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Scintigraphic assessment of the in vivo dissolution rate of a sustained release tablet

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Summary

The release of [^{99m}Tc]diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) from a matrix tablet formulation was measured by external scintigraphy in 4 healthy male volunteers. The rate determined was compared with that observed in vitro using a U.S.P. dissolution apparatus.

The in vitro release rate of [^{99m}Tc]DTPA was similar to that of chlorpheniramine, and therefore the labelled compound was used to model the release of this drug in vivo. The in vitro release of [^{99m}Tc]DTPA was pH-independent.

Introduction

Sustained release formulations offer several advantages over conventional preparations; for instance, prolongation of activity, reduced dependence on patient compliance and reduction of side-effects. It is possible to study the release characteristics of such systems using in vitro dissolution tests. However, it is often difficult to correlate the results obtained with pharmacokinetic parameters derived from in vivo measurements, particularly if the drug is administered for a local gastrointestinal effect (and thus low levels of the drug will be present in the blood), or if the drug is susceptible to variable degradation prior to absorption. In the latter case, it is difficult to discriminate degradation effects from those of poor in vivo dissolution and disintegration characteristics.

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The aim of the present study was to compare the in vivo and in vitro release of a drug from an oral sustained preparation, using the non-invasive technique of gamma scintigraphy to monitor the in vivo release of the drug from the base. The system investigated was that of a matrix tablet composed of hydroxypropyl methylcellulose ('Synchron'). Commercially, the antihistamine drug, chlorpheniramine, is incorporated into this matrix as a sustained release preparation. However, since practical considerations preclude labelling the drug directly with a gamma-emitting radionuclide, the non-absorbable, water-soluble chelate [^{99m}Tc]-labelled diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) was used to model the behaviour of a drug within the matrix. The release profile in vitro was compared, using a U.S.P. dissolution apparatus, with that of chlorpheniramine in solutions with a range of pH that the tablet might encounter in vivo.

Materials and methods

Preparation of tablets

Technetium-99m pertechnetate in 2 ml saline, obtained by elution from a generator (Amersham International, Amersham, U.K.) was used to prepare [^{99m}Tc]DTPA solution containing 75 MBq ^{99m}Tc in 9 mg DTPA, (C.I.S. Biomedical Products, London). This was added to 591 mg unlabelled DTPA and evaporated to dryness in an oven at 80°C for 10 min. The resulting powder was mixed with 5.4 g of hydroxypropyl methylcellulose. Tablets, each of nominal weight 300 mg, containing 30 mg DTPA were compressed on an instrumented Manesty F3 machine using 10 mm diameter flat-faced punches at an upper punch compaction pressure of 165 MNm^{-2}. Tablets outside the weight range 290–310 mg were rejected. At the time of administration, the tablets contained a mean of 4.4 MBq with a standard deviation of 0.1 MBq ($n = 8$).

Tablets of nominal 300 mg weight containing 30 mg chlorpheniramine were prepared by direct compression at 165 MNm^{-2} in the same manner as for the tablets containing [^{99m}Tc]-DTPA.

In vitro dissolution testing

The in vitro release rates of the [^{99m}Tc]DTPA and chlorpheniramine were measured using the U.S.P. rotating basket apparatus at 100 rpm (United States Pharmacopoeia, 1980). Solutions of hydrochloric acid and sodium hydroxide were used as the dissolution media over the pH range 1.0–8.5. Each dissolution test was carried out using 6 stations of the apparatus. Samples of dissolution media (2 ml) were removed periodically from the bath and replaced with 2 ml of the appropriate solution. The [^{99m}Tc]DTPA in the specimens was assayed using an automatic gamma-counter and the chlorpheniramine by UV spectrometry at a wavelength of 265 nm.

