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# Food-inspired innovations to improve the stability of active pharmaceutical ingredients

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## Abstract

Food-processing and pharmaceutical industries share a lot of stability issues against the same physical, chemical, and microbiological phenomena. They also share some solutions to improve the stability as the use of preservatives and packaging. Ecological concerns lead to the development of tremendous innovations in food. Some of these innovations could also be beneficial in the pharmaceutical domain. The objective of this review is to evaluate the potential application of these findings in the pharmaceutical field and the main limits in terms of toxicity, environmental, economic and regulatory issues. The principal factors influencing the shelf-life were highlighted through the description of the stability studies usually performed in the pharmaceutical industry (according to European guidelines). To counter those factors, different solutions are currently available as preservatives and specific packaging. They were described and debated with an overview of recent food innovations in each field. The limits of the current solutions in the pharmaceutical field and the innovation in the food field have inspired a critical pharmaceutical outlook. The active and intelligent packaging for active pharmaceutical ingredients of the future is imagined.

20 Key-words: Stability, pharmacy, food, preservative, packaging

### Highlights:

- Food-processing and pharmaceutical industries share a lot of stability issues.
- Temperature, humidity, oxidation, photolysis and biocontamination impact the stability.
- The current solutions for the conservation of medicinal products are not fully satisfactory.
- 25 • The food industry made a plethora of innovations in preservatives and packaging fields.
- The pharmaceutical packaging of the future may be inspired by food innovations.

### Abbreviations:

AMP: Antimicrobial peptides and proteins	40 GC: Gas chromatography
API: Active pharmaceutical ingredient	HPLC: High performance liquid chromatography
30 BHA: Butylated hydroxyanisole	ICH: International Conference on Harmonization
BHT: utylated hydroxytoluene	k: Degradation constant
CHMP: Committee for Medicinal Products Human Use	LAB: Lactic acid bacteria
CSE: Capillary zone electrophoresis	45 MIC: Minimal inhibitory concentration
DEHP: Di(ethylhexyl phthalate)	MS: Mass spectrometry
35 Ea: Activation energy	NMR: Nuclear magnetic resonance spectroscopy
EDTA: Ethylenediamine tetraacetate	PET: Polyethylene terephthalate
EFSA: European Food Safety Authority	pKa: Ionization constant
EssO: Essential oil	50 RFID: Radio Frequency Identification
Eur. Ph: European Pharmacopoeia	RH: Relative humidity

## 1. Introduction

55 Stability is a crucial point in the development of active pharmaceutical ingredients (API) and medicinal products. API quality will decrease with time under the influence of environmental factors like temperature, humidity, light, atmospheric oxygen, and microbial contamination. The classical degradation scheme will lead to a decrease in the efficacy of the medicinal product. The evaluation of stability is defined by the International Conference on Harmonization (ICH) guideline Q1A (R2) as the period during which no “significant change” occurs (ICH Q1A(R2), 60 2003). They are defined as:

1. “A 5 % change in API assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (*e.g.*, color, phase 65 separation, resuspendibility, caking, hardness, dose delivery per actuation);
4. Failure to meet the acceptance criterion for pH;

Or failure to meet the acceptance criteria for dissolution for 12 dosage units.” (ICH Q1A(R2), 2003)

Moreover, the control of microorganism contamination is also a critical issue for the pharmaceutical industry. Depending on the route of administration, a medicinal product must (parenteral route) or must not (enteral route) be 70 sterilized. The biocontamination and the quantification of endotoxins (previously called pyrogen substances) is a point of caution (European Pharmacopoeia 50102, 2017). So, one of the objectives of medicinal product formulation is to ensure the best possible stability. New strategies are being developed nowadays to achieve this goal: one can cite the incorporation for example in liposomes (Rashwan et al., 2021) or cyclodextrin (Rincon-Lopez et al., 2021) to protect the API, the development of freeze-drying (Dong et al., 2021; Simon et al., 2020) to reduce hydrolysis and thermo- 75 sensitivity, or, more recently, the boom in cocrystal (Guo et al., 2021). These innovations manifest the need for new strategies to improve stability in the pharmaceutical field.

Food and pharmaceutical industries share a lot of concerns. They are related to the impact of both industries on human/animal health and quality of life. Similarities are directly found related to the products they develop. One can cite: the origin of the products that may be extracted from both vegetables or animals (European Pharmacopoeia 80 50208, 2011) or *via* the use of similar synthesized compounds (such as preservatives, antioxidants, flavoring agents, *etc...*). The shelf-life of food products is also limited and may lead to potentially dramatic consequences associated with a loss of quality. As an example, oxidation can affect both lipids and proteins in foodstuff and medicinal products. The first case will impact the quality of food *via* organoleptic (flavor, color, texture) and/or nutritional deteriorations (Duncan and Chang, 2012; Kalogianni et al., 2020). For medicinal products, a decrease in the 85 concentration of the API accompanied by the formation of impurities will occur.

In the case of food safety, the shelf-life is mainly defined by the potential growth of microorganisms in prepacked food and the factors influencing their growth during storage until consumption (temperature, pH, environment, ...). Some products do not require a ‘best before date’ according to annex X in Regulation (EU) No 1169/2011(Regulation (EU) No 1169/2011). For the others, the EFSA (European Food Safety Authority) Panel on Biological Hazards

90 (BIOHAZ) developed a decision tree to help in the definition of a case-by-case shelf-life (EFSA Panel on Biological Hazards (BIOHAZ) et al., 2020).

For the improvement of the preservation and stability whether in the pharmaceutical or food industry, two approaches are to be considered using preservatives and/or specific packaging. Nowadays, ecological concerns lead consumers to prefer environmental friendly and safer solutions to eat fresh and less processed food. This demand has encouraged tremendous innovation in the food field. They are partly focusing on the discovery of new antioxidant and/or antimicrobial substances, mainly of natural origin (Bellucci et al., 2021), or the development of new packaging to increase the stability of food (Song et al., 2022; C. Sun et al., 2022) or to monitor its freshness (Y. Sun et al., 2022). Because food and pharmaceutical industries share similar issues in term of stability, the innovations developed in the food field may be transposed or at least inspire the emergence of innovative solutions to improve the stability of API and medicinal products.

The objective of this review is to evaluate the potential application of these findings in the pharmaceutical field. First, the stability studies usually performed in the pharmaceutical industry (according to European guidelines) will be described to highlight the main factors influencing the shelf-life of medicinal products. Vitamins will be taken as examples because of their use in both industries. In the next part, the current solutions to improve stability (preservatives and packaging) will be described and debated with the specific example of medicinal products marketed in France. An overview of recent innovations in each field will be presented. Finally, a critical pharmaceutical outlook will be given to imagine the drug packaging of the future.

## 2. Stability studies in the pharmaceutical industry

110 The stability and its demonstration are key points in the pharmaceutical field and the writing of marketing authorization applications. The ICH guideline Q1A(R2) (ICH Q1A(R2), 2003) recommends exploring the effects of temperature, relative humidity (RH), oxidation, pH, hydrolysis, and photolysis on the stability of new API and medicinal products (ICH Q1A(R2), 2003) or biotechnological/biological products (ICH guideline Q5C (ICH Q5C, 1995)). The recommendations help to assess significant changes in several storage conditions (physical, chemical, biological, and microbiological tests). The specifications of the “significant changes” have to be defined following ICH guidelines Q6A for chemical products (ICH Q6A, 1999) or Q6B for biotechnological or biological products (ICH Q6B, 1999). According to (4), stability studies may be divided into two parts: stability studies and forced degradation studies.

### 2.1. Stability studies

120 Stability studies include long-term, intermediate-term, and accelerated studies (ICH Q1A(R2), 2003) and lead to establishing the shelf-life of a medicinal product. Long and intermediate-term studies occur under normal storage conditions defined on the container label. The storage conditions vary according to the intended temperature of storage ( $25 \pm 2$  °C,  $5 \pm 3$  °C or  $-20 \pm 5$  °C), and the climatic zone. Four climatic zones were defined: I (temperate climate), II (subtropical and Mediterranean climates), III (hot, dry climate) and IV (hot, humid climate) (Grimm, 1998, 1986). The stability study also comprises accelerated testing, that occurs under exaggerated storage conditions. The obtained results help to evaluate the short-term storage outside the recommended storage conditions. In the literature, plethora

of stability studies of medicinal products and API are available. Most of them comes from hospital pharmacists and meets the need of stability studies in a real environment (D'Huart et al., 2018).

130 Except for parenteral, ocular and (more rarely) topical administration routes, medicinal products are not sterile. Thus, microorganisms may be present with a potential proliferation risk. They must be maintained below a defined threshold depending on the concerned strain. The contamination can occur during manufacturing (under Good Manufacturing Processing, GMP), despite the precautions (use of disinfectants, sanitizers, and sporicidal (EU Guidelines; Shintani, 2015)), or after the opening and the reclosing of multidose presentations. As mentioned in the guideline ICH Q1A (R2), stability studies include microbiological evaluation (ICH Q1A(R2), 2003). Section 2.6.12. of the European Pharmacopoeia (Eur. Ph.) suggests microbial enumeration to evaluate the microbiological contamination of non-sterile 135 products (Table 1) (European Pharmacopoeia 20612, 2021; European Pharmacopoeia 20613, 2021). These recommendations are required to establish the marketing authorization application but give no information about the degradation pathway, which is the case for forced degradation studies.

## 2.2. *Forced degradation studies*

140 Forced degradation study, also called stress testing, occurs under more severe conditions of temperature, light exposure, pH, or oxidation than the previously described one for stability accelerated studies. The corresponding collected data are very important and necessary to identify the degradation products and to establish the degradation pathways for the elucidation of the API intrinsic stability. This information will define the conditions of packaging and storage and enable the development of specific analytical methods to identify and quantify API and degradation 145 products: stability-indicating methods (Sautou, 2013).

The developpement of stability-indicating methods is of great importance in stability studies. The analytical methods should be separative (spectometric methods are not recommended). Chromatographic methods (High performance liquid chromatography (HPLC) and gas chromatography (GC)) are the most popular and widely used. But today, hyphenated analytical techniques are increasingly being developped to facilitate the isolation, detection and 150 identification of drug products. Most of the time, chromatographic methods are coupled to mass spectrometry (MS) (Jahani et al., 2022). Other techniques are gradually being introduced in stability studies as liquid chromatography coupled with nuclear magnetic resonance spectroscopy (NMR), capillary zone electrophoresis (CZE) (Jahani et al., 2022) or the use of solid phase microextraction techniques (SPME) to identify specific volatile organic degradation products (Jamrógiewicz and Pieńkowska, 2019).

