Section 5

Drug Solubility
### 9.2.5 Lifestyle Chemistry – Section 5 :::: Drug Solubility

**The solubility of drugs has an effect on the way in which the body responds to them**

| 9.2.5.a | Identify the parts of the digestive system |
| 9.2.5.b | Outline the role of the stomach and the small intestine in breaking down food |
| 9.2.5.c | Discuss the difference in pH of the stomach and the small intestine |
| 9.2.5.d | Explain why a knowledge of the solubility of materials can be used to design drugs for specific tasks |
| 9.2.5.e | Account for the absorption of a drug and its action on the body in terms of its solubility |
| 9.2.5.f | Identify that the manner of administration of a drug may be related to its solubility |
| 9.2.5.g | Identify the solubility of capsules, tablets, enteric coated tablets, and slow-release tablets |
| 9.2.5.h | Identify vitamins that are water-soluble and those that are fat-soluble and relate this to their toxicity |
| 9.2.5.i | Gather, process and analyse information from first-hand or secondary sources to relate the significance of solubility of a medication to their action on/in the body |
The alimentary canal

When you swallow food, it starts to move down a long tube called the *alimentary canal*. This tube runs from the mouth to the anus and food is squeezed along it by wave-like muscle movements called *peristalsis*.

Two important things happen to the food as it passes along the alimentary canal:

**The food is digested**

During digestion, chemical compounds called *enzymes* break the food down into simpler substances which can be carried in the bloodstream, and which will dissolve in the water within the cells of the body.

Digestion mainly takes place in the stomach and the small intestine but it starts in the mouth - an enzyme in saliva starts to break down starch into glucose as you chew your food.

**Digested food is absorbed into the bloodstream**

This mainly takes place in the small intestine - its walls are lined with tiny blood tubes that carry the digested food away.

Undigested matter passes into the large intestine and is pushed out of the anus when the toilet is used.
The stomach
After food has been swallowed, it passes down the oesophagus and into the stomach. The stomach has two main roles.

1. Mixing food with digestive juices. Contractions of strong muscles in the stomach walls thoroughly mix food with gastric juice.

2. Beginning the digestion of protein. The digestive juice in the stomach is called gastric juice. It oozes from thousands of tiny glands in the stomach lining. Gastric juice contains hydrochloric acid and an enzyme called pepsin. Pepsin begins the break-up of any proteins in the food (from foods such as meat and milk).

The stomach stretches as it fills with food. After it has been mixed and partly digested it becomes a thick paste, called chyme. Every now and then, a ring of muscles at the bottom of the stomach allows some mixed food to pass down into the small intestine.

The small intestine
The major roles of the small intestine are:

1. Digestion is completed in the small intestine. In the upper part of the small intestine, three more digestive juices are mixed with the food. These continue the process of digestion:

   **Bile**, which is made in the liver and stored in the gall bladder, breaks up fats into droplets small enough to be digested. It also neutralises the stomach acid.

   **Pancreatic juice** from the pancreas carries powerful enzymes that digest starches, fats and proteins.

   The walls of the small intestine secrete **intestinal juice**. This liquid (like pancreatic juice) digests starches, fats and proteins.

2. Digested food passes through the walls of the small intestine into the bloodstream. The small intestine has a very large surface area for absorption due to the millions of tiny bumps on the intestine walls. The bumps are called villi, and they contain the network of tiny blood tubes that carry the food away.

   Undigested droplets of fat are also absorbed by the villi. They pass into tiny tubes containing a liquid called **lymph** that drains into the blood elsewhere in the body.

The large intestine
Undigested matter such as cellulose passes into the large intestine. Here, water remaining from the digestive juices is absorbed so that it can be re-used by the body. Waste matter, now semi-solid, passes out of the body through the anus.
Notes Questions

1. Copy and complete the following flow chart showing the parts of the digestive system. Use the words supplied below. [3 marks]

   Mouth, (Bile from liver), Intestinal wall, Anus, Gall bladder, (Pancreatic juice), Stomach, Large intestine, (Gastric Juice), Pancreas, Small Intestine, (Intestinal juice), Oesophagus

   ![Flow Chart Diagram]

