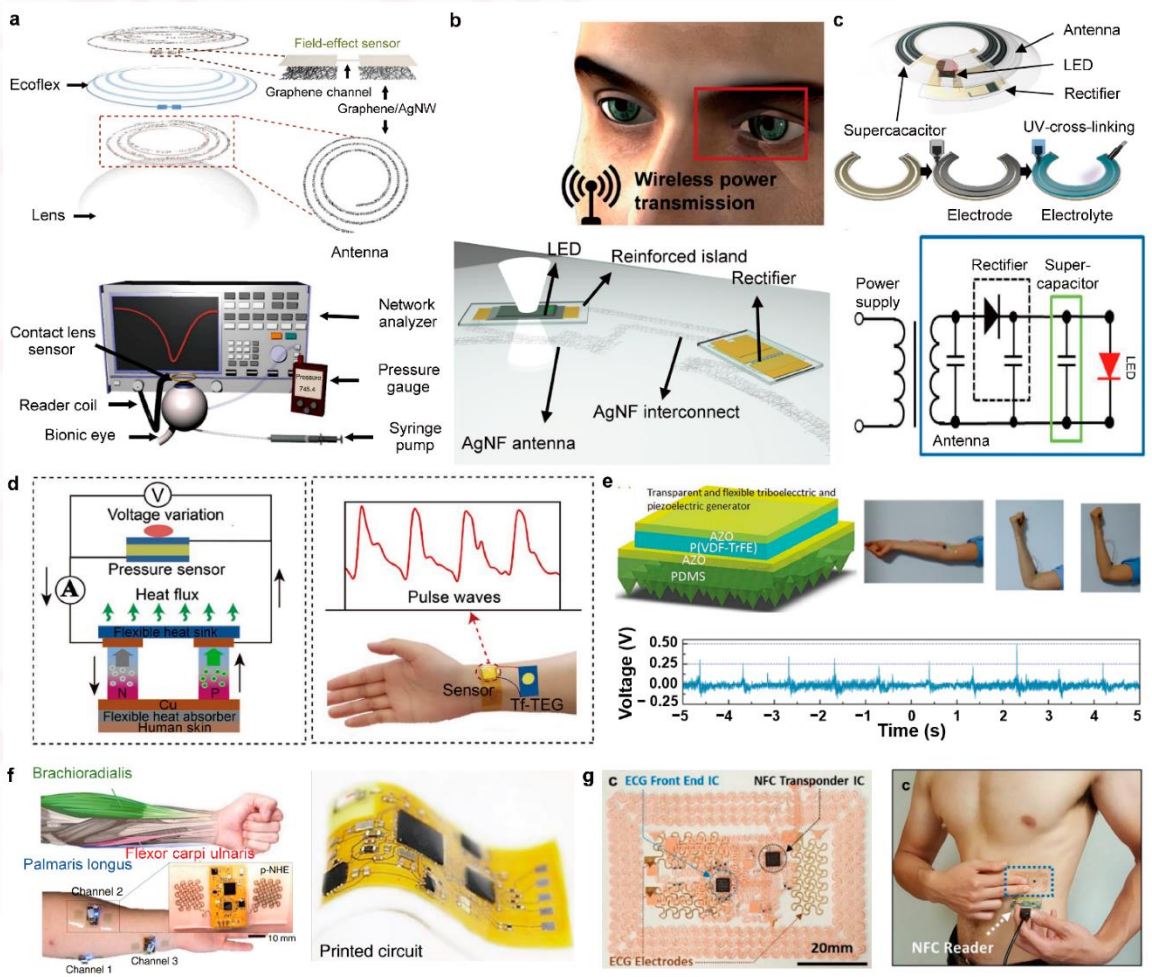
Active Preprogrammed

- Metered Insulin Pump
- Release can be altered by external source associated to the body



