Transdermal Drug Delivery System

Membrane Permeation Systems

- Transdermal systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, delivers the drug through the skin at a controlled rate to the systemic circulation

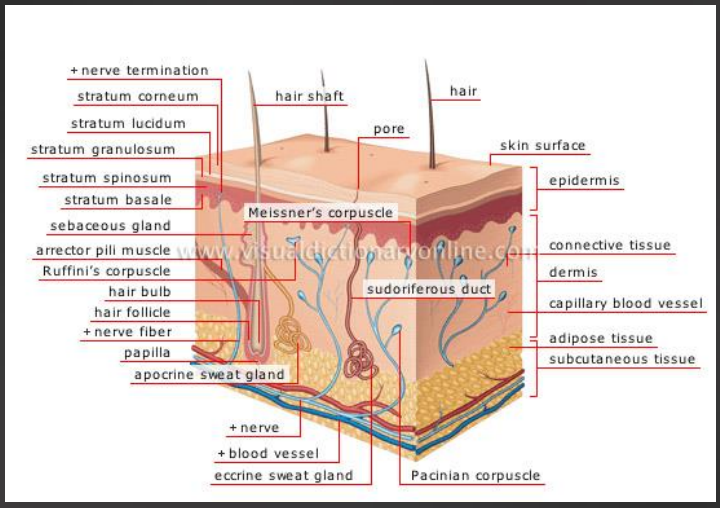
Advantages

1. Delivers a steady infusion of a drug over an extended period of time.
2. Less fluctuations
3. Increases the therapeutics value of many drugs by avoiding various problems like:
   - GI irritation
   - Low absorption
   - First pass metabolism
   - Short half life
   - Formation of metabolites that cause side effects
4. Lower dose than oral dosing
5. Improved patient compliance
6. Termination of therapy possible
7. Self administration is possible

Limitations

1. Drugs should penetrate the stratum corneum. Dose required if more than – 10 mg/day – TDDS difficult
   - Required dose – less than 5 mg/day
2. Skin irritation or contact dermatitis due to drug, excipients and permeation enhancers
3. The barrier function of skin changes from one site to another on the same person, from person to person and with age

Cross-section of skin



Skin

- Most extensive organ in the body
- Covers an area is 2 m^2
- Receives 1/3rd of all blood circulating
- Thickness – 1 mm

Epidermis

- Outermost layer
- Thickness – 150 µm
- Various layers
  - Stratum cornuem – stratified and extremely resilient
  - Stratum lucidum
  - Stratum granulosum
  - Stratum spinosum
  - Stratum germinativum

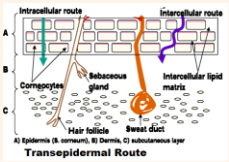
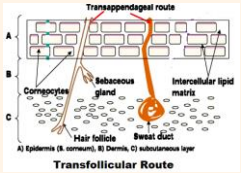
Stratum corneum

- Horny layer
- Rate limiting barrier that restricts the entry and exit of chemical substances
- 15 – 25 layers of flattened polygonal cells
- Interiors of these cells is crisscrossed with densely packed bundles of keratin fibers
- Thus it has 75 – 85% proteins (intracellular)
- Remaining is lipids (intercellular)

Dermis

- Thick – 2000 µm
- 80% protein (collagen)
- On a matrix of muco-polysaccharide (ground material)
- A rich bed of capillaries 20 µm deep
- Also contains – lymph capillaries, nerves, hair follicles, sebaceous glands and sweat glands