155 Forced degradation studies are recommended by the ICH guideline (ICH Q1A(R2), 2003), but while there is a brief description for temperature, relative humidity, and photolysis, none is available for hydrolysis, pH, or oxidation. Several research teams have worked to fill this gap and have proposed reviews that describe strategies for conducting forced degradation studies for chemical (Alsante et al., 2007; Bardin et al., 2011; Blessy et al., 2014; de Alvarenga Junior and Carneiro, 2019) or biotechnological API (Bardin et al., 2011; Nowak et al., 2017; Tamizi and Jouyban, 160 2016). Table 1 gathers the descriptions of the conditions of forced degradation studies according to the guidelines of reference documents (ICH, *Eur. Ph.*) to other reviews. The conditions described to carry out these studies may be different from those for the intrinsic stability of the API (specific functional groups in their chemical structure linked to their sensitivity to several physicochemical parameters). The objective is to reach a maximum of 10 to 20 % of degradation of the API to avoid any overdegradation.

165 Stability studies are essential but time-consuming. Some modern approaches aim to introduce a Quality-by-Design  
approach (QbD) to optimize the development of stability indicating method (Jahani et al., 2022). These approaches  
include reduced stability testing: “bracketing” and “matrixing” for the stability study of medicinal products (because  
of its limited application for API) (Sengupta et al., 2018; Dong and Huynh-Ba, 2020). Bracketing is the design of a  
170 stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or  
fill) are tested at all time points as in a full design (ICH Q1D,2002). Matrixing is the design of a stability schedule  
such that a selected subset of the total number of possible samples for all factor combinations would be tested at a  
specified time point. At a later time point, another subset of samples for all factor combinations would be tested (ICH  
Q1D,2002). However, before considering a reduced design, certain assumptions must be evaluated and justified (ICH  
Q1D,2002; Sengupta et al., 2018; Dong and Huynh-Ba, 2020).

Parameters	Forced degradation studies – Description by reference documents	Forced degradation studies – Description by review	Review of parameter stability of API
Temperature	10 °C increments (e.g., 50 °C, 60 °C, etc.) above accelerated testing - <i>ICH Q1A(R2)</i> (ICH Q1A(R2), 2003), <i>ICH Q1F</i> (WHO, 2018)	> 50 °C – 75 % RH (Alsante et al., 2007) 60 – 80 °C ± 75 % RH (Blessy et al., 2014) (Waterman and Adami, 2005a)	(Glass et al., 2004; Jelic, 2021)
Relative humidity (RH)	75% RH or greater - <i>ICH Q1A(R2)</i> (ICH Q1A(R2), 2003) <i>ICH Q1F</i> (WHO, 2018)	60 °C - 75 % RH or greater 1 to 10 days (WHO, 2008) 50 °C and increase by 10 °C steps (Bardin et al., 2011)	
Hydrolysis, pH	“The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.” <i>ICH Q1A(R2)</i> (ICH Q1A(R2), 2003)	HCl or H <sub>2</sub> SO <sub>4</sub> (0.1 – 1.0 M); pH = 2, 4 or 6 NaOH, LiOH or KOH (0.1 – 1.0 M); pH = 8 (Alsante et al., 2007; Blessy et al., 2014; WHO, 2008) HCl; pH = 3 and NaOH; pH = 9 (Bardin et al., 2011) HCl or NaOH (0.01 – 1 M) 2 h to 7 days (Sengupta et al., 2018)	(Waterman et al., 2002a; Waterman and Adami, 2005b)
Photolysis	Option 1: artificial daylight fluorescent lamp combining visible and ultraviolet outputs, xenon, or metal halide lamp (similar to D65/ID65 SO 10977 (1993)). Option 2: cool white fluorescent (ISO 10977 (1993)) and near ultraviolet lamp with a spectral distribution from 320 nm to 400 nm. ≥1.2 million lux hours and ≥ 200 W.h.m <sup>-2</sup> . <i>ICH Q1B</i> (ICH Q1B, 1996)	≥ 1.2 million lux hours (max 6 million lux hours), ≥ 200 W.h.m <sup>-2</sup> (Alsante et al., 2007) Metal halide, mercury, xenon, or ultraviolet-B fluorescent lamp 1 to 10 days (WHO, 2008) 1.2 to 6 × 10 <sup>5</sup> Lux.h (Sengupta et al., 2018)	(Ahmad et al., 2016; Albin and Fasani, 1998; Glass et al., 2004)
Oxidation	Not described	Under oxygen atmosphere, the presence of H <sub>2</sub> O <sub>2</sub> (up to 3 % (V/V)) or free radical and/or H <sub>2</sub> O <sub>2</sub> (5–20 mol) 3 % (V/V) H <sub>2</sub> O <sub>2</sub> 25 °C, 60 °C ; Peroxide control 25 °C, 60 °C ; Azobisisobutyronitrile 40 °C, 60 °C (Blessy et al., 2014) 3 % (V/V) H <sub>2</sub> O <sub>2</sub> 1 to 3 hours (WHO, 2008) 3 to 30 % (V/V) H <sub>2</sub> O <sub>2</sub> (Bardin et al., 2011)	(Waterman et al., 2002b)

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Microbiological contamination	Test on 10 mg or mL of product or 10 patches/films/container/...	(Kneifel et al., 2002)
	<p>Examination of the product:</p> <ul style="list-style-type: none"><li>- Membrane filtration method</li><li>- Plate-count methods (pour-plate method or surface-spread method)</li><li>- Most-probable-number method</li><li>- Microbiological examination of non-sterile products: microbial enumeration tests described for <i>Staphylococcus aureus</i>, <i>Pseudomonas aeruginosa</i>, <i>Bacillus subtilis</i>, <i>Candida albicans</i>, and <i>Aspergillus brasiliensis</i> Eur. Ph. 2.6.12. (European Pharmacopoeia 20613, 2021)</li><li>- Microbiological examination of non-sterile products: test for specified micro-organisms to control the presence of <i>Escherichia coli</i>, <i>Salmonella</i>, <i>Pseudomonas aeruginosa</i>, <i>Staphylococcus aureus</i>, <i>Clostridia</i>, <i>Candida albicans</i> Eur. Ph. 2.6.13. (European Pharmacopoeia 20612, 2021)</li></ul>	<p>Microbial determination methods in pharmaceutical quality control:</p> <ul style="list-style-type: none"><li>- Standard plate count</li><li>- Most probable number</li><li>- Direct epifluorescent filter techniques</li><li>- ATP detection of viable cells</li><li>- Impedance microbiology direct or indirect</li><li>- ELISA tests</li><li>- Immunomagnetic separation</li><li>- Polymerase chain reaction (PCR)</li><li>- Microarray and biochip technologies</li><li>- Phospholipid fatty acid analysis (Nemati et al., 2016)</li></ul>

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To illustrate the variety of experimental conditions found in the literature, a special focus on vitamins is given (Table 2). Vitamins are widely used in both pharmaceutical and food industries. Indeed, they are naturally present in fruits or vegetables (Munyaka et al., 2010; Sławińska et al., 2016) or added in processed food. For example, vitamin D or E may be added in dairy products (Guo et al., 2018; Pandya et al., 2019). In the pharmaceutical field, vitamins are incorporated in enteral and parenteral nutrition (Stawny et al., 2020; Temova and Roskar, 2016) or prescribed to cure vitamin deficiencies (Gayet-Wernicke encephalopathy (Jain et al., 2020), xerosis, (Kopecký et al., 2018) megaloblastic anemia (Socha et al., 2020) ...). The main indication of vitaminic supplements is as prophylactic treatment in children, elderly, and pregnant women to prevent rickets, osteoporosis-related fractures (Lips and van Schoor, 2011), or neural tube defects in newborns (Cawley et al., 2018) respectively. Several tests may be set up to define the stability of medicinal products and API. They also allow to evaluate their sensitivity to multiple environmental factors such as temperature, humidity, light, atmospheric dioxygen, and biocontamination. These different factors are also well known to limit the shelf-life of food products by impacting, in particular, food quality via organoleptic (flavor, color, texture) and nutritional deteriorations (Duncan and Chang, 2012; Kalogianni et al., 2020). As with medicinal products (Table 1), it is possible to track their influence on vitamins in food (Choe et al., 2005; Lavelli et al., 2021; Ottaway, 2010). Thus, vitamins illustrate the common characteristics between the food and pharmaceutical industries. The fact that the same molecules are found in both industries highlights that the same factors negatively impact the stability of both food and medicinal products (Fig 1.). These factors are described below.

### 2.2.1. Temperature and relative humidity

Temperature and relative humidity (RH) influence the stability of API. The increase of moisture content in a powder system enhances the degradation of sensitive ingredients (Mabey and Mill, 1978). In 2010, Hiatt *et al.* studied the influence of simultaneous variations of temperature and relative humidity on the stability of vitamin C (Table 2). They concluded that relative humidity had a much greater impact than temperature. The degradations observed are mainly described according to reaction schemes of oxidation and hydrolysis, in connection with the presence of dissolved dioxygen and humidity (Hiatt et al., 2010).

Temperature impacts the physical and chemical stability of APIs. Indeed, the increase in the Brownian motion leads to an energetic heat flux, which leads to their thermal decomposition (Jelic, 2021). For example, the stability of ergocalciferol (vitamin D<sub>2</sub>) went from 25 days at 25 °C to 1 day at 40 °C ( $\geq 95\%$  remaining). The stability of cholecalciferol (vitamin D<sub>3</sub>) fell from 15 days at 25 °C to less than 15 h at 40 °C ( $\geq 95\%$  remaining) (Table 2) (Grady and Thakker, 1980). For these reasons, pharmaceutical regulations impose to evaluate the thermal stability of drug substances and their sensitivity to moisture (ICH Q1A(R2), 2003). The experimental conditions of the studies of forced degradation are often poorly described. Arrhenius' equation makes it possible to set up an appropriate temperature and duration for the thermal studies (Alsante et al., 2007).

### 2.2.2. Hydrolysis and pH

In solution or suspension, API are mostly dissolved/dispersed in water. Hydrolysis is a phenomenon in which water induces the rupture of one or more chemical bonds of a compound. It is one of the major degradation pathways of medicinal products. In 1978, Mabey and Mill gathered the rate constants for hydrolysis in the water of 12 classes of organic compounds: alkyl/allyl/benzyl halides, epoxides, esters (aliphatic and aromatic acid esters), amides,

carbamates, phosphoric and phosphonic acid esters, and acylating and alkylating agents (Mabey and Mill, 1978). Carboxylic acid, ester, amide, lactone, lactam, imide, and carbamate are functional groups conferring to API an increased sensitivity to hydrolysis (Waterman et al., 2002a).

Hydrolysis is influenced by pH: acid and alkaline hydrolysis can be distinguished (Temova and Roskar, 2016). pH also impacts the ionization state of molecules. Ahmad *et al.* studied the photolysis of cyanocobalamin (vitamin B<sub>12</sub>, pK<sub>a</sub> = 3.3 at 25 °C (Ahmad et al., 2014)) in an aqueous solution at a range of pH from 1.0 to 12.0. Photochemical conversion of cyanocobalamin to hydroxocobalamin occurred after light exposure. The photochemical conversion to hydroxocobalamin was pH-dependent with a value of the zero-order rate constant from  $1.32 \times 10^{-7} \text{ mol.L}^{-1}.\text{min}^{-1}$  at pH 1.0 to  $0.050 \times 10^{-7} \text{ mol.L}^{-1}.\text{min}^{-1}$  at pH 7.0 (Table 2). These results were explained by the ionization state of cyanocobalamin (the molecule is 99.5% protonated at pH 1.0 and 99.9% neutral at pH 7.0 (Ahmad et al., 1992)).