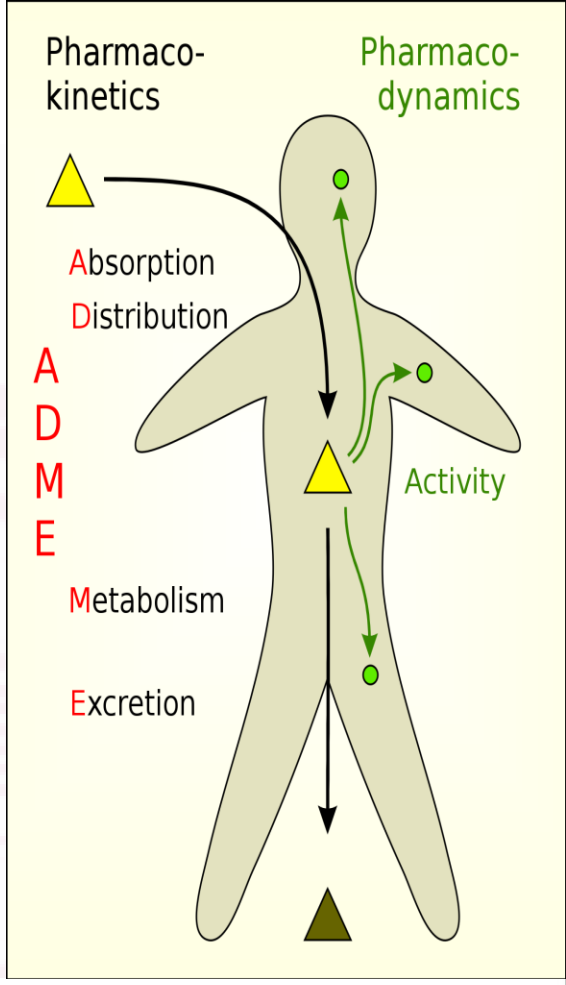
Active Self Programmed

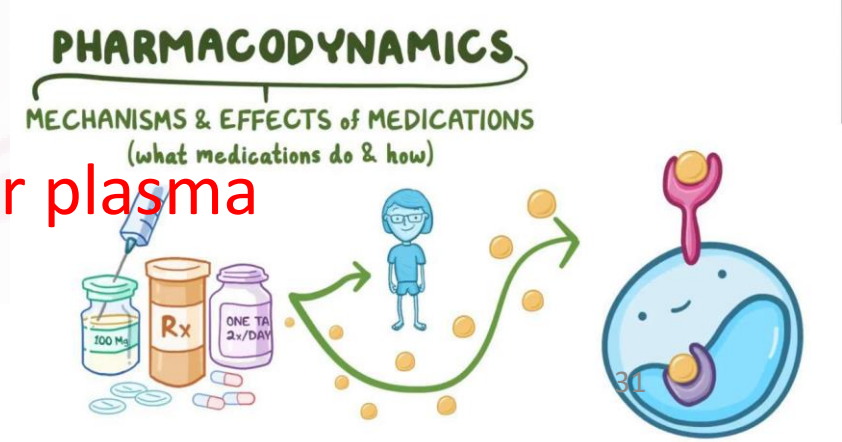
- Modulates release rate of drug in response to information registered by sensor
- By change in the biological environment such as blood sugar level in diabetes



