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Preparation and Evaluation of Free Oxygen Absorber in Pharmaceutical Preparations

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Ferrous compound was used as a free oxygen absorber (FOA). It was prepared from the chemical reaction of ferrous sulfate and sodium hydroxide under nitrogen atmosphere. The condition of reaction was investigated to obtain a product of high absorbing activity. A kinetic study was done when FOA was exposed to the air and the efficacy was tested.

Keywords free oxygen absorber; iron(II) compound; oxygen removal; chemical kinetics; iron–oxygen; deoxygenator

Introduction

The oxidation process is largely controlled by the environment *i.e.*, temperature, light, oxygen, oxidizing agent and trace metals. Several methods have been employed singularly or in combination to minimize oxidation; one of these is to exclude free oxygen from the preparation and the void space of the packaging. Free oxygen absorber (FOA) may be used to reduce or eliminate the free oxygen.

The present study was done to find a low cost FOA which is safe and effective for use in pharmaceutical products. The rate and extent of reactions between FOA and atmospheric oxygen were investigated, and the efficacy of FOA was also evaluated.

Experimental

Materials Iron(II) sulfate heptahydrate was purchased from E. Merck. All other chemicals used throughout the study were reagent or pharmaceutical grade. Packaging materials were obtained from Strong Pack Co., Ltd.: laminated kraft paper/low density polyethylene (kraft/LDPE, 40 g/m^2, 22 μm thickness), low density polyethylene (LDPE, 60 μm thickness), kraft paper/ethylene vinyl acetate (kraft/EVA, 20 μm thickness) and kraft paper/nylon/polyethylene/aluminum/polyethylene (kraft/nylon/PE/Al/PE) were obtained from Strong Pack Co., Ltd.).

Preparation of Iron(II) Compound Iron(II) compound was prepared by adding 120 ml of 6 N sodium hydroxide to 200 g of iron(II) sulfate heptahydrate under nitrogen atmosphere in a glove box (Gallenkamp, Ltd.). The very fine dispersion obtain was filtered through a filter paper (Whatman No. 1) while flushing with nitrogen gas. The precipitate collected was washed several times with fresh distilled water. The damp mass of iron(II) compound obtained was weighed and stored in an oxygen barrier bag (kraft/nylon/PE/Al/PE).

Preparation of Free Oxygen Absorber FOA was prepared by mixing the damp iron(II) compound with various ratios of fumed silica (Aerosil 200) in a mortar and pestle and passing it through a 20-mesh sieve. The powder was then put into oxygen permeable bags (40 mm × 50 mm) and heat sealed. The bags were kept in an oxygen barrier package (kraft/nylon/PE/Al/PE) until used.

Analysis of Iron(II) Compound An accurately weighed sample was placed in a 250 ml Erlen-meyer flask and 50 ml of 5% (w/v) of H_2SO_4 added. The solution was titrated with 0.1 N $KMnO_4$ to the first permanent pink color. Each ml of 0.1 N $KMnO_4$ was equivalent to 0.090 g of iron(II) hydroxide.

Determination of Moisture Content The moisture content was calculated from the weight lost by drying at 100 °C until the weight was constant.

Particle Size Measurement Sample of iron(II) compound from each preparation was dispersed in a small amount of 0.9% NaCl in a mortar and then rinsed with the electrolyte into a beaker. The electrolyte solution was added and sonicated so that discrete particles were observed under a microscope. Particle size was determined by a Coulter counter model D-industrial (Coulter Electronics Inc. U.S.A.). The culative weight oversized were calculated from the number of particles counted.[1] Duplicate measurements were performed for each preparation.

Chemical Kinetics Study a) Direct Exposure to Atmospheric Oxygen: Iron(II) compound was spread on a watch glass and left exposed to air at room temperature (30±2 °C). Samples were removed at suitable time intervals. The amount of unoxidized iron(II) compound was determined by titration with 0.1 N $KMnO_4$. All determinations were carried out in duplicate.

b) In an Oxygen Permeable Bag: About 1 g of FOA was placed in an oxygen permeable bag (kraft/LDPE) and suspended in the air at room temperature. The bag was removed at suitable time intervals and analyzed for the amount of residual iron(II) compound.

Determination of Oxygen Removing Efficacy Varying amounts of FOA were placed in 500 ml amber glass bottles (equivalent to 100 ml of oxygen at room temperature) and left at a temperature of 25±2 °C. The residual amount of oxygen in each bottle was monitored over time by means of a head space oxygen analyzer (model IL 307-02 SIE Supply and service).

Results and Discussion

Preparation of Iron(II) Compound Iron(II) sulfate reacted with sodium hydroxide solution forming a white precipitate. The precipitate gradually turned to a pale green precipitate during the preparation process. When left exposed to the air, it darkened and finally changed to a reddish brown. The average moisture content was 35.03%.