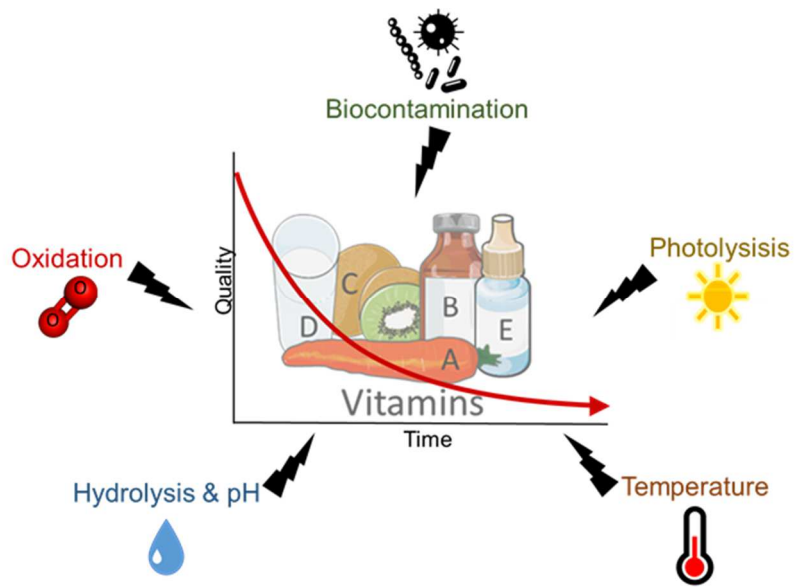
### 2.2.3. Photolysis

Photolysis is the degradation of molecules by their exposure to actinic light. The ICH guideline Q1B details the conditions to determine the photostability of a new API or medicinal product (ICH Q1B, 1996). The recommendation ensures that light exposure will not result in unacceptable change due to photodegradation. It will also give information on the necessity to use specific light-protective packaging. Photosensitivity can be conferred by some chemical groups such as double bond, carbonyl group, aryl chloride, nitroaromatic group, weak C–H bond, sulfides, alkenes, polyenes, and phenols (Ahmad et al., 2016; Albini and Fasani, 1998). For example, the structure of folic acid (vitamin B<sub>9</sub>), which has double bonds and carbonyl groups is very sensitive to photolysis. Indeed, a degradation of 80 % of a  $1.10^{-5} \text{ M}$  acid folic solution has been observed after only one hour of irradiation by UVA (Off et al., 2005).

### 2.2.4. Oxidation

A wide variety of mechanisms may lead to the oxidative degradation of API as autooxidation, electron transfer (transition metals could act as a catalyst), photooxidation, reactions with singlet oxygen, reactions with peroxides, *etc.* Oxidation can be induced by molecular oxygen or after a reaction with oxidizing agents (Waterman and Adami, 2005b). Some functional groups are more sensitive than others to oxidation such as alkenes, aromatic groups, ethers, thioethers, and amines (Hovorka and Schoneich, 2001). Oxidation reactions can lead to the formation of hydroperoxides or *N*-oxides or phenomena such as dehydrogenation or isomerization.

In 2009, Sabliov *et al.* (Sabliov et al., 2009) studied the photostability of  $\alpha$ -tocopherol (vitamin E) in oil form and after its solubilization in hexane. After 3 h, the half-lives were 17.5 h in oil and 9.0 h in hexane (Table 2). The authors explained this difference by the low solubility of dioxygen in oil compared to hexane (Bunsen coefficient = 0.116 and 0.329, respectively). Upon exposure to UVA,  $\alpha$ -tocopherol dissociates to form an anion which, in the presence of dissolved dioxygen, can undergo one-electron oxidation to ultimately form tocopheroxy and superoxide radicals (Sabliov et al., 2009). In 2011, Ribeiro *et al.* evaluated the sensitivity to oxidation of vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, and C in neonatal parenteral nutrition using 3 % and 10 % (V/V) of hydrogen peroxide for 6 h at room temperature. Vitamin B<sub>1</sub> showed higher sensitivity to oxidation than vitamins B<sub>2</sub> and B<sub>6</sub> (Table 2) (Ribeiro et al., 2011).



250

Fig. 1 Parameters reducing the stability of vitamins in foods and medicinal substances

Table 2 Stability studies on vitamins

Molecules	Degradation/Storage condition					Stability results		Ref
	Temperature	Relative humidity	UV light	Hydrolysis	Oxidation	Conditions	Results	
Sodium ascorbate and ascorbic acid (Vitamin C)	25 to 40 °C	54, 75, 85 or 98 %				40 °C – 98 % RH 40 °C – 98 % RH	Ascorbic acid: $k = 0.043 \text{ days}^{-1}$ Sodium ascorbate: $k = 0.302 \text{ days}^{-1}$	(Hiatt et al., 2010)
Ascorbic acid (Vitamin C)	4 and 25 °C - 14 days		Room fluorescent light or protected from light – 25 °C - 75 h		Sodium hypochlorite	4 °C 25 °C	14 days ** Between 10.6 and 13.4 days **	(Walker et al., 2019)
$\alpha$ -Tocopherol (Vitamin E)	40, 60, 120, and 180 °C - 6 h		365 nm - 100 W - 6 h			Heat degradation UV light	$t_{1/2} = 2.1 \text{ h}$ , $k = 0.325 \text{ h}^{-1}$ $t_{1/2} = 17.5 \text{ h}$ , $k = 0.040 \text{ h}^{-1}$	(Sabliov et al., 2009)
Ergocalciferol (Vitamin D <sub>2</sub> ) and Cholecalciferol (Vitamin D <sub>3</sub> )	25 and 40 °C - 56 days	Dry, 45 and 85 % - 56 days			Anaerobic condition - 56 days	25 °C: - Desiccator - 85 % RH - Anaerobic  25 °C: - Desiccator and anaerobic - 85 % RH  40 °C: - 85 % and 45 % RH	Ergocalciferol: - 7 days * - 25 days * - 56 days *  Cholecalciferol: - 56 days * - 15 days *  - Ergocalciferol: 1 day * - Cholecalciferol: < 15 hours *	(Grady and Thakker, 1980)
Cholecalciferol (Vitamin D <sub>3</sub> )	25, 45, 55 and 65 °C - 1 h			HCl – 70 °C - 5 h	Iodine solution - 1 h	Temperature: isomerization to pre-vitamin D <sub>3</sub> isomer  Iodine: cis/trans isomerization of vitamin D <sub>3</sub> (trans-vitamin D <sub>3</sub> ) and pre-vitamin D <sub>3</sub> (tachysterol)  Acidic: Acid-catalyzed isomerization product		(Mahmoodani et al., 2017)
Cholecalciferol (Vitamin D <sub>3</sub> )	25 and 60 °C – 24 h			0.1 M HCl 0.1 M NaOH	0,3 and 15 % (V/V) H <sub>2</sub> O <sub>2</sub>	Acidic condition  All other conditions	1 h *  24 h *  Degradation products: Tachysterol D <sub>3</sub> , D <sub>3</sub> Pre-vitamin D <sub>3</sub> , Trans-vitamin D <sub>3</sub> , Vitamin D <sub>3</sub> , Lumisterol D <sub>3</sub> , Hydroxy vitamin D <sub>3</sub>	(Temova and Roskar, 2016)
Cyanocobalamin (Vitamin B <sub>12</sub> )	25 °C		125 W high-pressure mercury-vapor fluorescent lamp (emission at 405, 436, 545 and 578 nm) – 6 h	pH = 1.0 – 12.0		$k = 1.32 \times 10^{-7} \text{ mol.L}^{-1}.\text{min}^{-7} - \text{pH} = 1.0$ $k = 0.050 \times 10^{-7} \text{ mol.L}^{-1}.\text{min}^{-7} - \text{pH} = 7.0$		(Ahmad et al., 1992)

Nicotinamide riboside (vitamin B <sub>3</sub> )	55, 65, and 75 °C		pH = 2.0, 5.0, 7.4	pH = 2.0 pH = 5.0 pH = 7.4	Ea = 75.4 (± 2.9) kJ/mol Ea = 76.9 (± 1.1) kJ/mol Ea = 82.8 (± 4.4) kJ/mol	(Campbell et al., 2019)			
Thiamine (Vitamin B <sub>1</sub> ) Riboflavin (Vitamin B <sub>2</sub> ) Pyridoxine (Vitamin B <sub>6</sub> ) Ascorbic acid (Vitamin C)	4 and 25 °C - 72 h	With or without photoprotection	Sulfuric acid 10 %	3 and 10 % (V/V) H <sub>2</sub> O <sub>2</sub> - 6 h	Residual quantity (%)		(Ribeiro et al., 2011)		
					Vitamin	B <sub>1</sub>	B <sub>2</sub>	B <sub>6</sub>	C
					3 % H <sub>2</sub> O <sub>2</sub>	74.7	80.6	98.4	
					10 % H <sub>2</sub> O <sub>2</sub>	59.8	60.9	92.4	
					4 °C	96.4 ± 3.1	99.4 ± 1.1	97.5 ± 1.0	94.4 ± 2.9
					25°C with photoprotection	92.4 ± 3.1	94.7 ± 9.2	93.1 ± 6.0	85.9 ± 1.1
					25°C without photoprotection	95 ± 7.6	99.0 ± 1.6	94 ± 5.0	87.8 ± 1.3
Thiamine (Vitamin B <sub>1</sub> )	4 and 25 °C - 5 days	With or without photoprotection			In prolonged parenteral nutrition admixtures for all conditions	5 days **			(Stawny et al., 2020)
Phytonadione (Vitamin K)	4.9 to 5.4 °C - 90 days	With or without photoprotection			Dissolved in SyrPalta Dissolved in cherry syrup	7 days ** 24 h **			(Lawson et al., 2019)

\*95 % remaining; \*\* 90 % remaining; Ea: Activation energy; k: degradation constant

### 2.3. Recent innovative research to improve the stability aspects in the pharmaceutical area

255 New strategies have already been developed in the pharmaceutical field to improve the stability. The first step is to manage storage conditions (Iudicello et al., 2021), but this solution often proves to be very limited. The formulation of the medicinal product has also an impact on its stability as the use of solid dispersion. Freeze-drying is being increasingly developed to reduce the thermo-sensitivity of biological medicinal products especially for vaccines (Dong et al., 2021) and antibodies (Simon et al., 2020). Another widely studied approach is the nano/microencapsulation especially for biological medicinal products as active peptides using nano- and microparticles, liposomes (Rashwan et al., 2021) or cyclodextrin (Rincon-Lopez et al., 2021) to protect the API. More recently, pharmaceutical cocrystals are multicomponent systems in which at least one component is an API and the others are pharmaceutically acceptable ingredients. Cocrystallization of an API with a cofomer is a promising and emerging approach to improve its stability by modifying its physico-chemical properties (Guo et al., 2021; Liu et al., 2022). Nevertheless, all solutions have limits. Chennell *et al.* tried to improve the stability of amphotericin B by solubilizing ophthalmic solutions in 2-Hydroxypropyl-Cyclodextrins but concluded that this formulation did not provide long-term stability (Chennell et al., 2020). Thus, these innovations demonstrate a strong need for the development of new strategies to improve stability in the pharmaceutical field.