Rational for Designing Controlled Release Dosage form

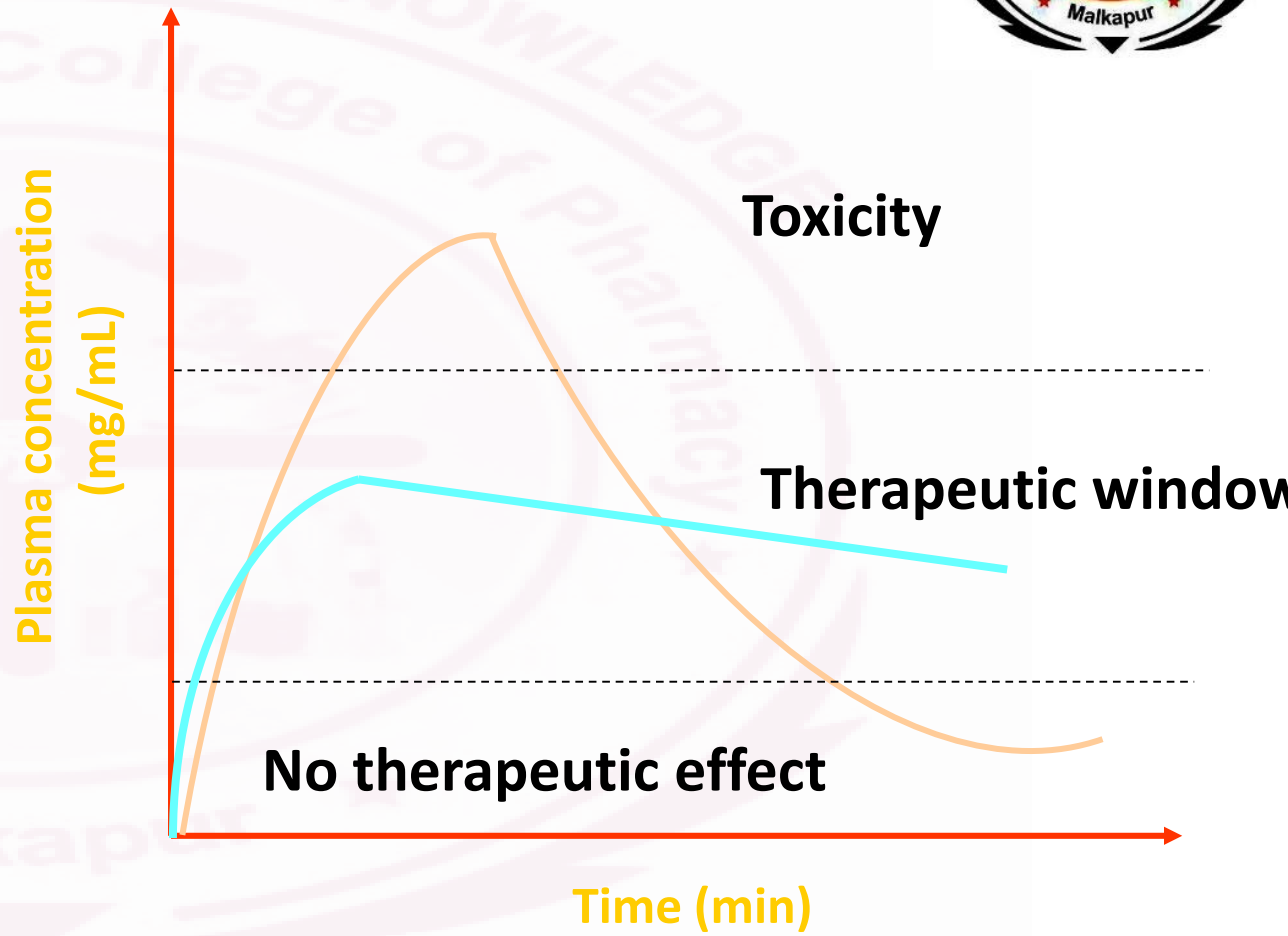
- Alter pharmacokinetic and pharmacodynamics of pharmacological active moieties
- Modification of molecular structure or physiological parameters for selected route of administration
- Drug action is designed property of rate controlled system and not the drug itself.
- The rate controlled drug delivery system ensure safety, improve efficacy and patient compliance
- Frequent dosing was minimized and better control over plasma concentration levels





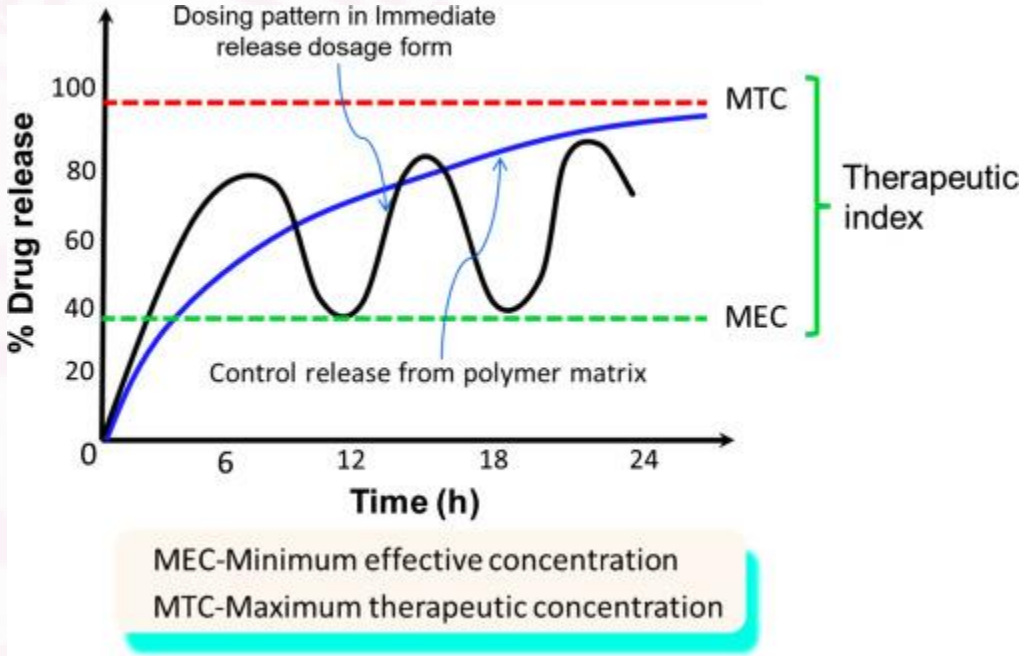
Rational for Designing Controlled Release Dosage form

