Controlled Release

Estimation of the Diffusion Coefficient

Stokes-Einstein Relation

- For free diffusion

$$D = \frac{kT}{6prh}$$

  - Assumes a spherical molecule
    - i.e., not valid for a long-chain protein

- *k* = Boltzman Constant
  - 1.38 x 10^{-23} J/K
- *?* = solvent viscosity (kg/ms)
- *T* is temperature (K)
- *r* is solute molecule radius
  - related to molecular weight

Stokes-Einstein Relation

- Radius, r, is related to MW

$$(MW) = NrV = Nr\left(\frac{4}{3}pr^{3}\right)$$

- Solve for r

$$r = \left[\frac{3(MW)}{4pNr}\right]^{1/3}$$

- Substitute into S-E eqn

$$D = \frac{kT}{6ph\left[\frac{3(MW)}{4pNr}\right]^{1/3}}$$

  - ❑ Note D is not a strong fn of MW

- N is Avagadro’s Number
- V is the molal volume of the solute.
- r is the hydrodynamic radius, which considers solvent bound to solute

Diffusion Coefficient

- Many drugs have a low molecular wt
  - 100 < MW < 500 g/mol
  - Not true for proteins and larger molecules
- Examples

Drug	**MW (g/mol)**	**D(cm^2/s) Aqueous**	**Note**
Caffeine	194.2	4.9×10^{-6}	Medium size
Insulin	41,000	8.3×10^{-7}	Huge size

Sutherland-Einstein Correlation

- Sutherland-Einstein Equation
  - More reliable prediction for smaller solutes.
  - Modification of Stokes-Einstein, which considers sliding friction between solute and solvent.

$$D = \frac{RT}{6pNrh}\left(\frac{br + 3h}{br + 2h}\right)$$

  - For large molecules, ß approaches infinity to reflect “no slip” conditions, and the equation reduces to the Stokes-Einstein relation

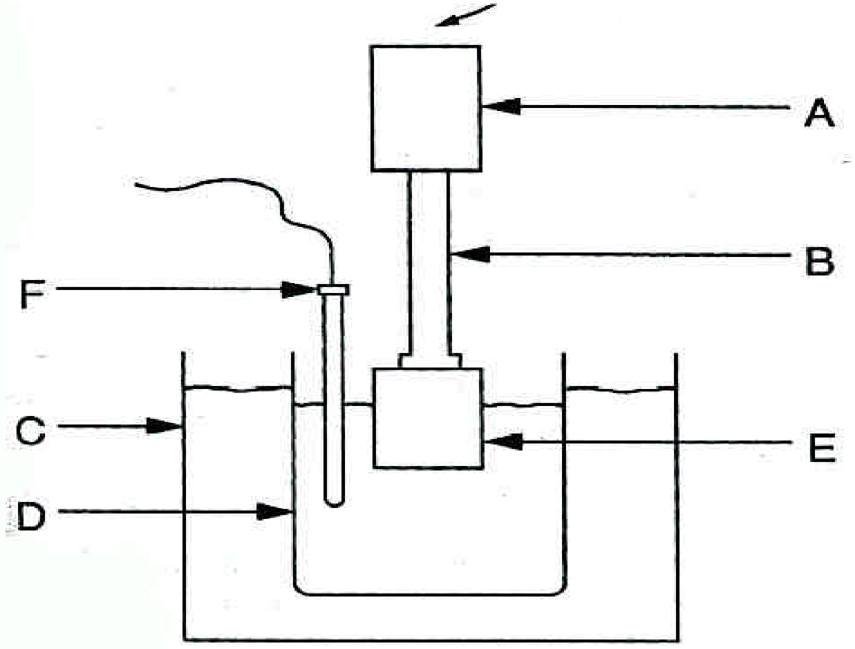
Wilke-Chang Correlation

- Semi-empirical modification of the Stokes-Einstein relation. 10-15% error.
- Widely used for small molecules in low MW solvents, at low concentrations.
- Involves
  - ❑ MW of solvent
  - ❑ Absolute temperature
  - ❑ Solvent viscosity
  - ❑ Solute molal volume at normal BP
  - ❑ Association factor of solvent (2.6 for water, 1.9 for methanol, 1.5 for EtOH)

