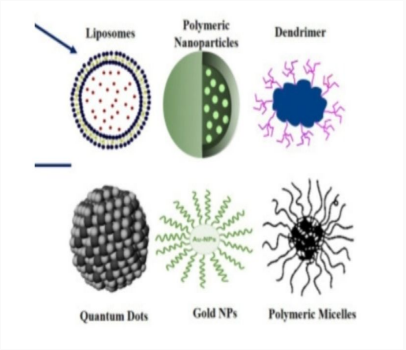
체내 약물 전달을 예측하는 수학 모델: 투입 약물 Dependent mathematical model

22-1 SEM 5조

- Drug Delivery & Release Kinetics
- Higuchi Model
- Korsemeyer-Peppas Model
- Weibull Model
- Wrap up

Drug Delivery

- 원하는 target tissue 등에 원하는 기간만큼, 원하는 양의 약물을 투입 및 유지하는 bt system
- 일반적으로,



Drug + Solid dosage form (capsule 등) 을 체내 투입

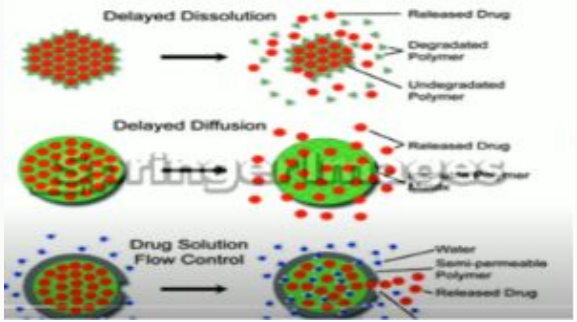
-> 체액 (fluid) 의 entry 로 discharge 되는 dosage form

-> **fluid 가 inner layer 에 도달하고 drug particle 이 dosage form 의 surface 로 이동**

-> surface 에서 target 지점으로 이동

Release Kinetics

- 체내의 Drug delivery 를 체외에서 예측하기 위해 사용하는 mathematical model 을 정립하기 위해선 Release Kinetics 를 기반으로 해야 함
- Release mechanism : 주로 diffusion



Diffusion: t에 대한 release exponent, 즉 dynamics 속도에 따라

- Fickian / Non fickian Diffusion
- Case 2 transport / Super case 2 transport

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.45 < n = 0.89	Non -Fickian transport
0.89	Case II transport
Higher than 0.89	Super case II transport

- Drug 의 종류, 농도, dosage form 의 종류 등이 영향을 미침

Release Kinetics- key base formulas

Noyes-Whitney Rule : Drug bulk -> Surface

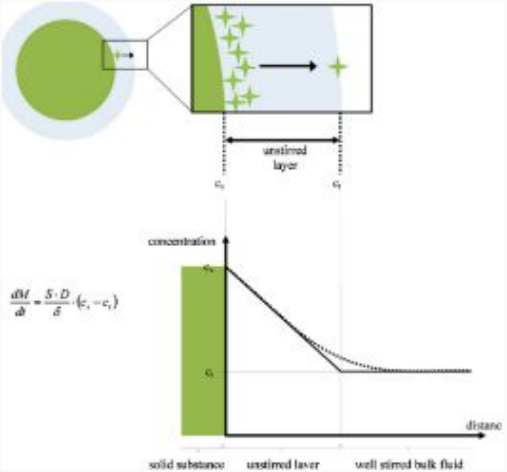
- dM/dt = KS (Cs - Ct)

Surface S 에서 Cs-Ct 농도차에 의해 dissolution 된 drug mass respect time

Nernst and Brunner Film Theory

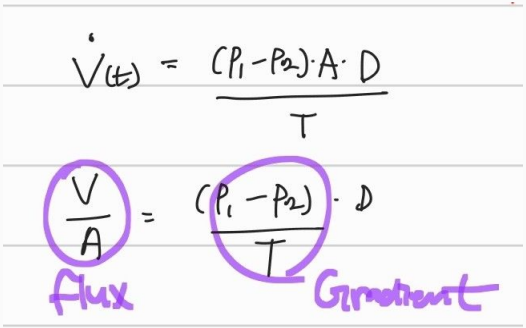
- K = DS/ hγ

D: diffusion coefficient, γ is the solution volume and h is the diffusion layer thickness.