- Conventional Dosage forms has variable dose and dosing interval
- The therapeutic window below which no therapeutic effect exist
- Above therapeutic window toxic effect was elicited
- Ratio of Median lethal dose (LD50) to median effective dose (ED50)
- Maximum drug concentration (Cmax) in blood that tolerated to minimum concentration (Cmin) needed to produce therapeutic effect



Rational

- The drug disposition shows pronounced linear one compartment characteristics. It has relationship between dosing interval and therapeutic index
- $\tau = \frac{t_{\frac{1}{2}}(lnT_1)}{ln2} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 1$
- Where $t_{1/2}$ – half life
- It will be necessary to dose the patient shorter than half life
- The half life replaced with mean residence time



Rational

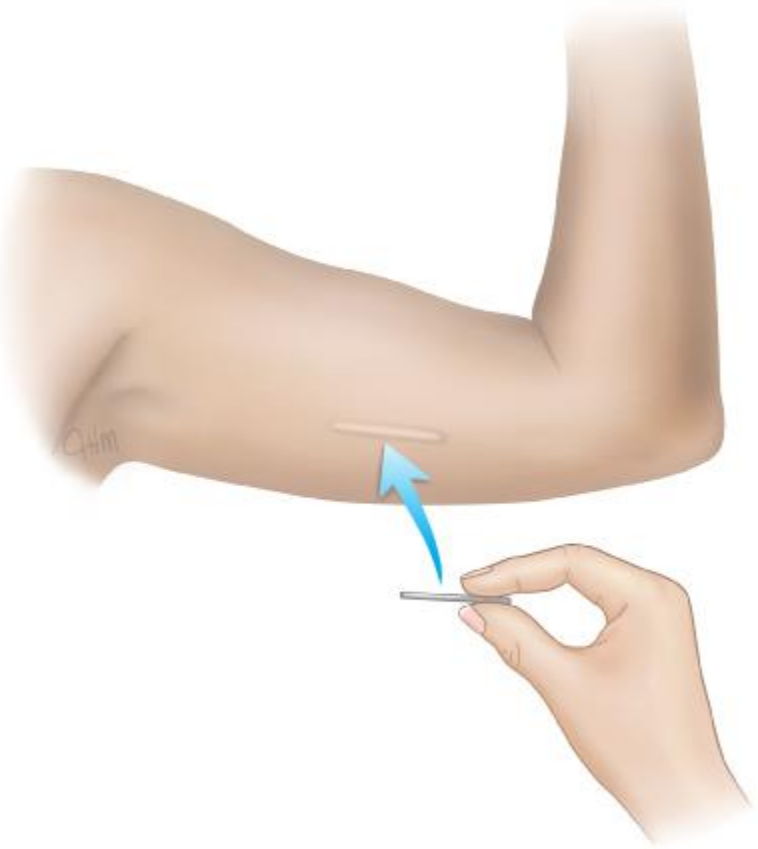
- Dosing – Interval can be decreased modification of drug molecule by decreasing rate of elimination (Kel)
- Modifying release rate of a dosage form to decrease rate of absorption (Kab)
- Kel and Kab may decreases the fluctuation in plasma levels during multiple dosing
- Helps to increase dosing interval without overdosing or under dosing
- For extension of rate of absorption formulation understand the physiological constraints of finite residence time at the absorption site
- E.g. if effective absorption time of drug is 9 – 12 h for orally administered drug, where lowering rate of absorption may pass the drug into large intestine and bacteria start degradation of drug.
- If half life is 6h then drug interval must be given not less than 12 h

Table 1. Usual Ranges of Therapeutic Serum Concentrations and Terminal Half-Lives in Humans

Drug substance	Therapeutic serum concentrations[a] (C^*_{min} to C^*_{max})	Terminal half-lives[b]
Digitoxin	14–30 µg/liter	6.3–11.3 days
Digoxin	0.9–2 µg/liter	1.4–2.2 days
Lidocaine	1.5–5 mg/liter	1.2–1.7 hr
Lithium	0.5–1.3 mEq	14.2–24.1 hr
Nortriptyline	50–140 µg/liter	18.2–35.0 hr
Phenytoin	10–20 mg/liter	18.7–27.6 hr
Procainamide	4–8 mg/liter	2.5–4.7 hr
Propranolol	20–50 µg/liter	1.1–9.9 hr
Quinidine	2–5 mg/liter	3.0–16.0 hr
Salicylates	150–300 mg/liter	2.9–22 hr
Theophylline	10–20 mg/liter	5.3–8.3 hr

[a]Data were obtained from Koch-Weser [26].
[b]Data were obtained from Pagliaro and Benet [27].

