International Journal of Pharmaceutics, 49 (1989) 115–119
Elsevier

IJP 01650

Development of a new coated-bead dosage form of sodium iodide I-131

Richard Dansereau [1] and Raymond Dansereau [2]

[1] *Norwich Eaton Pharmaceuticals, Inc., Norwich, NY (U.S.A.) and* [2] *Albany Medical Center, Albany, NY (U.S.A.)*

(Received 23 November 1987)
(Modified version received 1 July 1988)
(Accepted 5 July 1988)

Key words: Sodium iodide I-131: Coated bead dosage form; Decreased radiation hazard; film coating, aqueous; Film coating, HPMC

Summary

Sodium iodide I-131 is a commonly used radiopharmaceutical agent in the diagnosis and treatment of various thyroid conditions. The USP recognizes an aqueous solution and a capsule dosage form of sodium iodide I-131. The sodium iodide I-131 solution presents significant radiation hazards associated with spills and inhalation of volatile components. The capsule dosage form restricts the dosing flexibility and often requires that the patient take several capsules. This paper describes the development of a stabilized solid dosage form of sodium iodide I-131. The non-radioactive species was used in this study because it possesses the physical and chemical properties of the radioactive compound, but without radiation hazards. The sodium iodide was dissolved in a polymeric film and applied to nonpareil beads by conventional fluid-bed technology. The film coating protected the sodium iodide from degradation by environmental factors. The bead dosage form offers the physician and pharmacist infinite dosing flexibility because the specified dose can be filled into a single hard-gelatin capsule before dispensing. This dosage form also minimizes the hazards associated with spillage and overcomes the volatility problem associated with the solution dosage form.

Introduction

Sodium iodide I-131 is frequently used as a marker in nuclear medicine for radionuclide studies involving the thyroid. It is also used to measure thyroid uptake of iodine, and it is the preferred radiopharmaceutical agent for the identification and assessment of ectopic thyroid tissue. Therapy with sodium iodide I-131 is regarded as the treatment of choice for hyperthyroidism in patients over age 30. Sodium iodide I-131 is an important adjunct in therapy for thyroid carcinoma for ablation of postsurgical residual thyroid tissue in the neck and eradication of functioning local and distant metastases (Mettler and Guiberteau, 1986). The doses of sodium iodide I-131 that are used in the treatment of hyperthyroidism and in thyroid carcinoma range from approximately 100 megabecquerels (MBq) to several gigabecquerels (GBq).

Sodium iodide I-131 is commercially available for oral administration in aqueous solution and capsule form. The liquid dosage form provides the pharmacist and physician with infinite flexibility in dose selection, but it presents significant radiation hazards association with spills; an additional hazard, unique to handling solutions containing

Correspondence: R. Dansereau, Norwich Eaton Pharmaceuticals, Inc., Norwich, NY, U.S.A.

sodium iodide I-131, is the inhalation of volatile components containing airborne radiation (Haenchen et al., 1985). In solution, sodium iodide can be oxidized to iodine gas by oxygen: $4HI + O_2 \rightarrow 2I_2 + 2H_2O$ (Howard, 1976). Exposure to light, heat, and other oxidizing agents, such as chloride ions found in tap water, can accelerate the oxidation of the iodide. The capsule dosage form provides convenience of handling and lower exposure hazards but restricts the flexibility available to the physician for ordering a given dose without requiring the patient to take several capsules.

To reduce the hazards of handling sodium iodine I-131 for the radiopharmacist and to maintain dosing flexibility for the physician, an alternative dosage form is required. Rapidly dissolving beads, uniformly coated with a film that is impregnated with carrier-free sodium iodine I-131, would meet these requirements. This paper reports the development of such a system.

Materials and Methods

Film selection

Sodium iodide is a deliquescent material: it will gradually absorb moisture up to 5% (0.5 mol) on exposure to air. Sodium iodide also becomes brown in the air because of liberation of iodine. These circumstances indicate the need for a moisture-resistant film that prevents the degradation of sodium iodide to elemental iodine.

The film must also dissolve rapidly upon ingestion to assure maximum drug availability in vivo. The film-forming polymer should be water-based to circumvent the restrictions and regulations imposed by the use of organic solvents. Ghebre-Sellassi et al. (1982) described the film-forming, permeability, and solubility properties of Aquacoat (FMC Corporation, Philadelphia, PA)/hydroxypropylmethylcellulose (HPMC) films. The authors concluded that at high Aquacoat/HPMC ratios ($> 1.00:0.25$) based on total solids, the physical appearance, solubility, and permeability characteristics of the film were close to those obtained from plasticized Aquacoat formulation alone, whereas at low Aquacoat/HPMC ratios ($< 1.0:1.5$), the films showed a dramatic increase in water solubility and disintegrated quite rapidly. Based on this work, a film containing an Aquacoat/HPMC ratio of 5 : 1, representing a compromise between film permeability and solubility, was selected for use in this project.