270 As mentioned above, the pharmaceutical and food industries share a lot of stability issues against the same physical, chemical and microbiological phenomena. So, to counter the deleterious effects of environmental factors on stability, some solutions are already common to food and medicinal products, such as the use of preservatives. The current enthusiasm in the development of innovative solutions for food is leading to the discovery of new antioxidant and/or antimicrobial substances, mainly of natural origin (Bellucci et al., 2021). The innovation developed in the food field could be inspiring for the pharmaceutical field.

## 3. Preservatives: current knowledge and innovation

### 3.1. Preservatives in food and pharmaceutical industries

280 The low amount of consumed medicines compared to food explains that most of the daily intake of preservatives comes from food. The use of additives in food and medicinal products is regulated. Table 3 lists the preservatives used in both fields, and Table 4 lists the preservatives used in pharmacy with side effects. It should be noted that more preservatives are permitted in medicines than in food. The approved additives in food and the related maximum concentrations allowed are listed in Regulation (EC) No 1333/2008 (*Regulation (EC) No 1333/2008*). In the pharmaceutical industry, the authorized excipients are described in the Eur. Ph. Otherwise an appropriate specification for the excipient must be justified in the document for application for marketing authorization (Committee for medicinal products for human use (CHMP), 2007a).

290 Preservatives can be divided into two categories: antioxidants and antimicrobials. According to the Committee for Medicinal Products for Human Use (CHMP), antioxidants are “excipients which are used to improve stability of medicines by delaying the oxidation of active substances and other excipients.” and antimicrobials “preservatives normally added to prevent microbial proliferation arising under in use conditions.” (CHMP, 2007a). They can be obtained after extraction from the animal, plant, or microbial resources or after chemical synthesis (Carocho et al., 2014). Some compounds present both activities (*e.g.* citric acid, sodium citrate) (Hirshfield et al., 2003).

Table 3. List of allowed food preservatives and some also used in pharmacy (Bensid et al., 2020; Carocho et al., 2018; Regulation (EC) No 1333/2008; Thériaque)

Property	Chemical family	Molecules	Used in food ?	Used in pharmacy ?
Antioxidants	Tocopherol (E307-309)	Tocopherol-rich extract	Y	N
		Alpha-tocopherol, gamma-tocopherol, delta-tocopherol	Y	Y
	Ascorbate (E300-304)	Ascorbic acid, sodium ascorbate	Y	Y
		Calcium ascorbate	Y	N
		Fatty acids esters of ascorbic acid	Y	N
	Butylate (E319-321)	Tertiary-butylhydroxyquinone (TBHQ)	Y	N
		Butylated hydroxyanisole (BHA)	Y	Y
		Butylated hydroxytoluene (BHT)	Y	Y
	Erythorbate (E315-316)	Erythorbic acid, sodium erythorbate	Y	N
	Malate (E350-352)	Sodium malate, potassium malate, calcium malate	Y	N
	Tartrate (E334-337, 353-354)	Tartaric acid (L(+)-)	Y	Y
		Sodium tartrate, potassium tartrate, sodium and potassium tartrate	Y	Y
		Calcium tartrate	Y	N
		Metatartaric acid	Y	N
	Extracts of rosemary (E392)		Y	N
Ethylenediamine tetraacetate (EDTA) (E385)	Calcium disodium EDTA	Y	Y	
Antimicrobial	Inorganic acids	Nitrite and nitrate salts (E249–E252)	Y	Y
		Sulfur dioxide	Y	Y
		Potassium and sodium metabisulfites and sodium sulfite (E220–E228)	Y	Y
	Weak organic acids	Benzoic acid and sodium, potassium and calcium benzoate (E210–E213);	Y	Y (except for calcium benzoate)
		Sorbic acid, sodium and potassium sorbate (E200–E202);	Y	Y
		Propionic acid and potassium propionate (E280–E283);	Y	Y (except for potassium propionate)
		Acetic acid (E260)	Y	Y
		Lactic acid (E270)	Y	Y
	Parahydroxybenzoate	Ethyl parahydroxybenzoate (E214),	Y	Y

	and the esters	propyl parahydroxybenzoate (E216), Sodium propyl parahydroxybenzoate (E217), Methyl parahydroxybenzoate (E218), sodium methyl parahydroxybenzoate (E219)		
		Lysozymes (E1105)	Y	N
	Polyphenols	Hydroxybenzoic acid derivates (E215, 217)	Y	Y
		Anthocyanidin (E163),	Y	N
		Riboflavin (E101),	Y	Y
		Bacteriocin nisin (E234)	Y	N
Antioxidant and antimicrobial	Gallate (E310-312)	Propyl-gallate, Octyl-gallate, dodecyl-gallate	Y Y	Y N
	Citrate (E330-333, 380)	Citric acid, sodium citrate, potassium citrate, Calcium citrate, triammonium citrate	Y Y	Y N
	Adipate (E355-357)	Adipic acid, potassium adipate Sodium adipate	Y Y	N Y
	Lactate (E325-327)	Sodium lactate, potassium lactate, calcium lactate	Y	Y
	Phosphate (E338-343)	Phosphoric acid, sodium phosphates, potassium phosphates, calcium phosphates, magnesium phosphates	Y	Y

Y = used; N = not used



Table 4. Preservatives with side effects found in medicines with marketing authorization in France according to Theriaque® database extracted on October 2021 (EMA and CHMP, 2019; Theriaque)

<b>Excipient</b>	<b>Use</b>	<b>Number of registered medicines</b>	<b>Side effects</b>	<b>Administration routes</b>
<b>Sulfite derived</b>	Preservative antioxidant		May cause a severe allergic reaction and difficulty breathing.	Oral, parenteral, and respiratory
Sodium bisulfite ( <i>E222</i> )		8		
Sodium metabisulfite ( <i>E223</i> )		82		
Sulfur dioxide ( <i>E220</i> )		42		
Potassium metabisulfite ( <i>E224</i> )		7		
Sodium hydrosulfite		14		
Potassium sulfite ( <i>E228</i> )		1		
Sodium sulfite ( <i>E221</i> )		15		
Caramel ammonium sulfite		6		
<b>Synthetic Phenolic Antioxidant</b>	Preservative antioxidant		May cause local cutaneous reactions (ex: eczema) or eyes or mucous membrane irritation.	Topical
Butylated hydroxytoluene ( <i>E321</i> )		179 (including 40 topical medicines)		
Butylated hydroxyanisole ( <i>E320</i> )		231 (including 23 topical medicines)		
<b>Benzalkonium chloride</b>	Disinfectant and antimicrobial properties	141 (including: - eye route: 110 - cutaneous route: 1 - nasal route: 13 - vaginal route: 1 - respiratory route: 2)	May cause eyes irritation. Avoid contact with contact lenses (remove lenses before application and wait 15 minutes after the application to put them again). May discolor soft contact lenses. May cause a cutaneous reaction. May cause difficulty breathing especially for asthmatics. May cause nasal irritation and swelling inside the nose. May cause local irritation.	Ocular Topical (not ocular) Respiratory Nasal Vaginal
<b>Benzoic acid and benzoates</b> ( <i>E210–E212</i> )	Antibacterial and antifungal preservatives	336 (including: - 15 for neonates (including 2 for	An increase in bilirubinemia may increase neonatal jaundice which may develop into kernicterus	Oral, parenteral Topical
Sodium benzoate				
Potassium benzoate				

		premature) - 26 topical route)	May cause non-immunologic immediate contact reactions by a possible cholinergic mechanism	
<b>Bronopol</b>	Antibiotic preservative	3 (including 1 topical medicine)	May cause local cutaneous reaction (eczema)	Topical
<b>Chlorocresol</b>	Antibiotic preservative	5 (including 5 topical medicines)	May cause an allergic reaction.	Topical and parenteral
<b>Sorbic acid and salts</b> ( <i>E200-203</i> )	Antimicrobial agent	104 (including 12 topical medicines)	May cause local cutaneous reaction (eczema)	Topical
<b>Parahydroxybenzoates and their esters</b>	Antimicrobial agent		May cause an allergic reaction.	Oral, ocular, topical
Sodium propyl-p-hydroxybenzoate ( <i>E 218</i> )		69		
Sodium ethyl-p-hydroxybenzoate ( <i>E 215</i> )		9	May cause an allergic reaction with urticaria and difficulty breathing.	Parenteral and respiratory
Propyl-p-hydroxybenzoate		204		
Sodium methyl-p-hydroxybenzoate		88		
Parahydroxybenzoate ethyle		9		
Methylhydroxybenzoate		3		
Methyl-p-hydroxybenzoate		262		
Parahydroxybenzoate butyl		3		
Propyl, ethyl, methyl hydroxybenzoate		3		
Propylhydroxybenzoate		2		
<b>Organic mercury compounds</b>	Antimicrobial and antifungal properties		May cause an allergic reaction.	Ocular
Phenylmercuric borate		3 (including 3 ocular medicines)	May cause local cutaneous reactions (eczema) and depigmentation.	Topical (not ocular)
Phenylmercuric nitrate		2 (including 1 ocular medicine)		
Phenylmercuric acetate		0		
Thiomersal		8 (including 1 topical medicine, 5 ocular medicines)	(Thiomersal only) May cause an allergic reaction.	(Thiomersal only) Parenteral

### 3.2. Side effects related to the use of preservatives

The use of preservatives should be rational because of their potential impact on human health. A guideline published in 2019 by European Medicines Agency (EMA) described 49 excipients with side effects (EMA and CHMP, 2019). Among them, ten are antioxidants or antimicrobials. Some of these preservatives are also found in food (Table 3).

#### 3.2.1. Antioxidant preservatives with side effects

Most of the antioxidant preservatives are innocuous such as tocopherol, citric acid (Parke and Lewis, 1992), or propyl gallate (EFSA et al., 2020; Nguyen et al., 2021).

Nevertheless, some of them (sulfite-derived and synthetic phenolic antioxidants) present side effects (EMA and CHMP, 2019; Silva and Lidon, 2016). The reactions mainly observed by the sulfite derived class, are skin sensitivities such as dermatitis and respiratory sensitivities including bronchoconstriction. Other symptoms like urticaria, angioedema, abdominal pain, diarrhea, and anaphylaxis have also been described (Vally et al., 2009; Vena et al., 1994).