Percutaneous absorption

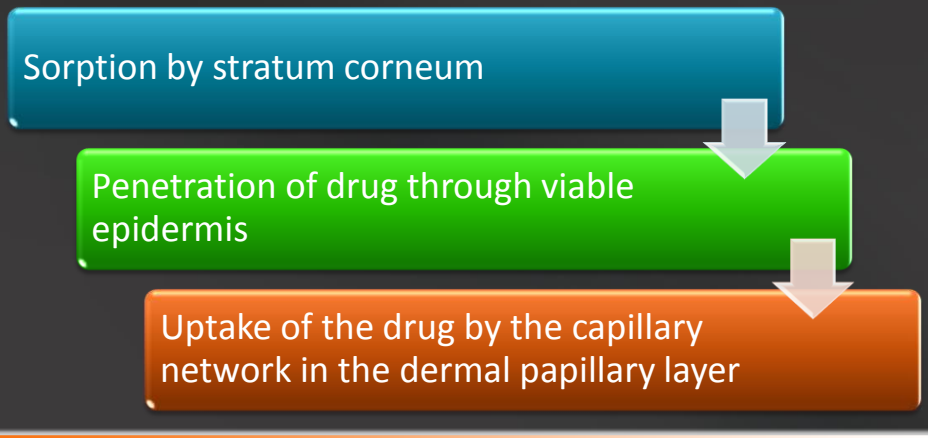
Criteria	Transepidermal	Transfollicular
Site for drug permeation	Stratum corneum	Pilosebaceous unit
Diagrammatic representation		
Importance of the route in drug permeation	Major route	Secondary route
Classification	Intracellular and intercellular	Via hair follicles, sebaceous glands and ecrine sweat glands (negligible)
Drugs have to partition through	Protein-lipid matrix of stratum corneum	Sebum

Number of times the drug has to diffuse	**Lot of times. It requires frequent crossings of cell membrane**	**Just once. Through the lipids in sebaceous pores**
Thickness of barrier layer	Thicker. Almost 1 µm	Thinner. Approximately 10^{-3} µm
Fraction of surface area of skin available for drug permeation	1	0.001
Duration of drug permeation	Drugs are absorbed over a longer duration	Shows transient diffusion of drugs
Lag time for drug absorption	Small molecules gets absorbed in minutes whereas large molecules may even take days to get absorbed	The lag time ranges from seconds to a few minutes
Steady state flux	Higher. Flux observed by this route is 30 times as compared to transfollicular route	Lower flux
Dedicated pharmacokinetic models	Available	Not available

Equation describing kinetics of drug permeation	**$R_{Transepidermal} = R_{stratumcorneum} +$ Rviable tissue-TransEpidermal** **$R_{TE} = R_{SC} + R_{vt-TE}$** **Where R = resistance offered**	**$R_{Transfollicular} = R_{sebum} +$ Rviable tissue-TransFollicular** **$R_{TF} = R_{Seb} + R_{vt-TF}$** **Where R = resistance offered**
Preferred by type of drug	Both hydrophilic and lipophilic drugs can pass through	Suitable for small hydrophilic non-electrolyte molecules
Examples of drugs known to permeate via the route	Clonidine, fentanyl, nicotine, nitroglycerine, estradiol, scopolamine, testosterone etc	Nitroglycerine, estradiol etc
Important characteristic of drug which makes it a suitable candidate	HLB	Small size, uncharged and hydrophilic
Preferred vehicles	Oily vehicles like oleic acid or petrolatums	Polar vehicles like propylene glycol, ethanol etc
Preferred dosage forms	Topical semisolids likes ointments, gels etc and transdermal patches	Liposomes and other small colloidal carriers
Drug permeation affected by	Dry skin, psoriasis, UV rays etc	Alopecia, hirsutism, hypertrichosis etc
Beneficial for	Systemic drug delivery (major), skin infections etc	Systemic drug delivery (minor), acne etc

Kinetics of transdermal permeation

- Transdermal permeation of drug involves the following steps:



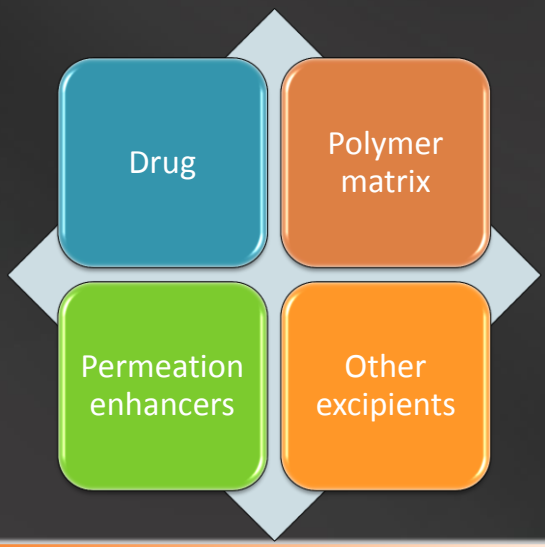
- Rate of permeation across the skin (dQ/dt) is given by:
- $\frac{dQ}{dt} = P_s(C_d - C_r)$ ---------- (1)
- Where;
  - C_d – conc of drug on stratum corneum (donor compartment)
  - C_r – conc of drug in the systemic circulation (receptor compartment)
  - P_s – overall permeability coefficient of skin tissues to the penetrant

