PHAR 7632 Chapter 12

Physical-Chemical Factors Affecting Oral Absorption

Physical-Chemical Factors Affecting Oral Absorption

Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to describe the physical-chemical factors that affects oral absorption
- be able to describe the pH-partition hypothesis as it applies to drug absorption and estimates values of Brodies D value
- be able to describe Fick's first law as it applies to drug dissolution

There are two major headings, which can be used to discuss this material as it affect oral drug absorption. These are:

1. the pH-partition theory and
2. the dissolution of drugs.

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pH - Partition Theory

For a drug to cross a membrane barrier it must normally be soluble in the lipid material of the membrane to get into membrane it has to be soluble in the aqueous phase as well to get out of the membrane. Many drugs have polar and non-polar characteristics or are weak acids or bases. For drugs which are weak acids or bases the pKa of the drug, the pH of the GI tract fluid and the pH of the blood stream will control the solubility of the drug and thereby the rate of absorption through the membranes lining the GI tract.

Brodie et al. (Shore, et al. 1957) proposed the pH - partition theory to explain the influence of GI pH and drug pKa on the extent of drug transfer or drug absorption. Brodie reasoned that when a drug is ionized it will not be able to get through the lipid membrane, but only when it is non ionized and therefore has a higher lipid solubility.

Brodie tested this theory by perfusing the stomach or intestine of rats, in situ, and injected the drug intravenously. He varied the concentration of drug in the GI tract until there was no net transfer of drug across the lining of the GI tract. He could then determined the ratio, D as:

$$D = \frac{\text{Total concentration in Blood}}{\text{Total concentration in GI Tract}}$$

Equation 12.2.1 Brodie's D Value

i.e.

$$D = \frac{[U]_b + [I]_b}{[U]_g + [I]_g}$$

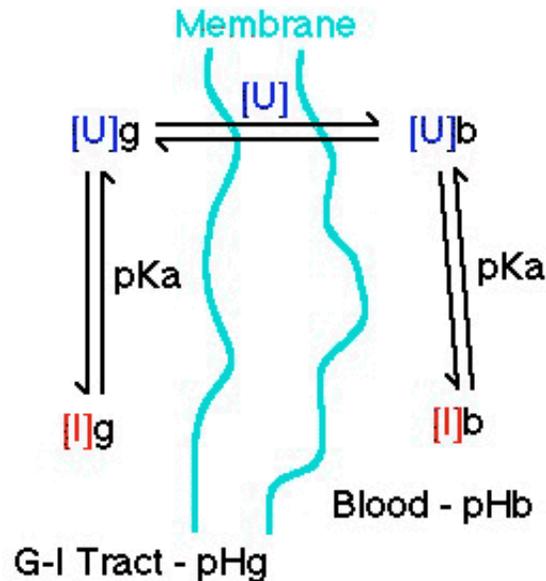**Equation 12.2.2 Brodie's D Value in Another Form**

Figure 12.2.1 Diagram Showing Transfer Across Membrane

These values were determined experimentally, but we should be able to calculate a theoretical value if we assume that only non ionized drug crosses the membrane and that net transfer stops when $[U]_b = [U]_g$

Brodie found an excellent correlation between the calculated D value and the experimentally determined values.

Review of Ionic Equilbrium

The ratio [U]/[I] is a function of the pH of the solution and the pKa of the drug, as described by the Henderson - Hasselbach equation

Weak acids

$$HA \rightleftharpoons H^+ + A^-$$

where HA is the weak acid and A^- is the salt or conjugate base

$$Ka = \frac{a_{H^+} \bullet a_{A^-}}{a_{HA}} \approx \frac{[H^+] \bullet [A^-]}{[HA]}$$