In vivo studies

Four healthy male volunteers (age 21–24 years) each swallowed a tablet contain-

ing approximately 4.4 MBq [^{99m}Tc]DTPA together with 100 ml of water. The subjects had fasted overnight and during the study were allowed a light lunch. Imaging was undertaken with the subjects standing, using a gamma camera having a 40 cm diameter field of view, fitted with a medium energy parallel hole collimator.

During the course of a study, each subject swallowed two doses, each of 2 MBq [^{113m}In]DTPA, administered in 200 ml of water at various times after administration of the tablet, to image the stomach and proximal intestines to identify the position of the tablet in the gastrointestinal tract. Anterior and posterior images, each of 10 s duration, were taken at 20-min intervals over a 6-h period and the data recorded on a computer for analysis. Subsequently, regions of interest were defined around images of the tablet and the activity remaining in the tablet quantified. Corrections were applied for background activity, arising from the [^{113m}In]DTPA solution and the released [^{99m}Tc]DTPA, and for radioactive decay.

The attenuation of the radiation by overlying tissues can cause erroneous estimates of the amounts of radioactivity in vivo when imaging is undertaken from one direction only (Tothill et al., 1980). The use of the geometric mean of the anterior and posterior count rates gives a result independent of the depth of the source (Whalley et al., 1981). In the present study, the geometric mean of the counts from anterior and posterior images was used to derive time–activity plots for the amounts of tracer remaining in the tablets.

Results and Discussion

Slow release preparations previously studied have included matrices based on gums (Choulis and Papadopoulos, 1975; Bamba et al., 1979); waxes (Dakkuri et al., 1978; Al-Shora et al., 1980) and synthetic materials such as silicones (Chien and Lambert, 1974; Chien et al., 1974; Gore and Banker, 1979). The basic process of release fom a matrix is leaching of the medicament by the surrouding fluid which is able to permeate into the matrix through pores and interparticulate spaces. The drug dissolves into this fluid phase and diffuses from the system via capillary channels. In the case of 'Synchron', the surface of the tablet swells to a gel-like consistency allowing drug release by a combination of diffusion and surface erosion.

The conventional method of evaluating a tablet formulation in vivo is to measure the plasma levels, or urinary excretion of the drug, over an appropriate period. Such techniques do not give an insight into the disintegration and dissolution behaviour of the dosage form within the gastrointestinal tract, and are inapplicable to locally-acting chemotherapeutic agents which are not absorbed.

Radiographic methods have been used to monitor externally the behaviour of tablets in vivo. These include the study of tablets containing barium sulphate (Buckley and Bliven, 1936) and more recently, Wagner et al. (1958) and Gruber et al. (1958) have investigated the passage of radiopaque tablets through the gastrointestinal tract. The location of the tablets in the latter studies were controlled by attaching a length of string to each tablet. Disintegration in vivo was monitored radiographically and by withdrawal of the tablets through the mouth.