- $P_S = \frac{K_S D_{SS}}{h_S}$ ---------- (2)
- Where;
  - K_s – partition coefficient for the interfacial partitioning of the permeant
  - D_{ss} – diffusivity for the steady-state diffusion of the penetrant
  - h_s – overall thickness of skin
- As A_s, K_s, D_{ss} and h_s are constant under a given condition – hence Ps can be considered a constant

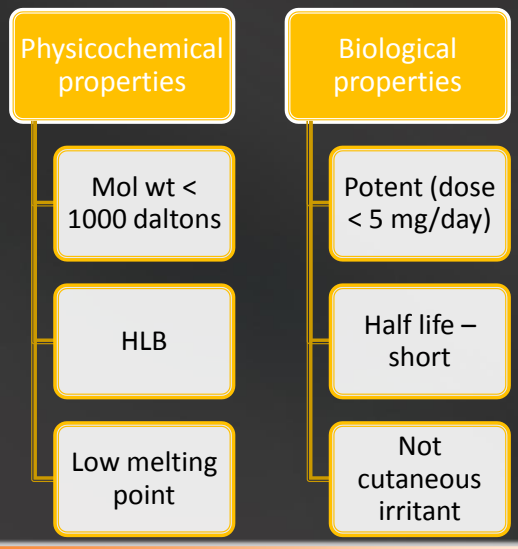
- Normally drug conc at stratum corneum (C_d) is substantially greater than drug conc in the body (C_r)
- Equation 1 becomes
- $\frac{dQ}{dt} = P_S C_d$ ---------- (3)
- To keep rate of skin permeation constant, the magnitude of C_d should remain fairly constant
- For keeping C_d constant, the drug should be released from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake (R_a)
- $R_r >> R_a$

- Since $R_r >> R_a$
- C_d is maintained at a level equal to or greater than the equilibrium (saturation) solubility of the drug in the stratum corneum (C_s)
- $(\frac{dQ}{dt})_m = P_s C_s$
- Where;
  - $(dQ/dt)_m$ – maximum rate of skin permeation
  - P_s – skin permeability coefficient
  - C_s – equilibrium solubility in the stratum corneum

