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THE EFFECT OF FORMULATION ON I-131 DISSOLUTION *IN VITRO* FROM SODIUM IODIDE CAPSULES

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ABSTRACT

Because of the importance of the bioavailability of I-131 for thyroid uptake studies and thyroid therapy, the present investigation was conducted to determine the influence of diluents, type of lubricant and the concentration of lubricant on the *in vitro* release rate of I-131 from I-131 sodium iodide capsules. Formulations and I-131 sodium iodide capsules were prepared in-house and dissolution profiles determined using the U.S.P. XXII Dissolution Test. Distilled water was employed as the solvent. Lactose only, calcium phosphate only, a mixture of dicalcium phosphate—Avicel PH 101 and a sodium phosphate formulation consisting of lactose, L-cysteine hydrochloride and sodium phosphate were chosen as diluents. Several concentrations of the lubricant magnesium stearate were employed. The influence of 3% or 5% talc as the lubricant was studied using the sodium phosphate formulation.

The results of the study demonstrated the influence of the formulation on the dissolution of I-131 when the concentration of magnesium stearate was held constant. This was particularly noted at a 3% concentration and to a lesser degree at a 1% concentration of magnesium stearate. The dissolution rate for I-131 from capsules prepared with the sodium phosphate—Avicel PH 101 formulation was slow and not influenced by varying the concentration of magnesium stearate. Using talc as the lubricant resulted in I-131 dissolution rates that were rapid for the sodium phosphate formulation. Based upon the findings it is apparent that the diluent and the lubricant can influence the dissolution rate of I-131 from sodium iodide labeled capsules. The relationship of *in vitro* dissolution profiles should be compared to the bioavailability of I-131 in animals to ascertain the importance of formulation in thyroid function studies and treatment.

INTRODUCTION

The knowledge that radioactive iodine will be treated in the same manner as the stable form has led to several applications of radioactive iodine in nuclear medicine. A common application is the radioactive iodine uptake (RAIU) study used to ascertain the functional status of the thyroid gland. The patient is administered a 5-10 μCi dose of I-131 as sodium iodide. Radioactivity in the thyroid gland is determined by detecting high energy gamma radiation with a crystal scintillation detector at 4 hr and 24 hr after administration. The percentage of the radioactive dose taken up by the thyroid is computed. A percentage range is considered normal with values below a certain number indicating a hypothyroid state and a higher than normal percentage indicating a hyperthyroid condition. At times the hyperthyroid condition is treated by administering a significantly higher (mCi) amount of I-131 to destroy a part of the functioning tissue using the beta and low energy gamma radiation emitted from the radioactive iodine.

The I-131 sodium iodide is commonly given as a capsule dosage form. Preparation of the dosage form is important in the utilization of the I-131 sodium iodide capsules. Variations in bioavailability in the gastrointestinal tract could lead to variations in the percentage uptake of I-131 by the thyroid gland. This would not be desirable for a product supplied by a given company or between two companies providing the same product. If in one situation a diagnostic capsule released the radioactivity slowly as compared to the normal rate of release than the radioactive iodine uptake value may appear lower and the patient may be mistakenly diagnosed as hypothyroid. If the same diagnostic capsule was given to a hyperthyroid patient the condition may not be diagnosed as the percentage uptake value may appear lower than the true value; i.e., normal. If the patient was diagnosed as hyperthyroid, a lower than true value would then be used to calculate the radioactive iodine to be given for therapeutic treatment. If the release from the therapeutic capsule was normal, an excessive radiation dose to the patient could result. The percentage uptake value from diagnosis is very important in calculations for treatment of hyperthyroid states.

Early work has demonstrated the influence of dosage form on I-131 uptake by the thyroid gland. Healthy individuals exhibited a lower thyroid uptake of I-131 from a capsule than from a liquid dosage form (1). Green, et. al. (2) also noted a lower thyroid uptake in patients receiving I-131 in capsules. They postulated that the difference was due to an incomplete dissolving of the capsule filler. The dissolution profiles for I-131 sodium iodide diagnostic capsules from three commercial vendors were determined by Yu (3) using the U.S.P. XXI dissolution test. The I-131 release rate in water was rapid for capsules from two of the vendors. The dissolution profile for the product from a third vendor resembled that of a sustained release capsule. Formulation appeared to influence the release of the I-131 from the capsules. Yu (4) repeated the study using I-131 sodium iodide therapeutic capsules from three commercial vendors. The I-131 release rate was rapid and complete at 35 min for all three of the products. The formulation for therapeutic capsules differed from the formulation for the diagnostic capsules that

exhibited a slow release rate. In particular, magnesium stearate was present in the diagnostic capsules. Yu reported that capsules containing magnesium stearate appeared to contract when placed into the dissolution media with a small residue remaining at the conclusion of the study.

