Influence of γ-irradiated biopharmaceutical films

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Influence of γ-irradiation on biopharmaceutical films

Sartorius: Dr S. Dorey, Dr F. Gaston | ECI - May 2017
Aix-Marseille University: Prof. N. Dupuy, Prof. S. Marque
Contents

1. Purpose and Scope
2. Materials & Methods
3. Approach and Results
4. Conclusion and Perspectives
Contents

1 Purpose and Scope

2 Materials & Methods

3 Approach and Results

4 Conclusion and Perspectives
Purpose and scope

- Sterilization of Single use plastic bags made of multilayer films with PE, EVA, EVOH, etc. is achieved by γ irradiation

- Sterilization purpose: to kill micro-organisms

- 25-40|45 kGy: common dose range

- γ rays generated with a $^{60}$Co source

- Norms (ISO 11137, ISO 11737) only deal with microbiological aspect
Purpose and scope

Unexpected phenomena could be observed even with in-purpose selected “γ-irradiatable” materials:

- Material color change
- Peptide oxidation
- pH shift
- Cell culture inhibition

Gamma irradiation necessarily leads to the creation of radicals, small molecules, and unsaturations in alkane chains

- are there any other impacts?
- if yes, what is the extent?
Contents

1. Purpose and Scope
2. Materials & Methods
3. Approach and Results
4. Conclusion and Perspectives
Materials and methods

- Multilayer PE based film (S80)
- 3 lots investigated
- Irradiated with a constant dose rate
- Several γ-doses investigated: 0, 30, 50, 115, 270 kGy
- Monitoring of the effects overtime

![Diagram of multilayer PE based film](image)

- EVOH (polyethylene vinyl alcohol)
- PE (polyethylene)
Materials and methods

**Emphasis of chemical modifications**
- ATR – FTIR
- Raman spectroscopy

**Emphasis of radicals**
- ESR Spectroscopy (electron spin resonance)

**Emphasis of extreme surface modifications**
- XPS (X-Ray Photoelectron Spectroscopy)

**Structural modifications**
- Tensile strength
- Gas permeability : WVTR

**Chemometrics**
- The data set size is huge → chemometric methods used (data in matrix)
  - PCA (Principal Component Analysis), AComDim (ANOVA in Common Dimension), SIMPLISMA (SIMPLE-to-use Interactive Self-modeling Mixture Analysis)
Discoloration

- Yellowing – Photography of S80 films after different irradiation doses

Yellowing of films increases with irradiation doses
Emphasis of radicals

- Problematics: coloration | oxidation of protein | acid release
- Hypothesis: oxidation due to the presence of hydroperoxydes (ROOH) and thus via radicals

- No ESR signal in non sterile films
- ESR signal in films irradiated at 30-50-115-270 kGy

- S80 film irradiated
- PE film irradiated
- EVOH films irradiated
Emphasis of radicals

Radical detection by electron spin resonance (ESR) in S80 film:

- Same signal for all irradiation doses
- Radicals in S80 should be:

  \[
  \begin{align*}
  \cdot C-OH \\
  CH_2
  \end{align*}
  \]

  \[
  \begin{align*}
  \cdot \cdot \cdot \\
  CH_2
  \end{align*}
  \]

  \[
  \begin{align*}
  \cdot \cdot \cdot \\
  CH_2
  \end{align*}
  \]

  \[
  \begin{align*}
  \cdot \cdot \cdot \\
  CH_2
  \end{align*}
  \]

- Stable radical: persistant over ~10-13 weeks
- Migration weakly probable
- This radical cannot be responsible of protein oxidation
- Protein oxidation is certainly due to hydroperoxydes issued from non observable radicals $R^*$

Degradation of γ-irradiated polyethylene-ethylene vinyl alcohol-polyethylene multilayer films: an ESR study
122 (2015) 169-179
Modification on film surface

- The presence of radicals leads necessarily to structural and chemical changes of the film surface
The presence of radicals leads necessarily to structural and chemical changes of the film surface.