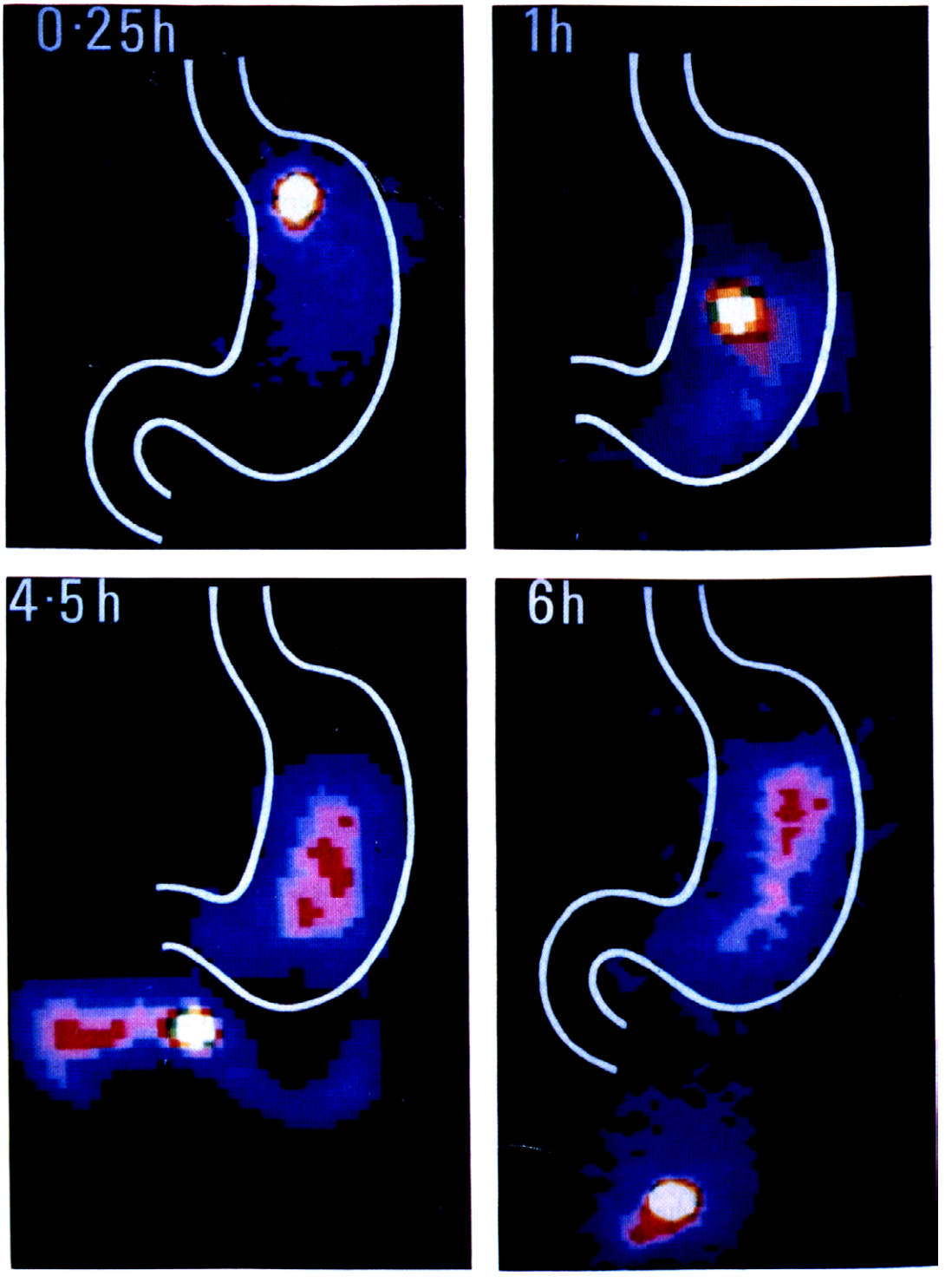

Fig. 1. Scintigraphic images of the tablet in the gastrointestinal tract at 0.25, 1, 4.5 and 6 h after dosing (composite from more than 1 subject)

The radiographic technique has two major limitations; first, quantitative data cannot be obtained, and secondly relatively large amounts of radiopaque materials have to be incorporated. The high density of these materials (e.g. barium sulphate 4.5 Mgm $^{-3}$) compared with the density of most drugs and excipients (varying from 1.0 to 1.5 Mgm $^{-3}$), (Lagas et al., 1980) could influence the transit rate along the gastrointestinal tract. Bechgaard and Ladefoged (1978) reported that an increase in density from 1.0 Mgm $^{-3}$ to 1.6 Mgm $^{-3}$ decreased the mean intestinal transit time of pellets from 7 to 25 h.

By labelling a material with a gamma-emitting radionuclide, it is possible to monitor the transit of the material using external scintigraphy. Alpsten et al. (1976) used a profile-scanning technique to study the release properties from different types of tablet in man. Formulation variables affecting the disintegration of capsules have also been investigated by this method (Casey et al., 1970; Hunter et al., 1980; Lagas et al., 1980).