TABLE 1

Formula for sodium iodide coating dispersion

Ingredient	Amount (% w/w)
Methocel E-5 Solution (10% w/w, per text)	23.1
Distilled water	31.0
Aquacoat (30% w/w)	38.6
Dibutyl sebacate	2.8
Sodium iodide	3.7
Chroma-Kote T1343-PK Dye Dispersion	0.8

A pink lake-dye dispersion system was added to the coating formula as a visual tracer to assist in determining the coating parameters. Chroma-Kote (Crompton and Knowles, Fairlawn, NJ) was selected because its components did not interfere with the assay procedures described in this test.

Preparation of the coating dispersion

The formula for the sodium iodide protective coating used in this study is listed in Table 1.

(1) A 10% w/w Methocel E-5 (HPMC) solution (Dow Chemicals, Midland, MI) was prepared in distilled water and deaerated overnight at 5 °C.
(2) The Aquacoat was plasticized with 24% w/w (based upon film former) dibutyl sebacate (Union Carbide, Jacksonville, FL). The dibutyl sebacate was added to the Aquacoat and mixed for 30 min with a Lightnin mixer (Mixing Equipment Co., Rochester, NY).
(3) The sodium iodide (Fisher Scientific Co., Fairlawn, NJ) was dissolved in a portion of the distilled water and added to the HPMC solution.
(4) The Chroma-Kote T1343-PK (Crompton and Knowles) was added with mild agitation to the HPMC solution.
(5) The HPMC mixture was added to the Aquacoat mixture and mixed for 20 min before coating and throughout the coating process.

Coating

In this study, stable forms of sodium iodide were used to represent the performance of sodium iodide I-131. Our laboratory was neither equipped nor licensed to handle radioactive materials; however, stable forms of iodine adequately reflect the physical and chemical characteristics of the radioactive species. Facilities that are currently equipped to manufacture pharmaceutical-grade sodium iodide I-131 may be appropriately modified to manufacture the coated beads.

Sodium iodide (10 mg) was applied to 1 g of Nu-Pareil PG beads, 710–840 μm (Ingredient Technology Corp., Pennsauken, NJ). The appropriate amount of sodium iodide was applied in an Aquacoat/HPMC dispersion to achieve an increase in bead weight of 5% w/w.

600 g of the 710–840 μm beads were coated in a fluidized-bed coating column (Strea-1, Aeromatic, Inc., Somerville, NJ) with an inlet coating temperature of 50 °C. The sodium iodide coating dispersion was pumped at a rate of 6 g/min into the atomizer, which operated at a spray pressure of 2 atmospheres and had a spray-nozzle orifice of 1.1 mm. After coating, the beads were dried on trays at 45 °C for 24 h.

Assay for iodide

An iodide-ion-selective electrode (Model 94-53, Orion Research, Inc., Cambridge, MA) and a single-junction reference electrode (Model 90-01, Orion) were used to determine iodide content. The electrodes were connected to a digital ion analyzer (Model 801A, Orion). The ion electrodes are responsive over a range of 127 ppt to 5 ppm of iodide ion concentration. Calibration curves were prepared just before all samples were analyzed.

The iodide concentration in the beads was determined by first stirring the specified quantity of crushed beads (1 g or 10 g) in 90 ml of distilled water for 30 min. The solutions were then filtered through Whatman No. 1 filter paper (Whatman Limited, U.K.). Before assay with the ion-selective electrode, 2 ml of ionic-strength adjuster (5 M $NaNO_3$, Fisher Scientific Co., Fairlawn, NJ) was added to the filtrate. The reported values represent the means of 5 sample determinations.

Detection of iodine

After the solutions were assayed for iodide, they were tested for the presence of elemental iodine. Of each iodide test solution 75 ml were manually mixed with 25 ml of carbon tetrachloride (Mallinckrodt, Paris, KY) in a 125 ml separatory funnel for 10 min. The endpoint for detection of iodine is the development of a red-violet color in the carbon tetrachloride layer. Latimer et al. (1951) demonstrated the usefulness of this technique to detect trace amounts of iodine.