   Alimentary Canal
   \[\downarrow\]
   \[\downarrow\]
   \[\downarrow\]
   \[\leftarrow\]
   \[\downarrow\]
   \[\leftarrow\] Gall bladder (Bile from liver)
   \[\downarrow\]
   \[\leftarrow\]
   \[\downarrow\]
   Anus

2. Use the two column method to outline the role of the stomach in breaking down food. [2 marks]

   **NB** Outline means sketch in general terms. It implies a relatively brief answer without great detail.

<table>
<thead>
<tr>
<th>Main sentence (idea)</th>
<th>Supporting sentence(s) (ideas or facts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The stomach mixes food with digestive juices</td>
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<tr>
<td>The digestion of protein begins in the stomach</td>
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</table>

3. Use the two column method to outline the role of the small intestine in breaking down food. [3 marks]

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.</td>
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<td>2.</td>
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</table>
9.2.5.c Discuss the difference in pH of the stomach and the small intestine

**pH differences - Stomach & the Small Intestine**

The pH of the stomach is about 3.0. The stomach gets this pH because of the acidity of gastric juice secreted by the walls of the stomach. The pH of the small intestine is about 8.0. The stomach acid is neutralised by the secretions of bile and pancreatic juice. These secretions of the liver and pancreas leave the intestine with an alkaline pH.

The stomach wall is protected from the acid by a lining of mucus. If this lining is broken an ulcer can develop on the stomach wall. Another problem with the acid environment of the stomach and its enzymes is that it destroys certain drugs (eg insulin), making oral administration difficult. Alternatively, a benefit is that the combined action of the acid and the enzymes kills bacteria in food.

One issue related to the pH difference is the operation of digestive juices. The different pH of the stomach and the small intestine provides an appropriate environment for the operation of particular digestive enzymes. Enzymes are chemicals that speed up the rate of chemical reactions in cells. Pepsin, an enzyme involved in the breakdown of protein, operates best in the stomach's acid pH. Access to the protein is made easier because the acid environment of the stomach denatures proteins. That is, the protein molecule unwinds making access by enzymes easier. Trypsin is another enzyme involved in the breakdown of protein. Trypsin operates best in the slightly alkaline pH of the small intestine.

A second issue is the absorption of drugs. The different pH of the stomach and the small intestine provides a different environment for the absorption of drugs. Most drugs are weak acids or weak bases. The solubility of a weak acid or a weak base is related to pH. The rate of break up and the rate of absorption are affected by differences in pH. The best pH environment for weak acid drugs to pass into the bloodstream occurs in the acidic stomach. The best pH environment for weak base drugs to pass into the bloodstream occurs in the alkaline small intestine.

**Notes Questions**

4. Rewrite each of the following statements so they are correct
   a. The pH of the stomach is about 5.
   b. Secretions from the liver (via the bile duct) cause the stomach to be acidic.
   c. The action of alkalis denatures protein.
   d. Trypsin is an enzyme that begins the digestion of protein.
   e. Trypsin operates best in a fluid of low pH.
   f. Most drugs are weak acids.
   g. Weak base drugs are absorbed through the stomach wall.
Drugs and solubility of materials

Most drugs are given orally in solid forms (tablets, capsules). This is mainly for convenience, economy, stability and patient acceptance. If drugs are taken in a solid form they must break up before the active ingredient is available for absorption. This break up converts drug molecules from the solid state to suspension in a liquid so that they can be dissolved. Therefore, a tablet needs to break up into granules, then into fine particles and then it eventually dissolves. The break-up of the solid form greatly increases the surface area of the drug in contact with digestive juices. This increases the amount of drug dissolved and absorbed. Various substances (lubricants, surfactants, binders, dispersants) are added to the tablet or capsule to assist with break-up, dissolving and absorption.

Normally, the availability of a drug for absorption decreases in the following order: solutions, suspensions, capsules/compressed tablets (regardless of shape) and finally coated tablets.

Different drugs perform different tasks. To design drugs for specific tasks it is helpful to have a knowledge of the solubility of the materials used and the solubility of the drugs. Solubility is the amount of solute that can dissolve in a given amount of solvent. A knowledge of solubility is important because solubility affects:

- How quickly a drug acts
- The ability of the drug to pass through the body membranes
- Where the drug dissolves
- How long the drug dosage acts

Example 1  **Fast acting drugs** - pain killers. To develop a fast acting, pain killing drug the designer needs to identify and select materials that are very soluble. This allows the pain killing drug to be quickly dissolved by the body and be transported to the appropriate area to relieve a person of pain.

