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Radiolabeling of an enteric coated tablet by (n,γ) radioactivation of erbium-170 for scintigraphic imaging

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Summary

Enteric coated tablets containing small quantities of a stable erbium isotope were irradiated in a neutron flux to produce radioactive tablets labeled with erbium-171. The radiolabeled tablets were used to monitor their transit through the GI tract in human volunteers using external scintigraphy. The absorbed radiation dose to the subjects was found to be within acceptable guidelines. The low toxicity of erbium oxide after oral administration makes the use of this agent ideal for the production of radioactive dosage forms that are difficult or impossible to radiolabel by conventional methods, and leads to products of high radiochemical purity.

Introduction

The performance and behavior of various dosage forms have been evaluated in vivo after oral administration using external scintigraphic imaging techniques (Digenis, 1982). These external imaging procedures require that the dosage forms be radiolabeled with a gamma-emitting radionuclide possessing a short half-life thereby minimizing the radiation exposure to the subjects. Frequently, radionuclides such as technetium-99m and indium-111 are employed as radioactive markers for dosage form scintigraphic studies (Davis et al., 1984; Jay et al., 1983). However, in some cases (e.g. prepared enteric coated tablets) it is not possible to incorporate the radiolabel without disrupting the integrity of the dosage form. We have recently applied the approach of neutron activation for radiolabeling intact dosage forms for external imaging that may overcome the limitations of the traditional labeling techniques (Parr et al., 1985). Using a [^{138}Ba]barium sulfate precursor, ^{139}Ba-labeled tablets were prepared for scintigraphic evaluation after oral administration to dogs (Parr et al., 1985). In this paper, we report on the neutron activation of erbium oxide [^{170}Er] in an enteric coated tablet and an uncoated tablet as a method for preparing ^{171}Er-labeled dosage forms. These tablets were administered to human volunteers to evaluate the suitability of the [^{171}Er]

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radiolabel for in vivo monitoring of dosage form behavior in the gastrointestinal tract.

Materials and Methods

Enteric coated tablets (300 mg) were manufactured using a direct compression method and were composed of 93.3% lactose, 5% starch, 1% magnesium stearate and 0.7% erbium oxide (enriched to $> 96\%$ ^{170}Er, ORNL, Oak Ridge, TN). These tablets were subsequently spray-coated with hydroxypropyl methyl cellulose phthalate (10% w/w) in acetone–ethanol (1 : 1 v/v) solution to obtain enteric coated tablets. The tablets were allowed to cure at 40°C for 24 h, and were then irradiated intact in a flux trap type 10 MW steady-state reactor (University of Missouri Research Reactor, Columbia, MO; 4.4×10^{13} n/cm$^2 \cdot$ s) for 10 min yielding ~ 800 μCi of ^{171}Er per tablet at the end of irradiation. After activation, the tablets were shipped from the reactor site to our imaging facilities via a commercial overnight carrier. The radioactive purity of the tablets was determined using a high resolution Ge(Li) detector interfaced with a multichannel analyzer.

The ^{171}Er-labeled enteric coated tablet was administered to one subject while a second subject received an uncoated ^{171}Er-labeled tablet prepared under similar conditions. Upon oral administration with 120 ml of water, the subjects, who had been fasted for a 6-h period, were placed in a supine position beneath the head of the gamma-scintillation camera (interfaced with a digital PDP-III computer) and the behavior of the tablet in the gastrointestinal tract was observed. The camera was fitted with a medium energy collimator with the pulse height analyzer adjusted to accept pulses from the 112 and 124 keV photons from ^{171}Er. Various parameters were determined for each tablet, such as disintegration rate, pyloric ejection time, site of disintegration, and gastric emptying. The position of the dosage forms relative to the stomach was determined by observing the tablets in a continuous dynamic mode using external radioactive markers placed over the xyphoid process and the umbilicus. This permitted us to track the dosage forms through the stomach, pylorus, into the duodenum and beyond.