Rational



- For other routes of administration, residence time is not the constraint
- The dosing interval can be lengthened to months or even years
- E.g. implants containing contraceptives may be effective for a year or two.

Rational

Progestin	Proprietary name	Number of units	Lifespan according to license	Countries registered in
LNG	Norplant	Six capsules	5 years	–
LNG	Jadelle®	Two rods	5 years	47
LNG	Sino-implant (II)	Two rods	4 years	19
ENG	Implanon NXT/ Nexplanon	Single rod	3 years	80

Notes: Norplant (Wyeth-Ayerst Laboratories, Philadelphia, PA, USA). Jadelle® (Bayer Schering Pharma, Turku, Finland). Sino-implant (II) (Shanghai Dahua Pharmaceuticals Co., Ltd, Shanghai, China). Implanon NXT®/Nexplanon® (Merck & Co, Inc., Whitehouse Station, NJ, USA).

Selection of Drug Candidate

- Drug candidate selection is difficult part of drug formulation development
- Failure leads to loss of valuable time and money
- All drug can not be suitable delivery using controlled drug delivery system
- Following strategy teaches us for lead optimization and selection of appropriate candidate for CDDS
  - Solubility
  - Partition coefficients
  - Oral bioavailability
  - salt and crystal forms
  - chemical stability

Selection of drug candidate

Parameter :	Preferred value
Molecular weight/ size:	< 1000
Solubility:	> 0.1 µg/ml for pH 1 to pH 7.8
Pka Non ionized moiety:	> 0.1% at pH 1 to pH 7.8
Apparent partition coefficient:	High Absorption
mechanism:	Diffusion
General absorbability:	From all GI segments
Release:	Should not be influenced by pH and enzymes

Selection of drug candidate

- Drug must posses characteristics suitable for controlled drug delivery
- Drugs having
  - Very short elimination half life
  - Very long elimination half life
  - Narrow therapeutic index
  - Rate of absorption
  - Mechanism of absorption
  - First Pass effect

Selection of Drug

- Physicochemical properties of drugs is most important for identifying performance of carrier or vice versa
- Physicochemical properties restrict or prohibit the place of drug in sustained or controlled release dosage form
- Significantly modify the performance
- Biological functional of drug is related to physicochemical properties
- Physicochemical properties are those that are determined from physicochemical experiment
- Biological properties are those that are determined from *In-vivo* experimental conditions like absorption, distribution, metabolism and excretion (ADME) as well as resulting from pharmacological studies

Selection of Drug

- **Aqueous Solubility**
- Based on solubility of drug in aqueous environment it get absorbed
- In some cases the site of absorption may be in the area of less soluble drug
- E.g. tetracyclin dissolves completely in stomach but highly absorbed in intestine
- Such drugs may be poor candidate for sustained/controlled release system.
- The system can be fabricated in a such way that the formulation will retained in stomach and gradually released into intestine
- Or by encapsulation of weakly basic drug with acidic polymer (weakly acidic drug with basic polymer)

