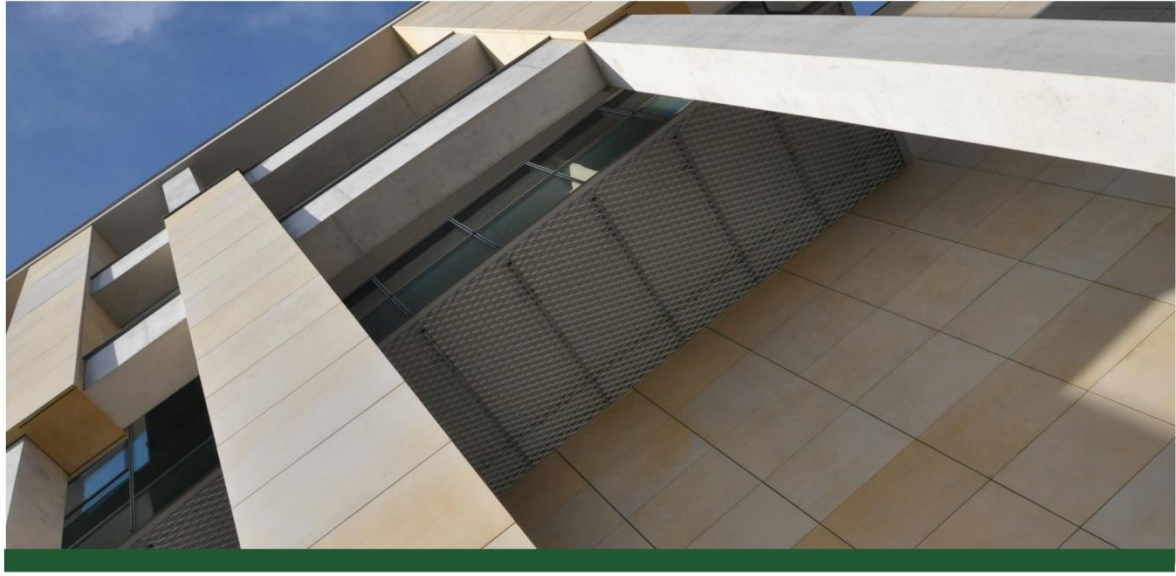

POZNAŃ UNIVERSITY OF ECONOMICS AND BUSINESS

New type of oxygen scavenger for pharmaceutical packaging

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3rd annual Stability of Science Conference October 2017, Dublin – Ireland

New type of oxygen scavenger for pharmaceutical packaging

Agenda

1. Introduction
   - The effect of oxygen on sensitive drug food products
2. The ways to protect products against harmful effects of oxygen
3. Characteristics of oxygen scavengers;
4. Examples of using oxygen scavengers to stabilize drugs in the pharmaceutical industry;
5. Traditional oxygen absorbers;
6. Humidity-neutral oxygen absorbers, Oxygen absorbing canisters
7. Nanoiron based composite oxygen scavenger,
8. Safety of the use of composites oxygen scavengers based on nanoiron,
9. Instead of conclusions

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Effects of oxygen on sensitive drug products

Oxygen is essential for life.

However, oxygen is also well-known source of degradation in many types of pharmaceuticals.

There are two sources of oxygen in a pharmaceutical packages, mainly:

(i) **oxygen present in the head space**, trapped during the filling process or remaining in the empty space in the container ("the head space") when the container is sealed;

(ii) **diffused oxygen**, that is transmitted through the material of the container over time after the container is sealed. The diffused oxygen enters the package slowly from the time the package is sealed until it is opened by the consumer.

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Effects of oxygen on sensitive drug products

Oxygen present in the container during pharmaceuticals shelf storage can cause adverse effects, most critically molecular changes leading to loss of potency.

According to the U.S. Pharmacopeia, the presence of oxygen can degrade pharmaceuticals by:

- causing color changes,
- producing odors,
- generation of by-products such as peroxides and radicals.

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Effects of oxygen on sensitive drug products

Oxidative degradation, after hydrolytic degradation, is one of the most common modes of degradation of a drug products.

In the worst case, the oxidative degradation may even be a source for adverse pharmacological effects.