Example 2  **Movement through membranes**  To move through the wall of the stomach or small intestine the chemical needs to be lipid soluble. To be transported by the blood the drugs need to be water soluble. Therefore the designer needs to select materials that can change from being water soluble to being lipid soluble. An understanding of solubility is therefore needed (read 9.2.5.e).

Example 3  **Enteric coated tablets**  Some tablets must be allowed to pass through the stomach before they release their drug into the intestines. This is because the acids in the stomach either destroy the drug or the drug irritates the stomach lining. In this instance, materials need to be used to prevent the tablet or capsule dissolving in the stomach. This is only possible with a knowledge of the solubility of materials.
Cartia is a tablet designed for the long term use of aspirin. It has an enteric coating that delays breakdown of the capsule until the tablet reaches the intestine. This is because aspirin has an irritating effect on the lining of the stomach. When aspirin is used as a pain killer the aim is for rapid response. Therefore, the drug is absorbed via the stomach. Short term irritation of the stomach is acceptable to ensure rapid pain relief. Cartia involves the long term use of aspirin and in this case it is better to avoid the irritation of the stomach.

Example 4  **Sustained release tablets**  A sustained release tablet are designed to release a drug slowly, producing a longer effect. The main advantage is an increase in time the drug acts. Only a fraction of the total dose is released immediately producing an effective level to begin with. The remaining dose is usually released at a constant rate to maintain the effective level. This means an optimum level of the drug can be maintained in the blood stream for a longer period of time. It also means that there is better patient compliance – taking a tablet once a day is easier than 4 times a day. (M.S. Contin is used to treat cancer patients - slow release morphine).

Example 5  Some drugs are not soluble. An antacid is insoluble and is not designed to be absorbed. The target of this medication is stomach acid. The substances in antacid tablets react with stomach contents to decrease acid content in the stomach.

A knowledge of solubility is therefore needed because the material used to make the tablet or capsule depends on the where and how the drug is absorbed. The tablet for a fast acting drug needs to be very soluble. Sustained release tablets need to be made from materials that dissolve slowly. Tablets that are meant to bypass the stomach must not dissolve in acids.

*Solubility is defined as the number of grams of solute that dissolves in one litre of the solvent, at 25°C. Any substance that has a solubility of less than 0.01 molL⁻¹ is considered insoluble. Several factors affect solubility including*
  *Particle size*
  *Temperature*
  *Acidity of solute*
  *Nature of the solvent (pH)*

**Notes Questions**

5. Define solubility
6. Name one reason why a drug would need to be fast acting
7. Explain why drugs need to change from being water soluble to lipid (fat) soluble.
8. Suggest two reasons why a drug should be enteric coated
9. Name a drug that is enteric coated.
10. Suggest why some drugs are released in a slow release form. Use examples in your answer.
9.2.5.e Account for the absorption of a drug and its action on/in the body in terms of its solubility

Solubility of drugs - their absorption and action

Pharmacology is the science of the nature and properties of drugs and their actions in the body. There are a large number of factors to be considered in the design of effective drugs.

For a drug to be effective it needs to be
- Absorbed
- Distributed through the body and then
- Interact with receptors in the target area (act on the body).

An important factor for the absorption, distribution and action of a drug is solubility. This solubility may refer to the solubility of the drug itself or the chemical carrier of the drug. Absorption is the movement of a drug from the site of administration into the blood. In the blood the drugs are either dissolved in blood plasma or attached to proteins in the blood. At the site of action the drug becomes attached to a receptor compound to carry out its function.

Oral intake of drugs

- the drug must be water-soluble and therefore dissolve in the stomach or small intestine before absorption can occur.
- Then the drug must cross several cell membranes of the stomach and/or intestine walls to reach the circulatory system (capillary - blood vessel). These membranes are mainly made up of lipids (a group of fat and fat-like substances). To cross this barrier the drug needs to be lipid soluble. In water-soluble form, drugs cannot pass through the lipid membranes.
- Once in the blood the drug is again in a water-soluble form and is then transported around the body. Alternatively, the drug is transported in the blood attached to a protein molecule.
- Finally, at the site of action the drug may again need to move across several cell membranes. Again it may need to return to its lipid soluble form to pass across this biological barrier.

