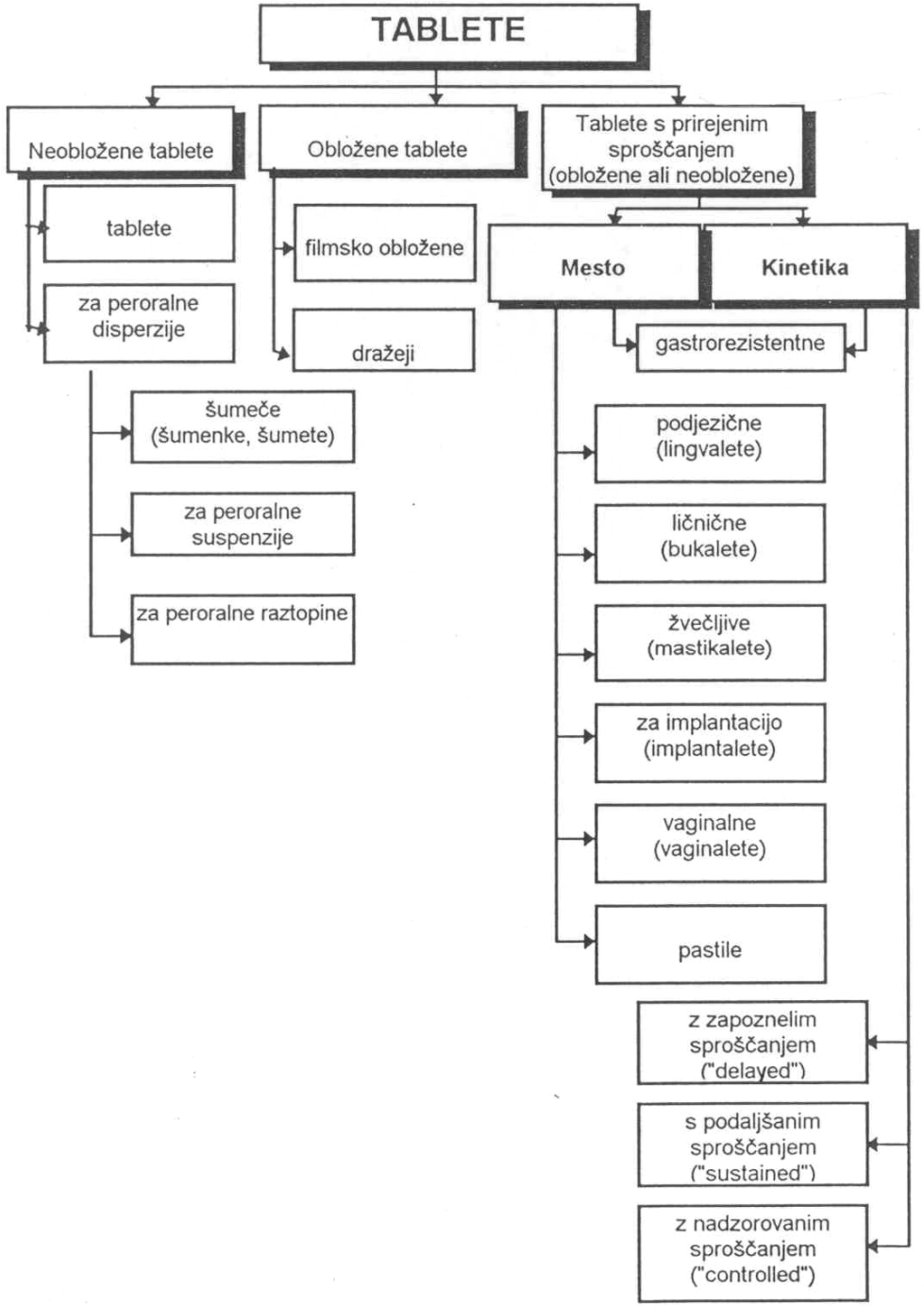


Modified release tablets

TERMINOLOGIJA

Table 1: Some names associated with oral sustained – release dosage forms

Constant release	Prolonged action
Continuous action	Prolonged release
Continuous release	Protracted release
Controlled action	Repeat action
Controlled release	Repository
Delayed absorption	Retard
Delayed action	Slow acting
Delayed release	Slowly acting
Depot	Slow release
Extended action	Spaced release
Extended release	Sustained action
Gradual release	Sustained release
Long acting	Sustained release depot
Long lasting	Timed coat
Long-term release	Timed disintegration
Programmed release	Timed release

4 glavne skupine:

- zakasnjeno sproščanje (delayed release)

- zadržano sproščanje (sustained release)

- večkratno/ponovljivo sproščanje (repeat release)

- kontrolirano sproščanje (controlled release)

USP XXI: modified release (spremenljivo/modificirano sproščanje): modificira čas in kraj sproščanja učinkovine iz pripravka; le 2 tipa pripravkov:

- **extended release (podaljšano sproščanje)**
- **delayed release (zakasnjeno sproščanje)**

Tudi v USP XXII (1995) je izraz "modified release" še definiran kot v USP XXI (tablete in kapsule) – enako kot extended in delayed release (2 tipa).