Content uniformity

One gram aliquots of the coated beads were tested for content uniformity according to the USP XXI (USP85) requirements for solid dosage forms.

Chemical stability

For the stability studies, the sodium iodide beads were stored under the following conditions: (a) in open Petri dishes at 25 °C; (b) in screw-capped amber bottles at 25 °C; (c) in open Petri dishes at 25 °C and 75% relative humidity; (d) in screw-capped amber bottles at 60 °C; and (e) in open Petri dishes in an Envira-Lite cabinet (Thermal Research, Inc., Iselin, NJ) (2000 ft-candles) at 25 °C

The beads (5 samples per interval) were assayed for iodide and iodine after 0.5, 2.0, 4.0, and 6.0 months. Because the detection of iodine is a qualitative test, a 10 g sample was used to maximize assay sensitivity.

Dissolution testing

Drug release was determined using 1 g of the coated beads. The USP Dissolution Apparatus 2 (VanderKamp 600, Van Kel Industries, Chatum, NJ) was used with 900 ml of dissolution medium at a stir speed of 50 rpm. The dissolution medium was stimulated gastric fluid (SGF), USP, without enzymes, pH 1.2–1.5. Samples of 5 ml were removed for assay every 2.5 min for 15 min. The sampled volume was replaced with fresh medium at each sample time. The 5-ml samples were taken from the center of the dissolution vessel using a 10-ml syringe (Becton Dickinson, Rutherford, NJ),

fitted with a 3-inch needle, and filtered through a 0.22 μm disposable filter (Gelman Scientific, Ann Arbor, MI). Two milliliters of the ionic-strength adjuster was added, and the samples were assayed directly with the iodide ion-selective electrode. The response variable measured was the cumulative amount of iodide ion dissolved. Six samples at each storage condition were assayed.

Results and Discussion

Initial testing of the coated beads indicated that the iodide was uniformly applied on the Nu-Pareil PG beads. The mean iodide content of 10 samples was 9.8 mg iodide per 1 g of beads, with a standard deviation of 0.42.

The results of the iodide-ion assay over the 6-month stability program are shown in Table 2. The limits-of-population means of the coated beads were calculated using the average iodide-ion content of a 10-g sample of beads. The results were within the 95% confidence intervals for the population mean of 95 mg $< u <$ 100 mg. As shown in Table 2 and Fig. 1, the average iodide ion values are within this limit. Based on these data, it can be concluded that no significant degradation of the iodide content occurred over six months under any of the conditions studied.

All samples were negative for the presence of elemental iodine. The absence of iodine, coupled

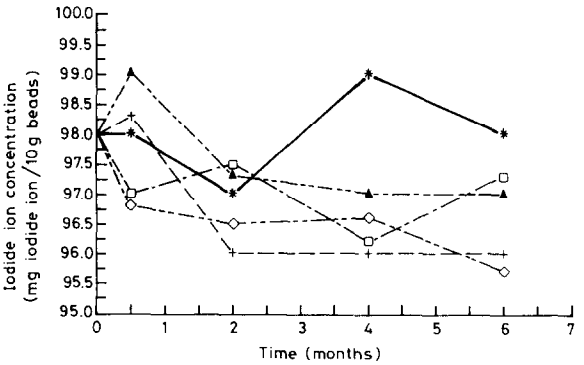

Fig. 1. Six-month chemical stability of sodium iodide-coated beads; *, open Petri dishes at 25 °C; +, screw-capped amber bottles at 25 °C; △, open Petri dishes at 25 °C and 75% relative humidity; ◇, screw-capped amber bottles at 60 °C; □, open Petri dishes in an Envira-Lite cabinet at 25 °C.

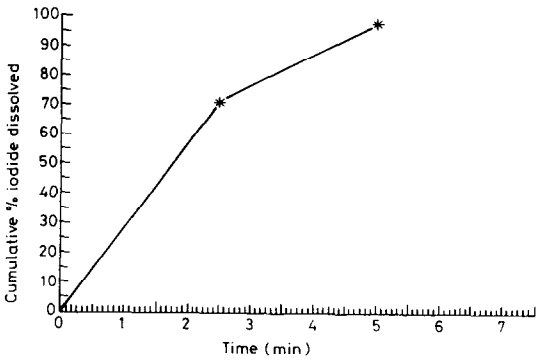

Fig. 2. Dissolution of sodium iodide-coated beads (1 g) in simulated gastric fluid.