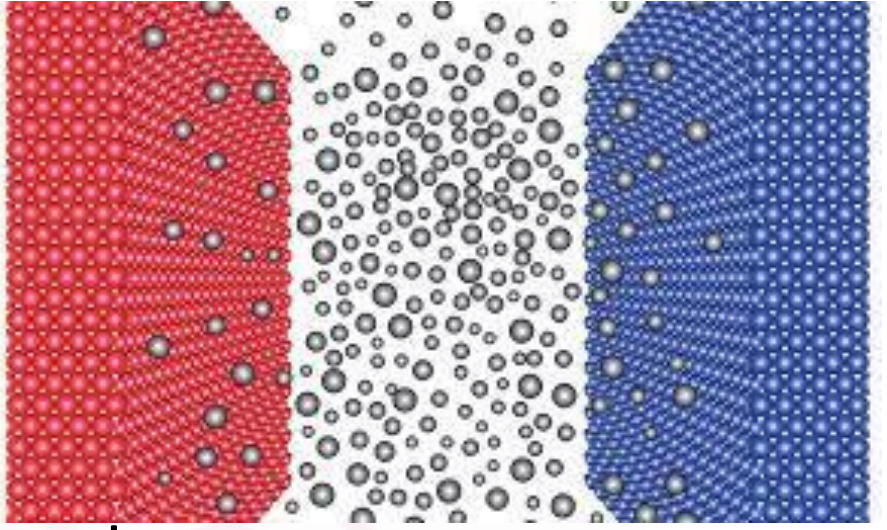
Selection of Drug

- **Aqueous solubility**
- Drugs having limited absorption by dissolution rate
  - Digoxin
  - Warfarin
  - Griseofulvin
  - Salicylamide.
- The activity can be prolonged by decreasing the solubility of drug
  - But this will occur inconsistent and incomplete bioavailability
- Diffusion system also has poor choice for slightly soluble drug
  - Driving force required for lower aqueous conc. will be decreases

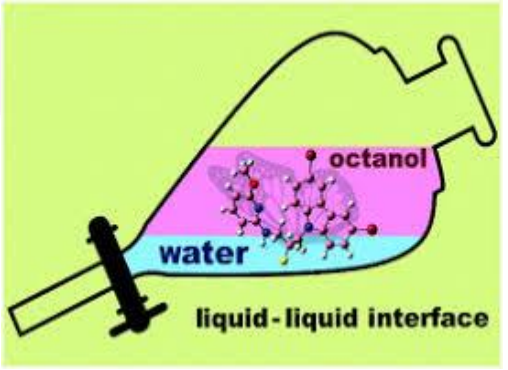
Selection of Drug

- **Aqueous Solubility**
- The selection of appropriate polymer for composite is bitterly impact on the distribution rate of drug
- Some antibiotics have good to excellent solubility but poor dissolution rate
- Slow dissolution of such drugs helps to achieve controlled drug release after incorporation into matrix system (Dissolution limited bioavailability may occur)
- Aqueous soluble drugs have limited loading efficiency in liposomes, microparticles, etc. and tend to leak out from the carriers