Ustrezni “dissolution testi” (po USP)

SPLOŠNO: oblike, ki delujejo daljši čas – biotransformacija in eliminacija sta podaljšani ($t_{1/2}$ je večji).

- retard oblike: ustrezen nivo koncentracije je vzdrževan skozi daljši čas

- depo oblike: sproščanje in absorpcija iz depoja (“skladišče”)

- npr. implantanti, oljna suspenzija i.m., hidroliza estra ...

RAZVOJ

Osnovna naloga "controlled release drug delivery systems" včasih

- zagotoviti sproščanje ničelnega reda:

- problem velike molekule (peptidi)

- ni 0. red vedno najbolj primeren

Razvoj novih biokompatibilnih polimerov – jih primanjkuje → ni razvoja implantantov.

Še v 50-ih letih so kadili "medicinske cigarete" pri astmi (do 60-ih). Veljalo je načelo – "delivery system" naj ne povzroča nobene škode; le nosilec učinkovine, ki ne razgrajuje učinkovine in omogoča polno razpoložljivost učinkovine telesu.

Pozna štirideseta leta – prvi pripravki z zadržanim sproščanjem komercialno dosegljivi – Smith, Kline&French. Ekonomsko in terapevtsko – slabo.

Pozna šestdeseta leta – dejanska doba "drug delivery systems" – ALZA Corporation (produkt je bil "controlled release product" – zanesljiv, ponovljiv sistem, katerega hitrost sproščanja ni odvisna od okolja, kjer se pripravek nahaja).

Table 2: Factors Influencing the *In Vivo* Performance of Sustained Release Dosage Formulatins

Physiological

- Prolonged drug absorption
- Variability in GI emptying and motility
- Gastrintestinal blood flow
- Influence of feeding on drug absorption

Pharmacokinetic/biochemical

- Dose dumping
- First-pass metabolism
- Variability in urinary pH: effect on drug elimination
- Enzyme induction/inhibition upon multiple dosing

Pharmacological

- Changes in drug effect upon multiple dosing
- Sensitization/tolerance

Table 3: Terminology

FDA Controlled release dosage forms	USP Modified release dosage forms
Oral dosage	
1. Prolonged release drug products	1. Extended release
2. Delayed release drug products	2. Delayed release
Intramuscular dosage	
1. Depot injections	
2. Water immiscible injections (i.e., oils)	
Cutaneous/subcutaneous dosage	
1. Implants	
2. Transdermal preparations	
Targeted dosage	
1. Ocusert	
2. Intrauterine devices (IUDs)	

Sustained release drug delivery systems

Razvoj teh sistemov odvisen od različnih faktorjev (Table 4).

Table 4: Factors influencing design of drug delivery system.

Factor	Considerations
Physicochemical propertiesof the drug	Aqueous solubility of the drug Size of the dose Stability of the drug Molecular size and diffusivity of the drug Partition coefficient of the drug pK_a of the drug Protein binding Type of dosage form
Biological properties of the drug	Absorption characteristics of the drug Biological half-life of the drug Body movement Distribution characteristics Duration of action of the drug Margin of safety of the drug Metabolism of the drug Role of diurnal variation Drug administration route Side effects of the drug

Factor	Considerations
Patient/disease factors	Acute or chronic therapy required Age and physiological state of the patient Ambulatory or bedridden patient Circadian changes in disease Duration of drug action desired Location of target area Pathology of disease state Route of drug administration

TEHNOLOGIJA IZDELAVE

Metode za zagotovitev zadržanega sproščanja:

1) biološke ali medicinske metode

2) kemijske metode

3) farmacevtske metode

Ad 1): Sprememba fizikalno-kemijskih in/ali bioloških lastnosti okolja.

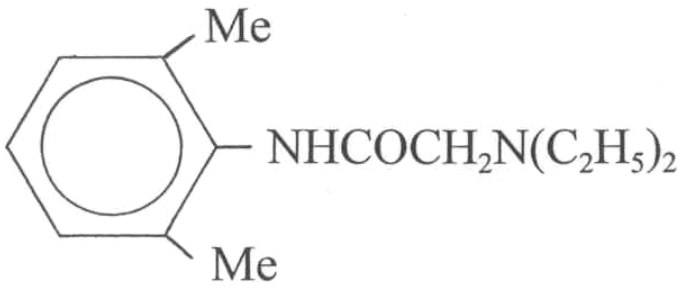
Aplikacija spojine 2.

- sprememba $t_{1/2}$ - inhibicija encimov

Ad 2): Sprememba fizikalno-kemijskih lastnosti učinkovine.