Basic components of TDDS

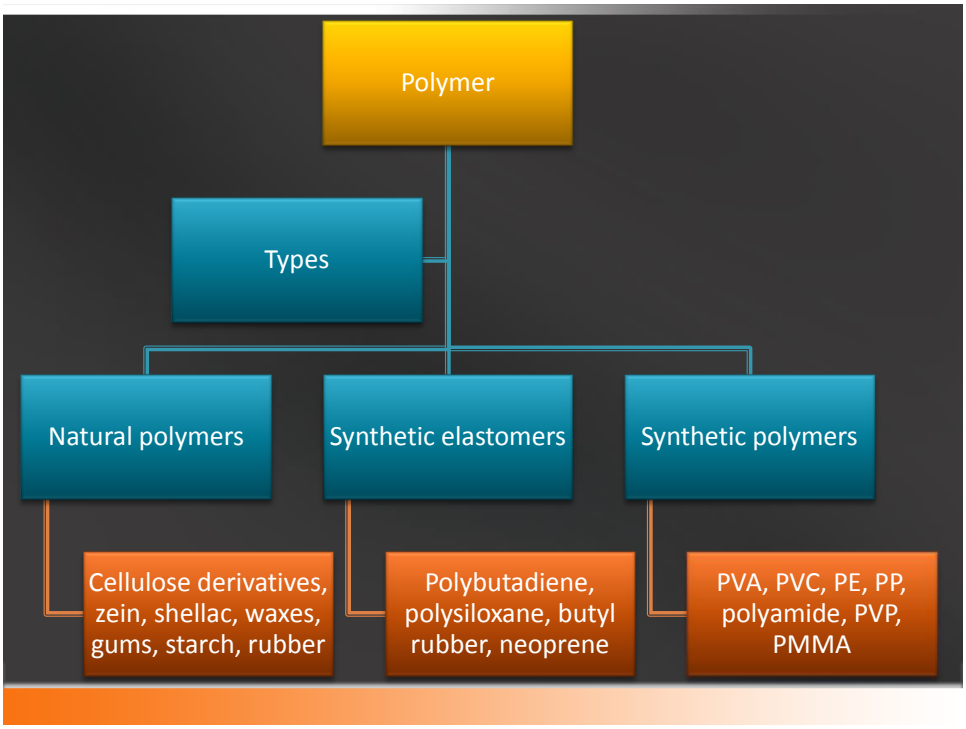


Drug - desirable properties



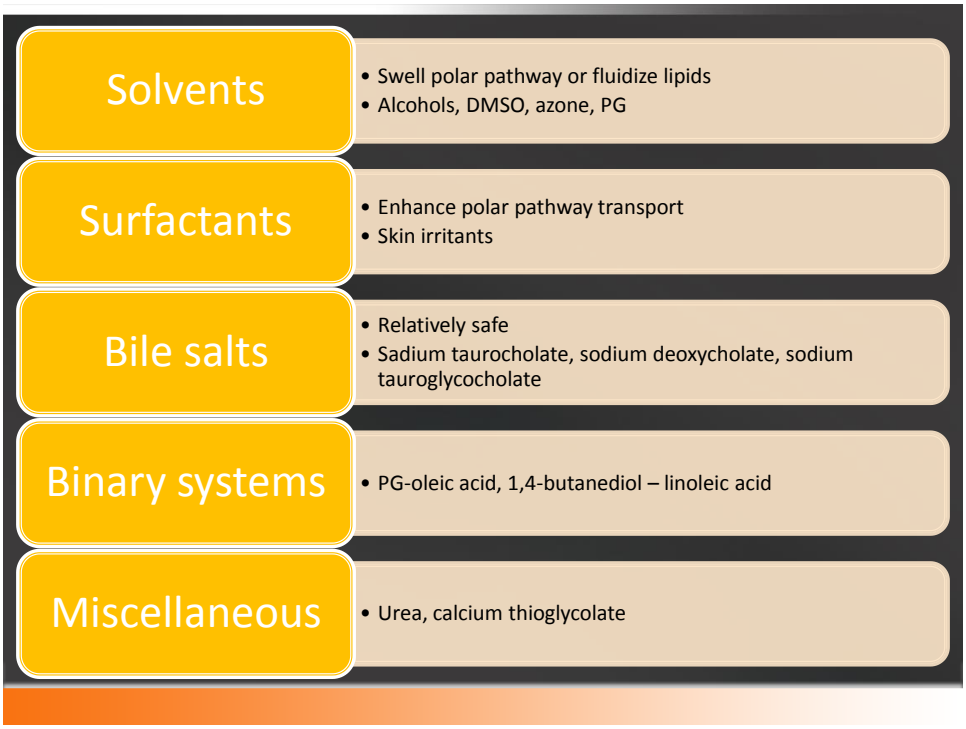
Polymer matrix - Ideal characteristics

1. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the drug diffuses properly and gets released through it
2. Should be stable, non-reactive with the drug
3. Should be easily manufactured and fabricated into desired product
4. Inexpensive
5. Polymer and its degradation products must be non-toxic to the host
6. Mechanical properties of the polymer should not deteriorate excessively when large amounts of drug is incorporated



Permeation enhancers

- They promote skin permeability by altering the skin as a barrier to the flux of a desired permeant
- The enhancement of flux across membrane reduces to considerations of:
  - Thermodynamics (lattice energies, distribution coefficients)
  - Molecular size and shape
  - Reducing the energy required to make a molecular hole in the membrane

