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In-vivo Monitoring of Dosage Forms*

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Abstract

The use of imaging techniques including gamma scintigraphy to follow the behaviour of drug formulations has revolutionized our knowledge of absorption and distribution in drug delivery. The development of gamma camera techniques as physiological tools to explore organ function became routine by the mid-seventies. Several research groups started to explore the applications of technique in drug delivery. Within 5 years, the utility of the technique became obvious and scintigraphy is now widely accepted as an important investigation tool in formulation research.

Gamma scintigraphy is especially useful in exploring sources of inter-subject variation, especially in examining food effects in pharmacokinetic estimations and establishing windows of absorption for oral delivery. As a tool to examine drug delivery to the lung and to the eye, scintigraphy is the method of choice.

Magnetic Resonance Imaging (MRI) became more generally employed in medicine two decades after the gamma camera. The superior soft-tissue contrast and resolution compared to computed X-ray tomography rapidly established MRI in clinical investigation. Recent applications in oral drug research has allowed the pharmaceutical scientist to explore new facets of delivery and ultimately combine MRI and scintigraphy in human clinical trials.

The need to image drug formulations

By the beginning of the next millennium our understanding of how new therapeutic targets can be addressed will have improved immensely; however, the question of how to deliver large hydrophilic pharmacons effectively remains a problem of crippling complexity. In pharmaceutical research much effort is expended in attempts to minimize inter- and intra-subject variation during treatment with therapeutic agents. This problem will be tougher with protein, gene and anti-sense technologies, attractive though they are with regard to exquisite targeting. The introduction of extremely potent agents which are transported erratically to the site of action has generated a well understood need for tools to follow the distribution of drug from delivery systems.

What are the sources of variation?

The influences contributing to the variability of absorption of a particular drug between and within individuals can be categorized into two principal sources: those arising from physiological variation including age, diet, posture and time of dosing and those ascribable to pharmaceutical factors including the selection of a different dosage form, route of administration or targeting mechanism for the active ingredient. The most familiar sources of physiological variation relate to the intake of food with the drug, where the energy density of the meal controls access to the site of absorption, the small intestine (Davis et al 1984). For example, formulation treatments to reduce release in the stomach behave more erratically as a function of continued food intake. An extreme example is seen with large enteric dose forms taken in the morning with a heavy breakfast. The inhibition of emptying by pyloric closure, and additional inhibitory meals—lunch and dinner—can result in a delay in the onset of action until late evening (Wilson et al 1989). An attempted classification of contributory effects as weak or strong is given in Figure 1 but the list is not exhaustive; for further reading, the reader is referred to reviews of the subject (Washington & Wilson 1995; Wilson & Washington 1995).

For a number of oral formulations, which will be the main focus of this article, the active ingredient is designed to act topically within the gut and hence is poorly absorbed. In the development of a

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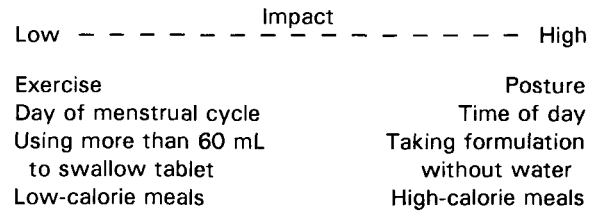

Figure 1. Physiological contributions to inter- and intra-subject variability in absorption.

sucralfate formulation in our laboratory many approaches were tried to increase oesophageal bioadhesion. Gamma scintigraphy, which will be described later, was pivotal in helping decide a strategy because the effectiveness of the formulation could not be measured from blood-level data. Some time after this particular project had ended, a promising avenue was discovered as illustrated in Figure 2. Use of a thermosetting gel resulted in a large increase in viscosity during swallowing and this provided the types of behaviour and distribution for which we had previously searched.

At the opposite end of the gut, the optimization of timed-release dosage forms was aided at various times by labelling the base and by fill-and-plug of a Pulsincap dosage form. In these experiments, measurement of displacement of the base and plug labels, with the subject positioned with anterior, back and side facing the camera, enabled the time of release to be followed (Wilson et al 1997a).

Imaging techniques

Early in the studies of the in-vivo behaviour of drug formulations, imaging techniques including X-ray contrast media were used to follow gastrointestinal transit. Fluorimetry is still used to position intubation tubes, but the considerable reduction in

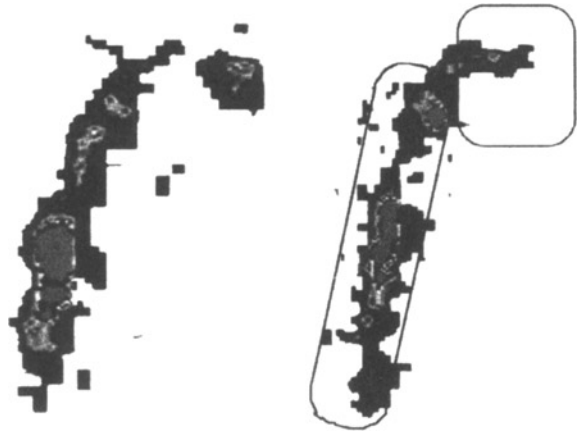

Figure 2. Oesophageal residence of a thermosetting polymer in man. Left panel: image at t = 0 min. Right panel: image at 10 min. Oblongs indicate regions of interest used to calculate residence time in the oesophagus and mouth.