Release Kinetics- key base formulas

Fick's 1st law : Surface-> Target tissue



$$J_B = -D_B \frac{dC_B}{dx}$$

J_B : 단위시간당 단위 면적을 지나는 원자의 수를 나타내는 Flux

D_B: B 원자의 확산계수

C : 농도

x : 방향

dC_B/dx는 x방향으로의 농도 변화율

- 정상상태에서만 적용 가능 (시간에 대한 농도 변화율 = 0)
- 정상상태에서 flux 는 일정히 유지.

Release Kinetics- Mathematical Models

- Statistical methods
- **Model dependent methods**
  zero order, first order, **Higuchi, Korsmeyer-Peppas model**, Hixson Crowell, Baker-Lonsdale model, **Weibull model**, etc.
- Model independent methods

Release Kinetics- Mathematical Models

- Higuchi model : describes the drug release from a matrix system, fickian diffusion
- Korsmeyer and Peppas: analyze both Fickian and non-Fickian release of drug from swelling and nonswelling polymeric delivery systems.
- Weibull : describes drug dissolution and release from dosage forms, it expresses the accumulated fraction of drug‘m’ in solution at time‘t’.

Higuchi model

Higuchi model

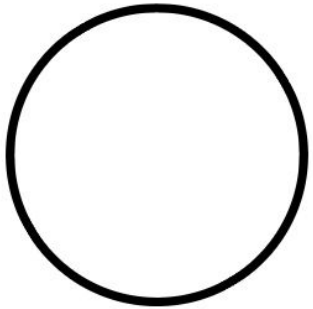
Two geometric systems

a homogeneous matrix

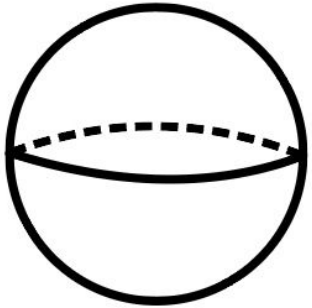
a granular matrix

Two mechanisms of release

planar surface



a sphere



Higuchi model

Release from a Planar System Having a Homogeneous Matrix

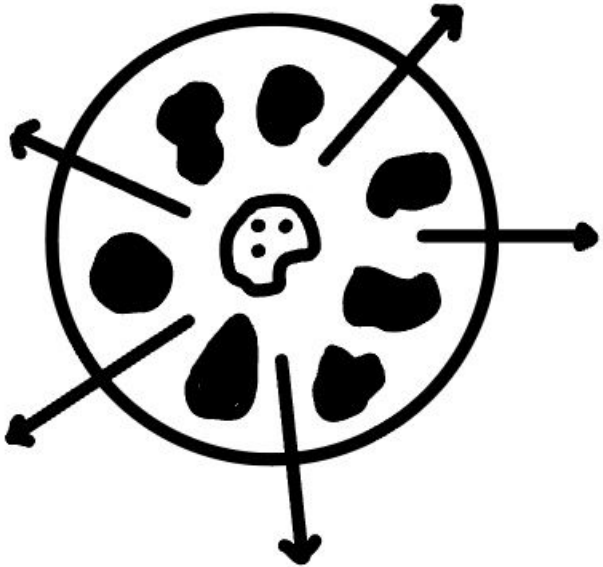
Release from a Planar System Having a Granular Matrix

Release from a Spherical Pellet Having a Homogeneous Matrix

Release by Leaching from Granular Spherical Pellet

Release from a Planar System Having a Granular Matrix

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s) C_s t}$$



Q = the amount of drug released after time t per unit exposed area.

D = the diffusivity of the drug in the homogeneous matrix media.

타우 = the tortuosity factor of the capillary system

A = the total amount of drug present in the matrix per unit volume.

Cs= the solubility of the drug in the matrix substance.

앱실론 = the porosity of the matrix.

Release from a Planar System Having a Granular Matrix

(i) $A > \varepsilon C_s$

(ii) $\varepsilon = \varepsilon_o + kA \quad \left(k = \frac{1}{\text{density of drug}}\right)$

$\Rightarrow \varepsilon \cong kA$

$$Q = A\sqrt{Dk/T(2 - kC_s)C_s t}$$

Korsemeyer-Peppas release model

Korsemeyer-Peppas release model

$$F = \frac{M_t}{M_\infty} = Kt^n$$

simple relationship which described drug release from a polymeric system equation

F=fraction of drug release at time t

M_t =amount of drug release at time t

M_∞ =total amount of drug in dosage form(amount released at infinite time)