Since I-131 release characteristics for commercial capsules have been observed to vary with formulation it appears important to determine the influence of formulation on the dissolution rate and dispersion of I-131 capsule contents. The present investigation was designed to ascertain the influence of diluents and lubricants on I-131 dissolution. In addition, the study was conducted to determine the usefulness of the U.S.P. dissolution test as a quality control procedure for I-131 sodium iodide capsules.

MATERIALS AND METHODS

Formulations

Several formulations were prepared. The components included water-soluble or water-insoluble diluents that were first granulated, then labeled with I-131 as sodium iodide followed by mixing with different concentrations of lubricants. Formulations and lubricant concentrations are presented in Table I.

Granulation

Granulations were prepared by adding the desired volume of 10% polyvinylpyrrolidone (PVP) to 1000 gm. of diluent in a stainless steel one quart capacity bowl of a planetary mixer. The diluent was wetted to produce a mass with a consistency of damp snow. The wet mass was forced through a 16 mesh wire screen except for sodium phosphate where a 12 mesh screen was utilized. Wet granulations were spread thinly on a shallow tray and dried at 116°F for 24 hr. Dried granulation was reduced in particle size by passing through a 20 mesh screen followed by a 30 mesh screen. The final particle size was approximately 590 μm. Dried granulations were stored in a closed container at room temperature.

Labeling Apparatus

A schematic illustration of the labeling apparatus is presented in Figure 1. As may be observed from the drawing, the granulation was placed in a two-ounce wide-mouth glass container attached to a mechanical shaker. A transfer pipet was positioned near the bottom of the glass container. The pipet was inserted through an opening in the center of a #4 rubber stopper. The rubber stopper was sealed to the glass container with tape. A butterfly needle was inserted into the tubing and firmly held with tape. The solution to be injected was contained in a 1 cc tuberculin syringe. The syringe was attached to the tubing of the butterfly needle for injection. The entire apparatus was placed behind a leaded body shield.

TABLE 1.
Formulations

A. Combination[a]
984 gm Sodium Phosphate, Dibasic
49 gm Lactose
1.08 gm L-Cysteine Hydrochloride

B. Lactose[b].

C. Calcium Phosphate[b]

D. Combination[b]
590 gm Dicalcium Phosphate
410 gm Avicel PH 101

[a]Studied with magnesium stearate concentrations of 1, 1.6, 3 and 5 % as well as 3 or 5 % talc
[b]Studied with magnesium stearate concentrations of 1 or 3 %