- sinteza analogov

lidokain



Me : H

- sinteza predzdravil (prodrugs)

kloramfenikolpalmitat – netopen in brez okusa, hidrolizira v GIT do kloramfenikola

Ad 3): Sprememba (oblikovanje) pripravka samega → preko spremenjene hitrosti raztapljanja, difuzije, ionske izmenjevalne smole idr.

NAČINI ADMINISTRACIJE

OSNOVNI: - oralno
- perkutano (absorpcija za sistemski učinek)
- parenteralno

OSTALI: bukalno, nazalno, v uterus, v oči idr.

ORALNO: pH, encimi, pretočnost ipd. Za absorpcijo sta najpomembnejša želodec in tanko črevo.

Tanko črevo: - 6 do 7 m dolgo (4.5 – 9.5 m)
- površina 3,5 m^2; z makro in mikrovili 10 – 30x večja; efektivna površina cca. 100 m^2

Vsebina želodca – tekoča; vzdolž GIT – na koncu tankega črevesja – "pasta".

Dozirne oblike: tablete, kapsule. Tekoče – redko (suspenzije, viskozni materiali).

- absorpcija v želodcu (lepljenje na steno, plavajoče tablete, nabrekanje)
- interakcije s substancami v GIT, metabolizem, flora

Čas prehoda skozi GIT: duodenum 5 min, jejunum 2 h, ileum 3 – 6 h (efektivni tranzitni čas).

GIT – želodec – konec tankega črevesja ~ 12 h

Sproščanje učinkovine: po 7 – 8 h več kot po 3 – 5 h

PERKUTANA ABSORPCIJA (SISTEMSKO DELOVANJE):

- **transdermal delivery system**
- **nitroglicerin prvi**

Koža – nepropustna bariera:

- **permeabilnost – pasiven proces**
- **proces raztapljanja in molekularne difuzije**
- **glavna bariera – stratum corneum**
- **stratum corneum – dvofazna lipido/proteinska heterogena membrana**
- **permeabilnost membrane korelira z vodotopnostjo in logP (lipid/protein)**
- **difuzija makromolekul bistveno nižja kot večina učinkovin**

Hitrost in obseg absorpcije skozi kožo zavisi:

- koncentracija učinkovine v pripravku

- narava topila, v katerem je učinkovina

- kontaktna površina

- “narava kože” (spol, starost, del telesa, bolezensko stanje, ...)

Primerne učinkovine za transdermalno aplikacijo:

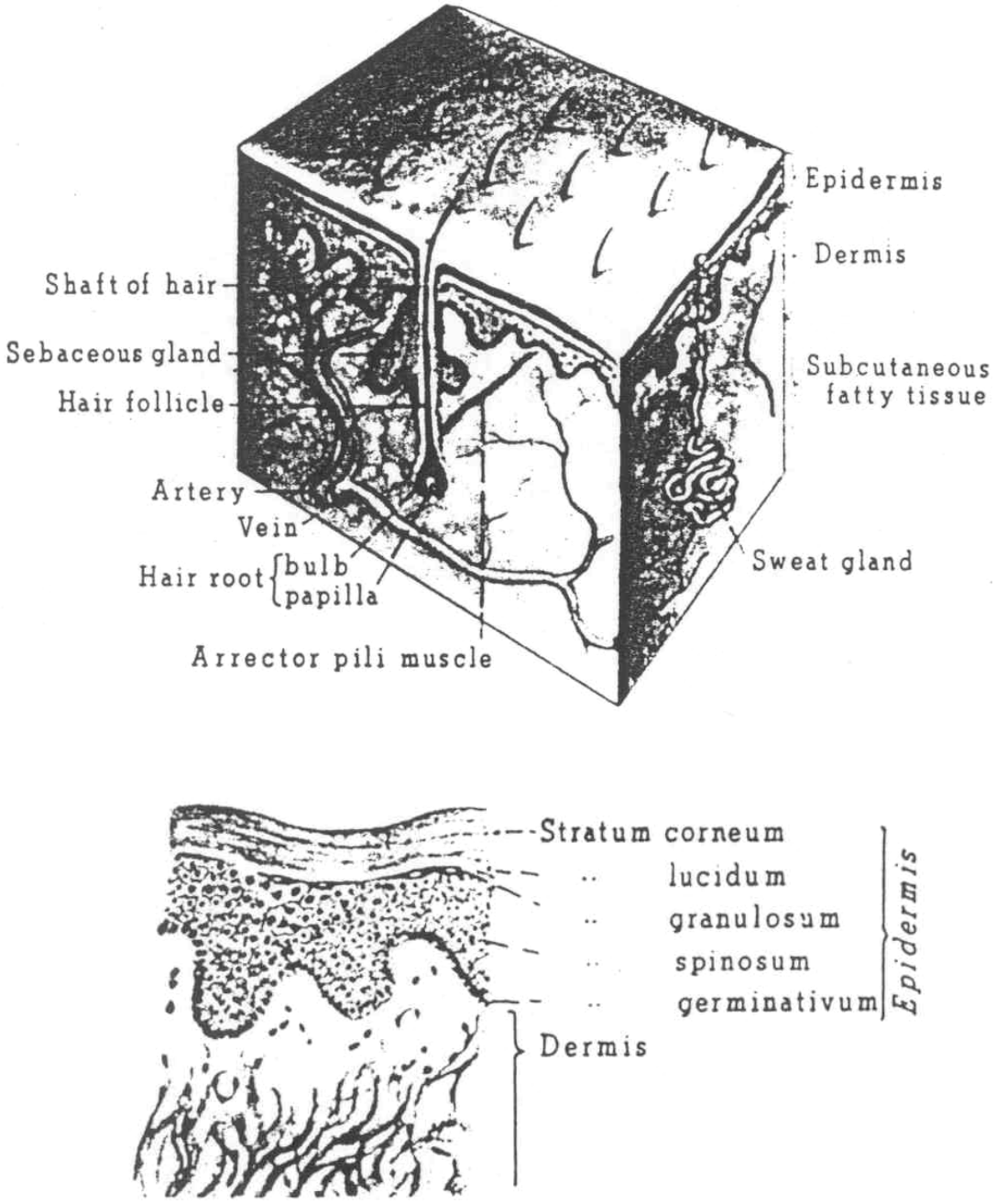
- učinkovite

- “first pass efekt”

- kratka razpolovna doba

- so lipofilne – problematične z vidka “prijaznosti” do pacienta

Figure 1: Three – dimensional view of the skin showing various skin tissue layers and appendages and cross – sectional view of various epidermal layers and the dermis. (From Jacob and Francone, 1970.)



PARENTERALNA ADMINISTRACIJA:

- intravenozno, intramuskularno, subkutano

- IV infuzija (mobilne infuzijske črpalke in implantanti kot “delivery devices”)

- IM, SK aplikacija: oljne raztopine, vodne in nevodne suspenzije, emulzije, pelete

- raztopina se obori “in situ” na mestu aplikacije (zaradi pH)

Hitrost in obseg absorpcije IM in SK injekcije zavisi od: pK_a, velikost molekul, difuzijski koeficient učinkovine, tip dozirne oblike (emulzija, oljna razt. idr.), temperatura in cirkulacija krvi na mestu aplikacije; gibanje pacienta, volumen in koncentracija učinkovine v injekciji.

Problemi – bolečine, poškodba tkiva.

ZADRŽANO SPROŠČANJE – PARENTERALNI PRIPRAVKI

- Kontinuirana IV infuzija razt. učinkovine

Najpomembnejši aplikaciji:

- subkutana in intramuskularna: obe aplikaciji sta bioekvivalentni

Subkutano – za neiritirajoče, vodotopne spojine: vol. injiciranja 0,5 – 1,5 mL

Intramuskularno – večji volumen (1 – 6 mL)

Factors Affecting Absorption from a Parenteral Sustained – Release Drug Delivery System

1. The pK_a of the drug
2. The pH of the formulation
3. The lipophilicity of the drug molecule
4. The solubility of the drug in biological fluids at the site of injection
5. The partition coefficient (in the tissue fluid and formulation vehicle) of the drug
6. The particle size of the drug molecule
7. The type of crystal of the drug molecule
8. The dissolution rate of the drug particles in the formulation vehicle
9. The presence and interaction of other ingredients in the formulation