Equation 12.2.3 Dissociation Constant - Weak Acids

taking the negative log of both sides
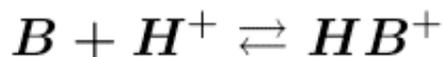
$$-logKa = -log[H^+] - log\frac{[A^-]}{[HA]}$$

and rearranging gives Equation 12.2.4 where pKa = -log Ka and pH = -log[H^+]

$$pKa - pH = log\frac{[U]}{[I]} = log\frac{[HA]}{[A^-]}$$

Equation 12.2.4 Henderson - Hasselbach Equation - Weak Acids

Weak Bases

$$B + H^+ \rightleftarrows HB^+$$

where B is the weak base and HB^+ is the salt or conjugate acid

$$Ka = \frac{a_{H^+} \bullet a_B}{a_{HB^+}} \approx \frac{[H^+] \bullet [B]}{[HB^+]}$$

Equation 12.2.5 Dissociation Constant - Weak Acids

taking the negative log of both sides

$$-logKa = -log[H^+] - log\frac{[B]}{[HB^+]}$$

and rearranging gives Equation 12.2.6 where pKa = -log Ka and pH = -log[H^+]

$$pKa - pH = log\frac{[I]}{[U]} = log\frac{[HB^+]}{[B]}$$

Equation 12.2.6 Henderson - Hasselbach Equation - Weak Bases

or alternately

$$Kb = \frac{[OH^-] \bullet [HB^+]}{[B]}$$

Equation 12.2.7 Dissociation Constant - Weak Base

taking the negative log of both sides

$$-logKb = -log[OH^-] - log\frac{[HB^+]}{[B]}$$

$$pKb - pOH = log\frac{[U]}{[I]} = log\frac{[B]}{[HB^+]}$$

Note that $K_a \bullet K_b = [H_3O^+] \bullet [OH^-] = K_w$ which is approximately 10^{-14}, thus pKb - pOH = pH - pKa and the equation above can be changed into Equation 12.2.6.

Table 12.2.1 Some Typical pKa Values for Weak Acids at 25 °C Martin 1993

Weak Acid	pKa
Acetic	4.76
Acetylsalicyclic	3.49
Ascorbic	4.3, 11.8
Boric	9.24
Penicillin V	2.73
Phenytoin	8.1
Salicyclic	2.97
Sulfathiazole	7.12
Tetracycline	3.3, 7.68, 9.69

Table 12.2.1 Some Typical pKa Values for Weak Bases at 25 °C Martin 1993

Weak Base	pKb
Ammonia	4.76
Atropine	4.35
Caffeine	10.4, 13.4
Codeine	5.8
Erythromycin	5.2
Morphine	6.13
Pilocarpine	7.2, 12.7
Quinine	6.0, 9.89
Tolbutamide	8.7

D Values and Drug Absorption

Even though the D values refer to an equilibrium state a large D value will mean that more drug will move from the GI tract to the blood side of the membrane. The larger the D value, the larger the effective concentration gradient, and thus the faster the expected transfer or absorption rate.
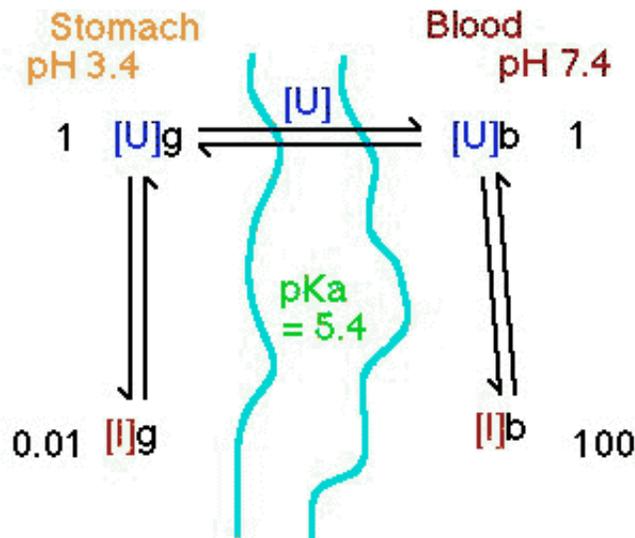
Figure 12.2.2 Diagram Illustrating Drug Distribution between Stomach and Blood

Compare D for a weak acid (pKa = 5.4) from the stomach (pH 3.4) or intestine (pH 6.4), with blood pH = 7.4