Diffusion Coefficients in Polymers

- For large pores
  - diffusion through liquid filled pores
  - Porosity, tortuosity, partition coefficient
- For small pores
  - Diffusion through liquid filled pores
  - Steric hindrance, friction
- For non-porous polymer networks
  - Complicated; various mechanisms proposed
  - Depends on crystallinity, swelling, crosslinking, rubbery vs. glassy state
- Predictions based on semi-empirical or empirical approaches

Measurement of D: rotating disk



(a)

Figure 4 (a) Rotating-disk apparatus for dissolution rate studies. Key: A, constant-speed motor; B, rotating shaft; C, water bath; D, reservoir; E, rotating disk; F, conductivity probe.

From Kydonieus, A., Treatise on Controlled Drug Delivery

Measurement of diffusion coefficient

- Rotating disk for measurement of D in liquids
  - Considers the rate of dissolution of a drug from a disk spinning in a liquid

$$Q = 0.62AD^{2/3}v_0^{-1.6}w^{0.5}C_s$$

  - Q is rate of dissolution
  - A is surface area of drug on disk
  - v_o is the kinematic viscosity of the solvent,
  - C_s is the drug solubility in the solvent
  - ? is the rotational speed of the disk
- Perform experiments at different ? . What plot will give a slope of D?
  - Q vs. $?^{0.5}$