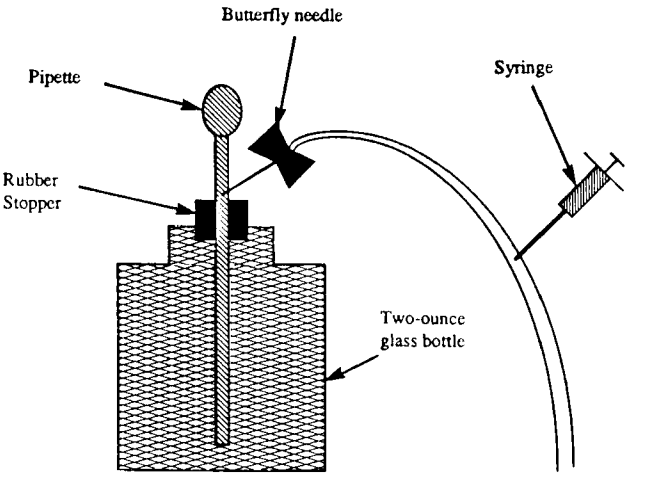

FIGURE 1
Labeling apparatus

Labeling Procedure

The granulation was dried at 49°C to reduce moisture to 4% or less before labeling. Moisture was determined with an OHAS Moisture Balance. The I-131 labeling solutions were prepared by mixing a solution of sodium iodide-131 in a mixture of distilled water and absolute ethanol (1:3). Approximately 0.4 mL (150-200 μCi/mL) was added to 2 gm of the granulation to be labeled for each diluent with the exception of calcium phosphate granulation where 0.2 mL of the labeling solution was added to 3 gm of the granulation. Addition of the labeling solution was accomplished while shaking the container vigorously. After injection of the labeling solution, the butterfly needle was clamped, the syringe was removed, and the container was shaken for 5 min. One more gram of the granulation was added followed by 5 min of shaking. An additional 1 gm of the granulation was added and the final mass was shaken for 10 min. The stopper was removed and the bottle containing the labeled granulation was placed in a desiccator for 24 hr. Moisture content was determined after 24 hr and the results are listed in Table 2.

Capsule Filling

A single capsule holder was prepared and placed in a hood behind a leaded body shield. The labeled formulation was placed in a 5 cc plastic syringe connected to a plastic tube having a diameter of 0.3 cm. Filling of the capsules by gravity was accomplished by tapping the syringe lightly. Capsule weight was determined before and after filling with an analytical balance to obtain the weight of the formulation within the capsule. Ten capsules were prepared for each formulation.

Dissolution Apparatus and Procedure

The apparatus consisted of 6 units. Each unit met the requirements described under Apparatus 2, U.S.P. XXII. Each unit consisted of a 1000 mL glass vessel and a motor driven metallic shaft connected to a paddle blade. The stirring element was placed at the prescribed distance of 25 ± 2 mm from the bottom of the glass vessel. All units were partially immersed in a water bath maintained at 37 ± 0.5°C.

A total of 6 capsules from each formulation and lubricant concentration (two at a time) were studied in repeated experiments. Each capsule was contained in a wire cage placed at the bottom of individual vessels containing 900 mL of distilled water. The speed of each stirring paddle was 50 rpm. One-milliliter samples were obtained from each vessel at specific intervals at the same position. An equal volume of distilled water was added to the vessel after sampling. Each sample was counted with a sodium iodide detection assembly. An aliquot of an I-131 reference solution was used to determine the counting efficiency of the detection assembly. Counting data were corrected for background, counting efficiency and decay as necessary. The data were expressed as a percentage of initial capsule activity. Initial activity in capsules was determined for water soluble labeled formulations by dissolving a known weight of formulation in distilled water and obtaining

TABLE 2.
Labeled Formulation Moisture Content

Formulation	% Moisture Content
A. Combination Sodium Phosphate, Dibasic Lactose L-Cysteine Hydrochloride	3.5
B. Lactose	4.0
C. Calcium Phosphate	0.5
D. Combination Dicalcium Phosphate Avicel PH 101	4.1

activity per milligram. Activity in a capsule prior to study was determined by ascertaining the weight of the formulation within the capsule using the method of tares. For formulations containing calcium phosphate or a mixture of dicalcium phosphate and Avicel PH 101, a Ge (Li) detector and standard sources of radioactivity were employed to determine the activity in each capsule prior to study.

RESULTS

Magnesium Stearate

The dissolution of I-131 from capsules containing the sodium phosphate, lactose and L-cysteine hydrochloride formulation (sodium phosphate formulation) with magnesium stearate is presented in Figure 2. The contents from capsules containing the formulation with 1% or 1.6% magnesium stearate dissolved quickly resulting in a rapid dissolution rate. The presence of 3% or 5% magnesium stearate reduced the dissolution rate for I-131 from the I-131 sodium iodide capsules. The dissolution profiles were very similar between 1% and 1.6% as well as between 3% and 5% magnesium stearate. As expected for a rapid release formulations, the standard deviations were greater at early sampling intervals.

The dissolution of I-131 from capsules containing lactose with 1% or 3% magnesium stearate is presented in Figure 3. At 55 min after initiation of the study, 100% of the I-131 was released from capsules containing 1% magnesium stearates. Only 45% of the activity was released at the termination of sampling for capsules prepared with 3% magnesium stearate.