Absorption

Other methods of drug delivery follow similar steps. The drug or the chemical transporting the drug generally need to be both water-soluble and lipid soluble to be absorbed, transported and to finally act on the body. For example, the intravenous injection of drugs directly into the vein, the drug must be water-soluble.
Notes Questions

11. Name are the three steps needed for a drug to be effective?

12. Consider the oral intake of a drug. For each part of the body listed, name whether a drug is water soluble or lipid soluble.
   - Stomach  water soluble
   - Stomach wall
   - Capillary wall
   - Small Intestine
   - Intestinal wall
   - Blood vessels
   - Biological barrier at the site of action

| 9.2.5.i | Identify data sources, gather, process and analyse information from first-hand or secondary sources to relate the significance of solubility of a medication to their action on/in the body |

Research

Research one drug and relate the significance of solubility of a medication to their action on/in the body. Possible drugs include alcohol, insulin, .................
Identify that the manner of administration of a drug may be related to its solubility

### Routes of Drug Administration

- **oral** - tablets, caps, solutions, syrups, elixirs, suspension, magmas, gels, powders
- **sublingual** (under your tongue) - tablets, lozenges
- **parenteral** (intravenous injection, intra muscular) - solutions, suspensions
- **transdermal** - ointments, creams, pastes, plasters, powders, aerosols, lotions, patches
- **conjunctiva** - contact lens, solutions, suspension, ointments
- **nasal** (inhalation) - solutions, sprays, inhalants, ointments
- **rectal** - solutions, ointments, suppositories

The oral route is the most common way of administering medicine today. Drugs administered orally are soluble. They are eventually dissolved somewhere in the digestive tract and then absorbed (except insoluble antacids that act in the stomach).

Many substances are poorly soluble in the digestive system (i.e., low water solubility). Companies use a number of strategies to increase water solubility. These strategies include reducing the size of the drug particles, dissolving the drug in another solvent (alcohol or detergents) or combining the drug with a carrier molecule.

Large drug molecules (e.g., insulin, growth hormone) present a different delivery problem. These complex proteins and peptides are commonly delivered by injection. These drugs are generally water-soluble, but cannot be delivered by oral methods because they can be destroyed by the enzymes in the digestive system. There has been significant progress in delivering some of these macromolecules via an inhaler (to the pulmonary blood system).

The different methods of drug delivery have certain advantages and disadvantages.

**Intravenous**
- No barriers to absorption since the drug is put directly into the blood.
- Very rapid onset for drugs. Good in an emergency.
- Accurate dose can be delivered
- Sterile techniques needed for administration
- IV drug administration is expensive and inconvenient compared to other routes.
- Other disadvantages include the risk of fluid overload, infection, and embolism.

**Oral**
- Two barriers to cross: epithelial cells and capillary wall.
- Easy, convenient, and inexpensive, no sterile techniques.
- Highly variable drug absorption influenced by many factors: pH, drug solubility and stability, food intake, other drugs, etc.
- This route would inactivate some drugs; first pass effect.
- Irritates internal surface of stomach and small intestine

[Source http://www.crnasomeday.com/pharmpages/chapfivepharm.htm]
The absorption of drugs from tablets and capsules is affected by
- Solubility
- Particle size
- Chemical form
- Crystalline structure.

If a drug is
- not soluble
- is damaged or made inactive by the stomach
- takes too long to reach the appropriate site for action
it may be necessary to find an alternative path into the body. These alternatives include injection, rectal administration, transdermal patches and gas via the lungs.

LIVER – The liver changes the form of many drugs to an inactive compound. The hepatic artery carries blood from the stomach to the liver. This gives rise to the FIRST PASS effect. That is, the first time a drug goes past the liver it remain in an active form to complete its task. This function of the liver can be also used to activate a drug – that is convert it into a different compound that makes it more soluble before it is transported around the body.