K=release rate constant

n =release exponents

Korsemeyer-Peppas release model

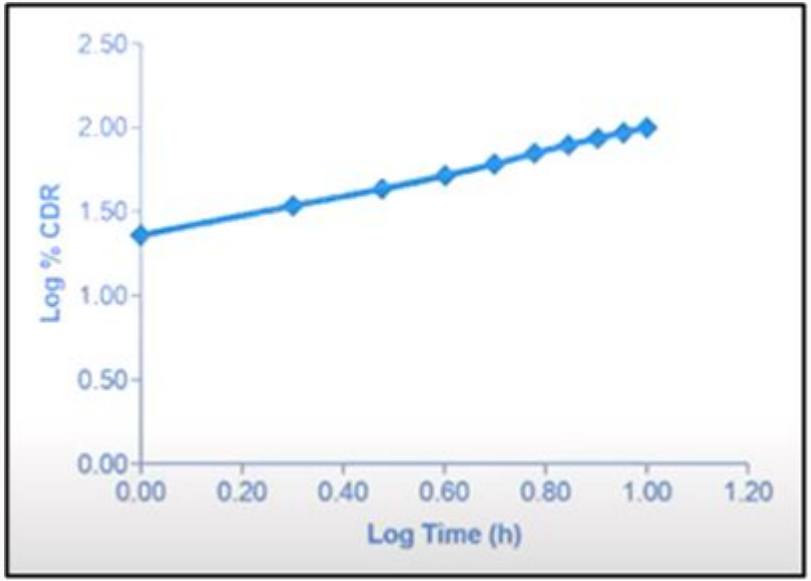
특징

-To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model

-To find out the exponent of n the portion of the release curve, where should only be used.

$$\frac{M_t}{M_\infty} < 0.6$$

Korsemeyer-Peppas release model



To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

Korsemeyer-Peppas release model

n이 0.45일 경우

-release behavior : fickian diffusion (Case 1)

-diving force: chemical gradient, square root of time dependent

release is rapid at first, then tailing off over time (처음에는 빠른 속도로 방출하지만, 시간이 지나면서 점점 속도가 줄어든다.)

-release mechanism : diffusion(확산)

Korsemeyer-Peppas release model

0.45<n<0.89일 경우

-release behavior : non-fickian transport

-diving force: release is rapid at first, slower than fickian release rate and again tails off over time

-release mechanism : diffusion and swelling.(확산과 팽창)

combination of both diffusion and erosion controlled release

Korsemeyer-Peppas release model

n이 0.89일 경우

-release behavior : Case 2 transport

-diving force: linear release

drug release rate is independent of time

Korsemeyer-Peppas release model

n> 0.89일 경우

-release behavior : super case 2

-diving force: erosion of polymeric chain

Weibull model

Weibull Model

- parametric model 중 하나
- 여러 지수 모델의 일반화

- 생존 데이터를 분석
- 위험율에 관한 연구
- 약물 용해 또는 약물 방출에 관한 데이터에서 사용

Weibull Model: 약물 용해/방출

$$M = M_0 \left[1 - e^{-\frac{(t-T)^b}{a}}\right]$$

The accumulated fraction of the drug 'M' in solution at time 't'

M: 약의 용해량

M_0: 총 방출 약물량

T: 용해 공정의 결과로 측정된 지연 시간

a: 시간 의존성을 설명하는 척도 매개변수

b: 용해 곡선의 모양

Weibull Model: 약물 용해/방출

→b=1일 경우, k=1/a인 식과 동일

$$M = M_0 \left(1 - e^{-k(t-T)}\right)$$

→b>1일 경우

곡선의 모양: sigmoidal with a turning point(S자형)

→b<1일 경우

b=1인 경우보다 가파르게 증가

Weibull Model: 약물 용해/방출

- 약물이 방출된 시간: inverse function of the Weibull equation

$$t_{(50\%\ \text{resp. } 90\%\ \text{dissolved})} = (-\,a \ln \frac{M_0 - M}{M_0})^{1/b} + T$$

- Weibull Model은 the release profiles of matrix type drug delivery을 비교하는 데 더 유용

Wrap up

- Model selection

drug, polymer 등의 특성에 따라 1차로 model 선택 후 실행 -> 이미 approved batches 기반으로 만들어진 F 분포 이용해 분산분석 -> model 최종선택

- Maintenance dose

유지 용량은 약물 투여의 유지 속도가 정상 상태에서의 제거 속도와 동일하다 고로, model 을 이용해 정상 상태의 condition 을 구하고, drug delivery 의 가장 핵심인 원하는 기간 동안 약물의 유지에 용이하게 활용 가능.