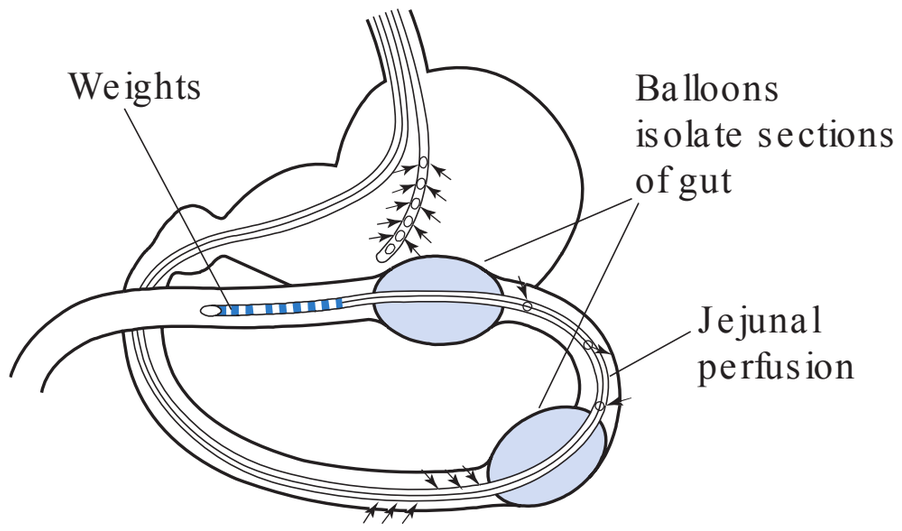

Fig. 21.7 • Diagram of the Loc-I-Gut.

occlude the region of interest. A tungsten weight is placed in front of the distal balloon to facilitate its passage down the gastrointestinal tract.

Drug absorption is calculated from the rate of disappearance of the drug from the perfused segment. This technique has afforded greater control in human intestinal perfusions, primarily because it isolates the luminal contents of interest, and has greatly facilitated the study of permeability mechanisms and the metabolism of drugs and nutrients in the human intestine.

Non-invasive approaches. There is concern that the invasive nature of perfusion techniques can affect the function of the gastrointestinal tract, in particular the fluid content, owing to the intubation process altering the absorption and secretion balance. To overcome this problem, several engineering-based approaches have been developed to evaluate drug absorption in the gastrointestinal tract. These include the InteliSite® and the Enterion®capsules and the MAARS® capsule.

The InteliSite capsule is a radiofrequency-activated, non-disintegrating delivery device. Either a liquid or a powder formulation can be filled into the capsule, the transit of which is followed by γ-scintigraphy (see later in this chapter). Once the capsule reaches its desired release site, it is externally activated to open a series of windows to the drug reservoir within the capsule. The Enterion capsule is similar in that it contains a drug reservoir and uses γ-scinitigraphy to locate the capsule in the gastrointestinal tract. However, its payload is released via an electromagnetic field triggering the actuation of a spring resulting in the instantaneous release of the formulation as a bolus. For both these systems, blood samples need to be taken to quantify drug absorption. The MAARS® system is a magnetic active agent release system and thus relies on a magnetic impulse to disassemble the capsule and release the drug; this is a simpler system and can contain a large volume of drug. More sophisticated systems with cameras incorporated into capsules, such as the M2A capsule, are being developed to visualize the gastrointestinal tract. These can be used to help design better products.

Presystemic metabolism

Presystemic metabolism is the metabolism that occurs before the drug reaches the systemic circulation. Therefore, for an orally administered drug, this includes the metabolism that occurs in the gut wall and the liver. As discussed above, perfusion models that involve both the intestines and the liver allow an evaluation of the presystemic metabolism in both organs. In other models it is sometimes possible to design mass balance experiments that will assess whether presystemic intestinal metabolism is likely to occur.

Intestinal cell fractions, such as brush border membrane preparations that contain an abundance of hydrolytic enzymes, and homogenized preparations of segments of rat intestine can also be used to determine intestinal presystemic metabolism. Drugs are incubated with either brush border membrane preparations or gut wall homogenate at 37 °C and the drug content analysed.

Various liver preparations, for example subcellular fractions such as microsomes, isolated hepatocytes and liver slices, are used to determine hepatic metabolism in vitro. These are classified as phase I metabolism, which mainly involves oxidation but can be reduction or hydrolysis, and phase II metabolism, which follows phase I and involves conjugation reactions. Microsomes are prepared by high-speed centrifugation of liver homogenates (100 000 *g*) and are composed mainly of fragments of the endoplasmic reticulum. They lack cystolic enzymes and cofactors and are therefore only suitable to evaluate some of the metabolic processes (phase I metabolism) of which the liver is capable. Hepatocytes must be freshly and carefully prepared from livers and are only viable for a few hours. It is therefore difficult to obtain human hepatocytes. Hepatocytes are very useful for hepatic metabolism studies as it is possible to evaluate most of the metabolic reactions, i.e. both phase I and II metabolism. Whole liver slices again have the ability to evaluate both phase I and II metabolism. As liver slices are tissue slices rather than cell suspensions, and because they