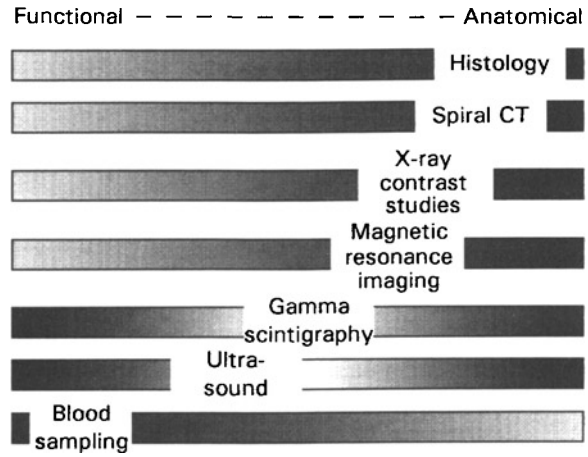

Figure 3. The spectrum of imaging and sampling techniques.

radiation exposure provided by scintigraphic investigation has enabled exciting developments in our understanding of windows of absorption and how drug formulations can be optimized. It is convenient to attempt to classify techniques in a spectrum from 'anatomical' through to 'functional' (Figure 3). This, however, is imperfect because although X-rays can be regarded as primarily a technique for examination of skeletal fractures, rapid X-ray monitoring provides functional information about swallowing and blood flow.

On the other hand, gamma scintigraphy gives quantitative functional data of the distribution of a radionuclide. When a functional target is included on the radiopharmaceutical compound an image of the tumour tissue can be produced which can be clearly discriminated from surrounding normal tissue. Thus the classification is somewhat arbitrary and only applies to these techniques with regard to what they tell us about formulation distribution in-vivo.

Magnetic-resonance imaging occupies a middle ground between gamma-camera imaging and X-ray techniques, and has superseded some old X-ray procedures. Ultrasound provides very low spatial resolution but is a useful technique for measuring flow in arteries and veins. Finally, there have been exciting developments in X-ray technologies, and much structural detail is provided by spiral Computer tomography (C.T.).

Gamma Scintigraphy

Gamma scintigraphy is an established method for in-vivo evaluation of drug-delivery systems and many reviews dealing with the applications of the technique have appeared since the early collaborations at Nottingham (Hardy & Wilson 1981; Wilson et al 1992). The limitations of the technique lie in the restricted number of radionuclides sui-

table for administration to man and for which a gamma camera can provide an image. Most studies are performed using $^{99}Tc^{m}$ or ^{111}In radiopharmaceuticals, which are well established in diagnostic nuclear medicine. These radionuclides are 'foreign' in terms of the structures of drug molecules and it is therefore not possible to use the technique to study drug biodistribution. In general, for the study of drug delivery systems, chelates or complexes of technetium or indium are incorporated by association within a component of the formulation, or used as probes which enable the behaviour of drugs to be predicted.

Radiopharmaceuticals based on $^{99}Tc^{m}$ are short-lived ($t^{1}/_{2} = 6{\cdot}03$ h) and formulations are prepared on the morning of administration. This is especially suitable for ophthalmic studies—here the low dose is an advantage for radiation-sensitive tissues such as the lens. ^{111}In is a longer-lived isotope ($t^{1}/_{2} = 2{\cdot}1$ days) enabling study over several days. The dose from ^{111}In is higher but acceptable for oral studies. Because the energies of the two isotopes can be gated in separate energy windows, dual-channel acquisition enables multiple phases labelled with ^{111}In and $^{99}Tc^{m}$ to be followed simultaneously. In this situation, where differential rates of disintegration occur, $^{99}Tc^{m}$ can be allowed to 'decay-out' enabling accurate determination of the two radionuclides; this is important where overlap of the ^{111}In energies causes cross-talk into the lower-energy $^{99}Tc^{m}$ channel. The 'decay-out' approach has also been used in our laboratories to measure lung deposition in which the patient breathes a radioactive gas with an extremely short half-life (for example [$^{81}Kr^{m}$]) while standing in front of the gamma camera (Ashworth et al 1991; Harnor et al 1993). While remaining in the same position, the subject actuates the pulmonary delivery device in which the contents are labelled with $^{99}Tc^{m}$. [$^{81}Kr^{m}$] has a half-life of 13 s and decays out quickly and exhaled material does not reduce the quality of the image. Overlay of the two images enables the extent of pulmonary deposition from the device to be calculated.

The use of neutron activation enables pilot-scale manufacturing facilities to be used, because the lanthanide earth precursors samarium or erbium oxides are not radioactive. Large atoms in this group absorb neutrons readily, leading to an increase of atomic mass. The change in the neutron/proton ratio causes changes in the internal nuclear binding forces which are accompanied by the emission of gamma and beta energy. Exposure to neutron fluxes of 10^{12} neutrons cm^{-1} for 2–4 min enables sufficient conversion to the γ-emitting radionuclides ^{153}Sm or ^{161}Er. Irradiation might be associated with physicochemical changes to polymers in the formulation and the conversion of potassium and sodium to their radioactive nuclides. The radionuclides ^{24}Na and ^{41}K can be left to decay before administration, reducing the radiation dose.