- ATR-FTIR spectra of non-sterile PE (i.e. 0 kGy) and γ-irradiated PE

- Global PCA → no evidence of impact of irradiation and ageing

- Unchanged PE peak positions | intensity

- The PE is not impacted globally

- Need to scrutinize zone by zone
Modification on film surface

- Chemometrics (PCA) outputs on the 1760-1680 cm\(^{-1}\) range:
  - Overlapping 0/30/50 kGy = minor impact below 115 kGy
  - Acids and unsaturated products ↝ with the gamma dose
Modification on film surface

- One possible mechanism

\[
\begin{align*}
\text{PE} + \text{PE} & \xrightarrow{\gamma} \text{PE} \cdot \cdot \cdot \text{PE} \\
\text{PE} \cdot \cdot \cdot \text{PE} & \xrightarrow{O_2} \text{PE} \cdot \cdot \cdot \text{PE} \cdot \cdot \cdot \text{PE} \\
\text{PE} \cdot \cdot \cdot \text{PE} \cdot \cdot \cdot \text{PE} & \xrightarrow{''H''} \text{PE} \cdot \cdot \cdot \text{PE} \cdot \cdot \cdot \text{PE} \\
\text{PE} \cdot \cdot \cdot \text{PE} \cdot \cdot \cdot \text{PE} & \xrightarrow{''H''} \text{PE} \cdot \cdot \cdot \text{PE} \cdot \cdot \cdot \text{PE}
\end{align*}
\]

- Short/long

pHmetry
IC
GC-MS
Modification on film surface

**ATR-FTIR analysis and chemometric analysis emphasize:**
- The polyethylene is globally weakly impacted
- Modifications taking place essentially > 115 kGy
- Modifications deal with chemical moieties having a high ε (coefficient of absorption)
- $\gamma$ dose $\Rightarrow$ impact on carboxylic acid generation and unsaturation

**XPS analysis confirms:**
- Oxidation occurs
- No trace of hydroperoxide detected
Modification in film core

- Material core chemical change on sample cross section by Raman spectroscopy – S80

Conditions:
- 5 µm step
- Spot of 1.3 µm
Modification in film core

Material core chemical change on sample cross section by Raman spectroscopy:

→ No modification observable by Raman spectroscopy of the PE and EVOH
Structural modifications

- Radicals could lead to:
  - Cross-linking or/and scission → changes in tensile features and thermal properties

- UTS ↗ - Elongation ↘
- UTS ↘ - Elongation ↗
Structural modifications

Tensile properties of S80 film:

- **UTS (MPa)**
- **Elongation (%)**

**MD = Machine Direction**

**TD = Transversal Direction**

**Constant**

**Drop from 115 kGy**

Identical observations with film/film welding
Modification on film core

Water permeability

Measured via the water vapor transmission rate (WVTR) (cm$^3$/m$^2$/24h):

- WVTR constant in the 0-270 kGy range

- PE thus slightly modified:
  - no scission or cross-linking took place in a way to influence the WVTR
By-products formation

Detection in extractables study

1 Jan C. J. Bart, Polymer Additive Analytics: Industrial Practice and Case Studies, Firenze University Press, 2006, p27
Contents

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Conclusion

What is the impact of the $\gamma$-irradiation on the S80 film?

- The S80 globally not impacted by the $\gamma$-irradiation
Conclusion

- Film handling features unchanged in the range 30-50 kGy
- No change of the WVTR
- PE globally not impacted
- PE and EVOH not globally impacted
- Presence of the hydroxyalkyl radical $R$-$\text{CH}_2$-$\text{C}^\cdot$$(\text{OH})$-$\text{CH}_2$-$R$
- WVTR
- PE slightly impacted
- Presence of carboxylic acids
- Presence of unsaturated products
Conclusion

What is the impact of the γ-irradiation on the S80 film?

- The S80 globally not impacted by the γ-irradiation
- Gamma irradiation is the starting point of the modifications
- Interactions of films with environment should be evaluated
Perspectives

- The principal plastic materials used for the fluid contact are mainly made up of semi-crystalline polymers:
  - Polyolefins (PE, PP & EVA)
  - PVC
  - Silicone (Siloxane, PDMS)
  - PA(X,Y)
  - Polyesters (PET, etc.)
  - Thermoplastic elastomer (TPE)

- Other materials are used to bring special features:
  - EVOH
  - Binding agents

Material behavior to gamma irradiation will be different
Acknowledgments

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