Selection of Drug

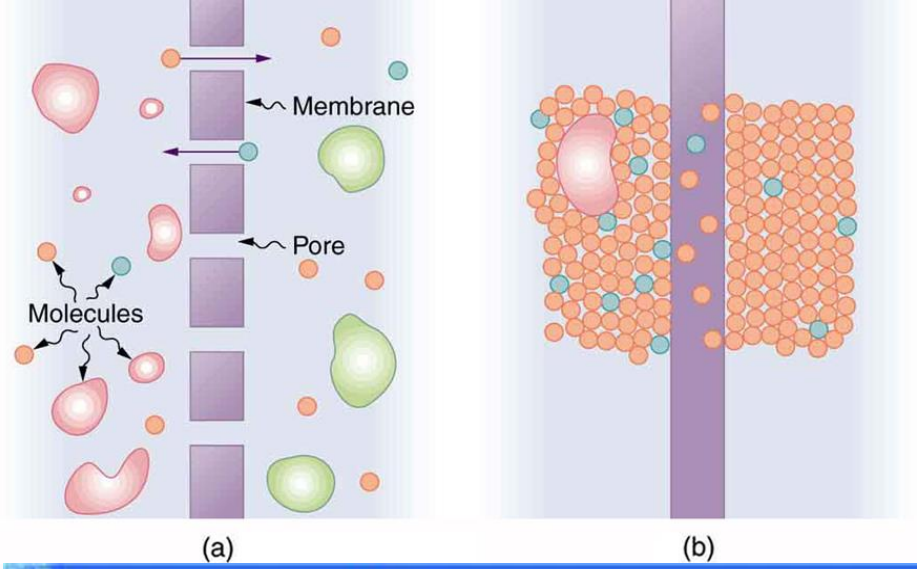


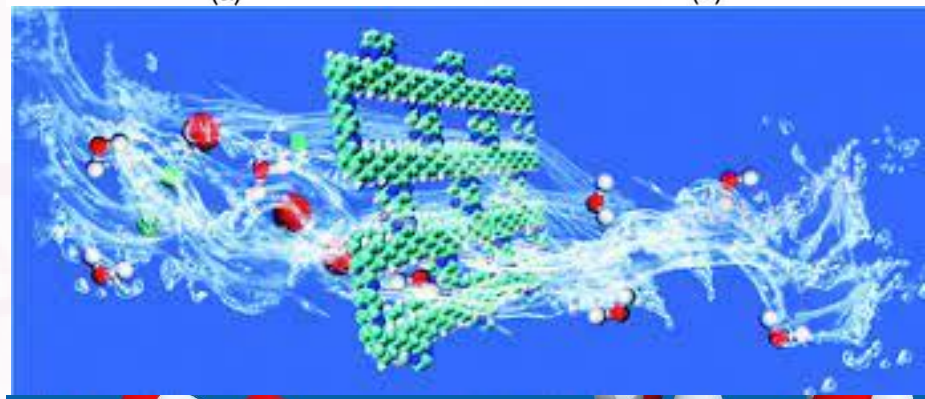
- **Partition Coefficient and Molecular Size**
- The factors influence permeation across biological membrane and diffusion across membrane or matrix
- Drugs with high pKa value (oil soluble drugs) readily permeated across membrane but unable to proceed further
- Drugs with low pKa value (water soluble drugs) cannot penetrate easily
- Balance in pKa is need to achieve optimum flux.
- Optimum n-octanol/water partition coefficient provides maximum flux approx. 1000

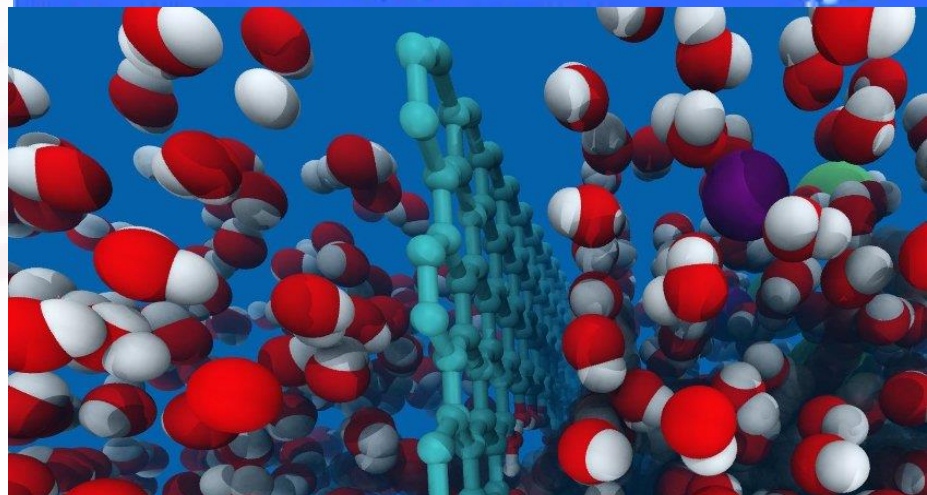


Selection of Drug

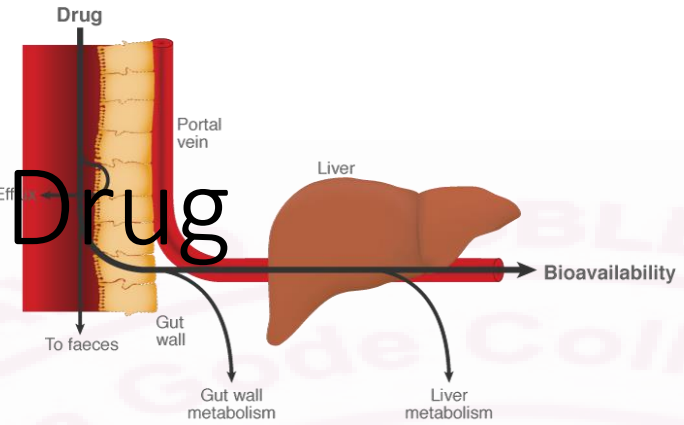
- **Partition Coefficient**
- The ability of drug diffuse through membrane is called diffusivity
- Diffusivity is related to molecular size as given by following equation
- $Log\ D = -S_v \log V + \ k_v = -s_M \log M + k_M$
- Where D- diffusivity, M – Molecular weight, V- Mol volume, S_v, S_M, k_V and k_M – constant for particular medium
- In Denser medium diffusivity decreases, while in lighter medium diffusivity was much higher
- Drugs having 150 – 400 D molecular weight have diffusivity in polymer medium was 10^{-8} cm^3sec^{-1}.