Measurement of D: permeation cell

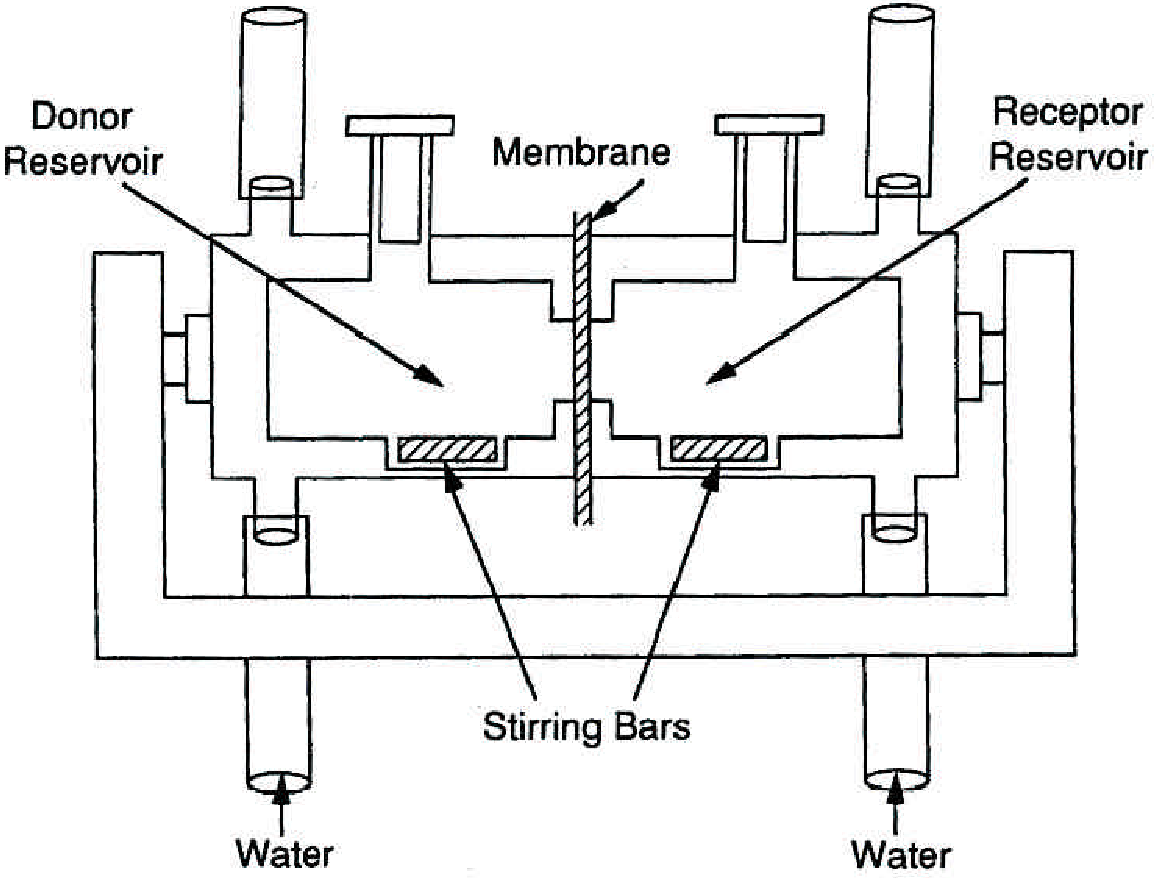


Figure 5 Two-cell system for diffusion coefficient measurement and membrane permeation experiment.

From Kydonieus, A., Treatise on Controlled Drug Delivery

Measurement of diffusion coefficient

- Two Cell Permeation System
  - For D in liquids or polymers
  - Two stirred cells divided by a membrane. Initially one contains the drug in suspension.

$$\left(\frac{dM}{dt}\right)_{\infty} = \frac{DKC_s}{l}$$

- LHS is the steady-state permeation rate
- K is the partition coefficient (membrane/solution)
- L is the membrane thickness

Measurement of diffusion coefficient

- More methods for polymers
- Direct release method – curve fitting from a release experiment.
  - Usually preferable to determine through independent experiments.
- Sorption and desorption from stirred finite volume
  - Simple experiment
  - Mathematics of diffusion through a solid will be investigated later