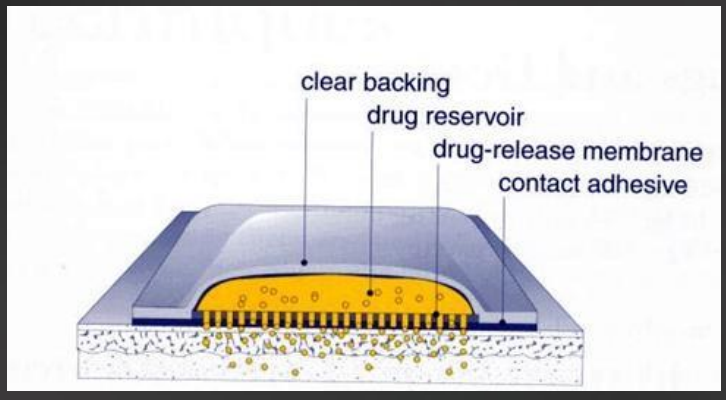


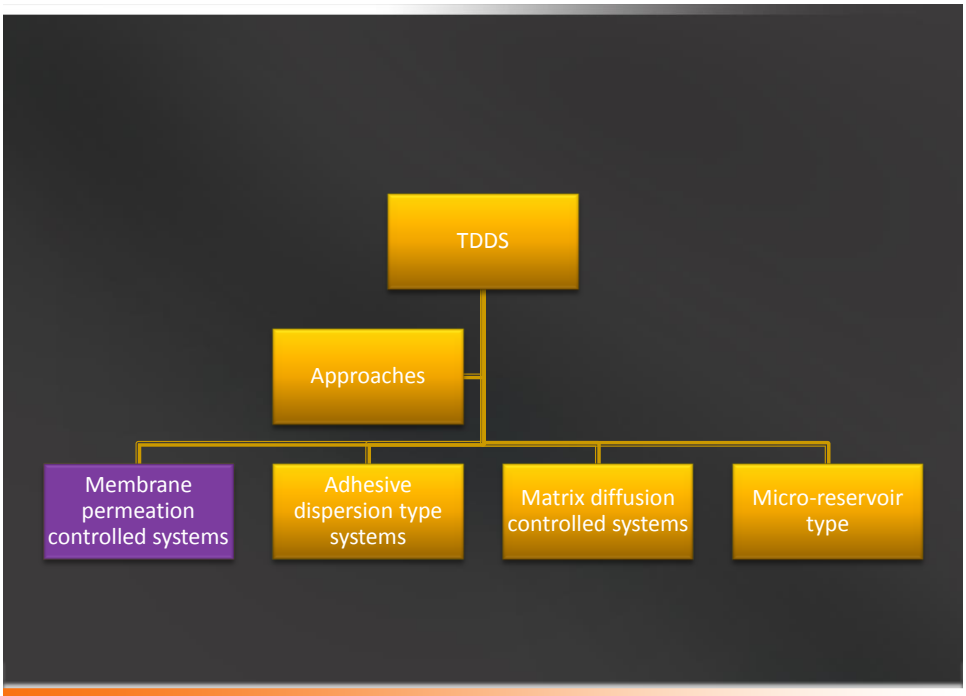
Other excipients

- Adhesives – ideal properties:
  - Should not irritate or sensitize the skin
  - Should adhere to skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc
  - Should be easily removed
  - Should not leave an unwanted residue on the skin
  - Should have intimate contact with the skin
  - Physically and chemically stable with drugs and other excipients
  - Should not affect permeation of drug
- Examples – polyisobutylene, acrylics and silicones

- Backing membrane
  - Should be flexible
  - Provide good bond to the drug reservoir
  - Prevent drug from leaving the dosage form from top
  - Accept printing
  - Impermeable
- Eg. Metallic plastic laminate, plastic backing with absorbent pad and aluminum foil, adhesive foam pad with aluminum foil