Stomach

$$\frac{[U]}{[I]} = 10^{pKa-pH} = 10^{5.4-3.4} = 10^2 = 100$$

Equation 12.2.8 Weak Acid from Stomach

$$\text{therefore } [I]_{stomach} = 0.01 \times [U]_{stomach}$$

Blood

$$\frac{[U]}{[I]} = 10^{pKa-pH} = 10^{5.4-7.4} = 10^{-2} = 0.01$$

Equation 12.2.9 Weak Acid from Blood

$$\text{therefore } [I]_{blood} = 100 \times [U]_{blood}$$

Therefore the calculated D value would be

$$D = \frac{\text{Total in blood}}{\text{Total in stomach}} = \frac{[U]_{blood} + [I]_{blood}}{[U]_{stomach} + [I]_{stomach}}$$

$$\text{replacing } [I]_{blood} \text{ and } [I]_{stomach} \text{ with the equivalent in terms of } [U]$$

$$\text{and setting } [U]_{blood} = [U]_{stomach} = [U]$$

$$D = \frac{[U] + 100 \bullet [U]}{[U] + 0.01 \bullet [U]} = \frac{101}{1.01} = 100$$

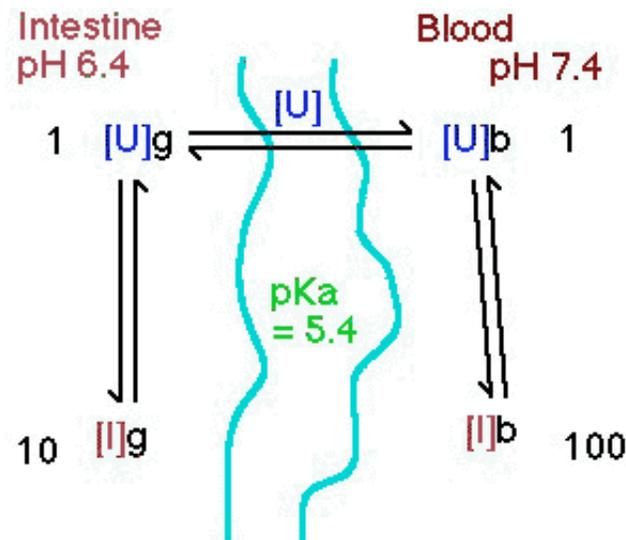**Equation 12.2.10 Brodie D Value - Weak Acid (Stomach)**

Figure 12.2.3 Diagram Illustrating Drug Distribution between Intestine and Blood

By comparison in the intestine, pH = 6.4

The calculated D value is (100+1)/(10+1) = 9.2

From this example we could expect significant absorption of weak acids from the stomach compared with from the intestine. Remember however that the surface area of the intestine is much larger than the stomach. However, this approach can be used to compare a series of similar compounds with different pKa values.

We have applied the pH - partition theory to drug absorption, later we will use this theory to describe drug re-absorption in the kidney.
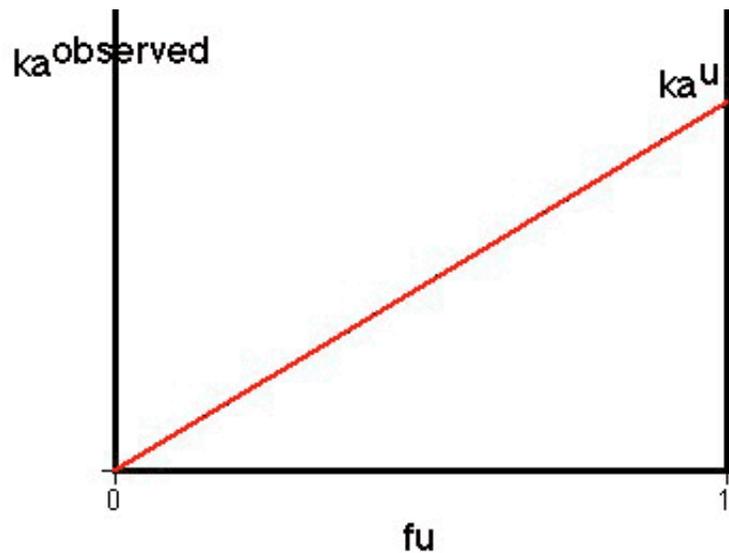
Figure 12.2.4 Plot of ka *versus* fu

With this theory it should be possible to predict that by changing the pH of the G-I tract that we would change the fraction non ionized and therefore the rate of absorption.