Dr. Steven W. Baertschi: „Overview of Pharmaceutical Oxidative Degradation Mechanisms”

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The ways to protect products against harmful effects of oxygen

- Protection against oxygen degradation can be addressed by modifying the active pharmaceutical ingredient (API) itself or by adjusting the formulation with, for example, antioxidants or specific coatings.
- In the pharmaceutical packaging industry, oxygen contamination can be reduced using a modified atmosphere such as nitrogen purging.
- Alternatively, vacuumed packed pharmaceutical products may also decrease the amount of oxygen with the head space.
- However, modified atmosphere or vacuumed packaging processes do not prevent later contamination from diffused oxygen.
- In fact, a package with a partial or full vacuum would likely increase the oxygen permeation rate of the package walls.

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The ways to protect products against harmful effects of oxygen

- Pharmaceutical packages have also employed the use of barrier films. In barrier film packaging processes, materials are used in the package walls which physically prevent oxygen from entering the package interior.
- Such processes, however, do not prevent contamination by head space oxygen, or prevent diffusion of oxygen from holes or voids in the package seals.
- This problem has been addressed in the food packaging industry by incorporating oxygen scavengers to reduce the amounts of oxygen within the food package.
- *However, protection against oxidation of pharmaceuticals with oxygen absorbers/scavengers has been relatively unknown.*

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Characteristics of oxygen scavengers

Oxygen scavenger are also called oxygen absorber or deoxidizer.

Based on the material components as well as the chemical and physical mechanisms of oxygen uptake, there are two major types of oxygen scavengers: inorganic and organic which can be classified into the following categories:

Inorganic: metal based oxygen scavenger

Organic: non-metallic

- ascorbic acid based oxygen scavenger
- enzymatic oxygen scavenger
- polymer based oxygen scavenger

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Characteristics of oxygen scavengers

Other classification of oxygen scavengers is based upon:

- **activation mechanism**: auto activated, water activated and UV activated,
- **scavenger form**: sachet, label and extrudable component,
- **reaction rate**: fast, medium and slow effect.

Commercial oxygen scavengers can be in the form of:

- **independent**, separate elements of the systems such as sachets, bags, strips, or labels, which are incorporated into or attached to the inside of the package. *They are the most widely used systems*.
- **systems integrated** into the packaging material itself, not visually perceptible as distinct elements = “stealth absorbers” – *current trend*.

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Characteristics of oxygen scavengers

Selection of oxygen scavenger: shape, size, ability to absorb oxygen, time to reach equilibrium, must be very strict and tailored to the needs and characteristics of each food (liquid, solid, dry, fat, water content, etc.), humidity effects and storage temperature.

Oxygen absorbers can lower the internal oxygen concentration to <0.0001 % when the scavenging chemical material and high barrier packaging are employed.

This lower level of oxygen can be maintained for long periods depending upon the oxygen permeability of the packaging material.

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Characteristics of oxygen scavengers

Limiting the oxygen exposure of oxygen sensitive pharmaceutical products in a packaging system, maintains the quality of the product and avoids degradation or damage due to oxygen contamination.

In addition, such packaging also keeps the product in inventory longer, thereby reducing costs incurred from waste and having to restock.

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Dr. Alisa Waterman: Oxygen sensitivity modelling and packaging implications

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Historically, there have been limited **examples of using oxygen absorbers to stabilize drugs in the pharmaceutical industry:**

- tablets of an anti-inflammatory drug were stabilized in large glass jars with oxygen absorbing sachets for six months at 50° C. (Japanese Patent No. SHO59-176247), 1984
- "L-Cysteine Ophthalmic Solution Stabilized with Oxygen Absorber," *Kyushu Yakugakkai Kaiho,* 44, 37-41 (1990).)
- tonic solutions of vitamin C were stabilized using a bottle cap having an oxygen absorber covered with a polyolefin (Japanese Patent No. SHO94-17056).
- cold remedy powders were stabilized in impermeable bottles by either nitrogen purging or with oxygen absorbers in the bottle (Japanese Patent No. SHO96-253638)
- the use of oxygen absorbers with parenterals (WO 9737628, U.S. Pat. Nos. 6,093,572; 6,007,529; and 5,881,534), 1997

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Examples of drugs stabilized by using oxygen scavengers

- Packaging for amorphous statins, Patent US20090071855
- Packaging for alitretinoin, Patent US20140262858 -
- Packaging for ivabradine hydrochloride, Patent WO2014030113A3
- Rheumatoid arthritis treatment, Patent US9682930; 2017,
- Stability of hormone formulations, Patent US20050020554; 2005
- A method for preventing the decomposition of water-soluble azunole; Japanese Patent No. JP 59-176247
- A package to protect pharmaceuticals, e.g., atorvastatin, PCT Publication No. WO 2006/008651