The class of synthetic phenolic antioxidants includes butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) (Rodil et al., 2012). Both can cause local cutaneous reactions, eye and mucous membrane irritations after local contact (EMA and CHMP, 2019). After their ingestion, they may also exacerbate urticaria (Goodman et al., 1990). They seem to play a role in tumor promotion, inducing DNA damage, cell apoptosis, carcinogenicity, and oxidative stress (Silva and Lidon, 2016; Xu et al., 2021). Nowadays, they are also suspected to be endocrine disruptors (Yang et al., 2018). Recently, the Scientific Committee on Consumer Safety (SCCS) asked for a scientific opinion on BHT in cosmetic products regarding its potential endocrine-disrupting properties. They conclude that BHT is slightly irritating with low acute toxicity. It also increases the activity of phase 1 and phase 2 liver enzymes, and a tumor-promoting effect was confirmed at high doses (Scientific Committee on Consumer Safety, 2021). But neither the *in silico* nor the *in vitro* data have indicated the endocrine disturbing properties. Nonetheless, no maximum concentration was considered as safe for use of BHT in cosmetic products according to the current available toxicological evaluation (Scientific Committee on Consumer Safety, 2021). Unfortunately, BHA was not evaluated in this study. The last statement from EFSA on the safety of BHA is dated from 2012 (EFSA, 2012). Contrary to their opinion given in 2011, no mention of a potential endocrine effect was reported (EFSA, 2011).

#### 3.2.2. Antimicrobial preservatives with side effects

Antimicrobial preservatives used in food and medicinal products include safe molecules such as acetic acid or lactic acid (Parke and Lewis, 1992). Others are incriminated to induce side effects. Parahydroxybenzoate compounds and their esters are effective against bacteria, more specifically gram-positive bacteria, yeast, and mold (Charnock and Finsrud, 2007). They may cause allergic reactions after administration by oral (Veien et al., 1996), ocular, topical, parenteral, or inhalation routes (EMA and CHMP, 2019). They are also suspected to be endocrine disruptors (Darbre and Harvey, 2008). Nevertheless, the EMA concluded on the absence of sufficient clinical evidence of additional parabens-related effects in humans. Methylparaben was not associated with side effects on the male and female reproductive organs during juvenile rats or in embryo-fetal development studies (CHMP, 2015). The opinion of the Scientific Panel on food additives (SCF) published in the EFSA showed an impact on the sperm production in the rats after four weeks of 10 mg /kg body weight/day of propyl-p-hydroxybenzoate (EFSA, 2004). The properties of

endocrinal disturbances of propyl p-hydroxybenzoate and sodium propyl-p-hydroxybenzoate stay disputed, but the European Union has prohibited their use in food since 2004 (Proposal for a Directive of the European Parliament).

Benzoic acid and its salts are also on the list of excipients with side effects. They are bacteriostatic antiseptics, active in an acidic environment. They may induce hypersensitivity response (Nair, 2001) and, depending on their concentration, membrane irritations (Johnson et al., 2017). Benzoic acid is particularly problematic for neonates because of its immature metabolizing enzymes. This immaturity leads to a risk of accumulation of benzoic acid followed by an increase in bilirubinemia (EMA and CHMP, 2017a, 2017b) which may cause newborn kernicterus. Non-conjugated bilirubin accumulates in brain resulting in sequelae such as cerebral palsy, hearing loss, or learning disabilities (Le Pichon et al., 2017).

Sorbic acid and sodium, potassium, or calcium salts inhibit the growth of bacterial and fungal cells (Brul and Coote, 1999; Sofos and Busta, 1981). The role in allergic dermatitis stays unclear (McEnery-Stonelake and Silvestri, 2014). Nevertheless, they appeared in the guideline published by EMA as excipients requiring precautions for use because of possible local skin reactions (EMA and CHMP, 2019).

Some preservatives are only used in medicinal products and not in food. This is the case of benzalkonium chloride, a cationic quaternary ammonium compound with disinfectant and antimicrobial properties. It is an established irritant (Ling and Highet, 2000; Saw and Hindmarsh, 2005) and allergen (Isaac and Scheinman, 2017; Wentworth et al., 2016).

Finally, marginal antimicrobial excipients are also found in marketed medicinal products. Organic mercurial compounds present adverse health effects including neurologic, renal, and developmental outcomes (Risher et al., 2002). Chlorocresol is a bacteriostatic agent efficient against gram-positive and -negative bacteria, yeast, and fungus (Summers et al., 1991). It is incriminated as an allergen and provokes contact dermatitis (Archer and MacDonald, 1984; Burry et al., 1975; Freitas and Brandão, 1986; Hancock and Naysmith, 1975). Bronopol (2-bromo-2-nitropropan-1,3-diol) belongs to the family of formaldehyde release agents. It is effective against both gram-positive and -negative bacteria, especially *Pseudomonas aeruginosa*, fungi, and yeasts (Kranke et al., 1996). It causes contact allergy (Kireche et al., 2011; Maibach, 1977; Schnuch et al., 2011).

Some preservatives are controversial without being on the EMA list. Nitrite and nitrate ions are considered safe at the concentration used in food and medicinal products (*Regulation (EC) No 1333/2008*). Nevertheless, the question of their carcinogenicity is debated. No study consistently highlights an increased risk of stomach cancer after ingestion of nitrate or nitrite ions (Bryan et al., 2012). However, ingested nitrite and nitrate ions may lead to the formation of *N*-nitrosocompounds with mutagenic, teratogenic, and diabetogenic properties, (Habermeyer et al., 2015).

Even though they represent a potential risk for patients, preservatives are still widely used in medicinal and food products. Table 4 lists all the excipients with side effects found in medicinal products with a marketing authorization in France according to the Theriaque<sup>®</sup> database (Thériaque). For each preservative, the administration routes concerned by the precautions of use and the potential side effects inventoried by the EMA are specified. It could be interesting to evaluate the distribution and quantity of additives with side effects in food. But no database enables to freely access the composition of the commercialized food products.

The safety assessment of preservatives is still ongoing. Nowadays, an emphasis is given to the evaluation of long-term toxicity, role as a potential endocrine disruptor, reproductive toxicity, carcinogenicity, mutagenic potential (ECHA et al., 2018), and environmental impact. Some of the available studies are questionable because they are limited to a few reported cases. The results are often obtained at concentrations, not related to the real intake of the population. For example, EDTA salt at a high concentration presents several side effects such as renal toxicity, fever, nausea, vomiting, fatigue, hypotension, arrhythmias, proteinuria, headache, anemia, and hypercalcemia (George and Brady, 2022). However, it is generally recognized as safe for the intended food use (Heimbach et al., 2000). The toxicity of a preservative depends on the concentration and the absorbed amount.

It is important to notice that all the conflicting results about safety contribute to the bad perception of the consumers of the “chemical” preservatives added in food (Bedale et al., 2016) but also, to a lesser extent, in medicinal products. This leads consumers to ask for safer and more “natural” options usually perceived as more innocuous than chemical compounds.

### 3.3. *Innovation in the field of food preservatives and potential application in pharmacy*

#### 3.3.1. **Innovation of food preservatives**

A current trend is the study of bio-based preservatives extracted from microorganisms or plants. As rosemary extract (E392) is authorized as a food preservative, a lot of essential oils (EssO) (Al-Maqtari et al., n.d.; Diniz do Nascimento et al., 2020; Falleh et al., 2020; Negi, 2012; Pandey et al., 2017; Prakash et al., 2015) and plant extracts (Eldien et al., 2020; Negi, 2012; Santos-Sanchez et al., 2017) are studied. The antimicrobial and antioxidant activities are related to the presence of a mix of dozens of chemically active compounds including polyphenols as phenolic acids, flavonoids, lignans, or stilbenes (Bensid et al., 2020; Chibane et al., 2019; Shahidi and Zhong, 2010). EssO and plant extracts are generally considered as “safe” by consumers, environmental friendly, and cost-effective choices for nutrition. However, the composition of EssO and plant extracts varies depending on the plant (genotype), the cultivation conditions (environmental conditions, agricultural practices of cultivation, time of collection), and the extraction method (Jing et al., 2019). The chemical composition is related to biological activity, which makes EssO and plant extracts highly variable compounds and as a result, the activity is questionable. For example, the minimal inhibitory concentration (MIC) of *Eucalyptus globulus* EssO is of the order of mg/mL while that of conventional antimicrobial preservatives is in the order of µg/mL (Vieira et al., 2017). This higher MIC is explained by the presence of impurities and/or related substances without any activity. The required concentration is not compatible with their usage in food because of the negative impact on the organoleptic properties of the product (strong odor or taste) (Androutsopoulou et al., 2021). About related substances and impurities, it should be noted that, the general monograph “Substances for pharmaceutical use” of the *Eur. Ph.* recommends to report, identify and/or qualify the organic impurities in active substances (European Pharmacopoeia 2034, 2021), which is not the case of EssO defined in “Herbal drug preparations” monograph. (European Pharmacopoeia 1434, 2010).

Other explored tracks are the antimicrobial peptides and proteins (AMP). These are small, mostly cationic compounds widespread in the immune system of prokaryotes and eukaryotes (Bahar and Ren, 2013). AMP exhibit antimicrobial activities (Yan et al., 2021) and/or antifungal properties (They et al., 2019). The more widely studied AMP are the bacteriocins produced by lactic acid bacteria (LAB) (Cleveland et al., 2001). Among them, nisin (E234) is a safe and efficient antimicrobial peptide used as a food preservative in more than 50 countries (Gharsallaoui et al., 2016).

Lactoferrin has also been approved by the EFSA as an antifungal preservative (*Commission Regulation No 2073/2005*). Peptides present high sensitivity to proteases and high-temperature treatment (Zhang et al., 2021). The low stability is a limit to the use. The activity is also affected by pH, high salt concentration, or the presence of cations. Even so raw materials are cheap, the lack of an optimized production process results in expensive extraction and purification process. The chemical synthesis of AMP could be an alternative to overcome this issue (Shwaiki et al., 2021; They et al., 2019).

Other marginal solutions are examined to regulate the spoilage of food that already contains bacteria (dairy products) using bacteria and especially LAB as *Lactobacillus ssp.* (Behera et al., 2018; Naghmouchi et al., 2020), virus as bacteriophages or their endolysins (bacteriophage-encoded enzymes) (Chang, 2020).

### 3.3.2. Pharmaceutical outlook

The use of new food preservatives may be inspiring for the pharmaceutical industry. However, the introduction of new preservatives in medicinal products is more complicated than in food: pharmaceutical legislation is stricter. A new preservative requires a full description in the *Eur. Ph.* or an appropriate specification in the file for an application for marketing authorization (CHMP, 2007b). A complete knowledge of the compound is necessary, particularly in terms of toxicology according to the dosage form and the route of administration. It is a powerful brake on the development of new excipients.

Considering a raw material extracted from natural resources, and even so natural preservatives are perceived by consumers as safer than chemical compounds, different problems occur. First, during the extraction process, several organic solvents may be used (Ben Hsouna et al., 2017) as for EssO (European Pharmacopoeia 20812, 2019). Consequently, the screening and quantification of residual traces must be evaluated (European Pharmacopoeia 20801, 2008). Second, EssO are mixtures of molecules (Ben Hsouna et al., 2017; Urbanaviciute et al., 2020; Vallverdu-Queralt et al., 2015) among them, some are bioactive (Ramsey et al., 2020). None of them should induce an adverse pharmacological effect. For better control, it is interesting to isolate the molecules behind the antioxidant or antibacterial activity even though, these activities often result from a synergistic effect.