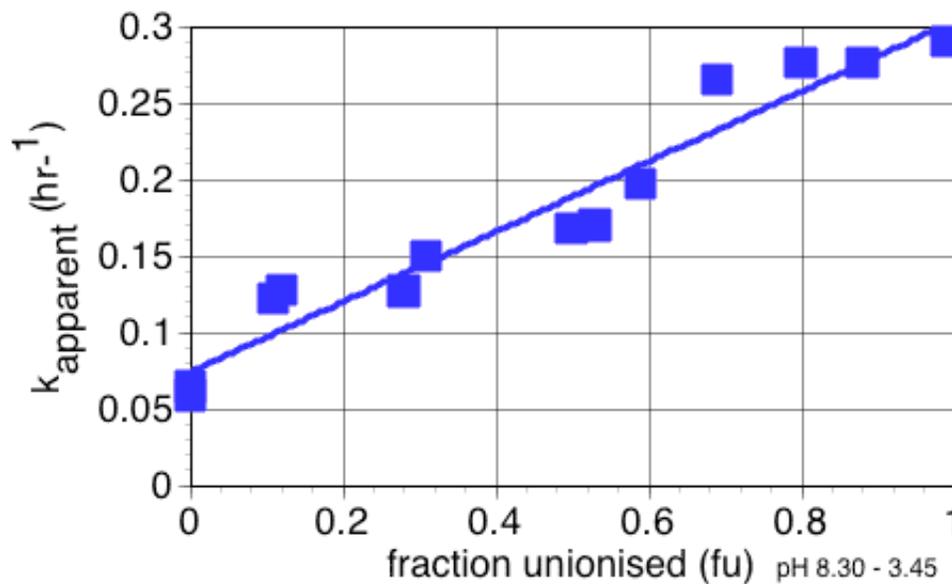Thus $ka_{observed} = ku \bullet fu$ assuming that the ionized species is not absorbed.

Figure 12.2.5 Plot of ka (apparent) *versus* fu for Sulfaethidole from Rat Stomach

Redrawn from Crouthamel, W.G., Tan, G.H., Dittert, L.W. and Dolusio, J.T.
1971 **Drug absorption IV. Influence of pH on absorption kinetics
of weakly acidic drugs**, *J. Pharm. Sci.*, **60**, 1160-63

For some drugs it has been found that the intercept is not zero in the above plot, suggesting that the ionic form is also absorbed. For example, results for sulfaethidole. Maybe the ions are transported by a carrier which blocks the charge, a facilitated transport process.

Calculator 12.2.1 Calculate the D Value for a Weak Acid
Starting with 100 units of a WEAK ACID

Drug pKa [5.4]

[HA]$_{GI}$ [   ]   [HA]$_{Blood}$ [   ]

GI pH [6.4]   [7.4] Blood pH

Total - GI [   ]   [A$^-$]$_{GI}$ [   ]   [A$^-$]$_{Blood}$ [   ]   Total - Blood [   ]

%U [   ]   (Calculate D)   [   ] %U
%I [   ]   D Value [   ]   [   ] %I

Calculator 12.2.2 Calculate the D Value for a Weak Base
Starting with 100 units of a WEAK BASE

Drug pKa [5.4]   Drug pKb [5.4]

[B]$_{GI}$ [   ]   [B]$_{Blood}$ [   ]

GI pH [6.4]   [7.4] Blood pH

Total - GI [   ]   [HB$^+$]$_{GI}$ [   ]   [HB$^+$]$_{Blood}$ [   ]   Total - Blood [   ]

%U [   ]   (Calculate D)   [   ] %U
%I [   ]   D Value [   ]   [   ] %I

Some items to consider

Item 1. A series of drugs, weak acids, have been developed. The best five drugs in the series have measured pKa values of 3.4, 4.7, 5.4, 4.2 and 5.1. Which drug has the highest D value in the stomach (pH 2.5)? Which drug would be better absorbed from the small intestine (pH 7.2).