Notes Questions

13. What is meant by oral intake of drugs and intravenous delivery?
14. Suggest three ways drugs may be delivered by transdermal means.
15. Name at least three problems related to oral delivery of drugs?
16. Name two advantages of delivering drugs being delivered intravenously.
17. Outline the first past effect.
9.2.5.g Identify the solubility of capsules, tablets, enteric coated tablets, and slow-release tablets

Tablet

Tablets are combinations of drug, binders and other substances compressed into hard masses that can disintegrate in water. A tablet must first disintegrate and then dissolve so that it is in soluble form. It is then absorbed, usually down a concentration gradient by diffusion. Tablets like capsules can be enteric-coated and prepared for sustained release.

Tablet Slow Release

The formulation of a slow release tablet allows it to dissolve slowly over time. The medication is released gradually as the medication travels through the Gastro Intestinal Tract. This allows an appropriate concentration of the drug to be maintained over a longer period of time.

Tablet Enteric-coated

The tablet is covered in a coating that doesn’t dissolve in the stomach: That is the tablet by passes the stomach. The tablet then dissolves in the small intestine as it has a different pH. Once in the small intestine the active medication may be released.

Capsule

Capsules can be divided into two main groups. In both kinds the gelatin coating must first dissolve. This occurs quickly in the acidic environment of the stomach.

- Type 1. Powder inside a gelatin cap. The gelatin dissolves then the powder must dissolve and mix with the gastric juices to form a solution and it is then absorbed.
- Type 2. Liquid inside a gelatin cap. The gelatin dissolves and the liquid is ready to be absorbed straight away.

Capsules may be "enteric coated", ie. made resistant to acid-disintegration in the stomach, or "delayed-action", which permit more sustained release of drug.

Notes Questions

18. Describe a tablet.
19. Explain why there is a need for slow release tablets.
20. Why is a tablet enteric coated? Give an example.
Vitamins

Vitamins are essential to all living humans. They provide the body with enzymes used as catalysts in chemical reactions between carbohydrates, fats and proteins and other substances, which produce body tissue and energy.

There are 13 different types of vitamins known to scientists. Vitamins are generally classified into two groups:

♣ **fat-soluble** (vitamin A, D, E and K) and
♣ **water-soluble** (8 varieties of B (B-complex vitamins) and vitamin C).

The absorption of fat-soluble vitamins is enhanced with dietary fat. Fat-soluble vitamins are so named due to the fact that they dissolve in fat because of their non-polar properties. Fat-soluble vitamins hold very specific functions within the body. They are absorbed by the intestines and carried by the lymph system to required areas of the body. Fat-soluble vitamins are responsible, in part, for the maintenance of the cell membranes. They are stored in the body in larger amounts than the water-soluble vitamins, which are not stored in the body in any significant degree. It is not so likely that deficiencies of fat-soluble vitamins occur, since it takes weeks or months for the body to empty its stores. Conversely, because they are stored in the body, fat-soluble vitamins are also more likely to reach toxic levels, a hazard generally ascribed to taking big doses of vitamin supplement and not through over-consumption of food. Fat-soluble vitamins are generally more stable than water-soluble vitamins and are thus less prone to destruction by heat, air and light.

Water-soluble vitamins can dissolve in water because they are polar molecules, having -OH groups, enabling hydrogen bonds to H₂O. Water-soluble vitamins are also absorbed by the intestines and carried through the circulatory system to areas where they will be utilised.

**Notes Questions**

21. Which vitamins are fat soluble?
22. Which vitamins are water soluble?
23. Give a reason why fat soluble vitamins can be toxic.
24. Give a reason why water soluble vitamins can be toxic.
HSC Style Question – High Band

1. Discuss the difference in pH of the stomach and the intestine. [5 marks]

This question is unstructured and requires an extended answer

In order to answer such a question, you must provide some structure.

