A further crucial factor in establishing bioequivalence, or in determining the influence that the type of dosage form, route of administration, etc., have on the bioavailability of a given drug, is the proper design, control and interpretation of such experimental studies.

Assessment of site of release in vivo

There are many benefits of being able to assess the fate of a dosage form in vivo and the site and release pattern of the drug. Particularly for drugs that show poor oral bioavailability, or in the design and development of controlled- or sustained-release delivery systems, the ability to follow the transit of the dosage form and the release of drug from it is advantageous. The technique of gamma-scintigraphy is now used extensively and enables a greater knowledge and understanding to be gained of the transit and fate of pharmaceuticals in the gastrointestinal tract.

Gamma (γ)-scintigraphy is a versatile, non-invasive and ethically acceptable technique that is capable of obtaining information both quantitatively and continuously. The technique involves the radiolabelling of a dosage form with a γ-emitting isotope of appropriate half-life and activity. Technetium-99m is often the isotope of choice for pharmaceutical studies because of its short half-life (6 hours). The radiolabelled dosage form is administered to a subject who is positioned in front of a γ-camera. γ-Radiation emitted from the isotope is focused by a collimator and detected by a scintillation crystal and its associated circuitry. The signals are assembled by computer software to form a two-dimensional image of the dosage form in the gastrointestinal tract. The anatomy of the gastrointestinal tract can be clearly seen from liquid dosage forms, and the site of disintegration of solid dosage forms identified. The release of the radiolabel from the dosage form can be measured by following the intensity of the radiation. By co-administration of a radiolabelled marker and a drug in the same dosage form, and simultaneous imaging and the taking of blood samples, the absorption site and release rate of a drug can be determined (for example with the InteliSite capsule described earlier in this chapter). When used in this way, the technique is often referred to as *pharmacoscintigraphy*.

Biopharmaceutics Classification System

As a result of the plethora and variability of biopharmaceutical properties of existing and potential drugs, an attempt has been made to classify drugs into a small number of categories. A scientific basis for a Biopharmaceutics Classification System (BCS) has been proposed that classifies drugs into four classes according to their dose, their aqueous solubility across the gastrointestinal pH range and their permeability across the gastrointestinal mucosa.

The scheme was originally proposed for the identification of immediate-release solid oral products for which in vivo bioequivalence tests may not be necessary. It is also useful to classify drugs and predict bioavailability issues that may arise during the various stages of the development process and is now utilized widely by many regulatory authorities.

The four classes are defined in terms of high and low aqueous solubility and high and low permeability:

- Class I – high solubility/high permeability
- Class II – low solubility/high permeability
- Class III – high solubility/low permeability
- Class IV – low solubility/low permeability.

A drug is considered to be highly soluble where the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range 1–8. The volume is derived from the minimum volume anticipated in the stomach when a dosage form is taken in the fasted state with a glass of water. If the volume of aqueous media needed to dissolve the drug in pH conditions ranging from 1 to 8 is greater than 250 mL then the drug is considered to have low solubility. The classification therefore takes into account the dose of the drug as well as its solubility.

A drug is considered to be highly permeable when the extent of absorption in humans is expected to be greater than 90% of the administered dose. Permeability can be assessed using one of the methods discussed earlier in this chapter that has been calibrated with known standard compounds or by pharmacokinetic studies.

Class I drugs. Class I drugs will dissolve rapidly when presented in immediate-release dosage forms, and are also rapidly transported across the gut wall. Therefore (unless they form insoluble complexes, are unstable in gastric fluids or undergo presystemic clearance) it is expected that such drugs will be