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New type of oxygen scavenger for pharmaceutical packaging

Recently, **the need for effective oxygen absorption solutions for pharmaceutical packaging** has been intensified by three trends:

1. The demand for increased shelf life allowing for cost optimization in drug manufacturing and distribution.
2. A higher proportion of molecules in the drug pipeline in Classes II and IV. These classes of molecules are often formulated with new galenic forms, which make them more sensitive to oxygen.
3. Potentially greater scrutiny by the U.S. Food and Drug Administration (FDA) regarding maintenance of potency to the end of shelf life.

[source: Protecting pharmaceuticals with 'humidity-neutral' oxygen scavengers; Healthcare packaging, December 5, 2012]

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Traditional oxygen absorbers

•Traditional oxygen-absorbers include metal-based absorbers such as particulate-type iron (e.g., hydrogen reduced iron, electrolytically reduced iron, atomized iron, and milled pulverized iron powders), copper powder, and zinc powder. A preferred metal-based absorber is an iron powder.

• In a typical iron-based oxygen absorber system, every gram of iron can react with about 300 cm^3 of oxygen (at 1 atm.) or effectively remove oxygen from about 1500 cm^3 of air..

• A moisture-holding material may be incorporated with the absorber to provide a self-activated system. *Water provides the activation mechanism used in most applications.*

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Traditional oxygen absorbers

• carry a major drawback since they need moisture to perform properly. The requirement for moisture precludes their use in a dry packaging environment, as moisture is another major pathway to degradation of the drug product.

• Unlike food applications where the products often have a high water content, pharmaceuticals usually do not contain significant water content required to cause the oxygen absorption reaction.

• Second, to maintain their stability, most pharmaceuticals have to be kept in dry conditions. They often utilize a desiccant to remove any headspace moisture and absorb moisture that enters the package from the outer atmosphere.

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Humidity-neutral oxygen absorbers

In order to avoid dependency between moisture and oxygen management, an organic polymer-based, humidity-neutral oxygen scavenger were elaborated.
They offer **several advantages**:

•• The ability to work under conditions ranging from 0 –to 100% relative humidity.

•• High performance at an affordable cost.

•• Simple configurations (canisters and packets) that are compatible with standard filling lines.

•• The ability to work in tandem with desiccants, or even be mixed with desiccants within the same packet or canister.

[source: Protecting pharmaceuticals with 'humidity-neutral' oxygen scavengers; Healthcare packaging, December 5, 2012]

New type of oxygen scavenger for pharmaceutical packaging

Examples of patents on modern oxygen scavengers for pharmaceutical packaging:

- Oxygen scavenger for low moisture environment and methods of using the same; US**2005**0072958
- Oxygen scavenging pharmaceutical package and methods for making same; US**2006**0076536
- Kit comprising a packaging material and oxygen absorber; Patent WO**2013**034273A1
- Package and device for simultaneously maintaining low moisture and low oxygen levels; US**2007**0163917
- Packaging system for oxygen-sensitive drugs; US9248229; 2016; US9545473, 2017
- Oxygen-impervious packaging with optional oxygen scavenger… EP 1835897 A2; WO2006071844A2)

Oxygen absorbing canisters

• For ease of manufacturing (packaging) and to assure there are no incidences of accidental ingestion of absorbers, a cartridge or canister rather than a sachet is preferred with solid dosage forms.

• Some challenges associated with the use of cartridges include:

- the level of oxygen permeability of the cartridge or canister and the pharmaceutical acceptability of the cartridge plastic.

- the plastic materials and additives (plasticizers) should have GRAS (generally regarded as safe) status.

• More preferably, the materials have been previously used in pharmaceutical packaging and have a proven record of pharmaceutical acceptability (e.g., minimal leaching of materials from the cartridge or canister to the dosage form) or acceptance by the appropriate governmental agency for use with pharmaceuticals.

New type of oxygen scavenger for pharmaceutical packaging

Oxygen absorbing canisters

Its oxygen absorption mechanism is based on the chemical reaction of C=C double bonds with oxygen.The reaction is followed by chain scission or the breaking of the molecular bond into side groups.

