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Report

Radiolabeling of Intact Dosage Forms by Neutron Activation: Effects on *In Vitro* Performance

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Compressed tablets containing various quantities of stable isotopes of Ba, Er, and Sm for use in neutron activation studies were evaluated for the effect of stable isotope incorporation on tablet hardness and disintegration times. At concentrations likely to be used in scintigraphic studies employing neutron activation as a radiolabeling method, no significant effect on *in vitro* parameters were observed. While the incorporation of stable isotopes influenced tablet hardness to a greater degree than disintegration time, irradiation of tablets in a neutron flux of 4.4×10^{13} n/cm^2 sec had a direct effect on tablet disintegration time. Thus, future neutron activation studies should focus on minimizing the amount of stable isotope to be incorporated with the formulation while using the shortest feasable irradiation time.

KEY WORDS: neutron activation; barium-138; erbium-170; samarium-152; tablet hardness; tablet disintegration; radiolabeling.

INTRODUCTION

The performance and behavior of various dosage forms have been evaluated *in vivo* after oral administration using external imaging techniques (1). These external imaging procedures require that the dosage forms be radiolabeled with a gamma-emitting radionuclide which is suitable for imaging and possesses a short half-life. Current radiolabeling techniques involve the incorporation of a radioactive isotope into the formulation prior to manufacturing the dosage form (2). This method of incorporating the radioactive isotope into the dosage form prior to its manufacture has a number of limitations that have been described elsewhere (3).

We have recently applied the approach of neutron activation for radiolabeling intact dosage forms for external imaging that may overcome the limitations of the previous techniques (4). The neutron activation approach involves the incorporation of a *stable* isotope into the dosage form prior to its manufacture, followed by neutron irradiation of the intact dosage form. Thermal neutron irradiation converts the carefully selected stable isotopes into radioactive isotopes that can be detected by external imaging devices. Using this approach various dosage forms have been radiolabeled with ^{139}Ba, ^{171}Er, and ^{153}Sm for *in vivo* scintigraphic evaluations. Of primary concern is the effect of this radiolabeling procedure (which includes the incorporation of the stable isotope as well as the irradiation procedure) on the *in vitro* behavior of the dosage forms.

A significant amount of work has been reported on the effect of various excipients (i.e., starch, magnesium stearate) and their concentrations on the *in vitro* behavior of various pharmaceutical preparations (5). Other investigators have considered the effect of gamma irradiation, used to sterilize various pharmaceutical preparations, on the stability of a number of compounds such as ampicillin (6), penicillin G (7,8), and antipseudomonal penicillins (9) and its effect on some pharmaceutical products (10). We were interested in determining the effects of the incorporation of stable isotopes and thermal neutron irradiation on the *in vitro* performance of lactose tablets. These tablets were subjected to hardness and disintegration tests and were compared to the appropriate controls.

Table I. Composition of 300-mg Tablets[a] Manufactured for the *In Vitro* Evaluation of the Effect of Barium Sulfate, Erbium Oxide, or Samarium Oxide Incorporation and Neutron Irradiation on Tablet Hardness and Disintegration

	Stable isotope		Lactose	
Formulation No.	mg	% of total	mg	% of total
1	0	0	282	94.0
2	1	0.33	281	93.7
3	5	1.7	277	92.3
4	10	3.3	271	90.3
5	20	6.7	262	87.3
6	30	10.0	252	84.0
7	40	13.3	242	80.7
8	50	16.7	232	77.3

[a] Each tablet (300 mg) also contained 3 mg (1%) of magnesium stearate and 15 mg (5%) of starch.