Item 2. A series of drugs, weak bases, have been developed. The best five drugs in the series have measured pKa values of 10.4, 9.7,

9.4, 8.2 and 8.7. Which drug candidate has the highest D value in the stomach (pH 2.5)? Which drug would be better absorbed from the small intestine (pH 7.2).

References

- Shore, P.A., Brodie, B.B., and Hogben, C.A.M. 1957. **The Gastric Secretion of Drugs: A pH Partition Hypothesis**, *J. Pcol., Exp., Therap.*, **119**, 361-369
- Hogben, C.A.M., Tocco, D.J., Brodie, B.B., and Schanker, L.S., 1959. **On the Mechanism of Intestinal Absorption of Drugs**, *J. Pcol., Exp., Therap.*, **125**, 275-282
- Crouthamel, W.G., Tan, G.H., Dittert, L.W. and Dolusio, J.T. 1971 Drug absorption IV. Influence of pH on absorption kinetics of weakly acidic drugs, *J. Pharm. Sci.*, **60**, 1160
- Martin, A. 1993 **Physical Pharmacy**, 4th ed., Lea & Febiger, Philadelphia

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PHAR 7632 Chapter 12

Physical-Chemical Factors Affecting Oral Absorption

Drug Dissolution

So far we have looked at the transfer of drugs in solution in the G-I tract, through a membrane, into solution in the blood. However, many drugs are given in solid dosage forms and therefore must dissolve before absorption can take place.

Figure 12.3.1 Dissolution and Absorption

If absorption is slow relative to dissolution then all we are concerned with is absorption. However, if dissolution is the slow, rate determining step (the step controlling the overall rate) then factors affecting dissolution will control the overall process. This is a more common problem with drugs which have a low solubility (below 1 g/100 ml) or which are given at a high dose, e.g. griseofulvin.

There are a number of factors which affect drug dissolution. One model that is commonly used is to consider this process to be diffusion controlled through a stagnant layer surrounding each solid particle.
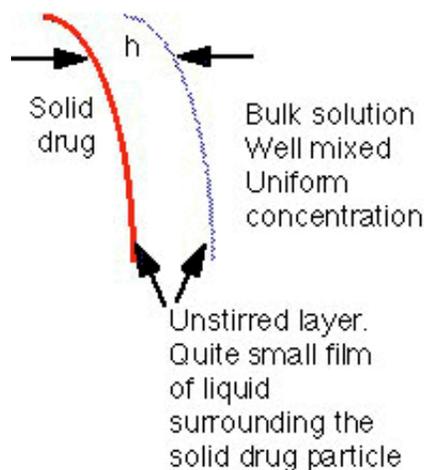

Figure 12.3.2 Diagram Representing Diffusion Through the Stagnant Layer

A physical model is shown in Figure 12.3.2

First we need to consider that each particle of drug formulation is surrounded by a stagnant layer of solution.

