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THE PREPARATION AND CHARACTERIZATION OF SAMARIUM CHELATES AS MARKER COMPOUNDS FOR SUBSEQUENT IN-VIVO DISSOLUTION STUDIES

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Gamma scintigraphy has been used for many years to study the in-vivo fate of pharmaceuticals. Conventional methods of radiolabelling using short lived radionuclides are suitable for simple dosage forms but problems associated with contamination of production facilities, scale-up difficulties and time available for preparation are encountered with complex dosage forms. To overcome these difficulties the technique of neutron activation has been applied. This involves the incorporation of a stable isotope (eg. samarium-152 (Sm)) into the formulation prior to manufacturing. Exposure of the intact product to a neutron source converts the isotope into a gamma emitting material. The aim of the present work was to produce a number of chelates of Sm which could be incorporated into controlled release formulations for the subsequent assessment of in-vivo dissolution characteristics.

Chelates of Sm were prepared (Table 1) by dissolving Sm_2O_3 (BDH, Poole) in sufficient 1M HCl to produce a solution of 1mg $SmCl_3$ mL^{-1}. This was added to the sodium salt of the chelating agent in a 10:1 molar excess, and evaporated to dryness in a rotary evaporator. The complexes were subsequently irradiated in a neutron flux ($1x10^{12}$ n cm^{-2} s^{-1}) for 15 min to generate the gamma emitting species, Sm-153. Chelate stability was determined by dissolving the activated complexes in a range of dissolution media (pH2, pH5, pH7 and water) and monitoring the resulting solutions at 0 and 21 h using cellulose TLC plates with pyridine:ethanol:water (1:2:4) as the solvent. The complex was located using autoradiography and quantified by cutting the TLC plates into 1cm transverse strips and counting in an automated gamma counter (Compugamma). Individual chelates could be distinguished by TLC; unchelated Sm-153 (as the chloride) remained at the origin whilst activity of all the Sm-153 chelates moved away, to varying extents, from the origin. Little difference was observed in the R_f values of the various chelates at 0 and 21 h for the range of dissolution media used suggesting a high degree of stability.

Tablets (120mg) were prepared from spray dried lactose 64%, hydroxypropylmethylcellulose (Methocel K4M) 28%, magnesium stearate 1% and chelate 7%, using 0.62cm shallow, concave punches on a single punch tableting machine (Manesty F3). Prior to compression the chelate was dissolved in 1mL of water and adsorbed onto the lactose. The tablets were irradiated as detailed above and release of chelate monitored using the USP XXI dissolution apparatus 1 (Caleva 7ST)in 900mL of phosphate buffer (pH7.4) at 100 rpm. Samples were withdrawn periodically and assayed for radioactivity in an automated gamma counter (Daly 1982). The rate of release from the HPMC tablets was independent of the chelate incorporated (Fig. 1).

Figure 1. Release of Sm complexes from HPMC matrix tablets.

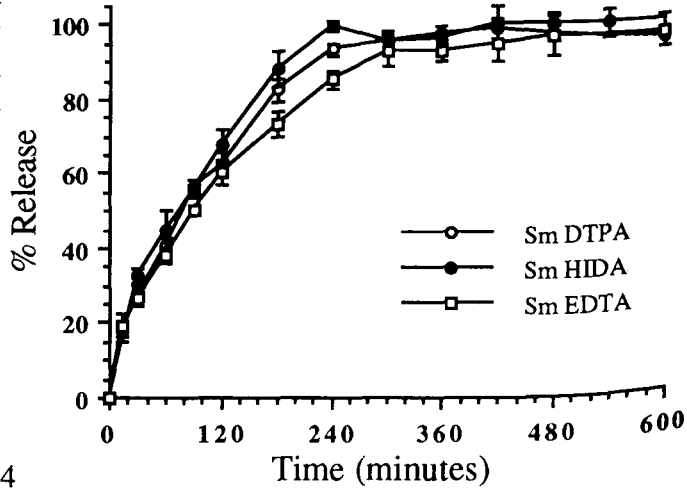

Table 1. Chelates

DTPA - Diethylenetriaminepentaacetic acid
HIDA - N-(2,6-Dimethylphenylcarbamoyl-methyl)-iminodiacetic acid
EDTA - Ethylenediaminetetraacetic acid

Daly, P. B. et al (1982) Int. J. Pharm. 10: 17-24