The pale green precipitate may be composed of iron(II) hydroxide ($Fe(OH)_2$) and iron(II) ferrite ($Fe(OH) \cdot O \cdot Fe(OH)_2$) as suggested by Mayne.[2] The structure of iron(II) precipitate is complex and varies with preparation conditions. For simplicity, the amount of iron(II) was calculated as equivalent to the amount of iron(II) hydroxide ($Fe(OH)_2$).

The particle size and size distribution of 3 lots of damp iron(II) compound were measured by a Coulter counter. Table I shows a typical cumulative weight percent oversize at each equivalent spherical diameter. The geometric mean diameters and standard deviations were calculated from linear regression lines of the log-probit plots of diameters

TABLE I. Typical Particle Size Analysis of Iron(II) Compound

Equivalent spherical dia. (μ)	Cum.%w oversize	
	Sample 1	Sample 2
50.9	5.21	9.02
40.4	14.85	18.13
32.4	25.48	27.80
25.7	38.19	41.44
20.4	50.93	52.94
16.2	61.36	62.32
13.2	70.43	72.60
10.9	81.24	81.69
8.7	90.25	90.39

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Table II. Oxidation of Damp Iron(II) Hydroxide with Atmospheric Oxygen

Time (h)	Iron(II) hydroxide remaining %(w/w)
0	100.0
1	99.84
2	99.59
4	98.62
7	96.15
500	27.57

against cumulative weight percent oversize. The geometric mean diameters (±S.D.) for 3 lots were 20.56 (0.53), 21.90 (0.52) and 19.42 (0.50) μm. These values were found to be not significantly different ($p > 0.05$) indicating uniformity within a lot and between lots.

Oxidation of Damp Iron(II) Compound Damp iron(II) compound was oxidized upon exposure to air. The amount of iron(II) hydroxide remaining at a specific time is shown in Table II; after 7 h of exposure, only 3.9% was oxidized. It took 500 h (3 weeks) to reduce iron(II) hydroxide to 27.5% of the original amount. The slowness of reaction was due to the limited accessible surface area of the compound.

Effect of Absorbent on the Oxidation of Iron(II) Compound The reaction rate would be faster if the effective surface area of iron(II) compound were increased by the addition of some absorbent such as fumed silica (Aerosil 200) or which would absorb the moisture and prevent agglomeration.

FOA was prepared from damp iron(II) compound mixed with varying amounts of fumed silica at a ratio of 11 to 20 parts silica to 100 parts by weight of the compound. Increasing the amount of fumed silica resulted in improved flowability and an increase in porosity and accessible surface area. The percentage remaining of iron(II) compound after 8 h of exposure to atmospheric oxygen was found to be 44, 41, 40 and 39 for the amounts of fumed silica of 11, 14, 17 and 20 parts of fumed silica. It can be seen that these products reacted with free oxygen about 15 times faster than damp iron(II) compound. The ratio of 17 : 100 of fumed silica to damp iron(II) compound was then selected for subsequent study.

Selection of Oxygen Permeable Bags The oxygen permeable bags used to hold FOA had high oxygen permeability, flexibility, heat sealability, printability and good appearance. The bags were 40 mm × 50 mm, made from laminated kraft/EVA, kraft/LDPE and LDPE and were filled with FOA and suspended in the air. The percentage of FOA remaining after 8 h of exposure in the three types was found to be 77, 70 and 69, respectively. The amount of iron(II) hydroxide reacted was about half that without a bag since oxygen had to permeate through the multilayer laminate. The permeability to oxygen of all packaging materials tested was in the same order of magnitude. Laminated kraft/LDPE was therefore selected for further study because it is available at low cost.

Chemical Kinetic Study a) Direct Exposure to Atmospheric Oxygen When FOA was directly exposed to atmospheric oxygen, the amount of iron(II) hydroxide remaining at each time interval was as shown in Fig. 1. The initial amount of 0.24 g decreased almost linearly during the first 4 h until 45% remained, and the reaction proceeded slowly thereafter. After 8 h of exposure to air, 63% of iron(II) hydroxide was reacted. Assuming the particles of iron(II) hydroxide were spherical, thus the surface thickness of 2.8 μm had been converted to iron(III) oxide.

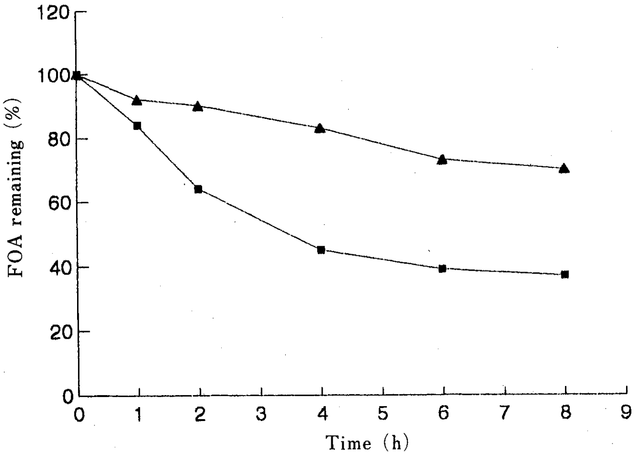

Fig. 1. Plot of the Amount of Iron(II) Hydroxide Remaining Following Direct Exposure to Air

■, FOA; ▲, FOA in kraft/LDPE bag.