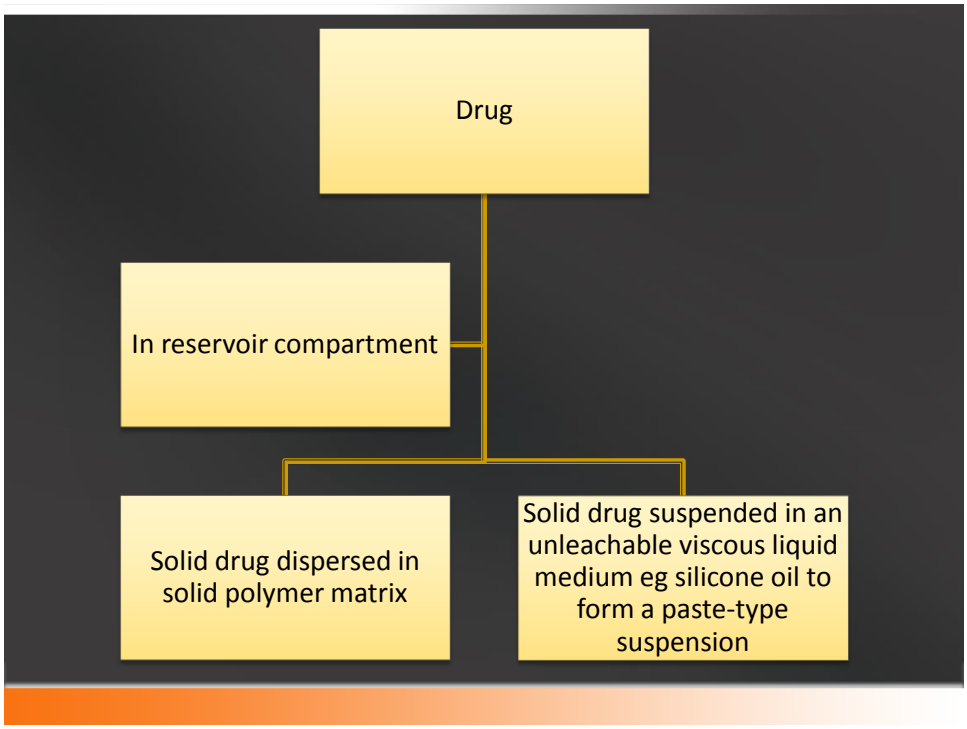
Normal transdermal patch

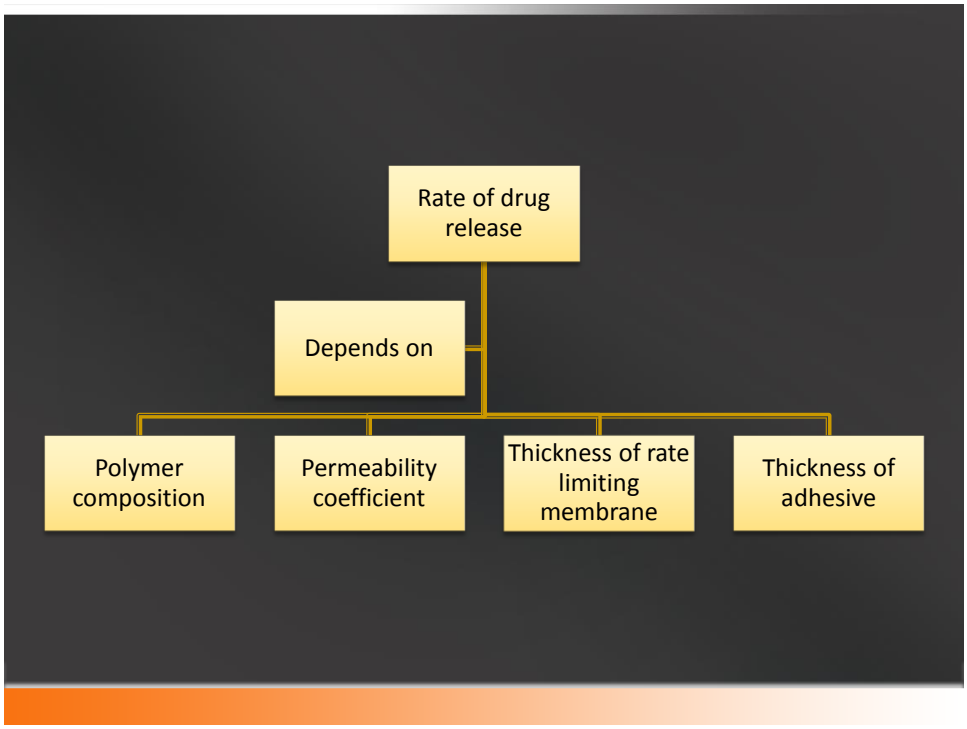




Membrane permeation-controlled systems

Drug reservoir	• Totally encapsulated in a shallow compartment molded from drug-impermeable metallic plastic laminate
Rate controlling membrane	• Microporous or non-porous • Eg ethylene vinyl acetate copolymer (EVA)
Adhesive	• Silicone or polyacrylate adhesive