TABLE 2

Iodide-ion content (mg) in 10 g of coated beads over the six-month stability program

Months	25 °C [1]	25 °C [2]	75% Relative humidity, 25 °C [1]	60 °C [2]	Envira-Lite cabinet, 25 °C [1]
0.0	98.0 [3]	–	–	–	–
0.5	98.0 (3.0)	98.3 (3.5)	99.0 (3.0)	96.8 91.9)	97.0 (2.9)
2.0	97.0 (2.9)	96.0 (3.3)	97.2 (4.1)	96.5 (2.9)	97.5 (3.9)
4.0	99.0 (3.2)	96.0 (3.2)	97.0 (3.3)	96.6 (3.6)	96.2 (3.4)
6.0	98.0 (2.9)	96.0 (3.0)	97.3 (3.0)	95.7 (2.8)	97.0 (2.1)
Slope (k)	0.08	−0.38	−0.27	−0.12	−0.28

Each value is the mean (S.D.) of 5 sample determinations.

[1] Open Petri dishes.

[2] Screw-capped amber bottles.

[3] Average value from content uniformity assay.

with the total recovery of iodide, indicates that the coating successfully prevented the oxidation of iodide to iodine.

The dissolution profile of the beads at the time of manufacture is shown in Fig. 2. The film coating dissolved rapidly, releasing approximately 70% of the iodide ion within 2.5 min and a total of 99% within 5 min. The dissolution rates of the beads after 0.5, 2.0, 4.0, and 6.0 months, at all storage conditions, were within the range of 95–100% iodide dissolved within 5 min.

The extremely rapid dissolution of the Aquacoat/HPMC film in SGF resulted in the desired release of sodium iodide from the beads. This characteristic should assure maximum drug availability upon administration.

This sodium iodide I-131 coated-bead dosage form would allow the pharmacist to dispense the appropriate quantity of beads to meet the therapeutic needs of each patient. Ideally, the pharmacist would load the beads into a single hard-gelatin capsule for administration, thus providing greater convenience for the patient. Should the beads be spilled during capsule preparation, it is unlikely they would contaminate any dry surfaces with which they come in contact, and the radiation hazard to safety personnel during the cleanup would be minimal. If the patient's condition dictated, the pharmacist would also have the option of dissolving the beads in an aqueous medium for provision of a liquid dosage form. The physician would have maximum flexibility in selecting a particular dose, and both the pharmacist and the physician would be protected from possible internal exposure to radiation.

Conclusions

In this study, stable forms of sodium iodide were used to reflect the physical and chemical properties of the radioactive species. This paper has described the development of a stabilized oral dosage form of sodium iodide I-131 providing several advantages over the aqueous solution and current capsule dosage form.

(1) It offers the flexibility of filling the prescribed amount of sodium iodide I-131 into a single hard-gelatin capsule.

(2) The coated-bead dosage form reduces the potential for internal radiation hazard to both the pharmacist and the dispensing physician.

(3) The sodium iodide dissolves rapidly from the protective coating, thus ensuring maximum drug availability upon dosing.

(4) The Aquacoat/HPMC polymer coating protects the sodium iodide from degradation by environmental factors (heat, light, moisture).

The Aquacoat/HPMC polymer coating was an ideal polymer combination because it simplified materials processing and protected the sodium iodide. This coating system may also be useful for other low-dose therapeutic agents that are moisture- and light-sensitive.

Acknowledgements

The authors would like to thank Mark Stella for his assistance in developing the chemical analysis techniques.

References

Ghebre-Sellassi, I., Banker, G.S. and Peck, G.E., Water-based controlled-release drug delivery System, *Pharmaceutical Technocology Conference*, Pharmaceutical Technology Publications, Oregon, 1982, pp. 234–247.

Haenchen, M., Eichling, J. and Glasgow, G., Assessment of the airborne activity levels during I-131 thyroid therapies. Poster presented at the *30th Annual Health Physics Society Meeting*, Chicago, June 1985.

Howard, B.Y., Safe handling of radioiodinated solutions. *J. Nucl. Med. Technol.*, 4 (1986) 28–30.

Latimer, W. and Hildebrand, J., Group VII. The halogens. In *Reference Book of Inorganic Chemistry*, The Macmillan Company, New York, 1951, pp. 162–163.

Mettler, F.A. and Guiberteau, M.J., Thyroid and parathyroid. In *Essentials of Nuclear Medicine Imaging*, 2nd Edition, Harcourt Brace Jovanovich, Orlando, 1986, pp. 89–115.