After an initial period we will have a steady state where drug is steadily dissolved at the solid-liquid interface and diffuses through the stagnant layer. If diffusion is the rate determining step we can use Fick's first law of diffusion to describe the overall process.
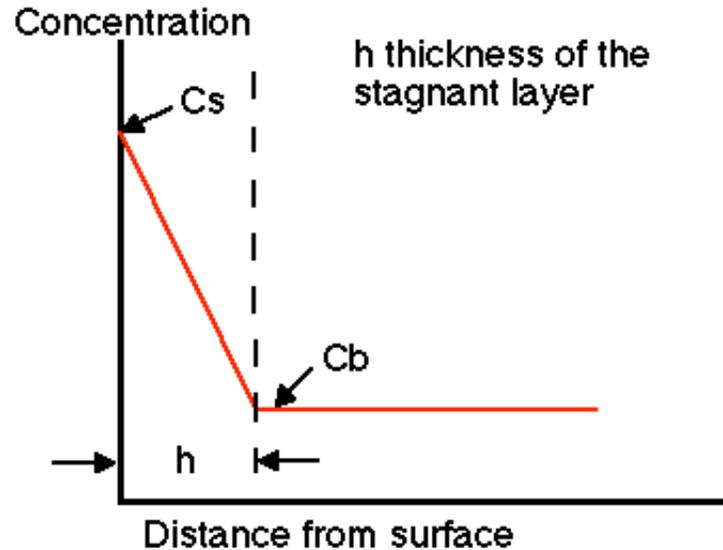
Figure 12.3.3 Plot of Concentration Gradient

If we could measure drug concentration at various distances from the surface of the solid we would see that a concentration gradient is developed. If we assume steady state we can used Fick's first law to describe drug dissolution.

Fick's first law

By Fick's first law of diffusion:

$$\text{Rate of Solution} = \frac{D \bullet A \bullet (Cs - Cb)}{h}$$

Equation 12.3.1 Fick's first Law of Diffusion applied to Dissolution

where D is the diffusion coefficient, A the surface area, Cs the solubility of the drug, Cb the concentration of drug in the bulk solution, and h the thickness of the stagnant layer. If Cb is much smaller than Cs then we have so-called "Sink Conditions" and the equation reduces to

$$\text{Rate of Solution} = \frac{D \bullet A \bullet Cs}{h}$$

Equation 12.3.2 Fick's First Law - Sink Conditions

with each term in this equation contributing to the dissolution process.

Surface area, A

The surface area per gram (or per dose) of a solid drug can be changed by altering the particle size. For example, a cube 3 cm on each side has a surface area of 54 cm^2. If this cube is broken into cubes with sides of 1 cm, the total surface area is 162 cm^2. Actually if we break up the particles by grinding we will have irregular shapes and even larger surface areas. Generally as A increases the dissolution rate will also increase. Improved bioavailability has been observed with griseofulvin, digoxin, etc.
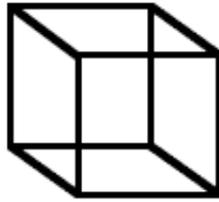
$$A = 1 \times 6 \times 3 \times 3 = 54$$

Figure 12.3.4 Reducing Particle Size Increases Surface Area

Methods of particle size reduction include mortar and pestle, mechanical grinders, fluid energy mills, solid dispersions in readily soluble materials (PEG's).

Diffusion layer thickness, h

This thickness is determined by the agitation in the bulk solution. *In vivo* we usually have very little control over this parameter. It is important though when we perform *in vitro* dissolution studies because we have to control the agitation rate so that we get similar results *in vitro* as we would *in vivo*.
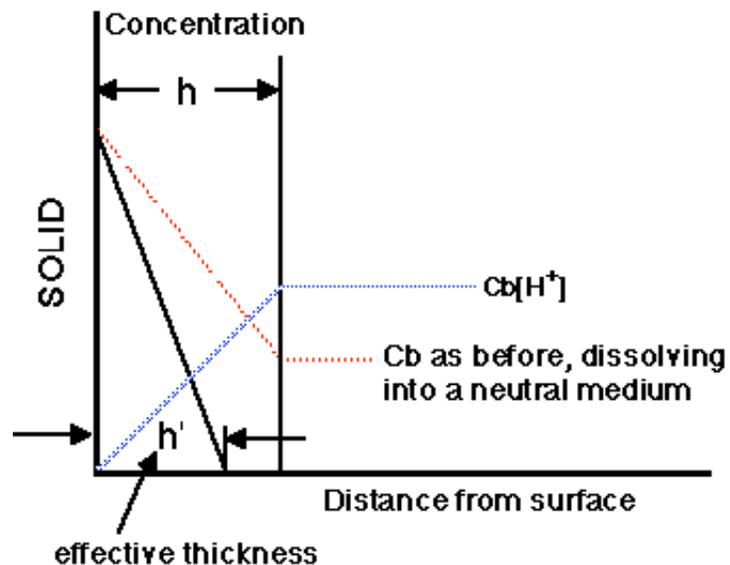
Figure 12.3.5 Plot of Concentration *versus* Distance for Dissolution into a Reactive Medium