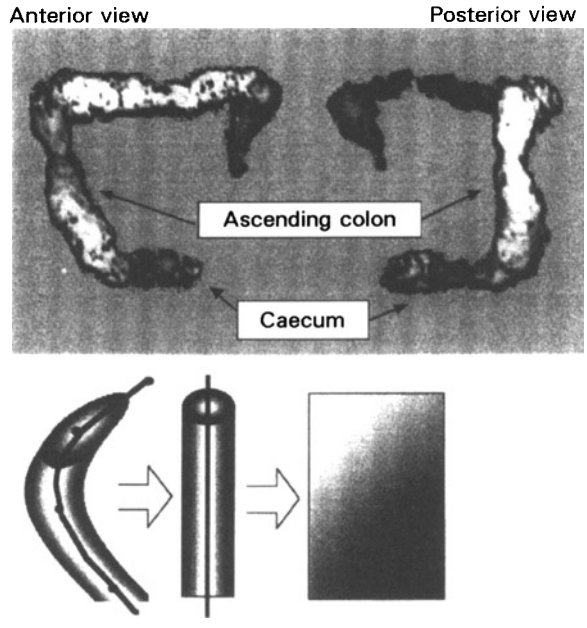

Figure 4. Three-dimensional image of the colon after dosing with ^{111}In-labelled resin in a Pulsincap system. The schematic diagram below shows the principle behind estimation of the surface coating by finding the midpoint of the colon in each segment, straightening and then unravelling the surface.

Dual-headed cameras, which enable acquisition of tomographic images, have recently become more common. Fastest acquisition is typically 20 min so dynamic processes in the gut are difficult to follow. We have used three-dimensional imaging to follow the distribution of contents from a Pulsincap dosage form with activities as low as 1 MBq. Figure 4 shows the coating of the colon from this dosage form. Further development of this technique should enable indexes of topical delivery to be constructed by determining the centre of the distribution and deconvoluting the shape of the object into a simple cylinder. Unwrapping of the cylinder would then enable the extent of coating to be determined, as illustrated in the figure.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) appeared as a clinical tool in the early eighties. The excellent soft-tissue contrast and resolution furnished by the technique rapidly established MRI in clinical centres throughout the world. Conventional NMR signals of tissue are derived from the resonances of water and lipid when tissue is placed in a strong magnetic field and a frequency-selective r.f. pulse is applied across the sample. Certain nuclei, nota-

bly ^{1}H and ^{13}C, can assume two orientations only, a low-energy orientation parallel to the magnetic field or an antiparallel high-energy orientation. The absorption of r.f. energy causes the proton to spin-flip to this higher state, generating a signal before saturation.

Oils can be imaged against the watery surroundings of the stomach contents because the differences in resonance frequency (chemical shift) and the relaxation properties of the fat and water protons enables the operator to manipulate and optimize contrast. This has proved useful for the study of oil-filled capsules in the gastrointestinal tract, where the flumes of oil released as the soft gelatin capsule ruptures can be directly observed (Wilson et al 1997b). Smaller units are harder to study and contrast agents such as gadolinium-diethylenetriaminpentacetic acid (DTPA) are incorporated into the formulations.

Enhancements of the imaging technique requires the development of agents with parameters which almost exactly match those for new therapeutic systems. It is interesting to note there is a perceived need in radiology and MRI to develop agents with longer circulation times and which as a consequence become distributed to tissues other than the liver and spleen (for example the lymph nodes). The small bowel poses great problems—the poor contrast and overlap of loops of the intestine confound image quality. Perfluorocarbons and silicone oils have been used to improve definition, but the volumes administered are sometimes large. In this respect, gamma scintigraphy remains the technique of choice for investigation of the gut, despite poor anatomical resolution.

MRI offers great flexibility, but because the image contrast depends on several factors, including proton density, the T_1 and T_2 values (relaxation time constants) of the tissue environment and the flow patterns within the area of interest, and is confounded by problems such as movement artefacts, the study of formulations is fraught with difficulties. The contrast of real-time images is usually poor and therefore definition is inherently unsatisfactory unless the material of interest can be gated; spin-echo sequences give high definition but require long acquisition times.

Conclusions

The two major imaging techniques currently employed for in-vivo evaluation of formulation behaviour have significant limitations. Gamma scintigraphy is an excellent tool for the evaluation of nearly all routes of administration (the exception being transdermal delivery), and the ingenuity employed to obtain probes with a desired distribution to assess organ function offer rich diversity in physicochemical properties. The development of faster three-dimensional techniques would offer great advantages with regard to gastrointestinal, pulmonary and ophthalmic administration, and the availability of multi-headed machines to researchers might provide another technical advance. Access to MRI is extremely restrictive but the promise of being able to combine scintigraphic and MRI tomographic images offers an immense wealth of possibilities in pharmaceutical research.

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