Fig. 1 shows a series of typical images of radiolabelled 'Synchron' tablets following administration. At 15 min and also at 1 h after dosing, the tablet could be seen in the stomach, which was delinated by the [^{113m}In]DTPA. Later images show the tablet in the small intestine with the stomach and intestine visualized using the [^{113m}In]DTPA. In each of the 4 volunteers, the tablet left the stomach between 1 and 2 h.

The in vitro study of chlorpheniramine release from the tablet gave a similar profile to that of the [^{99m}Tc]DTPA, which was therefore considered to be a satisfactory model for the drug (Fig. 2). There was agreement between the in vitro release data for [^{99m}Tc]DTPA and the in vivo data obtained using gamma scintigraphy (Fig. 3).

The release profile in vivo did not change noticeably when the tablet left the stomach, implying that the release rate was pH-independent. As seen in Fig. 4, the release profiles of the [^{99m}Tc]DTPA in vitro in acid and alkaline conditions were

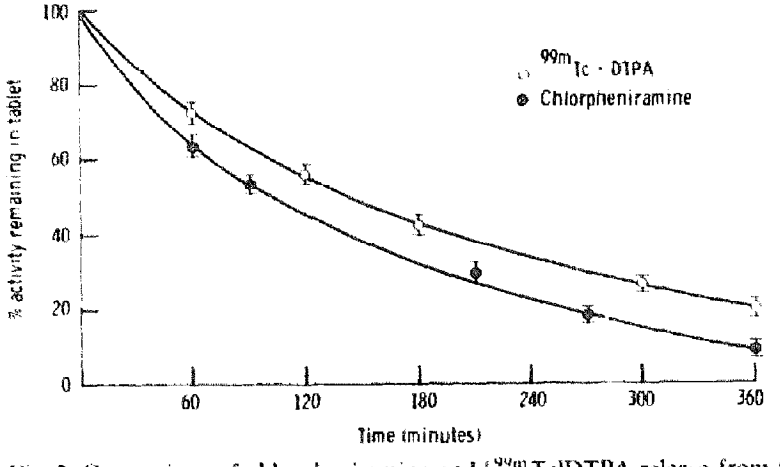

Fig. 2. Comparison of chlorpheniramine and [^{99m}Tc]DTPA release from tablets in vitro at pH 1.0 using the U.S.P. dissolution apparatus ○, [^{99m}Tc]DTPA, ●, chlorpheniramine. Mean ± 1 S.E.M., n = 6.

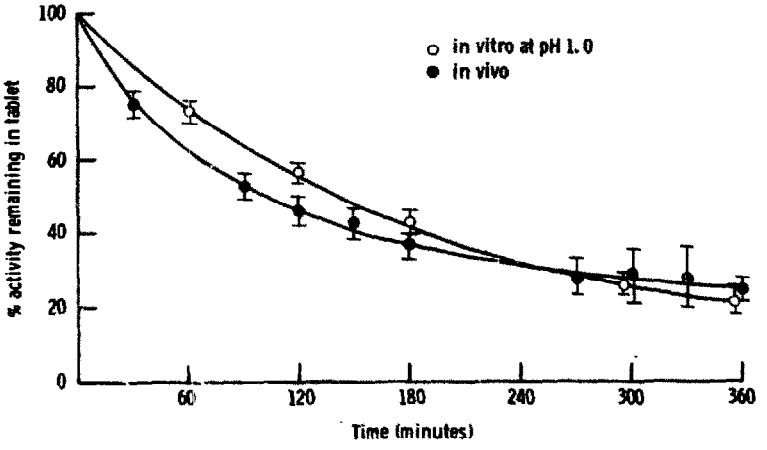

Fig. 3. Comparison of the in vitro and in vivo release of [^{99m}Tc]DTPA from hydroxypropyl methylcellulose matrix tablet. ○, in vitro results at pH 1.0, n = 6; ●, in vivo results, n = 4. Mean ± 1 S.E.M. for each plot.