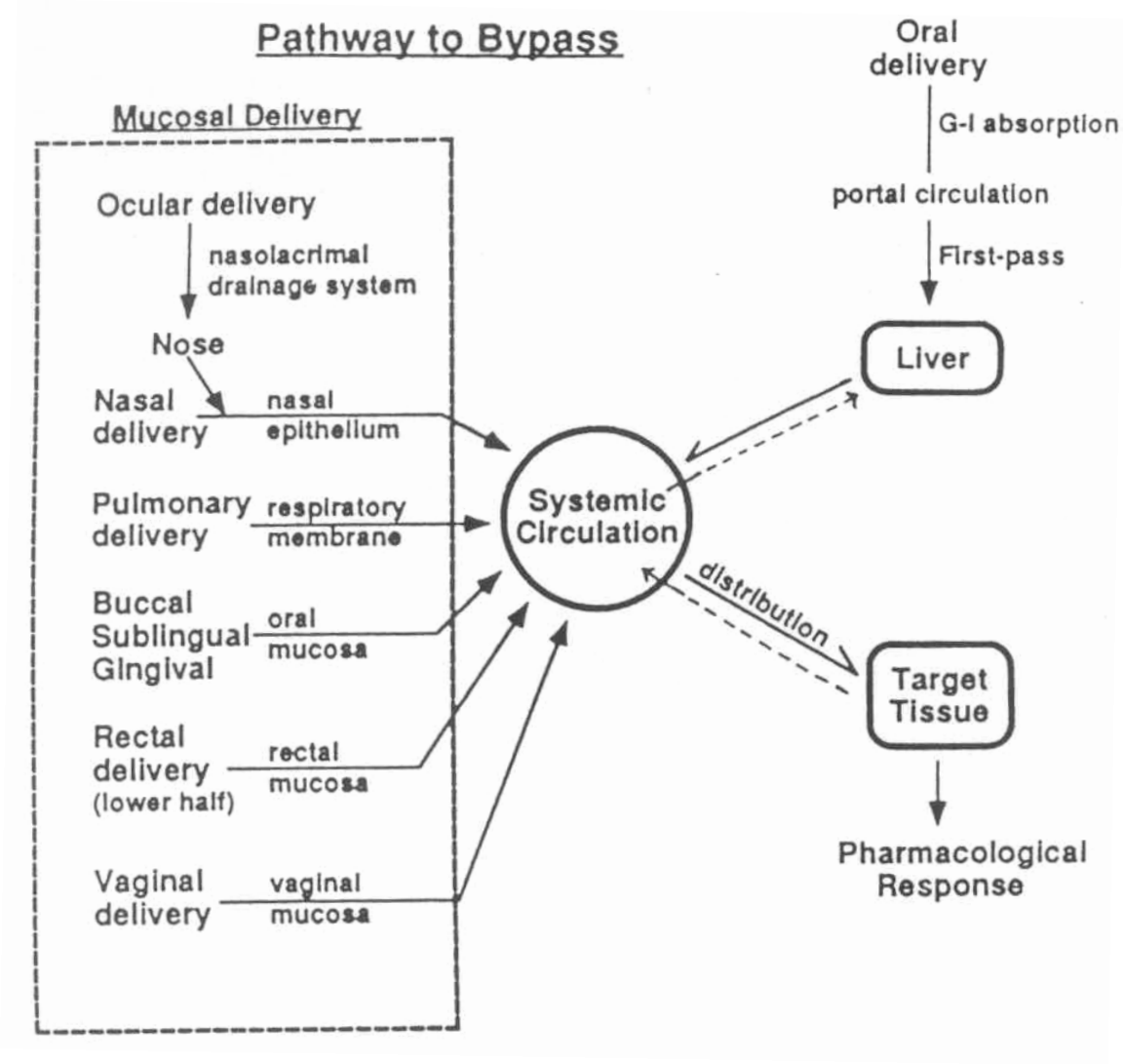
Methods used in parenteral sustained – release drug delivery systems:

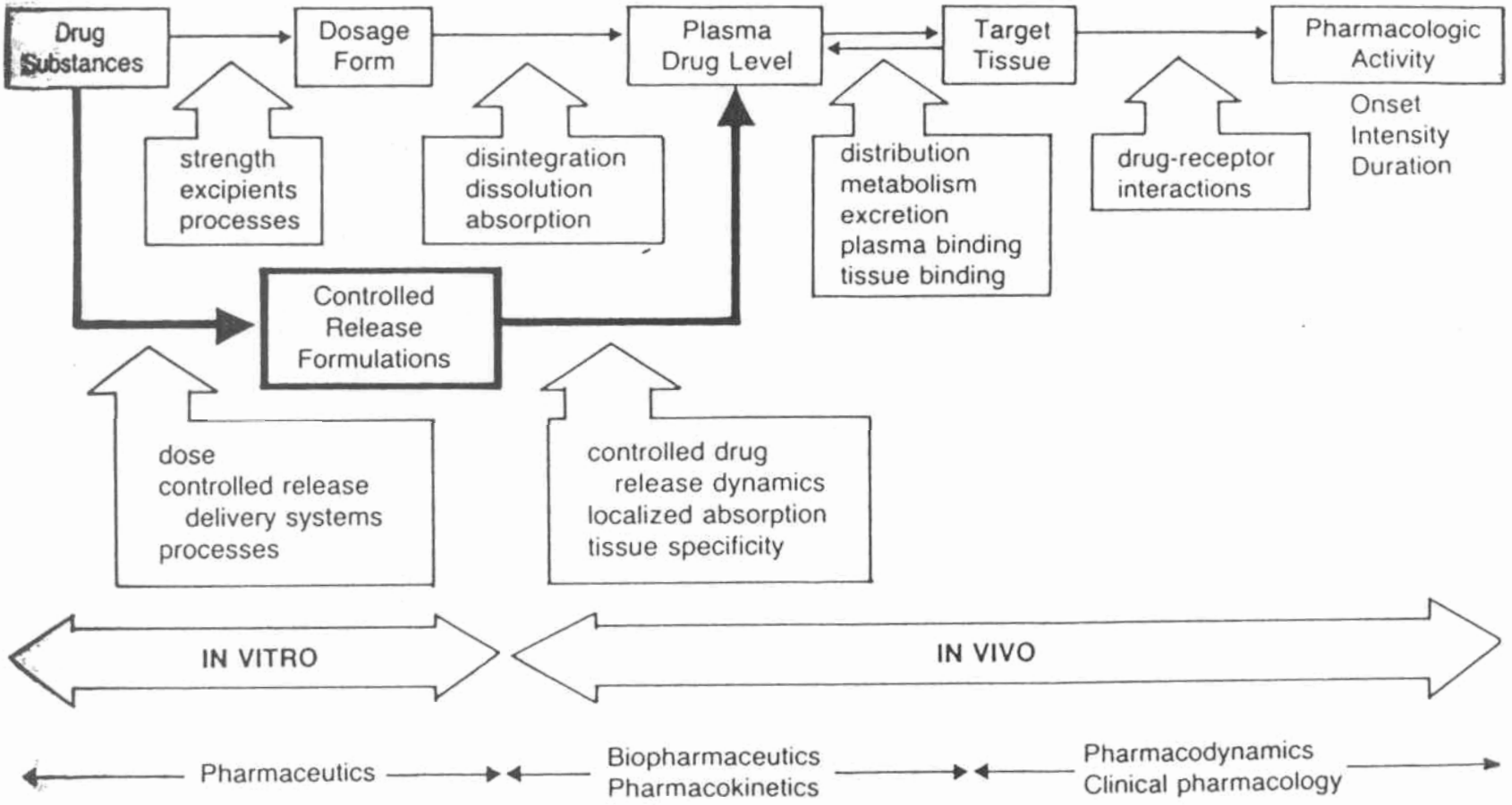
Method	Rate – Limiting Step
Aqueous suspension	Dissolution
Reducing solubility	Dissolution
Drug – polymer dispersion	Dissolution, diffusion
Microencapsulation	Dissolution, diffusion
Oil solution	Partitioning
Oil suspension	Dissolution, partitioning
Emulsion	Partitioning
Complexation	Dissociation