➢ STEP 1 Identify (& highlight) the important words in the question
➢ STEP 2 Recall definitions of these important words (if necessary)
   ▶ Discuss – Identify issues and provide points for and/or against
   ▶ Difference in pH
➢ STEP 3 Use the structure provided below to answer the question

<table>
<thead>
<tr>
<th>Basic information</th>
</tr>
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<tbody>
<tr>
<td>What is the pH of the stomach and the small intestine?</td>
</tr>
<tr>
<td>What causes the difference between the pH?</td>
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</table>

<table>
<thead>
<tr>
<th>Issue 1</th>
<th>Operation of digestive juices</th>
</tr>
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<tbody>
<tr>
<td>Points for</td>
<td>and/or Points against</td>
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<table>
<thead>
<tr>
<th>Issue 2</th>
<th>Absorption of drugs</th>
</tr>
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<tbody>
<tr>
<td>Points for</td>
<td>and/or Points against</td>
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</table>

<table>
<thead>
<tr>
<th>Marking Criteria</th>
<th>Marks</th>
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<tbody>
<tr>
<td>Outlines basic facts about the pH of the stomach and the small intestine Identifies at least two issues Provides points for and/or against for each issue</td>
<td>5</td>
</tr>
<tr>
<td>Outlines basic facts about the pH of the stomach and the small intestine Identifies one issue Provides points for and/or against for this issue</td>
<td>3 – 4</td>
</tr>
<tr>
<td>Outlines basic facts about the pH of the stomach and the small intestine</td>
<td>1 - 2</td>
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</tbody>
</table>
**HSC Style Question – Mid Band**

2. Explain why knowledge of the solubility of materials can be used to design drugs for specific tasks.  
   [3 marks]

   *NB* **Explain** means to relate cause and effect

<table>
<thead>
<tr>
<th>Marking Criteria</th>
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</thead>
<tbody>
<tr>
<td>Define solubility</td>
<td></td>
</tr>
<tr>
<td>Identify important effects of solubility on drug design</td>
<td></td>
</tr>
<tr>
<td>Use examples to show how an understanding of solubility is used to design drugs</td>
<td>3 - 4</td>
</tr>
<tr>
<td>Outlines examples of different drugs and how solubility varies</td>
<td>1 - 2</td>
</tr>
</tbody>
</table>

**HSC Style Question – Mid Band**

3. Use the information above to account for the absorption of a drug and its action on the body in terms of its solubility  
   [4 marks]

   *NB* **Account for** means to state reasons for, report on. Give an account of; narrate a series of events or transactions
Extra bits
Extra bits
Extra bits
Extra bits
Extra bits
Extra bits
Additional information for the chemically capable

Most drugs are weak acids or bases. In an aqueous environment the drugs exist as charged (ionized) or uncharged (unionized) forms. The unionized form is soluble in lipids. As such it diffuses readily across cell membranes. The ionized form cannot penetrate the cell membrane easily because it is not soluble in lipids.

Drug absorption is determined by
- the physical properties of drugs (eg particle size)
- the chemical properties of drugs
  - acid or base
  - solubility in water and solubility in lipids
- the pH of the fluid in which the drug dissolves
- rate of blood flow
- the method of administration.

Absorption can only occur after the drugs enter solution.

As a drug moves through the body, it must cross membranes. Some important factors to consider here are:
- A membrane, consisting of a lipid barrier, surrounds the cells of the body.
- There are three ways that a substance can cross cell membranes (the lipid barrier)
  - Passing through channels and pores in the membrane – only very small molecules can cross membranes in this way.
  - Transport systems – Carriers transport the substance (needing energy to do so)
  - Diffusion across the membrane
    - pH dependent ionisation – In an acid medium a weak acid is not charged (unionised). Because it is not charged (unionised) it can travel across the lipid membrane. In an alkaline medium a weak acid is charged (ionised). Because it is charged (ionised) it cannot travel across the lipid membrane by diffusion. In an alkaline medium a weak base is uncharged (unionised). Because it is uncharged (unionised) it can travel across the lipid membrane. In an acid medium a weak base is charged (ionised). Because it is charged (ionised) it cannot travel across the lipid membrane by diffusion.
    - pH partitioning – Drugs will collect on whichever side of a membrane will favour their ionisation. For example, the pH of the stomach is about 3. The pH of blood plasma is about 7.4. Weak acids will ionise more in a higher pH. Therefore, weak acid drugs will tend to travel from the stomach to the blood capillaries.

Further background reading may be found at the following web sites

http://www.viterbo.edu/personalpages/faculty/DWillman/p431_action.htm
http://www.merck.com/pubs/mmanual/section22/chapter298/298b.htm
http://www.elon.edu/shouse/pharmacology/pharm1/Lecture1.html