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Formulation Factors Affecting Oral Absorption

Student Objectives for this Chapter

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

- be able to describe various dosage forms and the expected bioavailability and pharmacokinetic consequences of each dosage form
- be able to describe formulation components which affect the oral absorption of drug products

The role of the drug formulation in the delivery of drug to the site of action should not be ignored. With any drug it is possible to alter its bioavailability considerably by formulation modification. With some drugs an even larger variation between a good formulation and a bad formulation has been observed. Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet. This order may not always be followed but it is a useful guide. One example is the results for pentobarbital. Here the order was found to be aqueous solution > aqueous suspension = capsule > tablet of free acid form. This chapter will briefly discuss each of these formulation types particularly in regard to the relative bioavailability.

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Solution Dosage Forms

Drugs are commonly given in solution in cough/cold remedies and in medication for the young and elderly. In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form. The rate limiting step is often the rate of gastric emptying. Since absorption will generally be more rapid in the intestine.

When an acidic drug is given in the form of a salt, it may precipitate in the stomach. However, this precipitate is usually finely divided and is readily redissolved and thus causes no special absorption problems. There is the possibility with a poorly water soluble drug such as phenytoin that a well formulation suspension, of finely divided powder, may have a better bioavailability.

Some drugs which are poorly soluble in water may be dissolved in mixed water/alcohol or glycerol solvents. This is particularly useful for compounds with tight crystal structure and higher melting points that are not ionic. The crystal structure is broken by solution in the mixed solvent. An oily emulsion or soft gelatin capsules have been used for some compounds with lower aqueous solubility to produce improved bioavailability.

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Suspension Dosage Forms

A well formulated suspension is second only to a solution in terms of superior bioavailability. Absorption may well be dissolution limited, however a suspension of a finely divided powder will maximize the potential for rapid dissolution. A good correlation can be seen for particle size and absorption rate. With very fine particle sizes the dispersibility of the powder becomes important. The addition of a surface active agent will improve dispersion of a suspension and may improve the absorption of very fine particle size suspensions otherwise caking may be a problem. As a suspension ages there is potential for increased particle size with an accompanying decrease in dissolution rate. Smaller particles have higher solubility and will tend to disappear with the drug coming out of solution on larger particles.

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Capsule Dosage Forms

In theory a capsule dosage form should be quite efficient. The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents. The capsule contents should not be subjected to high compression forces which would tend to reduce the effective surface area, thus a capsule should perform better than a tablet. This is not always the case. If a drug is hydrophobic a dispersing agent should be added to the capsule formulation. These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder. Tightly packed capsules may have reduced dissolution and bioavailability.

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Tablet Dosage Forms

The tablet is the most commonly used oral dosage form. It is also quite complex in nature. The biggest problem is overcoming the reduction in effective surface area produced during the compression process. One may start with the drug in a very fine powder, but then proceeds to compress it into a single dosage unit.

Ingredients

Tablet ingredients include materials to break up the tablet formulation.

- Drug - may be poorly soluble, hydrophobic
- Lubricant - usually quite hydrophobic
- Granulating agent - tends to stick the ingredients together
- Filler - may interact with the drug, etc., should be water soluble
- Wetting agent - helps the penetration of water into the tablet
- Disintegration agent - helps to break the tablet apart

Coated tablets are used to mask an unpleasant taste, to protect the tablet ingredients during storage, or to improve the tablets appearance. This coating can add another barrier between the solid drug and drug in solution. This barrier must break down quickly or it may hinder a drug's bioavailability.

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Sustained Release Dosage Forms

Another form of coating is enteric coated tablets which are coated with a material which will dissolve in the intestine but remain intact in the stomach. Polymeric acid compounds have been used for this purpose with some success. This topic and the area of sustained release products has been discussed in more detail in other courses.

Benefits

- for short half-life drugs, sustained release can mean less frequent dosing and thus better compliance.
- reduce variations in plasma/blood levels for more consistent result.

Problems

- More complicated formulation, may produce more erratic results. A sustained release product may contain a larger dose, i.e. the dose for two or three (or more) 'normal' dosing intervals. A failure of the controlled release mechanism may result in release of a large potentially toxic dose.
- more expensive technology

Types of products

- erosion tablets
- waxy matrix
 - matrix erodes or drug leaches from matrix
- coated pellets
 - different pellets (colors) have different release properties
- coated ion exchange
- osmotic pump
 - insoluble coat with small hole. Osmotic pressure pushes the drug out at a controlled rate.

Results - reduced side effects

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In Vitro Testing

Disintegration

Disintegration time is the time required for the tablet to break down into particles which can pass through a sieve while agitated in a specified fluid. Indicates the time to break down into small particles. Not necessarily solution. In the process of tablet manufacturer the drug is often formulated into a granular state (that is small but not fine) particles. This is done as the granule often has better flow properties than the a fine powder and there is less de-mixing leading to better uniformity. The granules are then compressed to produce the tablet. The disintegration test may lead to an end point of tablet to granule only, although the granules may be larger than the seive opening.



Figure 24.7.1 Movie Illustrating Table Disintegration

Dissolution

The time it takes for the drug to dissolve from the dosage form is a measure of drug dissolution. Numerous factors affect dissolution. Thus the dissolution medium, agitation and temperature are carefully controlled. The dissolution medium may be water, simulated gastric juice, or 0.1M HCl. The temperature is usually 37°C. The apparatus and specifications may be found in the U.S.P. The U.S.P. methods are official however there is a wide variety of methods based on other apparatus. These are used because they may be faster, cheaper, easier, sensitive to a particular problem for a particular drug, or developed by a particular investigator.

Dissolution tests are used as quality control to measure variability between batches which may be reflected by *in vivo* performance. Thus the *in vitro* test may be a quick method of ensuring *in vivo* performance. Thus there has been considerable work aimed at defining the *in vitro/in vivo* correlation.

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