Some components of a parenteral suspension:

I. Drug
II. Solvent
    A. Dextrose and sodium chloride solution for injection
    B. Fixed oils meeting USP requirements
    C. Lactated Ringer's solution for injection
    D. Ringer's solution for injection
    E. Sodium chloride solution for injection
    F. Water for injection
    G. Cosolvents used as aportion of aqueous vehicle
        1. Polyethylene glycol 300
        2. Propylene glycol
        3. Sorbitol
III. Surfactants
    A. Lecithin
    B. Spans
    C. Tweens
IV. Macromolecule polymers
    A. Methylcellulose
    B. Nonantigenic gelatin
    C. Polyvinylpyrrolidone
    D. Carboxymethylcellulose sodium
V. Miscellaneous

Figure 2: Various mucosal routes as potential pathways to bypass the hepato – gastrointestinal first – pass elimination associated with oral administration




Drug Substances
Dosage Form
Plasma Drug Level
Target Tissue
Pharmacologic Activity
Onset
Intensity
Duration
strength
excipients
processes
disintegration
dissolution
absorption
distribution
metabolism
excretion
plasma binding
tissue binding
drug-receptor interactions
Controlled Release Formulations
dose
controlled release
delivery systems
processes
controlled drug release dynamics
localized absorption
tissue specificity
IN VITRO
IN VIVO
Pharmaceutics
Biopharmaceutics
Pharmacokinetics
Pharmacodynamics
Clinical pharmacology

Scheme 1

Figure 3: Drug release and absorption across skin tissues for localized therapeutic action in tissues directly underneath the site of drug administration or for systemic medication in tissue remote from the site of topical drug application.

