Influence of pH on Drug Absorption from the Gastrointestinal Tract

A Simple Chemical Model

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In this article we describe a simple laboratory activity in which the gastrointestinal tract is modeled by a pair of test tubes containing aqueous solutions of different pH in contact with ethyl acetate. The aqueous solutions represent the aqueous contents of different sections of the gastrointestinal tract and the ethyl acetate, which is insoluble in water, represents the lipid component of the tissue that lines it. Students use the model to observe the effect of pH on the ability of different drugs to move from water into ethyl acetate and then relate their observations to the accepted pattern of absorption of drugs from the gastrointestinal tract. Pharmacology texts always provide an explanation for this pattern of behavior in terms of the influence pH on the ionization of weak acids and bases and, consequently, on their solubilities in water (*1*). However, without supporting laboratory experience, students having little background in chemistry often find the explanation difficult to understand and apply.

Methods

The substances used as drugs were aspirin (a weak acid, also known as acetylsalicylic acid), 3-aminophenol (a weak base), and paracetamol (a neutral substance, also known as acetaminophen or *p*-hydroxyacetanilide). The ethyl acetate used was of analytical grade. The phosphate buffer used was NaH_2PO_4, 0.2 mol L^{-1}/Na_2HPO_4, 0.2 mol L^{-1} (1:19, pH = 8.0). Micropipets were used for sampling ethyl acetate and for applying the samples to 50×30-mm sections of Merck thin-layer chromatography plates. These were plastic sheets coated with a layer of silica gel HF_{254}. After application of the sample and evaporation of the ethyl acetate, the silica layer was viewed under ultraviolet light of wavelength 254 nm. If the ethyl acetate sample contained the test drug it was visible at the point of application as a dark spot against a fluorescent background.

Experiment

Each test drug was supplied to students as two 50-mg samples in separate test tubes. To the first test tube was added 3 mL of hydrochloric acid solution of pH 1.5. To the second tube was added 3 mL of phosphate buffer of pH 8. Ethyl acetate (2 mL) was added to each test tube and the contents subjected to vortex mixing for 1 min. If the two layers formed an emulsion, this was broken by centrifugation. Otherwise the layers were separated simply by standing for a few minutes. Two microliter portions of the ethyl acetate layer in each test tube were spotted about 1 cm apart on a small silica sheet. The ethyl acetate was allowed to evaporate and the sheet was viewed under ultraviolet light. Students reported the concentration of drug present in the ethyl acetate as high, medium, or low according to the intensity of the spot seen.

Results and Discussion

The usual set of observations made is set out in the table below.

Drug Concentration in Ethyl Acetate Layer

Aqueous Layer pH	Drug		
	Aspirin	3-Aminophenol	Paracetamol
1.5	high	low	high
8	low	high	high

When a drug is ionizable, as aspirin and 3-aminophenol are, then the solubility in water is influenced by pH. This point is highly relevant to an understanding of drug absorption from the gastrointestinal tract because the pH of its aqueous contents varies from 1.2 to 3 in the stomach to about 8 in the intestine (*2*). At the gastric pH of 1.2–3, the weak base 3-aminophenol is almost fully ionized and it has a high solubility in water, low solubility in ethyl acetate. Aspirin, a weak acid, is hardly ionized at all at pH < 3 and has a low solubility in water, high solubility in ethyl acetate. In the model system, this extreme difference between the extent of ionization of the drugs and the effect of this on their solubilities explain why aspirin achieves a high concentration in the ethyl acetate layer but 3-aminophenol achieves only a low concentration. It also explains why weak acids are absorbed more rapidly from the stomach than weak bases: un-ionized weak acids are able to dissolve in the lipid material of the stomach wall and diffuse across into the blood stream, but ionized weak bases are retained in the aqueous contents of the stomach.

At the intestinal pH of 8 the weak base 3-aminophenol is no longer fully ionized (although it is still partially ionized) and it has a lower solubility in water, higher solubility in ethyl acetate than it had at pH 1.5. On the other hand, aspirin is fully ionized at pH 8 and has a high solubility in water, low solubility in ethyl acetate. This explains the observations made in the model system of high ethyl acetate concentration for 3-aminophenol and low ethyl acetate concentration for aspirin. It also explains why weak bases are absorbed from the intestine at a faster rate than weak acids: at the intestinal pH of 8 weak bases are not as highly ionized as weak acids and so dissolve more readily in the lipid material of the intestinal wall.

Paracetamol achieves a high concentration in ethyl acetate regardless of the pH. This drug does not ionize at all unless the pH is well above 8 and under all physiological conditions it exists entirely in the form of neutral molecules. It has a much higher solubility in ethyl acetate than in water and so passes readily from water to ethyl acetate. Drugs of this type are absorbed from both the stomach and the intestine.

Conclusion

The activity described is very simple to carry out. It can be completed, then thoroughly discussed, in a 2-hour laboratory class. It has been our subjective experience that it provides students with a convincing illustration of the validity of the explanation for the pH-dependence of drug absorption given in their pharmacology texts and increases their confidence in their ability to apply this explanation in related situations.

Literature Cited

1. Lehne, R. A.; Crosby, L.; Hamilton, D.; Moore, L. *Pharmacology for Nursing Care*; Saunders: Philadelphia, 1990.
2. Tortora, G. J.; Anagnostakos, N. P. *Principles of Anatomy and Physiology*, 5th ed.; Harper and Row: New York, 1987.