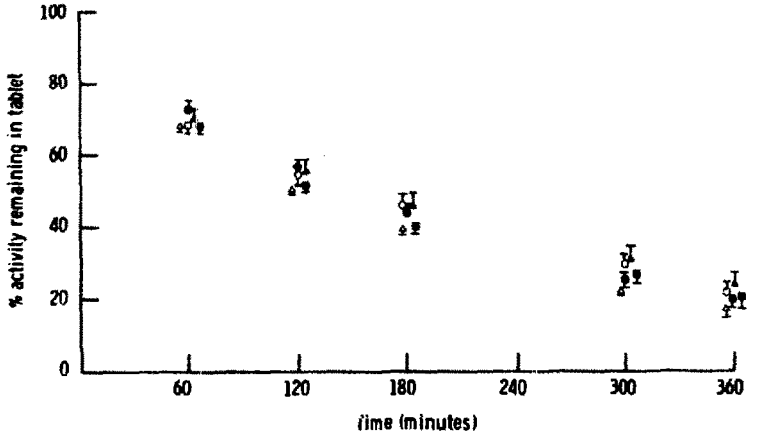

Fig. 4. Release of [^{99m}Tc]DTPA from the hydroxypropyl methylcellulose matrix determined in vitro in the pH range 1.0–8.5 using the U.S.P. dissolution apparatus: ●, pH 1.0; ▲, pH 3.0; ○, pH 4.0; ■, pH 6.0; and △, pH 8.5 Mean +/− 1 S.E.M. for each determination, n = 6 per group.

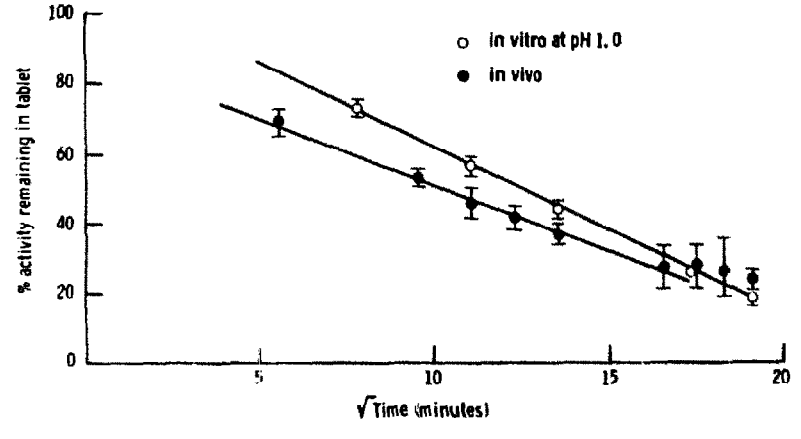

Fig. 5. In vivo and in vitro release of [^{99m}Tc]DTPA from tablets compared as a function of $\sqrt{time}$ after Higuchi (1963). Mean ± 1 S.E.M. for each plot.

similar, supporting these findings. The investigation of the release profiles of acidic and basic drugs are presently being undertaken to examine the pH-dependence of drug release from this matrix.

The in vitro and the in vivo plots of [^{99m}Tc]DTPA release as a function of the square-root of time, conform to the predicted relationship for a three-dimensional leaching or extraction from a spheroid pellet (Higuchi, 1963), the in vivo results deviated from linearity after 4.5 h (Fig. 5).

Conclusions

The present study has demonstrated the similarity between drug release rates measured in vivo and in vitro from the tablets of hydroxypropyl methylcellulose base. The study illustrates the potential of gamma scintigraphy in assessing the effects of formulation variables on the in vivo disintegration and dissolution of oral sustained release dosage formulations.

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