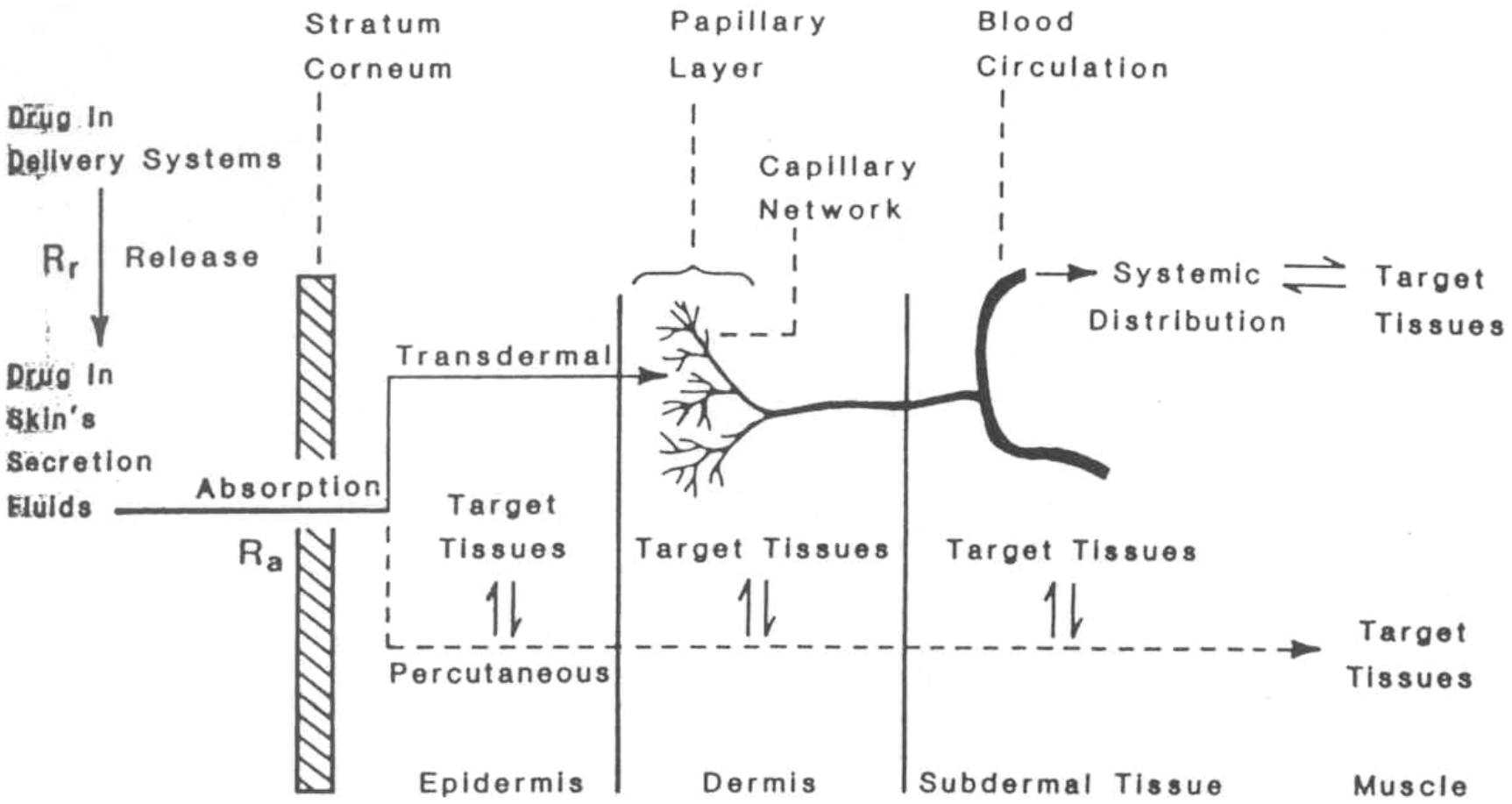
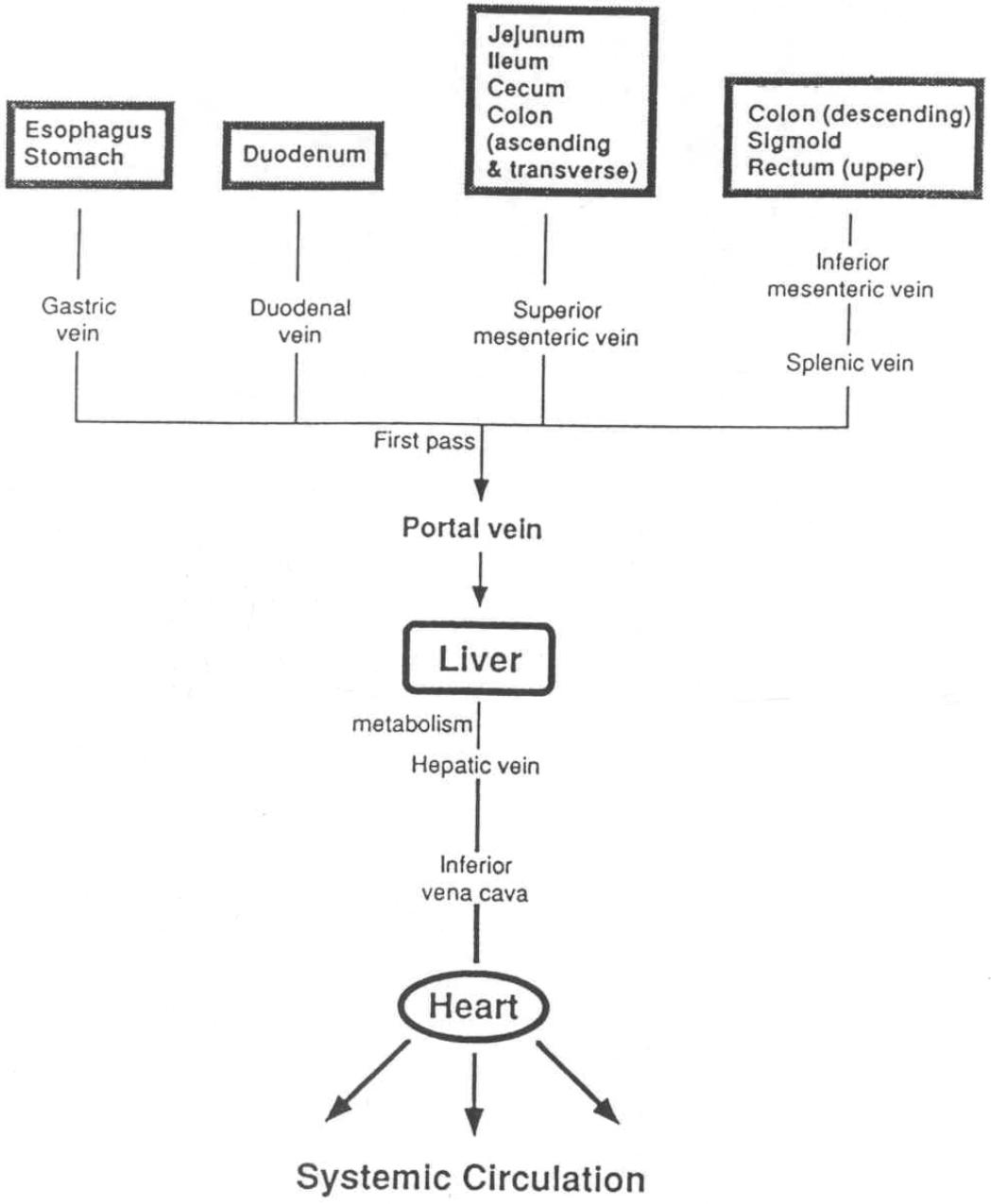