The apparent thickness of the stagnant layer can be reduced when the drug dissolves into a reactive medium. For example, with a

weakly basic drug in an acidic medium, the drug will react (ionize) with the diffusing proton (H^+) and this will result in an effective decrease in the thickness of the stagnant layer.

The effective thickness is now h' not h. Also the bulk concentration of the drug is effectively zero. For this reason weak bases will dissolve more quickly in the stomach.

Diffusion coefficient, D

The value of D depends on the size of the molecule and the viscosity of the dissolution medium. Increasing the viscosity will decrease the diffusion coefficient and thus the dissolution rate. This could be used to produce a sustained release effect by including a larger proportion of something like sucrose or acacia in a tablet formulation.

Drug solubility, Cs

Solubility is another determinant of dissolution rate. As Cs increases so does the dissolution rate. We can look at ways of changing the solubility of a drug.

Salt form

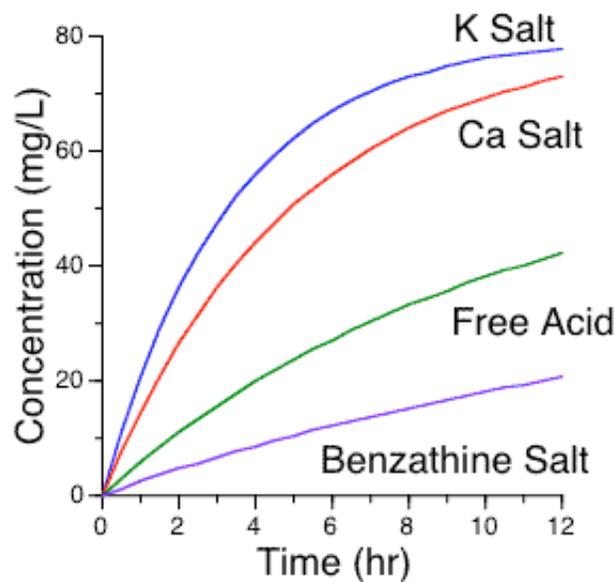If we look at the dissolution profile of various salts.

Figure 12.3.6 Plot of Dissolved Drug Concentration *versus* Time

Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base, therefore if the drug can be given as a salt the solubility can be increased and we should have improved dissolution. One example is Penicillin V.
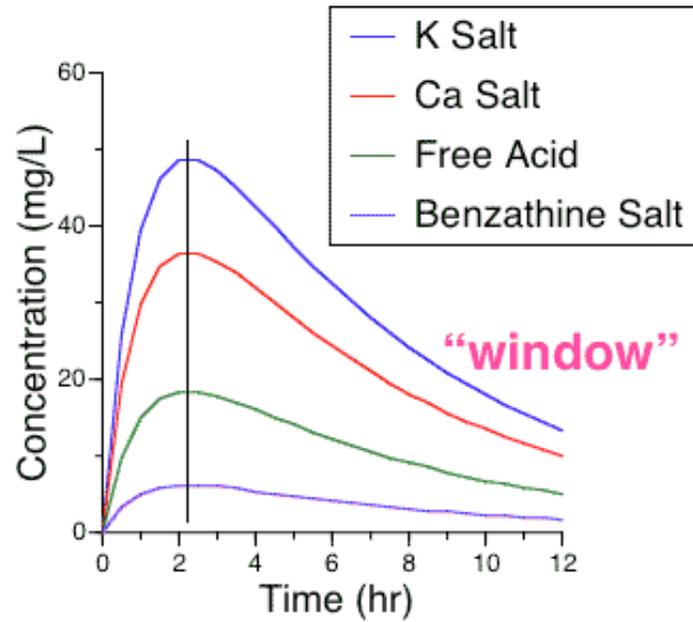
Figure 12.3.7 Plot of Cp *versus* Time

This can lead to quite different Cp *versus* time results after oral administration.