D values for small solutes in liquids

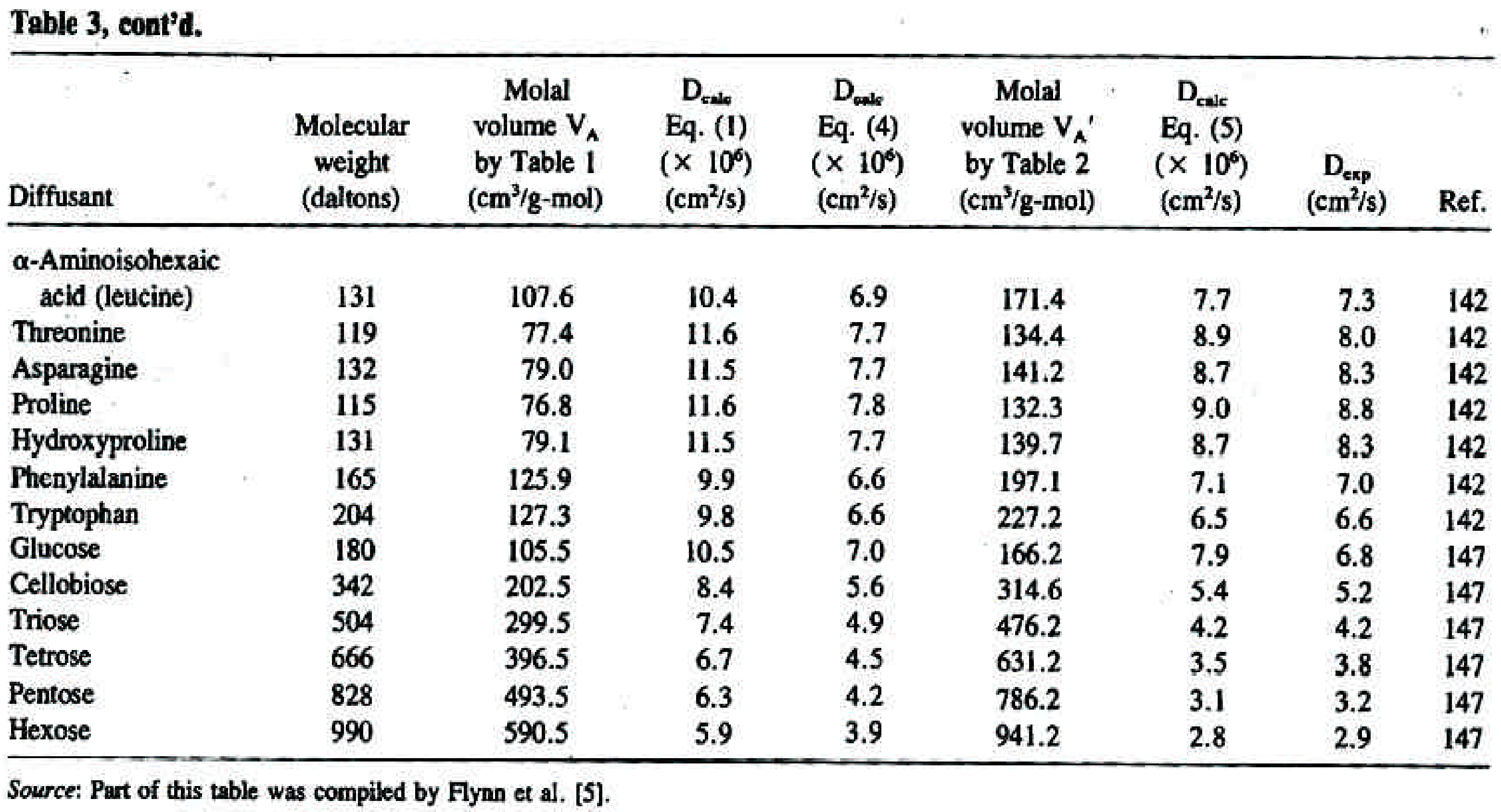


Table 3, cont'd.

Diffusant	Molecular weight (daltons)	Molal volume V_A by Table 1 (cm^3/g-mol)	D_{calc} Eq. (1) ($\times 10^6$) (cm^2/s)	D_{calc} Eq. (4) ($\times 10^6$) (cm^2/s)	Molal volume V_A' by Table 2 (cm^3/g-mol)	D_{calc} Eq. (5) ($\times 10^6$) (cm^2/s)	D_{exp} (cm^2/s)	Ref.
α-Aminoisohexaic acid (leucine)	131	107.6	10.4	6.9	171.4	7.7	7.3	142
Threonine	119	77.4	11.6	7.7	134.4	8.9	8.0	142
Asparagine	132	79.0	11.5	7.7	141.2	8.7	8.3	142
Proline	115	76.8	11.6	7.8	132.3	9.0	8.8	142
Hydroxyproline	131	79.1	11.5	7.7	139.7	8.7	8.3	142
Phenylalanine	165	125.9	9.9	6.6	197.1	7.1	7.0	142
Tryptophan	204	127.3	9.8	6.6	227.2	6.5	6.6	142
Glucose	180	105.5	10.5	7.0	166.2	7.9	6.8	147
Cellobiose	342	202.5	8.4	5.6	314.6	5.4	5.2	147
Triose	504	299.5	7.4	4.9	476.2	4.2	4.2	147
Tetrose	666	396.5	6.7	4.5	631.2	3.5	3.8	147
Pentose	828	493.5	6.3	4.2	786.2	3.1	3.2	147
Hexose	990	590.5	5.9	3.9	941.2	2.8	2.9	147

Source: Part of this table was compiled by Flynn et al. [5].

From Kydonieus, A., Treatise on Controlled Drug Delivery

D values for small solutes in polymers

Solute	Polymer	Diffusion Coefficient (cm^2/s)
Hydrocortisone	Silicone rubber	4.5×10^{-7}
	EVA	1.18×10^{-11}
	PVA terpolymer	4.31×10^{-12}
	Poly(EVA)	2.8×10^{-9}
Salicylic acid	PMMA	9.55×10^{-15}
	PVA	4.37×10^{-11}

From Kydonieus, A., Treatise on Controlled Drug Delivery