Disadvantages:

- the reaction of C = C double bonds with oxygen can cause strange odors,
- need for additional use of odor absorbers,
- high opacity,
- Under ambient conditions, one 1g Pharmakeep canister will remove substantially all oxygen contained in the headspace of a 100 cm^3 container = rate ?
- Cryovac and Chevron introduced (ultraviolet photoinitiated) oxygen absorbing plastics; The plastics are reported to be capable of absorbing 45-78 cm^3 of oxygen per gram of plastic.
- Fe = 300 cm^3 !

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Oxygen absorbing canisters

- Canisters – have capacity but works slowly
- Whether a scavenger can adequately protect a drug product from oxidation depends on its ability to quickly lower the oxygen level below the critical concentration threshold in relevant use conditions such as temperature and humidity.
- There is a still a need in the pharmaceutical packaging art to provide a pharmaceutical packaging which effectively reduces or eliminates the amount of oxygen contact with a solid or liquid dosage pharmaceutical product.

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Oxygen absorbing canisters

It is therefore desirable to:

- remove the relatively small amount of head space oxygen quickly, before the high oxygen concentration can damage or degrade the packaged product,
- remove diffused oxygen more slowly but continuously while the package is on the shelf, to prevent a significant buildup of oxygen over time.

A package capable of quickly removing head space oxygen and absorbing diffused oxygen over time would provide significant protection for oxygen-sensitive products.

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New type of oxygen scavenger for pharmaceutical packaging

Nanoiron based composite oxygen scavenger

- The problem: large iron sizes in traditional oxygen scavengers and the need for moisture to activate it.
- In order to eliminate this effect it is necessary to significantly reduce the size of iron. The use of nano-sized iron makes such a possibility.

- Novel potential oxygen scavengers based on iron containing kaolinite or iron nanoparticles have been evaluated for broad application as active packaging systems in a variety of oxygen-sensitive foods, increasing the reaction activity of iron powder and then the oxygen absorption capacity of oxygen scavengers.

[M.-J. Khalaj, H. Ahmadi, R. Lesankhosh, G. Khalaj, *Study of physical and mechanical properties of polypropylene nanocomposites for food packaging application: Nano-clay modified with iron nanoparticles*, Trends in Food Science & Technology 51, 41-48, 2016]

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Nanoiron based composite oxygen scavenger

- Nanoparticles exhibit a range of unique, novel and significant material properties, and catalytic activities in comparison with their analogous larger-sized materials.
- The most obvious difference between nanoparticles and larger colloids or bulk materials is their extremely high surface area.
- For any surface-area-limited heterogeneous chemistry, this alone makes iron nanoparticles particularly interesting, but the reactivity of nanoparticles is not due entirely to surface area.
- A large quantity of energy is stored in nanoparticles as surface-free energy, and this added energy can mean added reactivity.

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Nanoiron based composite oxygen scavenger

Why nanoiron?

- zero valent iron nanoparticles of a diameter 1-100 nm and with a surface area in the range 20-40 m^2/g, provide 10-1,000 times greater reactivity than granular iron, which has a surface area < 1 m^2/g .
- An important property of oxygen scavengers is their reaction rate. A strategy to increase the reaction rate is the reduction of particle diameters. The area of spheres increases by factor 10 when the particle diameter decreases be factor 10.
- For example iron powder with a particle diameter of 10 nm instead of 10 mm will have a 1000 times bigger surface area.
- Due to the fact that the passivating layer of metallic iron is several micrometres thick and forms in dry conditions or at very low relative humidity such iron powder is already active in conditions of dehydrated and dry foods.

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Nanoiron based composite oxygen scavenger

- The activity and effectiveness of nano iron and its price depend on the method of its production.
- The conditions of synthesizing the nanoparticles have significant influence on the properties of synthesized product. Using the same substrates in the nanoiron precipitation, depending on the conditions and the procedure of the process, may lead to products having completely different properties or even composition.
- The conditions of wet chemical synthesis methods effect on the characteristics and reactivity of nano scale zero valent iron (ZVI) obtained.

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- There are known methods of wet synthesizing the iron nanoparticles.
- One of commonly used methods of synthesizing the iron nanoparticles is the chemical reduction of iron's salts in the solution using borohydride.
- Important adjustments in the reaction condition have been made.
- It has been found that in the so far not used reaction conditions, obtained nano-iron has specific properties, what has been patented by us.