Drug
In reservoir compartment
Solid drug dispersed in solid polymer matrix
Solid drug suspended in an unleachable viscous liquid medium eg silicone oil to form a paste-type suspension


Rate of drug release
Depends on
Polymer composition
Permeability coefficient
Thickness of rate limiting membrane
Thickness of adhesive

Pros and cons

Constant rate of drug release	Accidental breakage can lead to dose dumping

Intrinsic rate of drug release

- $\frac{dQ}{dt} = \frac{C_R}{\frac{1}{P_m} + \frac{1}{P_a}} \quad ----------\ -(6)$
- Where;
  - Cr – drug conc in reservoir compartment
  - Pm – permeability coefficient of the rate controlling membrane
  - Pa – permeability coefficient of the adhesive layer

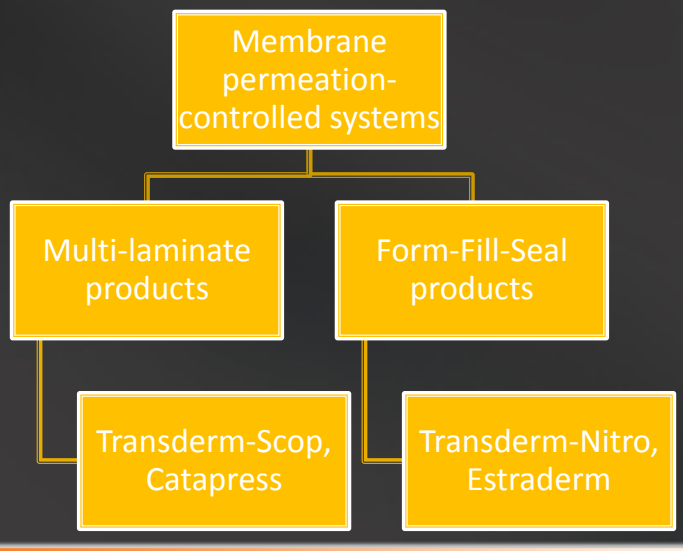
- $P_m = \frac{K_{m/r} D_m}{h_m}$ ---------- (7)
- $P_a = \frac{K_{a/m} D_a}{h_a}$ ---------- (8)
- Where;
  - $K_{m/r}$ and $K_{a/m}$ – partition coefficients for the interfacial partitioning of drug from reservoir to the membrane and from the membrane to the adhesive respectively
  - D_m and D_a – diffusion coefficients in the rate controlling membrane and adhesive layer respectively

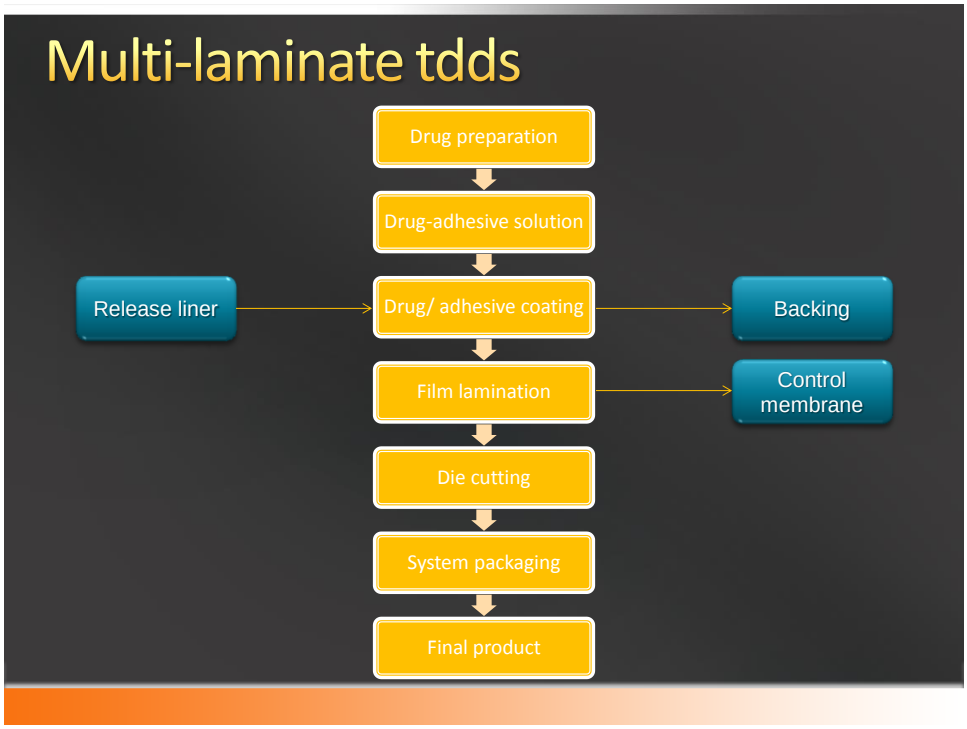
- Substituting equations (7) and (8) for P_m and P_a in equation (6), we get:
- $\frac{dQ}{dt} = \frac{K_{m/r} K_{a/m} D_m D_a}{K_{m/r} D_m h_a + K_{a/m} D_a h_a} C_R$
- Where;
  - dQ/dt – intrinsic rate of drug release from a membrane modulated drug delivery system