The t_{peak} values are similar thus ka is probably the same. C_{peak} might show a good correlation with solubility. Maybe site limited (only drug in solution by the time the drug gets to the 'window' is absorbed). Use the potassium salt for better absorption orally. These results might support the use of the benzathine or procaine salts for IM depot use.
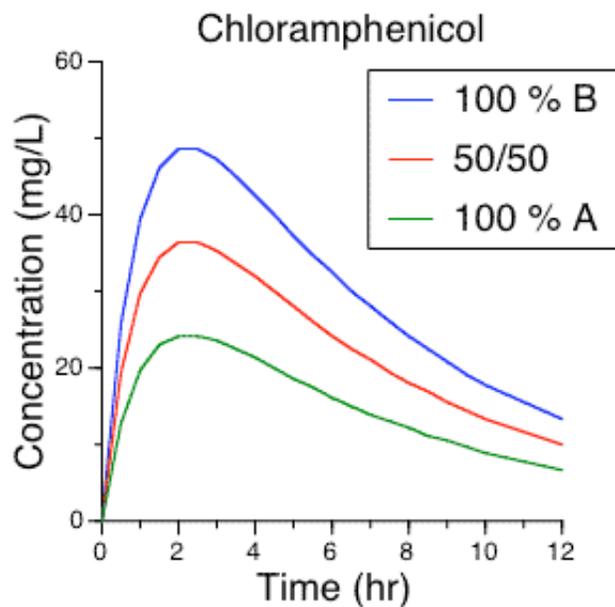
Crystal form

Figure 12.3.8 Plot of Cp *versus* Time for Three Formulations of Chloramphenicol Palmitate

Redrawn from Figure 6 in the paper by Aguiar et al. 1967

Some drugs exist in a number of crystal forms or polymorphs. These different forms may well have different solubility properties and thus different dissolution characteristics. Chloramphenicol palmitate is one example which exists in at least two polymorphs. The B

form is apparently more bioavailable.

The recommendation might be that manufacturers should use polymorph B for maximum solubility and absorption. However, a method of controlling and determining crystal form would be necessary in the quality control process. Shelf-life could be a problem as the more soluble (less stable) form may transform into the less soluble form. In time the suspension may be much less soluble with variable absorption.

Some items to consider

Item 1. In this Chapter we have assumed that the absorption process is uncomplicated and can be represented as a single first order process. Occasionally an additional process may be necessary. With sustained release products an additional dissolution step may be necessary.

A drug was administered as an IV injection, and oral solution and two tablet formulations (one rapid and the other a slow release tablet). A dissolution step was included to model the two tablet formulations. Parameters values included kel = 0.077 hr^{-1},V = 81.3 L, ka = 0.113 hr^{-1}. The two tablet formulations required kd = 0405 hr^{-1} or 0.0261 hr^{-1}. The dose were 25000 mg (Dose1 IV bolus), 20300 mg (Dose2 Oral solution), 19000 mg (Dose3 Oral rapid release tablet) and 21600 mg (Dose3 Oral slow release tablet). Simulate the concentration *versus* time curves after each dose. Bevill et al., 1977. Explore the problem as a Linear Plot - Java Applet

References

- Aguiar, A.J., Krc, J., Kinkel, A.W., and Samyn, J.C. 1967 **Effect of Polymorphism on the Absorption of Chloramphenicol from Chloramphenicol Palmitate**, *J. Pharm. Sci.,* **56**(7), 847-853
- Bevill, R.F., Dittert, L.W. and Bourne, D.W.A. 1977 Disposition of Sulfonamides in Food-Producing Animals IV: Pharmacokinetics of Sulfamethazine in Cattle following Administration of an Intravenous Dose and Three Oral Dosage Forms, *J. Pharm. Sci.*, **66**, 619-23

Student Objectives for this Chapter

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