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Nanoiron based composite oxygen scavenger

- The obtained nano-iron formulations were introduced into various polymer matrices to obtain composites to be used as oxygen scavengers.
- The preferred polymer matrix for testing is silicone.
- Silicone is well permeable for oxygen and it is well known for the very high barrier to moisture.

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Nanoiron based composite oxygen scavenger

- It has been found that the obtained nano-iron, both powdery and in the polymer matrix, actively absorbs oxygen also under anhydrous conditions.
- nano-iron (both ZVI and ZVIB) has an oxygen absorbing capacity of 250 cm^3 /g which is close to theoretical.
- ZVI, on the other hand, is different from ZVIB's rate of absorption.
- ZVI removes 90% of oxygen within 3 hours and remaining amount during the day, while ZVIBs acts slowly and removes 50% oxygen within 24 hours and has removed the oxygen completely from the packaging in the third day.

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Nanoiron based composite oxygen scavenger

- The introduction (dispersion) of nano-iron into the silicone matrix does not substantially affect the initial rate of oxygen absorption by ZVI. The highest absorption took place in the first day. The composite absorb 60% of oxygen within 1 hour and has removed the oxygen completely from the packaging in the third day.
- Interesting results were also obtained in the case of PVA encased iron. The highest absorption also took place in the first day and 40% of oxygen has been removed in 1 hour follow by complete removal on the fourth day.

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Nanoiron based composite oxygen scavenger

The practical utility of composites oxygen scavengers based on nanoiron has been investigated for a range of oxygen-sensitive food products such as coffee, crisps, peanuts, ham, bread and biscuits, milk powder.

There are intensive research into the use of **Nanoiron based composite oxygen scavengers** for the protection of pharmaceuticals.

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Safety of the use of composites oxygen scavengers based on nanoiron

- The question of safety of the use appears not only in the case of ZVI but also ferrous iron based oxygen scavengers. There is no clear conclusion that (nano) iron is in any case toxic.
- LD_{50} for iron is 16g / kg body weight, which means you would have to eat about 160 absorbers to get deadly poison.
- Oxygen scavenger's , like those with silica gel designed to absorb moisture, are labeled "Do not eat" because of the possible toxicity if the contents of the sachet would be eaten. However, small children and dogs cannot read.
- No cases of iron intoxication following the ingestion of oxygen absorbers have been reported but iron intoxication in a dog consequent to the ingestion of oxygen absorber sachets in pet treat packaging were described.

Safety of the use of composites oxygen scavengers based on nanoiron

- Nano-iron based oxygen scavengers in packaging rather will not be used in sachets but as an integral part of the package.
- However, in this case there is concern about the migration of nano iron from the packaging material to the packed product.
- Examination of the specific migration made by Hamilton Co. on composites oxygen scavengers based on nanoiron did not reveal the migration even traces of the nano-iron contained in the cross-linked silicone matrix to the test fluid imitating the food products, including the fats.

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Safety of the use of composites oxygen scavengers based on nanoiron

- Interestingly, zero valent iron modified bentonite and kaolinite are approved by the European Food Safety Authority (EFSA) as non-nanoform species.
- Consequently, EFSA (2011) Guidance on the application of nanoscience and nanotechnologies in the food and feed chain should be followed for the commercialization of composites oxygen scavengers based on nanoiron.
- FDA's Approach to Regulation of Nanotechnology Products have also to be taken into account.

EFSA CEF Panel (EFSA Panel on Food Contact Materials, E., Flavorings and Processing Aids), *Scientific Opinion on safety assessment of the active substance, iron (0) modified bentonite as oxygen absorber, for use in active food contact materials*. EFSA Journal 11(10): 3400, p. 12, 2013.

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Instead of conclusions

Nanoiron based oxygen scavengers - Foltynowicz Z., Kozak W., Stoińska J., Urbańska M., Muc K., Forysiak A. Kublicka K.,

- Japan Patent nr JP6093713 (2017); *for the commercialization*

- PCT/PL2011/050055 (2011);
- WO2012091587A1; WO2012091587A4 (05.07.2012)

- EPO, 2013; EP2658666A1
- Israel, 2013, nr 227146
- USA, 2013, US2014004232A1; **Urgently for sale !**

New type of oxygen scavenger for pharmaceutical packaging

Nanoiron based composite oxygen scavenger

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