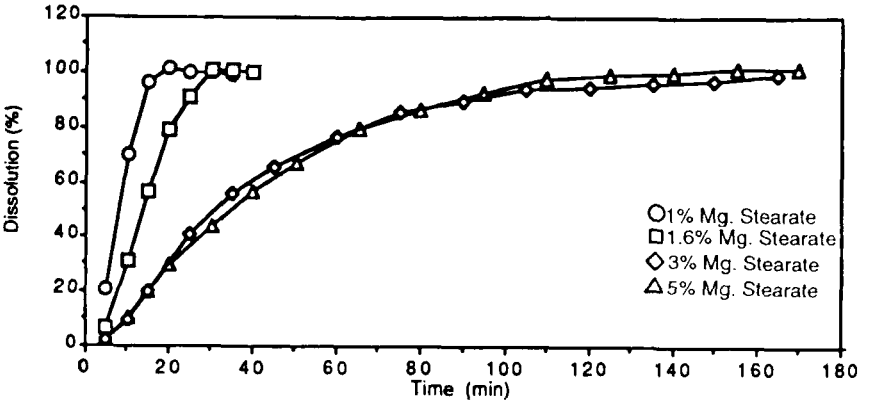

FIGURE 2
Sodium phosphate formulation with 1%, 1.6%, 3%, or 5% magnesium stearate

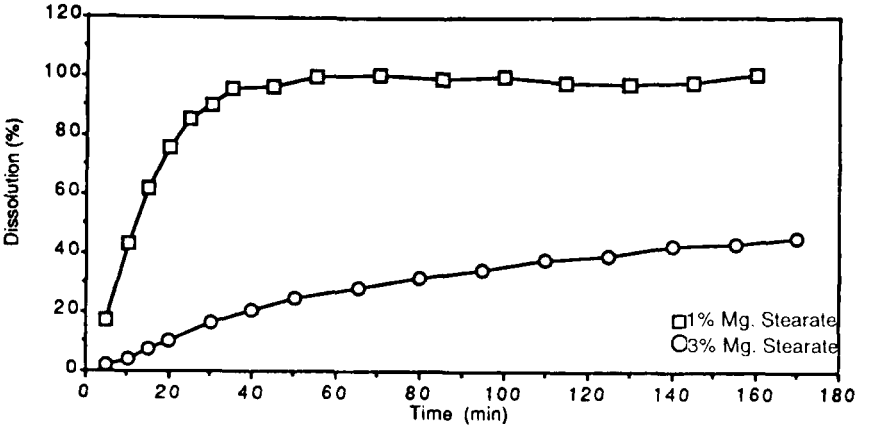

FIGURE 3
Lactose formulation 1% or 3% magnesium stearate

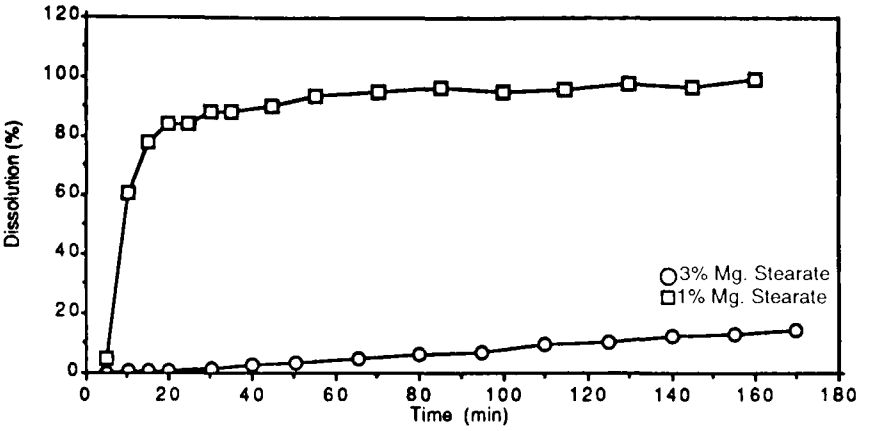

FIGURE 4
Calcium phosphate formulation with 1% or 3% magnesium stearate

As may be observed in Figure 4, the dissolution of I-131 from capsules made with the calcium phosphate formulation and 1% magnesium stearate was rather rapid. However, only 15% of the I-131 activity was released at the termination of sampling for capsules with 3% lubricant. Subjective observation indicated that the contents of the capsules with 3% lubricant appeared to contract followed by deposition of residues at the bottom of the vessel.