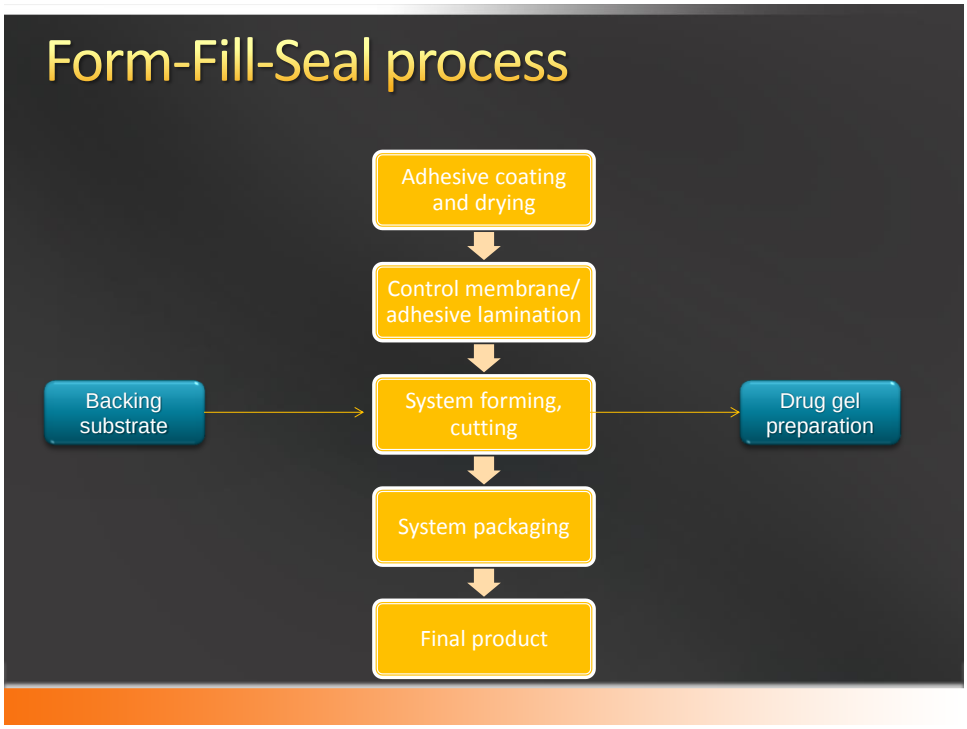
Examples

Nitroglycerine	• Transderm-Nitro (Ciba) • Once a day for angina pectoris
Scopolamine	• Transderm-Scop (Ciba) • 72 hrs prophylaxis of motion sickness
Clonidine	• Catapres – Boehringer Ingelheim • 7 days therapy for hypertension
Estradiol	• Estraderm – Ciba • 3 – 4 days for treatment of menopausal syndrome

Production




Multi-laminate tdds
Drug preparation
Drug-adhesive solution
Release liner
Drug/ adhesive coating
Backing
Film lamination
Control membrane
Die cutting
System packaging
Final product


Form-Fill-Seal process
Adhesive coating and drying
Control membrane/ adhesive lamination
Backing substrate
System forming, cutting
Drug gel preparation
System packaging
Final product