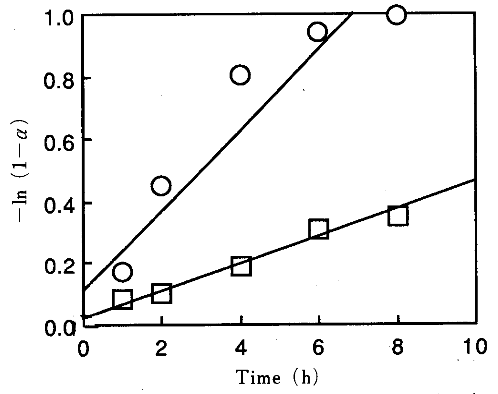

Fig. 2. Plot of $-\ln(1-\alpha)$ *vs.* t for FOA □, and FOA in a Bag ○.

The reaction between iron(II) hydroxide and oxygen is a complex phenomenon, involving reaction between iron(II) hydroxide and oxygen at the interface and diffusion of oxygen through the product layer. The reaction may be chemically developed or diffusion controlled or both. Hancock and Sharp[3] observed a generalized equation for the kinetics of solid state chemical reaction which facilitates comparison of experimental data with a theoretical model. In its simplest form, this equation can be written as

$$\alpha = 1 - \exp(-Bt^m) \qquad (1)$$

or

$$-\ln \ln(1-\alpha) = \ln B + m \ln t \qquad (2)$$

where α is the fraction reacted in time t, B is a constant related to frequency and linear rate of reacted surface and m is a constant varying according to the geometrics of the system. A plot of $\ln \ln(1-\alpha)$ against $\ln t$ would be linear if the range of α is limited to 0.15 to 0.50.

Equation 2 for $0.15 \leq \alpha \leq 0.05$ was applied to the data in Fig. 1. A regression line with a slope (m) of 1.12 ($r = 0.9883$)

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was obtained indicating a chemically controlled reaction. Plotting of f(α) *vs.* t over the whole range of α, one could differentiate between the chemically controlled models. Figure 2 is the best fit obtained for first order kinetics which is described by the equation

$$-\ln(1-\alpha)=kt \quad (3)$$

The first order reaction rate constant of $0.129\,h^{-1}$ was obtained from the slope of the linear regression line.

b) Oxidation in an Oxygen Permeable Bag Reduction of the amount of FOA in an oxygen permeable bag (kraft/LDPE) suspended in air at room temperature is shown in Fig. 1. The data were tested for conformance with Eq. 2 and a slope (m) of 0.92 ($r=0.9947$) was obtained. This relation also fit the chemical controlled reaction. Figure 2 shows good agreement of the data over the entire range of α to the first order reaction. The first order reaction rate constant of $0.0414\,h^{-1}$ ($r=0.9894$) was obtained from the linear regression line.

The reactions of both FOA and FOA in a bag follow first order chemical kinetics, but the reaction rate of FOA in an oxygen permeable bag was about 3 times slower than without the bag. Therefore, the permeability of free oxygen through the laminated plastic films also plays a significant role.

Oxygen Removing Efficacy of FOA FOA in a bag was suspended at room temperature in a 500 ml tightly closed amber glass bottle. The approximate oxygen content in the bottle was 100 ml or 4.46×10^{-3} mol which required about 2 g of FOA for complete reaction. Therefore, the amount of FOA used for testing was 4.4, 3.8 and 2.0 g. The concentration of free oxygen in the bottle was monitored over time, and Table III shows the amount of residual oxygen in the bottle with FOA. After 8 h, the content of free oxygen was reduced by half for 4.4 and 3.8 g of FOA. The reaction proceeded slowly thereafter, but the quantitative amount could not be accurately monitored. At this rate, FOA was only partially effective. Improvement in the reaction rate as well as identification of more suitable packaging materials is necessary for some readily oxidized compounds.

TABLE III. Oxygen Removing Efficacy of Free Oxygen Absorber in a 500 ml Bottle of Air at Room Temperature

Time (h)	Free oxygen (%)		
	4.4 g FOA	3.7 g FOA	2.0 g FOA
0	21.0	21.0	21.0
2	16.1	13.2	—
4	14.3	12.3	18.0
6	10.3	11.8	—
8	10.1	11.4	16.0

References

1) British Standard 3406 Part 5: 1983.
2) J. O. Mayne, *J. Chem. Soc.*, **1953**, 129.
3) J. D. Hancock and J. H. Sharp, *J. Am. Ceram. Soc.*, **55**, 74 (1972).