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Table II. Physical Parameters of Stable Isotopes (11) Used for Neutron Activation of Intact Dosage Forms

Compound	Water solubility (g/100 μl)	Density g/ml	Compressibility (cm^2/kg) × 10^6
Barium sulfate	0.000222	3.51	
Erbium oxide	0.00049	9.066	2.39
Sarmarium oxide	0.000054	7.520	3.34

MATERIALS AND METHODS

Tablets were manufactured using a direct compression method and were composed of lactose, magnesium stearate, starch, and either barium sulfate, erbium oxide, or samarium oxide at the concentrations indicated in Table I. Each tablet weighed approximately 300 mg and was manufactured using a ⅜-in. concave punch and die set and a compression force of 4000 lb. The barium sulfate-containing tablets were irradiated in a neutron flux of 4.4 × 10^{13} n/cm^2 sec for 15 min, and tablets containing erbium oxide or samarium oxide were irradiated under the same flux for 10 and 5 min, respectively. After irradiation, the tablets were stored until the radioactivity produced decayed to background levels.

The effect of stable isotope incorporation into the formulation and the effect of neutron irradiation on tablet hardness and disintegration time were tested. Tablet hardness was determined using an Erweka tablet hardness tester and determining the force needed to crack the tablet in half. Tablet disintegration time was determined by placing one tablet in each chamber of a Vanderkamp USP disintegration apparatus, which was then placed in 900 ml of distilled water (pH 6.5) maintained at 37°C. Tablet disintegration time was recorded as the time at which no solid residue remained on the wire mesh located on the bottom of each chamber.

RESULTS AND DISCUSSION

Neutron activation has been used to radiolabel various intact dosage forms by the conversion of stable isotopes of barium, erbium, and samarium into radioactive isotopes. The inorganic complexes of these elements used in neutron activation studies possess varying physical and chemical properties (summarized in Table II) and may account for differences in tablet hardness and disintegration. The effect of increasing amounts of barium sulfate, erbium oxide, and samarium oxide on tablet hardness is shown in Fig. 1. A significant effect ($P < 0.05$) was observed by incorporation of 0.33% (w/w) of barium sulfate. However, below concentrations of 0.33 and 10% of erbium oxide and samarium oxide, respectively, no effect on tablet hardness was observed. At greater concentrations, the pressure required to crack the tablets gradually decreased. The effect of incorporating these same materials on tablet disintegration times is shown in Fig. 2. The incorporation of barium sulfate yielded an unusual result in that significant differences in tablet disintegration were observed at barium sulfate concentrations between 0.33 and 3.3% (w/w). Erbium oxide and samarium oxide showed no observable effects at concentrations of 16.7 and 3.3% or less, respectively.

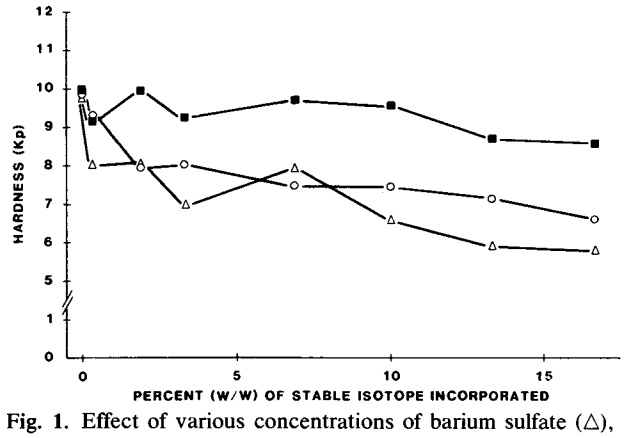

Fig. 1. Effect of various concentrations of barium sulfate (△), erbium oxide (○), and samarium oxide (■) on the hardness of 300-mg direct compression tablets.

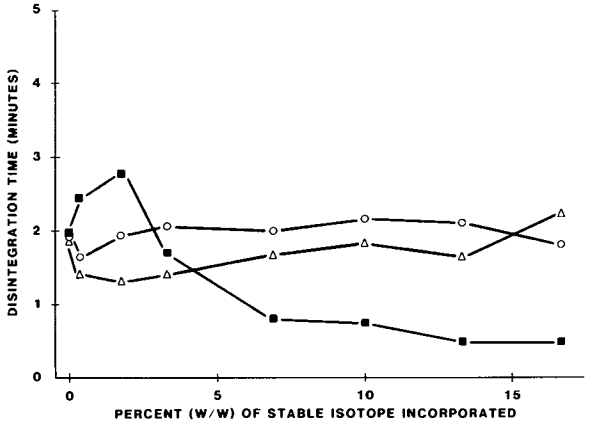

Fig. 2. Effect of various concentrations of barium sulfate (△), erbium oxide (○), and samarium oxide (■) on the disintegration time of 300-mg direct compression tablets.