TABLE 1

ISOTOPES OF INTEREST IN NEUTRON ACTIVATION OF INTACT DOSAGE FORMS *

Stable isotope	Cross-section (barns)	Radio-active isotope	Half-life	Photon energies (MeV)
Ba-138	0.4	Ba-139	83 min	0.166
Er-170	9.0	Er-171	7.5 h	0.112 0.124 0.296 0.308
Sm-152	210.0	Sm-153	46.7 h	0.103
Na-23	0.53	Na-24	15 h	1.369 2.754
K-41	1.2	K-42	12.36 h	1.525

* From "Table of Isotopes", 6th Edn., C.M. Lederer, J. Wiley & sons, New York, 1967.

Results

The radionuclidic purity of the tablets after neutron irradiation was $> 99\%$ as indicated by Table 2. The linear gamma spectrum of the product (Fig. 1A) demonstrated the presence of ^{171}Er with its characteristic photon energies of 112, 124,

TABLE 2

RADIONUCLIDIC PURITY OF IRRADIATED TABLETS

Isotope	Activity	
	(μCi)	%
Enteric coated tablet		
Na-24	5.1	0.64
K-42	1.3	0.16
Er-171	793.0	99.20
Uncoated tablet		
Na-24	5.02	0.66
Er-171	750.0	99.01
K-42	1.7	0.22
Mn-56	0.80	0.11

