5. \[ pK_a = 3.5 \]

\[ \text{pH} = pK_a + \log \frac{\text{salt}}{\text{acid}} \]

For aspirin, since it's an acid, the protonated acid (HA) form is neutral, and the deprotonated salt (A⁻) is polar.

\[ 10^{(\text{pH} - pK_a)} = \frac{\text{salt}}{\text{acid}} \]

- **Stomach**
  - For \( \text{pH} = 1 \)
  
  \[ \frac{\text{salt}}{\text{acid}} = 10^{(1.0 - 3.5)} = 3 \times 10^{-3} \]

  The compound is mainly in its protonated form (nonpolar) so it is absorbed in the stomach mainly in the deprotonated form (polar).

- **Intestines**
  - For \( \text{pH} = 6 \)
  
  \[ \frac{\text{salt}}{\text{acid}} = 10^{(6.0 - 3.5)} = 320 \]

6. For \( \text{pH} = 1 \),

\[ \frac{\text{salt}}{\text{acid}} = 10^{(1.0 - 0.6)} = 2.5 \]

Caffeine is a basic drug, so it is lipophilic at lower pH's and will absorb in the intestines.

7. \( pK_a = 5.1 \)

\( pK_{a2} = 9.7 \)

To extract from \( H_2O \), needs to be in neutral form so miscible with organic, lipophilic solvent.

Isoelectric pH = \( \frac{5.1 + 9.7}{2} = 7.4 \)

Neutral form at this pH so can extract out of aqueous phase into nonpolar phase.
dissolve sample at acidic pH so drugs are in polar form ($BH^+$)

9. L-L extraction = aqueous phase and nonpolar phase

H₂O soluble = powdered sugar + cornstarch

organic layer = cocaine + amphetamine in neutral forms \( \text{adjust pH} \)

\[
\begin{align*}
\text{Cocaine (Fig p. 104)} & \quad \text{pK}_a = 8.6 \\
\text{amphetamine (Fig p. 105)} & \quad \text{pK}_a = 9.8
\end{align*}
\]

\[ \text{pH 2 units above 9.8 or ~12 to be in neutral forms} \]

SPE Procedure - see example Problem 4.6, p. 113

1. dissolve basic drugs 2 pH units above 9.8 as before ~12 so in neutral form (drugs now in basic buffer)

2. select C₁₈ SPE column (Table 4.4 p 110)

   a very nonpolar state, phase used to remove hydrophobic species from aqueous solutions. Neutral forms will bind to column.

3. condition column by first rinsing with organic solvent (methanol) to remove organic contaminants, then with same basic buffer (pH = 12) used to dissolve drugs, rinse 2nd time

4. introduce sample onto column

**NOTE:** the book suggests a dilute acid wash at this point to "remove acidic contaminants". This makes no sense for 2 reasons: (1) basic drugs bound to column will be soluble in acid, (2) bases will remove acid contaminants, not weak acids.
(5) Strip bound contaminants off dry column with hexane.

(6) Elute drugs with:

NOTE: The book now suggests removing basic drugs with organic solvent (alcohol + methylene chloride) + NH₃. Instead,

(7) Elute neutral form of the drugs using organic solvent such as (Merck Index).
1. (a) Diazepam structure: MST Webbook — 2 amine groups but only 1 protonated; $pK_a = 3.4$

(b) basic since amine, but weak — $pK_a + pK_b = 14$

$$pK_b = 14 - 3.4 = 10.6$$

(c) $pH = pK_a + \log \frac{\text{salt}}{\text{acid}} \leftarrow B^+ \equiv 0.010 M$

\[ B + H_2O \rightleftharpoons BH^+ + OH^- \]

\[ B^+ + OH^- \rightleftharpoons BH \]

\[ I \quad 0.010 \quad - \quad - \]

\[ C \quad -x \quad +x \quad +y \]

\[ E \quad 0.010 -x \quad x \quad x \]

\[ x = \sqrt{\frac{(0.010 - x)(0.010)}{2.5 \times 10^{-11}}} \]

Since $k_b$ is so weak, assume $x \ll 0.010$

Since $k_b = 10^{-10.6} = 2.5 \times 10^{-11}$

$$x^2 = k_b = 10^{-10.6} = 2.5 \times 10^{-11}$$

$$x = 5.0 \times 10^{-7}$$

$$pOH = 6.3$$

$$pH = 14 - 6.3 = 7.7$$

(d) Assuming extracting from aqueous phase, adjust the pH so diazepam is in its neutral form; so raise pH 2 units greater than $pK_a \approx 5.4$. Then do L-L extraction into miscible organic phase such as chloroform.