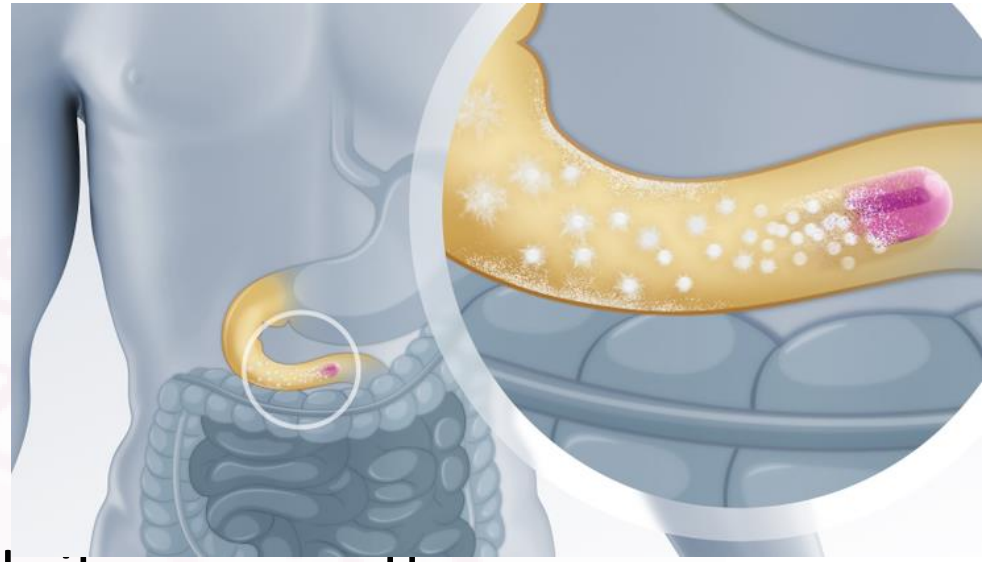






Selection of Drug

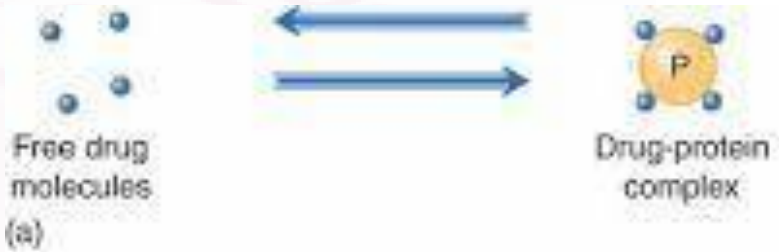


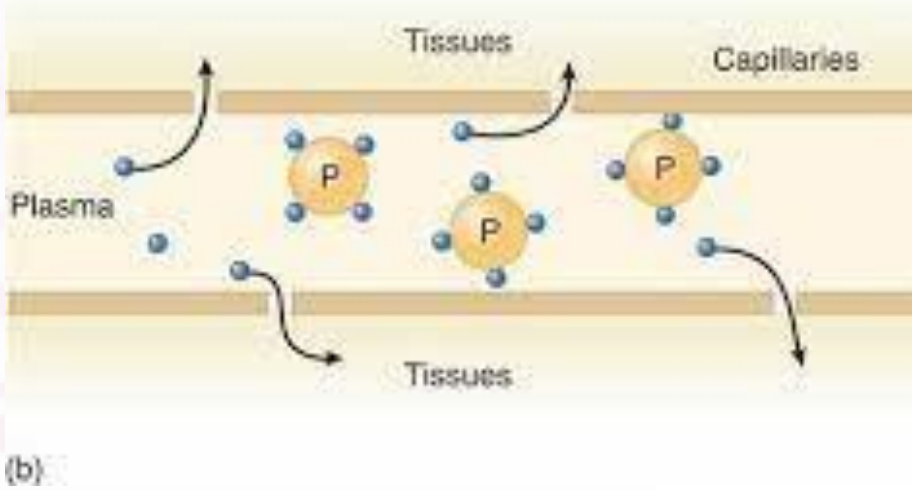


- **Drug Stability**
- Exposure of drug into the environment at the targeted site ensures the drug stability
- The stability consideration is depends on physicochemical characteristics
- The drugs that are unstable in stomach are modified to lower soluble form or delayed release until reach to the small intestine
- Unsuitable for the drugs like unstable in small intestine or extensive gut wall metabolism
- E.g. nitroglycerin is unstable in small intestine could not been administered using controlled release system.

Selection of drug

- **Protein Binding**
- Many drugs bind to plasma affects duration of drug action
- Blood proteins are recirculated without elimination
- Drug protein binding provides prolong drug release profile
- Quaternary ammonium compound bind to mucin in GI tract
- Drug bound to mucin increases absorption rate if bound drug act as depot
- After washing or degradation, the total concentration of drug decreases at absorption site





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Thank you...!!!