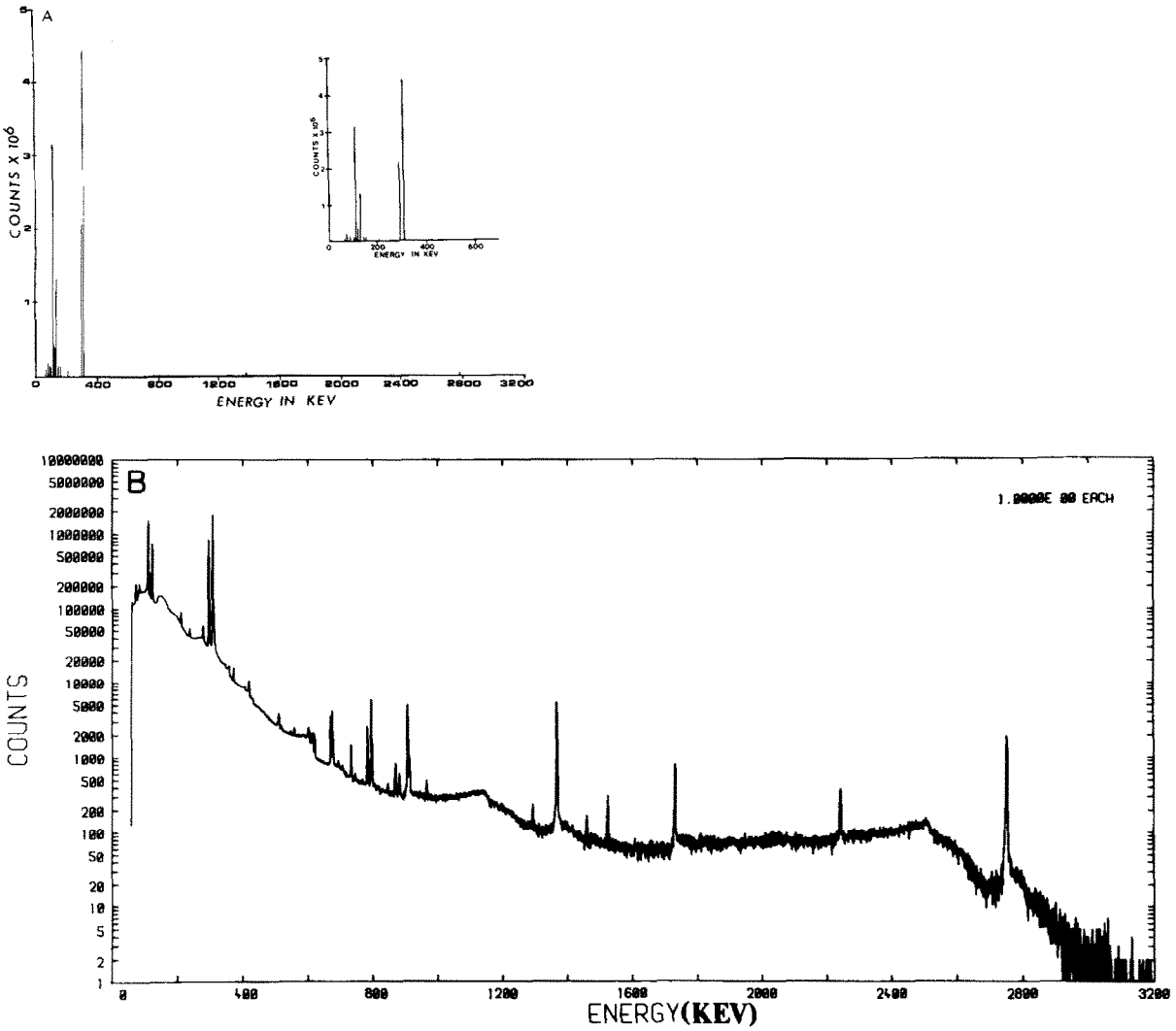


Fig. 1. Linear (A) and log (B) plots of the gamma spectrum of the enteric coated tablet after a 10-min neutron irradiation showing major gamma photons of ^{171}Er at 112, 124, 296 and 308 keV. Note the presence of minor quantities of ^{24}Na (1369 and 2754 keV) and ^{42}K (1525 keV).

196 and 308 keV. The logarithmic spectrum (Fig. 1B) revealed minute quantities of the impurities ^{24}Na, ^{42}K and ^{56}Mn. These impurities arose from minor contaminants in the other tablet components (lactose, starch, magnesium stearate).

In the subject receiving the uncoated tablet, a rapid disintegration time was observed (less than 15 min) with a subsequent gastric emptying time of 47 min. Representative scintiphotos at various times that trace the movement of this tablet through the gastrointestinal tract appear in Fig. 2. The gastric retention time of the ^{171}Er-labeled enteric coated tablet was found to be 68 min and disintegration was observed to begin 12 min after the tablet had been ejected from the pyloric region. The tablet appeared to completely disintegrate after an additional hour as depicted in Fig. 3. The subjects were scanned 18 h after administration of the radiolabeled tablets and, in both cases, the radioactivity was observed in the large

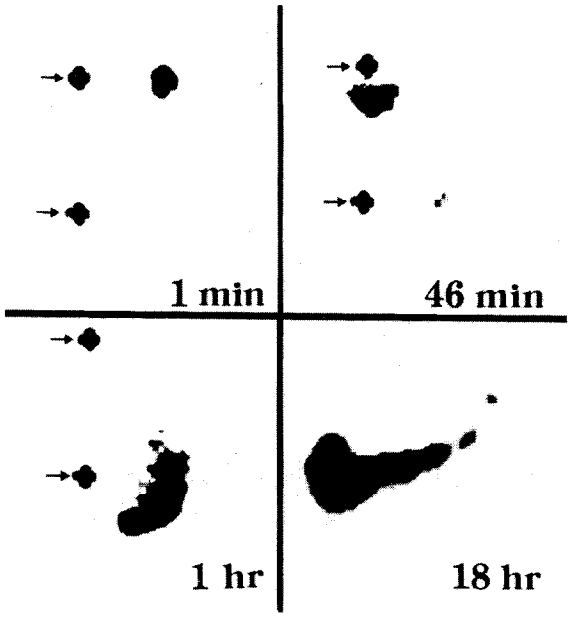
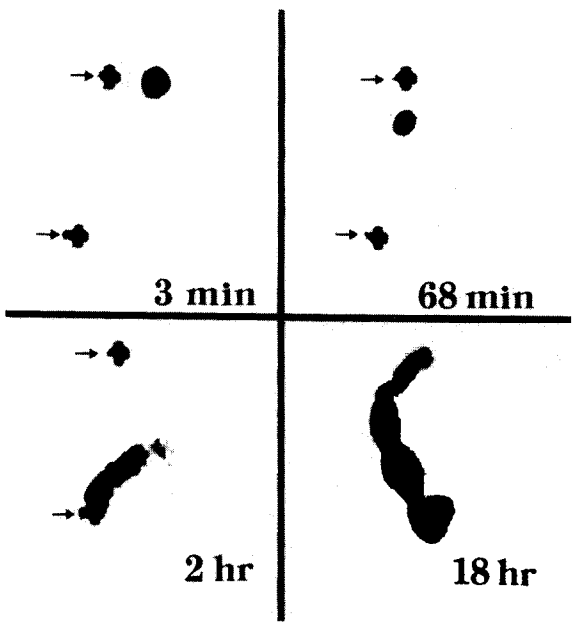