Figure 4: Various circulatory pathways that a drug molecule takes following its absorption from the various segments of gastrointestinal tract.



For many decades treatment of an acute disease or a chronic illnes has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables, as drug carries. Even today these conventional drug delivery systems are the primary pharmaceutical products ...

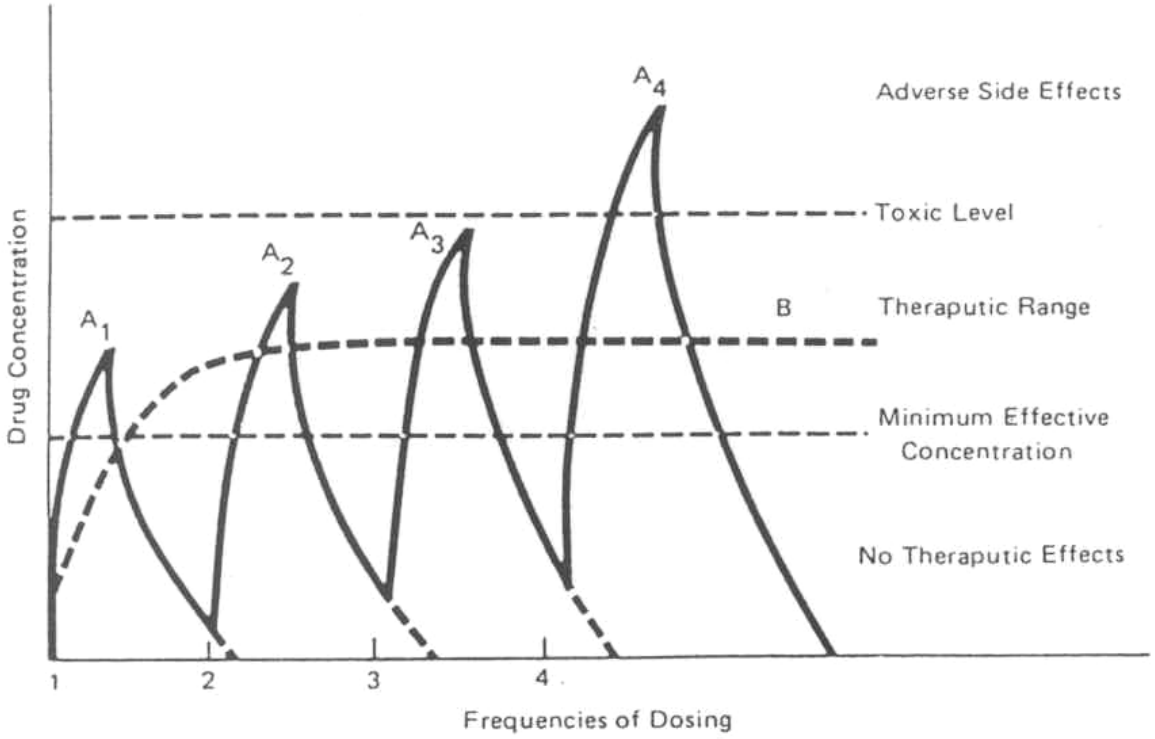


Figure 5: Hypothetical drug concentration profiles in the systemic circulation resulting from the consecutive administration of multiple doses of an immediate–release drug delivery system (A_1, A_2,...) compared to the ideal drug concentration profile (B) required for treatment.

Figure 6: 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.