The effect of exposing the tablets to an intense thermal neutron flux on *in vitro* hardness and disintegration was also evaluated. Neutron irradiations in a flux of 4.4 × 10^{13} n/cm^2 sec for up to 15 min had no apparent effect on the hardness of tablets that did not contain a stable isotope but was observed to increase in irradiated tablets containing Ba, Er, or Sm (Table III). A direct correlation between irradiation time and tablet disintegration time was observed for tablets with and without stable markers (Fig. 3). Thus, tablet disintegration time appeared to be more sensitive to the irradiation

Table III. Effect of Irradiation Time on the Hardness (K_p) of 300-mg Compressed Tablets Containing Various Quantities of Stable Isotope

Irradiation time (min)	Stable isotope	% incorporated 0	3.3	10.0
0	Sm	9.91 ± 0.90	9.28 ± 0.51	9.55 ± 0.63
	Er	9.91 ± 0.90	8.08 ± 0.85	7.48 ± 0.60
	Ba	9.91 ± 0.90	7.05 ± 0.48	6.58 ± 0.49
5	Sm	10.08 ± 0.74	11.06 ± 0.59	10.81 ± 0.88
10	Er	10.54 ± 0.83	9.97 ± 1.03	10.03 ± 0.70
15	Ba	10.09 ± 0.93	9.34 ± 1.12	7.97 ± 0.73

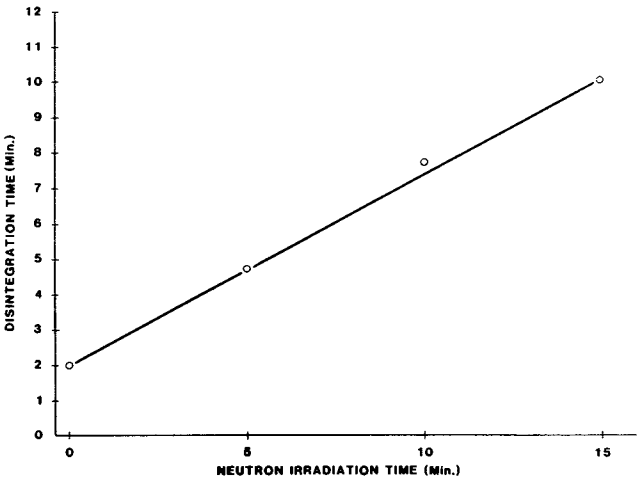

Fig. 3. Effect of neutron irradiation on the disintegration time of 300-mg direct compression tablets.

procedure than was tablet hardness. Conversely, the incorporation of stable isotopes affected tablet hardness significantly without affecting disintegration times.

These studies showed that for scintigraphic studies of dosage forms radiolabeled by the neutron activation method, the amount of stable marker incorporated into the dosage form and the neutron irradiation time should be minimized. In current studies, we have limited the amount of erbium oxide and samarium oxide to less than 1% of the formulation weight and have limited irradiation times to 2 min for erbium-containing dosage forms and 1 min for samarium-containing dosage forms (^{152}Sm has a much larger neutron capture cross section than ^{170}Er). Under these restrictions, we have radiolabeled enteric-coated tablets and multiparticulate dosage forms prepared under industrial scale conditions. The radiolabeling procedure had little or no effect on the drug dissolution profiles of these dosage forms and no drug radiolysis was observed to occur. The neutron activation approach has been shown to be an effective method for radiolabeling dosage forms that are difficult or impossible to radiolabel by conventional techniques without affecting dosage form integrity.

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