*Eur. Ph.* requires the quantification and identification of all active substances in medicinal products. Active substances are all the molecules characterized by activity including antimicrobial and/or antioxidant effects. Therefore, the use of EssO as preservatives in the pharmaceutical industry will require the identification and quantification of all the active components. Third, the compound or extract must be compatible with pharmaceutical manufacturing processes. It may include extreme conditions of pressure (compression of powder to make tablets) (Antikainen and Yliruusi, 2003) or temperature (freeze-drying (Ogienko et al., 2017), sterilization (CHMP and CVMP, 2019)). Studies on the impact of matrices or processing steps on the AMP activity are still needed for which low stability is a current obstacle (Zhang et al., 2021).

Considering the targeted population, food is consumed by everyone. In contrast, medicinal products are, in the majority, intended for sick people for whom physiological functions are partially impaired. EDTA is generally recognized as safe for the intended food use (Heimbach et al., 2000). However, EDTA is capable of massively exacerbating inflammation and inducing colorectal carcinogenesis at presumed safe doses in two mouse models of inflammatory bowel disease (Evstatiev et al., 2021). Thus, it might be interesting to consider the safety of excipients for a specific diseased population. The introduction of new preservatives into medicinal products must be assessed on

450 a benefit/risk basis. The current addition of preservatives is justified to increase stability. The addition of antimicrobial preservatives, even so they have side effects, is safer for the patient than the risk of infection from biocontamination. However, if the person is not sick (vaccine, contraception) the risks for its health must be about zero.

455 Food is limited to oral administration. In pharmacy, medicinal products are administered via several routes (oral, buccal, nasal, ocular, topical, rectal, vaginal, parenteral). Side effects of excipient vary depending on it (Table 4). For example, oregano or clove EssO can cause skin dermatitis and citrus EssO is photosensitizing after skin application (Farrar and Farrar, 2020).

460 Reducing the amount of excipient in medicinal products is another way to reduce the induced side effects. Immobilized preservatives are active through contact or low release in the product. That reduces the amount of preservatives ingested by the patient. The benefit of antimicrobial and/or antibacterial activity is retained while the risk of side effects is reduced.

## 4. Packaging

465 In the food and pharmaceutical fields, the main role of the packaging is to ensure and maintain the feature of the product until its use by consumers. It protects the product against light (Kucuk and Caner, 2005; Lennersten and Lingnert, 1998), impacts, gas, and moisture (ICH Q1A(R2), 2003). It also fulfills other functions as identification of the product, information of the consumers (composition, use-by date, storage conditions), or traceability (Data Matrix/barcode, batch number, batch recall).

470 Food packaging can take many different forms as long as it complies with the European regulation on the provision of food information to consumers (*Regulation (EU) No 1169/2011*). In the pharmaceutical field, packaging comprises the immediate and the outer packaging defined by the directive 2001/83/EC of the European Parliament (*Directive 2001/83/EC*).

475 Glass is the most inert and impermeable container material and is mainly utilized for the packaging of liquid products but because of its weight and its brittleness, it is more and more replaced by polymeric materials. Eur. Ph. describes the polymeric materials allowed for the manufacture of pharmaceutical containers: polyethylene, polypropylene, poly(vinyl chloride), polyolefins, poly(ethylene terephthalate), and poly(ethylene-vinyl acetate) (European Pharmacopoeia 30202, 2022; European Pharmacopoeia 90003, 2008). These plastics may be used with or without additives to modify the flexibility, malleability, or durability of the container or affect the stability of the contents by the addition of antioxidants (Table 5). Multilayer packaging also improves the properties of packaging materials. They are made of an inert inner layer in contact with food, an adhesive middle layer, and an outer layer that must offer mechanical stability and printability. They combine the benefits of each monolayer in terms of enhanced barrier properties, mechanical integrity, and functional properties (Anukiruthika et al., 2020).

480 Content/container interactions exist and they are divided into 4 main categories, which are adsorption, absorption, permeation, and extraction. Adsorption is a saturable surface interaction with a fast kinetic. It is influenced by the contact surface, temperature and increased with the amount of non-ionized forms of molecules. This quantity is related to the ionization constant (pKa) of the molecule and the pH of the solution (Adams et al., 2008). Absorption is a not saturable phenomenon that takes place when an API penetrates a container, usually made of plastic polymer (Gonyon

et al., 2013). If the molecule crosses all the container thickness and evaporates, the interaction is called permeation. It leads to the loss of the migrant compound into the environment (Roberts et al., 1980; Treleano et al., 2009). The last category of contain/container interaction is extraction. This event occurs when the container releases a molecule in the contained solution. Di(ethylhexyl phthalate) (DEHP) is a plasticizer used to improve the mechanical properties of PVC bags or tubes. It is not chemically bound to PVC and may migrate after contact with surfactants or oily agents. Multilayer infusions bags may also release plasticizers as phthalates (dibutyl phthalate, diethyl phthalate) or adhesive as caprolactam (Haned et al., 2018). The use of adequate material for human medicine is therefore of major importance. In the food field, the food/packaging interactions are mainly studied in relation to their impact on the sensory experience of the consumers; for more information, please refer to the review of Duncan and Webster (Duncan and Webster, 2009).

Some innovations have already been developed in the field of packaging to limit the use of preservative. For ophthalmological products, multi-dose containers require antimicrobial and antifungal preservatives to avoid contamination after opening. In a similar way, a new eye drops multi-dose bottle using a 0.2  $\mu\text{m}$  filter was developed. (Chauhan and HSU, 2021). Other innovation to upgrade the quality of the medicinal product, may be inspired by food field.



Table 5 Plastic additives described by Eur. Ph. Eur

Name	Use	Name	Use
Di(2-ethylhexyl) phthalate or DEHP	Plasticizer	2,2'-bis(octadecyloxy)-5,5'-spirobi[1,3,2-dioxaphosphinane]	Antioxidant
Epoxidized soy oil	Plasticizer and stabilizer	Diocetyl 3,3'-thiodipropionate	Antioxidant
Epoxidised linseed oil	Stabilizer	Plastic additive 18	Antioxidant
Butylhydroxytoluene	Antioxidant	Oleamide	Slip and anti-block agent
Ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate]	Antioxidant	Erucamide	Antiblock agent
Pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]	Antioxidant	Copolymer of dimethyl succinate and (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol	Antioxidant
Tris(2,4-di-tert-butylphenyl) phosphite	Antioxidant	Tris(2-ethylhexyl) trimellitate	Plasticizer
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6-(1H,3H,5H)-trione	Antioxidant	Bis(2-ethylhexyl) terephthalate	Plasticizer

## 4.1. Innovation in the field of food packaging

### 4.1.1. Innovation in material

Due to ecological concerns, petroleum-based non-biodegradable packaging materials are more and more abandoned in favor to more suitable packaging made of biodegradable and/or bio-based plastics (Hong et al., 2021; Jariyasakoolroj et al., 2020). The latter is made from renewable raw materials that can be reconstituted by natural processes. They include biopolymers as microbially-originated polymers, polysaccharides, or proteins-based polymers (Asgher et al., 2020; Wang et al., 2018). Biodegradable plastics are defined as polymers that can be degraded by microorganisms of the environment into water, carbon dioxide, and biomass. They may be composed of polylactic acid, cellulose nanofibers, gelatin, ... (Chisenga et al., 2020; Nur Hanani et al., 2014). This type of packaging includes thin films and coatings that can be directly applied or wrapped on food (Janjarasskul and Krochta, 2010; Mohamed et al., 2020; Trajkovska Petkoska et al., 2021).

### 4.1.2. Active packaging

Active packaging is defined in the European regulation No 450/2009 as the packaging with “deliberately incorporated components that would release or absorb substances into or from the packaged food or the environment surrounding the food” (*Commission Regulation (EC) No 450/2009*). They are more and more studied in food to improve product shelf-life. This subject generates a huge enthusiasm. In October 2021 the terms “active packaging” and “food” led to 4,402 results in Web of Science®, including 470 reviews more than three-quarters of which were written the last 5 years.

Active packaging may be categorized into 2 classes: active scavenging systems and active releasing systems (Yildirim et al., 2018). Table 6 brings an overview of the several active packaging strategies studied in food and the associated reviews.

The active scavenging systems bring together the systems removing undesirable compounds such as oxygen, carbon dioxide, ethylene (catalyst gas in fruit maturation), or moisture. Reduction of the dioxygen percentage in the atmosphere leads to increased shelf life of the products by limiting the oxidation (Sanjeev and Ramesh, 2006) and reducing the microbiological development (Caleb et al., 2013). Moisture reduction minimized the hydrolysis phenomena, and the microbiological development (Gaikwad et al., 2019). Some oil and fresh food are already stored in modified atmosphere packaging with various combinations of CO<sub>2</sub>, O<sub>2</sub>, N<sub>2</sub>, and air or vacuum packaging (Ghidelli and Pérez-Gago, 2018; Singh et al., 2012; Wilson et al., 2019). The modified atmospheres also include dry modified atmospheres in which humid air has been pulled out.

Active scavenging systems modulate the concentration of gas as oxygen (Dey and Neogi, 2019; Gaikwad et al., 2018) or ethylene (Awalgaonkar et al., 2020; Gaikwad et al., 2020; Sadeghi et al., 2021) and moisture (Gaikwad et al., 2019) in food packaging (Table 6). Absorbing agents often take the form of sachets, films, or pads and scavenge the residual dioxygen or ethylene, or absorb moisture. Active packaging may also act by improving the barrier properties of the packaging material. This active barrier prevents the permeation of dioxygen from the environment inside the packaging or the increase of moisture. Finally, ethylene can also be degraded by oxidation with potassium or sodium permanganate from the packaging (Awalgaonkar et al., 2020; Gaikwad et al., 2020; Sadeghi et al., 2021).

540 The other active packaging is obtained by the incorporation of active substances such as antioxidants or antimicrobials  
at the surface or inside the packaging. The antioxidant and antibacterial active packaging may be categorized  
according to three mechanisms of action. First, the antioxidant or antibacterial activity may be *in situ* and corresponds  
to a surface or contact phenomenon. Then, the antioxidant or antibacterial compounds may be released. This release  
may also be controlled to match the food deterioration kinetic (Kuorwel et al., 2015). Several techniques allowed the  
545 development of active material as the coating of an active compound at the surface of a polymer or its direct  
incorporation into the polymer matrix. These active compounds include synthetic and natural antioxidants  
(Dominguez et al., 2018; Kuai et al., 2021; Vasile and Baican, 2021), EssO (Ribeiro-Santos et al., 2017; Sharma et al.,  
2021), and bacterial antimicrobial peptides (Santos et al., 2018), nanoparticles, nanofibers and nanocomposites  
(Ahmad et al., 2021; Alfei et al., 2020; de Azeredo, 2013; Sothornvit, 2019; Zhang et al., 2020) (Table 6).