Fig. 2. Anterior scintigraphic images of an ^{171}Er-labeled uncoated tablet at selected times after oral administration to a human volunteer. The arrows indicate the position of external markers placed over the xyphoid process and the umbilicus. Note the position of the intact tablet in the stomach (1 min), the disintegrated tablet in the pyloric region (46 min), the tablet contents in the small intestine (1 h), and ^{171}Er-activity in the transverse colon 18 h after administration.



intestine, primarily in the ascending and transverse colon (Figs. 2 and 3).

Discussion

Neutron activation, a widely applied technique used in trace metal analysis and in the production of various radionuclides (Greene, 1968), may be employed for radiolabeling intact pharmaceutical dosage forms. This approach involves the incorporation of a carefully selected stable isotope during the manufacture of the dosage form and subsequently irradiating it with a neutron flux. The (n,γ) interaction of thermal neutrons with the stable isotope produces a *radioactive* isotope that can be used for external scintigraphic studies in humans.

The factors guiding the selection of the stable isotope precursors are: (1) absence of toxicity and chemical reactivity; (2) acceptable dosimetry of the resultant radionuclide for human studies and suitability for detection by conventional gamma cameras; (3) high natural abundance of the stable isotope or availability of the isotopically enriched species at reasonable cost; and (4) large neutron capture cross-section of the stable isotope. Neutron activation has recently been used in pharmaceutical systems for the production of iron-59 in ferrous chloride tablets for the study of iron absorption (Christensen et al., 1984). However, the physical properties of this isotope prevent it from being useful for human studies. Our previous work with ^{139}Ba-labeled tablets (using a ^{138}Ba precursor) showed this to be an adequate radionuclide for imaging studies in humans in terms of gamma photon energy and absorbed radiation dose. However, the relatively low neutron capture cross-section of ^{138}Ba and the short half-life of

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Fig. 3. Anterior scintigraphic images of an ^{171}Er-labeled enteric coated tablet at selected times after administration to a human volunteer. The arrows indicate the position of external markers placed over the xyphoid process and the umbilicus. Note the position of the intact tablet in the stomach (3 min) and pyloric region (68 min), the tablet after disintegration in the small intestine (2 h), and ^{171}Er-activity in the ascending colon 18 h after administration.

^{139}Ba limited the usefulness of this isotope for many scintigraphic dosage form studies. In the present work, we have employed an enriched erbium isotope (^{170}Er) for the production of ^{171}Er-labeled tablets after neutron activation. Erbium-171 has a longer half-life than ^{139}Ba making it suitable for many GI transit studies of radiolabeled dosage forms, and its precursor, ^{170}Er, has a markedly increased neutron capture cross-section compared to ^{138}Ba (Table 1). This was accomplished using only 2 mg of erbium oxide-170 (> 96% enriched) in a 300 mg tablet and a 10-min irradiation time. Under these conditions, enough ^{171}Er was produced that 50 μCi remained in each tablet approximately 30 h after irradiation. Thus, the high yield of ^{171}Er permitted overnight delivery of the irradiated tablets with enough radioactivity remaining the following day for the scintigraphic imaging studies. If the delivery time were reduced to 7.5 h, then the amount of erbium oxide-170 incorporated into each tablet could be reduced 8-fold. Alternately, the radionuclidic purity of the product could be further improved by using shorter irradiation times.