Capsules containing the formulation dicalcium phosphate—Avicel PH 101 and either 1% or 3% magnesium stearate released the I-131 activity slowly (Figure 5). As for calcium phosphate, the contents appeared to contract and deposit within the containment vessel.

Talc

Dissolution profiles for capsules containing talc as the lubricant were determined and compared to magnesium stearate. As can be noted in Figure 6, sodium phosphate formulation containing 3% or 5% talc resulted in a rather rapid dissolution of I-131 while comparable percentages of magnesium stearate as the lubricant produced slower dissolution rates for I-131.

Comparison of Diluents with Magnesium Stearate

The dissolution profiles for I-131 from different formulations containing 1% magnesium stearate are presented in Figure 7. With the exception of dicalcium phosphate—Avicel PH 101, almost 90% of the activity was released by 30 min. The dicalcium phosphate-Avicel PH 101 formulation is not acceptable for I-131 capsules prepared with 1% magnesium stearate as the lubricant. Increasing the percentage

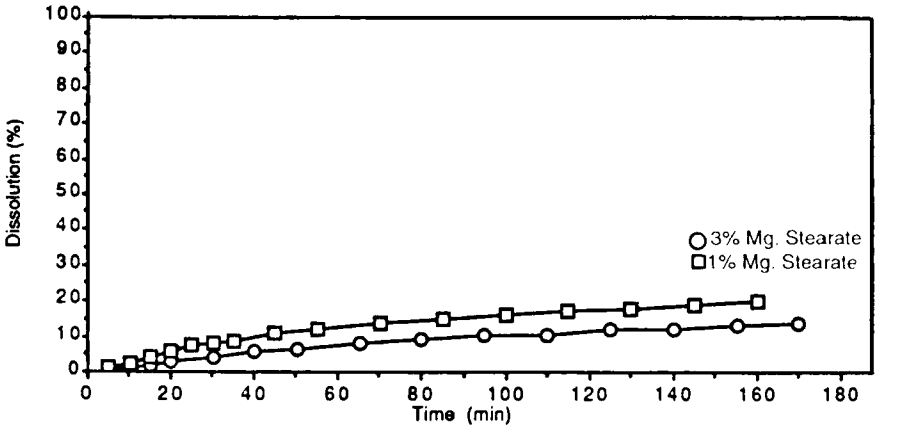

FIGURE 5
Dicalcium phosphate-avicel PH 101 formulation with 1% or 3% magnesium stearate