550 Active packaging may also be obtained by using bioactive polymers as packaging material, such as chitosan that  
exhibits intrinsic antimicrobial activity (Vasile and Baican, 2021). Some of those active packaging are already  
available on the market, as extensively detailed by Drago *et al.*, which gathered and described all of them in 2020  
(Drago et al., 2020)

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**Active packaging  
strategies  
studied in food**

**Examples of active agents**

**Related reviews**

**Active scavenging systems (absorber)**

Dioxygen scavenger	<p>Metallic or iron: iron powder or salt, ferrous oxide, platinum group metals</p> <p>Organic and unsaturated hydrocarbon: Ascorbic acid and its salts, tocopherol, hydroquinone</p> <p>Inorganic: Sulfite, thiosulfate, titanium dioxide</p> <p>Polymer: Oxidation-reduction resin, polymer metallic complex</p> <p>Enzyme: Glucose oxidase, laccase, ethanol oxidase</p> <p>Micro-organisms: yeast-wax, aerobic microorganism</p> <p>Nanoactive film: montmorillonite nanoparticles, nanoparticles of metallic iron or metal</p>	(Dey and Neogi, 2019; Gaikwad et al., 2018)
Moisture scavenger	<p>Organic: fructose, sorbitol, cellulose, and their derivatives</p> <p>Inorganic: calcium and potassium chloride, silica gel, bentonite</p> <p>Polymeric r: starch copolymers, polyvinyl alcohol, absorbent resin</p>	(Gaikwad et al., 2019)
Ethylene absorber	<p>Silicate-based ethylene absorber: Zeolite, Japanese Oya stone, cristobalite</p> <p>Regenerable sorbents: Propylene glycol, hexylene glycol, phenylmethylsilicone</p> <p>Catalytic oxidizers: Potassium permanganate, potassium dichromate, palladium</p> <p>Electron-deficient dienes or trienes: Benzene, pyridines, diazines triazines</p> <p>Nanomaterials: silver, titanium oxide, palladium nanoparticles</p> <p>Commercial blocking system: 1-methylcyclopropene, silver thiosulfate, aminoethoxyvinylglycine</p>	(Awalgaonkar et al., 2020; Gaikwad et al., 2020; Sadeghi et al., 2021)

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**Active releasing systems (emitter) - *Antimicrobial and antioxidant packaging systems***

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Antioxidant releaser	Synthetic antioxidants: BHA, BHT, TBHQ (tert-butylhydroquinone) Organic acids: sorbic, ascorbic, citric acid Natural antioxidants: phenolic compounds, ascorbic acid, $\alpha$ -Tocopherol, thymol Plant extracts: rosemary, green tea, citrus Enzymes: lysozyme, lactoferrin Others: EDTA	(Dominguez et al., 2018; Kuai et al., 2021; Vasile and Baican, 2021)
Essential Oils Or their main component	Chemical compounds: Terpenes (phenols, flavonoids, flavanols), hydrocarbons (aliphatic, alkanes, and aromatic hydrocarbons) EssO: Oregano, rosemary, clove, coriander, cinnamon, thyme	(Ribeiro-Santos et al., 2017; Sharma et al., 2021)
Bacterial antimicrobial peptides	Natural: Bacteriocins (nisin, pediocin, lactocin, enterocins) Synthetized	(Santos et al., 2018)
Nanostructuration	Nanoparticles: metal (Ag, Au, Cu), metal oxide (TiO <sub>2</sub> , ZnO, MgO) Electrospun nanofibers with antimicrobial and/or antioxidant agents Bionanocomposite films: Nanoclays (montmorillonite nanomaterial), nanocrystals (starch, cellulose, chitin) Nanoencapsulation of antimicrobial and/or antioxidant compounds	(Ahmad et al., 2021; de Azeredo, 2013; Sothornvit, 2019; Vasile and Baican, 2021; Zhang et al., 2020)

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### 4.1.3. Intelligent packaging

The EFSA defines intelligent packaging materials as “materials and articles that monitor the condition of packaged food or the environment surrounding the food” (EFSA, 2009). Thus, intelligent packaging does not directly act on the food or its environment to increase stability but makes their control possible by six-fold functions: monitoring, detecting, recording, sensing, tracking, and communicating (Kalpana et al., 2019). It informs the consumers on the food quality using three methods indicators, sensors, or data carriers (Fig. 2).

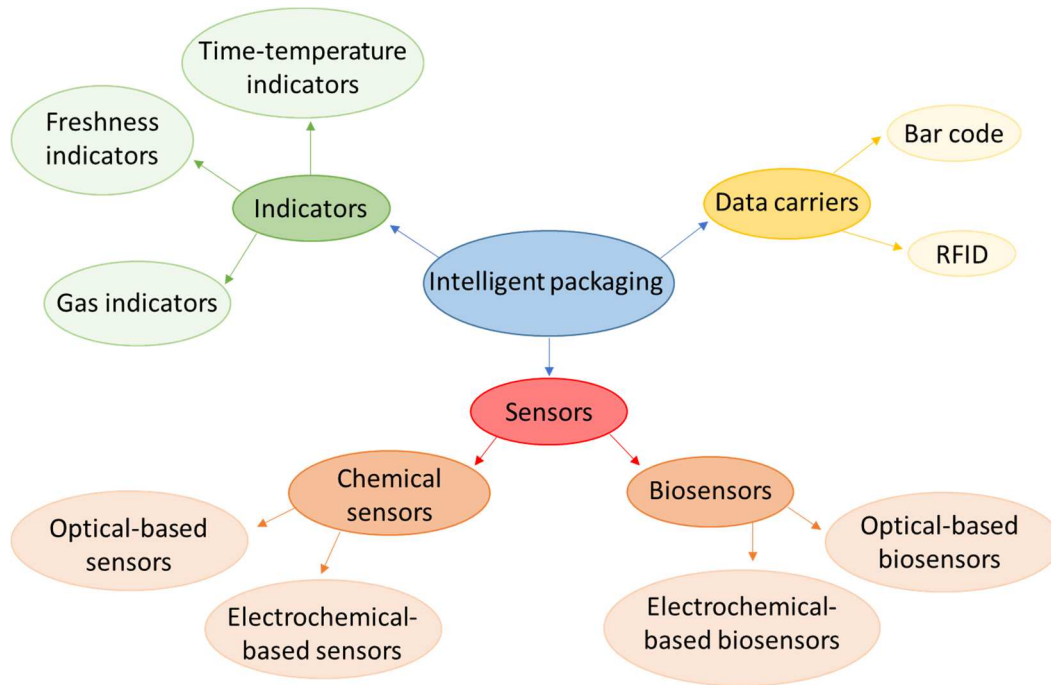


Fig. 2 Different classes of intelligent packaging (Müller and Schmid, 2019); RFID: Radio Frequency Identification

Indicators can detect the modification of the environment and can communicate it in a qualitative or semi-quantitative way often through a visible change (Drago et al., 2020). The color change of the indicator is mainly due to the presence of colorimetric redox dyes or enzymatic reactions (Dodero et al., 2021). The indicators are divided into three categories: time temperature, freshness, and gas indicators. Time-temperature indicators follow the temperature of storage according to two subcategories. Critical temperature indicators indicate the exposition of the food to a temperature impacting its quality (Wang et al., 2015). Complete or partial history indicators record the temperature profile along the food supply chain (Ahari and Soufiani, 2021). These systems may be used to control the pasteurization and sterilization process. Freshness indicators monitor pH changes, which variations may be induced by the growth of food spoilage microorganisms (Wu et al., 2021). Finally, gas indicators indicate the variations in carbon dioxide, dioxygen, or other gas concentrations, especially in modified atmosphere packaging. Water vapor or relative humidity by also be communicated by indicators (Ahari and Soufiani, 2021).

A sensor is a device providing quantitative signals after the measurement of chemical, biological, or physical parameters. Sensors are divided into three parts. The receptor enables the detection and quantification of chemical analytes. Then the transducer converts the change detected in a signal for the indicator. Sensors are divided into chemical sensors and biosensors. Chemical sensors are composed of a chemical receptor detecting volatile chemical compounds or gas. Biosensors are made of organic or biological material (DNA, enzymes, antibodies, ...) and monitor

allergens and organic compounds (Drago et al., 2020). Both are subdivided into electrochemical or optical-based sensors. Electrochemical-based sensors are based on redox reactions on an electrode surface generating an electrical signal while optical-based sensors generate optical signals (color, fluorescence, or chemiluminescence) (Dodero et al., 2021). Finally, the edible sensor is the last new concept (Kuswandi et al., 2020).

585 Data carriers store and transfer data, which underlines their importance as traceability supports. They are divided into bar code or 2D bar code (Quick Response code (QR code) and Data Matrix) and Radio Frequency Identification (RFID) system (Müller and Schmid, 2019). Data carriers, especially bar codes or 2D bar codes, have been printed a long time ago on food packaging. A lot of intelligent packaging equipped with indicators is already available on the market, mainly outside of Europe, unlike sensors that are mainly at a development state. For more information about  
590 active and intelligent packaging please refer to the extremely exhaustive and up-to-date reviews written by and by Drago, *et al.* (Drago et al., 2020) and Firouz, *et al.* (Firouz et al., 2021) published in 2020 and 2021 respectively.

#### 4.1.4. Pharmaceutical outlook of innovations in packaging

##### 4.1.4.1. Smart packaging for the pharmacy industry

Some innovations in food preservation are already found in pharmacy. Indeed, a number of the above-mentioned  
595 methods are already adopted in commercialized medicinal products as multilayer infusion bags (Haned et al., 2018), or the addition of nitrogen in the packaging of some solutions or powders for injectable products (Luveris 75 UI - Résumé des caractéristiques du produit; MYOVIEW 230 microgrammes - Résumé des caractéristiques du produit.; Mahajan et al., 2005) to obtain an inert or modified atmosphere. Active packaging is also already present on the pharmaceutical market: omeprazole capsules (Mopral®) is stored in a high-density polyethylene bottle with a  
600 desiccant capsule (Mopral 20 mg, - Résumé des caractéristiques du produit.) that is a dioxygen and moisture scavenger. These examples are encouraging for the translation of more innovations from food to pharmacy and reflect a need in the area of pharmacy stability. Smart packaging should be both intelligent and active. The future of pharmaceutical packaging should be smart (Fig. 3) and could incorporate both active primary packaging and intelligent secondary packaging. The primary container could be a multilayer packaging. The external layer may provide dioxygen and  
605 moisture barrier activities using dioxygen and or moisture scavenging as Di Maio *et al.* that studied and analyzed the oxygen absorption of a three-layers structure composed of polyethylene terephthalate (PET) as external inert layers, and PET with a polymeric oxygen scavenger as the core reactive layer (Di Maio et al., 2017). This type of container could help to reduce the amount of antioxidant needed to protect oxidation-sensitive API like epinephrine. Nowadays, huge amounts of preservatives are added to improve its stability, for example epinephrine injection solution contains  
610 0.65 mg/mL of metabisulfite, an antioxidant excipient that is known to cause severe allergic reactions when administered parenterally (Table 4) (Adrénaline Renaudin 1 mg/ml - Résumé des caractéristiques du produit.).