An important consideration in choosing stable precursor isotopes for in vivo scintigraphic studies after neutron irradiation is their toxicity. Barium sulfate has been administered orally in large doses as a contrast agent for radiographic studies of the GI tract. Thus, toxicity was certainly not a concern in the case of tablets containing barium isotopes. Erbium oxide was been tested for toxicity in rats after oral administration. No deaths were observed at doses up to 1000 mg/kg (Bruce et al., 1963). Toxicology studies of erbium and other lanthanide metal oxides have been performed in mice and monkeys (Hutcheson et al., 1975) and these lanthanides have been used as nutritional markers in man (Luckey et al., 1977). In all cases, essentially 100% of the markers were recovered in fecal matter after oral administration. Thus the use of erbium oxide as a constituent of a tablet formulation posed no health hazard to the subjects.

In addition to toxicity, the absorbed radiation dose by the subjects resulting from the ingestion of ^{171}Er-labeled tablets was also a concern. Table 3 lists the calculated absorbed radiation dose to various organs after oral administration of ^{171}Er tablets and compares these values to the absorbed doses obtained from other radionuclides. For comparison, the radiation dose obtained during an upper GI X-ray series is also included. The absorbed dose rates, as calculated by the Radiopharmaceutical Internal Dose Information Center (Oak Ridge Associated Universities, Oak Ridge, TN, U.S.A.) were found to be within acceptable limits and, thus, were approved by an Institutional Review Board.

Contamination of tablet components with trace amounts of sodium and potassium is inevitable and leads to the formation of the radionuclidic impurities ^{24}Na and ^{42}K (see Table 1 for cross-sections and half-lives). Several approaches may

TABLE 3

RADIATION DOSE (Rads/50 μCi) RECEIVED BY SUBJECTS *

Organ	Isotope				
	Ba-139	Er-171	Sm-153	Tc-99m	In-111
Stomach	0.13	0.09	0.06	0.0065	0.0285
Intestine – small	0.11	0.175	0.145	0.0125	0.090
Intestine – upper large	0.085	0.44	0.7	0.0220	0.200
Intestine – lower large	0.019	0.39	1.45	0.0145	0.365
Ovaries	0.0002	0.017	0.013	0.0046	0.0750
Testes	0.0000075	0.001	0.00065	0.00022	0.0055
Bladder	0.0048	0.0044	0.00325	0.0012	0.0205
Total body	0.0016	0.0065	0.008	0.0009	0.0105

Note: the usual absorbed radiation dose for an upper GI X-ray series is 20 rads.

* Calculated by the Radiopharmaceutical Internal Dose Information Center (Oak Ridge Associated Universities, Oak Ridge, TN).

be taken to reduce the presence of these contaminants. By handling all materials and tablets with gloved hands, one can prevent the transfer of sodium from skin to tablet prior to irradiation. Various approaches at reducing the sodium and potassium contents of bulk materials have been successfully applied when the presence of ^{24}Na and ^{42}K interfere with subsequent analyses. The use of epithermal neutrons (as opposed to the thermal neutrons routinely used) may significantly reduce the activation of sodium and potassium without affecting the yield of other isotopes (e.g. ^{171}Er, ^{153}Sm). Finally, if the presence of sodium or potassium cannot be avoided as with dosage forms containing sodium salts of drugs, a longer-lived isotope such as ^{153}Sm, ($t_{1/2}$ 46.7 h) can be employed. In this case, the activity due to ^{24}Na or ^{42}K would be allowed to decay to background levels before administration of the dosage forms. However, we would expect the longer $t_{1/2}$ of ^{153}Sm to result in higher radiation absorbed doses (Table 3). We are currently studying the use of this radionuclide for radiolabeling dosage forms with varying amounts of sodium and potassium.

Neutron activation has been shown to be useful as a labeling technique for certain dosage forms that might otherwise be difficult or impossible to radiolabel. The radionuclides we have employed for scintigraphic dosage form evaluations provide high quality images with a minimal absorbed radiation dose to the subjects. The various isotopes available for these studies allow a great deal of flexibility and permit the radiolabeling of almost any type of dosage form. We are currently studying the effect of barium, erbium and samarium incorporation with subsequent irradiation on tablet performance (dissolution and disintegration time, hardness, etc.) as well as drug radiolysis in these dosage forms.

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