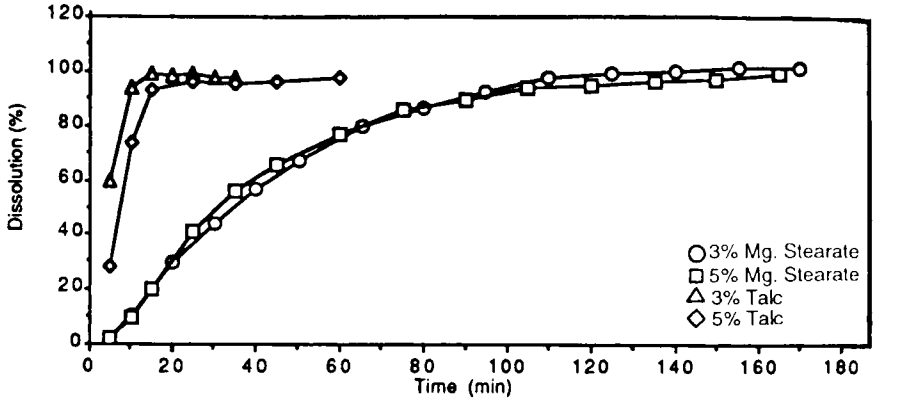

FIGURE 6
Sodium phosphate formulation with talc *vs* magnesium stearate

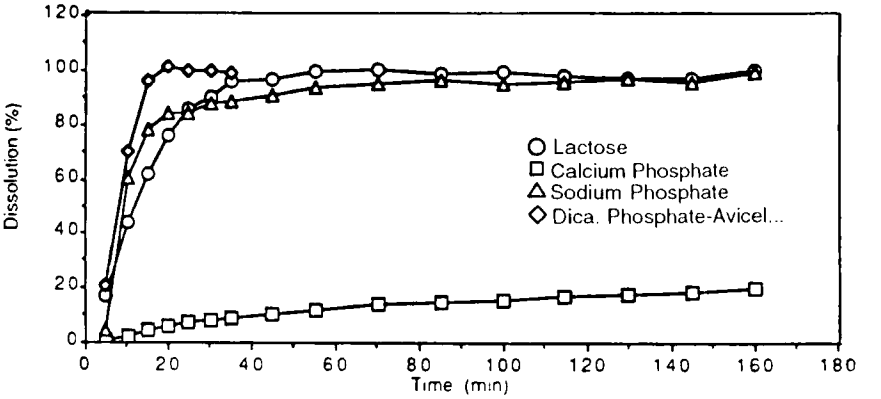

FIGURE 7
Sodium phosphate, lactose, calcium phosphate or dicalcium phosphate-avicel PH 101 formulations with 1% magnesium stearate

of lubricant to 3% resulted in rather unacceptable release rates for I-131 with all formulations except for sodium phosphate (Figure 8).

CONCLUSIONS

The results of the investigation illustrate the importance of diluent and lubricant in regard to the availability of I-131 from sodium iodide I-131 capsules. Dissolution rates were affected by varying the formulation while employing the same concentration of lubricant. The concentration of the lubricant was another variable that was found to influence the potential for release of I-131 from sodium iodide capsules. Variation in concentration did not always influence the I-131 dissolution rate as was illustrated by the study of the dicalcium phosphate—Avicel PH 101 formulation using magnesium stearate as the lubricant. Avicel PH 101 which is microcrystalline cellulose may have absorbed the I-131 applied as a solution. The concentration of lubricant may not have been an important factor because of the absorbing characteristic of the Avicel PH 101. Poor dissolution *in vitro* with microcrystalline cellulose may not indicate a lack of bioavailability *in vivo*, as demonstrated by studies previously conducted by Franz and Peck (5).

The results of the study of talc and magnesium stearate as lubricant using the same formulation indicate that the choice of lubricant may be important for a given situation. It would appear that talc will permit a more rapid release of I-131 from sodium iodide capsules prepared with the sodium phosphate formulation. However, the lubricating characteristics of talc may necessitate a higher concentration of the lubricant than needed with magnesium stearate and, thus, produce a release pattern similar to that observed for the magnesium stearate.

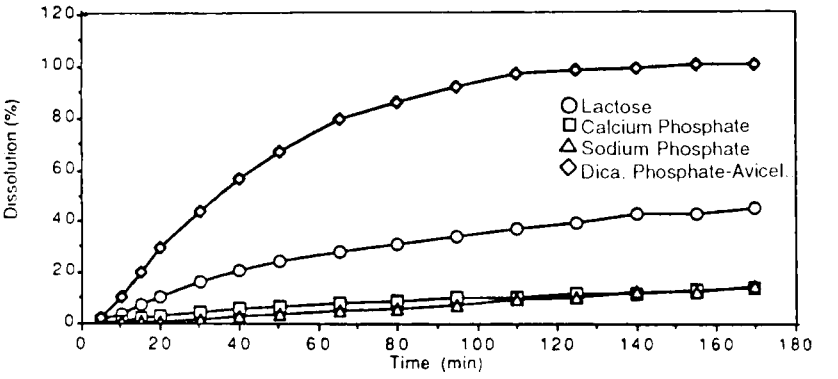

FIGURE 8
Sodium phosphate, lactose, calcium phosphate or dicalcium phosphate-avicel PH 101 formulation with 3% magnesium stearate

Based upon the data, it appears that knowledge of dissolution profiles for capsules containing I-131 is important in the utilization of the capsules in diagnosis or therapy related to the thyroid. However, further work must be conducted before drawing conclusions and making recommendations. The *in vivo* characteristics of the capsules should be determined and related to *in vitro* dissolution profiles. The influence of formulation and lubricant on filling capsules should be studied. The results of the investigation do indicate that consideration should be given to employing the U.S.P. XXII dissolution test for capsules as a quality control measure.

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