The inner layer could offer antioxidant and/or antimicrobial activity thanks to the controlled release of harmless preservatives or the use of an active nanostructured surface. Packaging enabling a slow and controlled release of preservatives could present an interesting benefit in the pharmaceutical industry (Kuai et al., 2021). A release of  
615 preservatives at the same kinetic as the degradation of the API could help to reduce the initial amount of incorporated preservatives. This reduction may permit to stay under the concentration threshold of excipients with known effects (EMA and CHMP, 2019) and to reduce the amount of preservatives administered to patients without affecting the stability of the product. Active packaging with *in situ* antioxidant or antibacterial activity as nanostructured surface

620 provides only surface activity without compound release (Topuz and Uyar, 2020). It could reduce the amount of  
preservatives needed to zero. This active primary container can then be placed in an intelligent secondary container  
equipped with an indicator discernible by the human eye to monitor temperature change, sterilization status or  
microbial contamination as needed. Intelligent packaging may be beneficial notably for the traceability of medicinal  
products. Nowadays, all the secondary packaging of medicinal products presents a printed Data Matrix to allow better  
625 traceability. Data Matrix theoretically makes all the medicinal packaging intelligent, because of their ability to  
communicate information as a batch number or expiry date. Their use could go further, as in 2021, Chelliah *et al.*  
described an intelligent packaging to help the medicine administration to the elderly. They proposed using RFID to  
monitor each medication intake and provide patients with comprehensive information, including therapeutic functions  
(Chelliah et al., 2021). This proposal uses smart packaging in another area than drug stability and is closer to a smart  
pillbox that could help to improve patient observance.

630 The potential intelligent secondary container may use indicators and/or sensors. Time-temperature indicators could  
record the temperature change or indicate an exposition to critical temperatures (Nesic et al., 2020). These indicators  
added on the surface of the secondary packaging could help to better control of the cold chain for pharmacists and  
patients. For example, it could be applied for medicinal products that are very sensitive to temperature changes, such  
as insulin, especially when stored in patients' homes (Heinemann et al., 2021). Freshness indicators, that monitor the  
635 apparition of microbial spoilage (Wu et al., 2021), could also be added to over-the-counter oral solutions or eye drops.  
Products without prescription are often used for self-medication and the storage conditions are not necessarily  
respected at the patient home. The addition of an easy-to-read visual indicator on their packaging could help the  
patient not to use the contaminated product. Finally, in an environmental-friendly approach, both primary and  
secondary containers should ideally be manufactured with bio-sourced material with high recyclability.

640 The case of the edible packaging material can be discussed. Many tablets are coated to modify their palatability or  
liberation kinetic profile (Sakai et al., 2018). Inspired by edible coatings applied on fresh food, it could be interesting  
to take advantage of this coating to improve their stability. The Tablets are dry forms often kept in a blister pack. This  
physical presentation already provides high stability and most of them present a weak sensitivity to oxidation and  
hydrolysis. However, if they are unpacked to be stored in a pillbox or when they are in multidose packaging this  
645 “edible” coating could be profitable. The eventual impact on the release profile of the API due to modification of the  
coating would require attention.



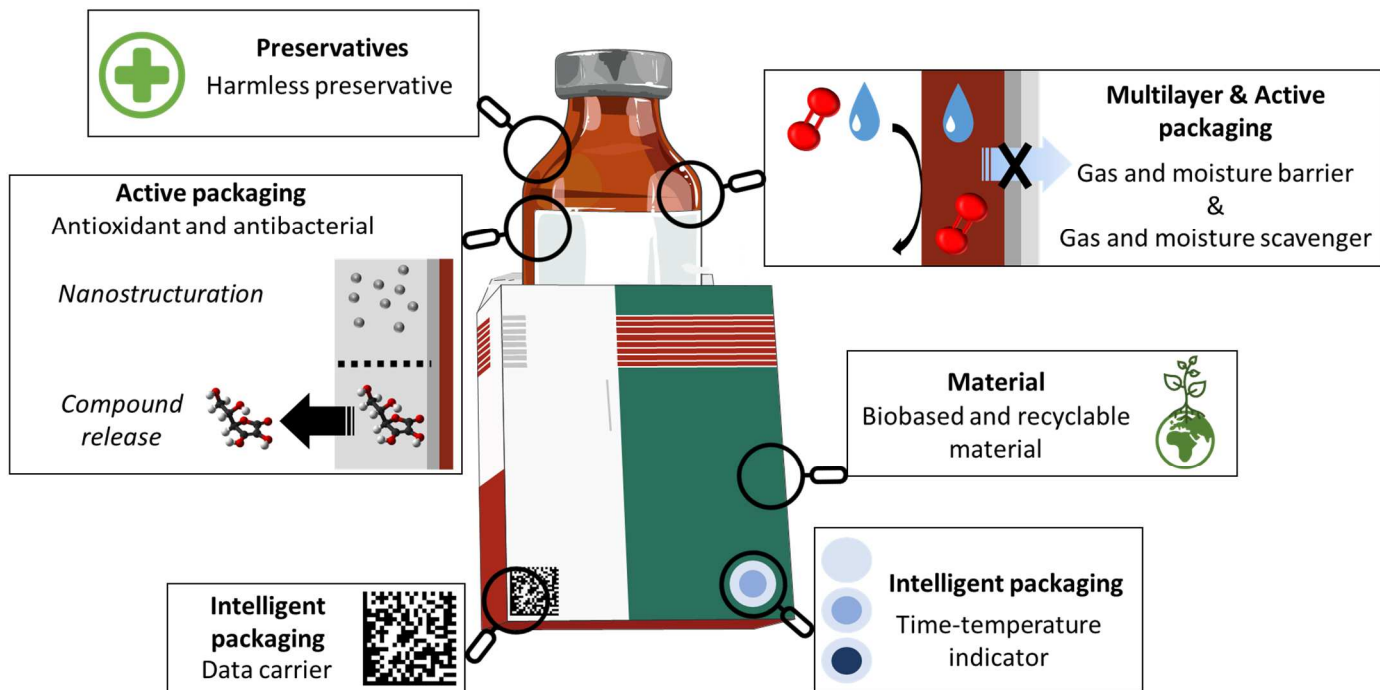


Fig. 3 Theoretical ideal smart pharmaceutical packaging

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#### 4.1.4.2. Limits

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Some issues limit the use of active or intelligent packing at an industrial scale even in the food field. Scaling up the techniques from lab batch to pilot batch is often difficult and numerous developed materials remain at a lab scale. Their utilization as commercialized packaging will require a constraining manufacturing process. It should be ensured that those processes do not impact the expected activity of the material especially after treatment with several conditions of temperature, pressure, or shearing force. For example, if the material is employed to make an active syringe, it should resist first to a sterilization process and then to the shearing stress generated by the passage of the plunger in the body of the syringe. This shearing stress must not cause the surface coating to come off because of the risk of accidental administration of the coating. The activity of the developed materials must also be compatible, in terms of activity duration, with real storage conditions. As mentioned above, dry physical forms are quite stable and their shelf-life can reach several years. In comparison, reconstituted injectable solution should be stored for a maximum of 24 hours. The active packaging may present a high interest in liquid medicinal products.

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Another problem in relation to the passage from the food to the pharmaceutical domain is the administration route and the targeted population. For example, some active packaging includes microorganisms (Table 6). Even so these microorganisms can be harmless for healthy people, the liberation of bacteria or yeasts to immunosuppressed people can be critical. Moreover, medicines may be injected in parenteral routes. If bacteria may be safe after oral administration, their introduction into the systemic system is more harmful even for a patient without immune deficiency.

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Finally, the main litigious question about the new packaging is their safety and their potential interactions with food and, in our case, with the medicinal product. Currently, toxicity studies are limited (Bumbudsanpharoke and Ko, 2015). The information mainly comes from the extrapolation of the toxicity studies of the compound in solution and not directly incorporated in packaging. The existing guideline (*Directive 2001/83/EC*) to study the interaction between packaging and the medicinal product could be adapted to cover the new interactions induced by the new packaging. The update should principally focus on the migration of active compounds from packaging to the product. Eur. Ph.

670

675 already imposes the quantification and the identification of the active substance in medicine that is all the molecules showing an activity. It includes antimicrobial and/antioxidant preservatives, EssO, or nano-objects that could be released by the packaging. To predict the potential migration of nanoparticles from packaging, appropriate analytical techniques should be developed (Kuorwel et al., 2015) to allow the redaction of monographs. The development of these techniques could be easier in pharmaceutical than in food industry (Hannon et al., 2016), because of less complex matrices due to their perfectly known composition. The adjuvants of the packaging are potential extractables based on content/container interactions described in part 4: they must be defined and their safety must be evaluated.

#### 680 4.1.4.3. Legislation

Intelligent packaging in food is more widespread outside of Europe due to the stricter legislation in this part of the world (Müller and Schmid, 2019). The Commission Regulation 450/2009/EC defines active and intelligent material in direct contact (*Commission Regulation (EC) No 450/2009*) and Regulation 1935/2004 mentioned that intelligent packaging should not transfer constituents in quantities that could put in danger human health or affect the composition or organoleptic properties of food (*Regulation (EC) No 1935/2004*). The pharmaceutical legislation is even more restrictive. An evolution and an update of the legislation would be required to be consistent with the development of innovations.

#### 685 4.1.4.4. Environment

Does the adjunction of an antimicrobial product on a packaging impact its recyclability? Antimicrobial compounds impact the microorganisms behind the decomposition of the material (Ahari and Soufiani, 2021). The presence of potential antimicrobial compounds in the environment may also have an impact on the development of bacterial resistance (Karkman et al., 2018). The addition of new properties to packaging should balance the benefit and the ecologic impact. The newly produced materials, especially if they are nanostructured, may be considered as a new waste that we must learn how to treat (Giese et al., 2018; Vogel et al., 2016). RFID system does not respect recyclability and sustainability mechanisms (Lopez-Gomez et al., 2015). At the same time, the bar code only requires to be printed without modification in the recyclability of the packaging material. The question is to know if the increase of information stored in RFID system offset the negative environmental impact.

## 690 5. Conclusion

The stability is a key point in pharmacy as stability studies represent an essential step in the development of a new API or a new medicinal product. This evaluation allows to highlight the parameters that influence the degradation. To improve the stability, some solutions already exist but are not completely satisfactory, so we must turn to new innovations. As mentioned, the pharmaceutical and food industries share common stability problems related to the same physical, chemical and microbiological phenomena. Thus, the innovation developed in the food field must be a source of inspiration in this search for solutions. As it has been described, new preservatives with natural origin like essential oils or antimicrobial peptides and proteins can be an alternative to replace the notorious antimicrobial preservatives used in medicinal products. The immobilization of preservatives, surface with intrinsic antioxidant or antimicrobial activities, material that reduce oxygen permeation, could also increase the stability of medicinal product and make it possible to reduce or stop the addition of preservatives. Finally, the development of intelligent packaging could help pharmacists and patients to monitor product stability. All these innovations would reduce the impact on

710 health of preservatives with known effects and, combined with the other innovations, contribute to a better preservation of medicinal products. Today, the limits to their utilization are mainly the lack of knowledge about toxicity, environmental, and legislative issues. These issues will need to be addressed to allow patients and pharmacists to take advantage of the potential benefits offered by all food innovations.

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# Packaging of the future

