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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.
- 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 ± 2 °C, 5 ± 3 °C or -20 ± 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 ₂ SO ₄ (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 ⁻² . <i>ICH Q1B</i> (ICH Q1B, 1996)	≥ 1.2 million lux hours (max 6 million lux hours), ≥ 200 W.h.m ⁻² (Alsante et al., 2007) Metal halide, mercury, xenon, or ultraviolet-B fluorescent lamp 1 to 10 days (WHO, 2008) 1.2 to 6 × 10 ⁵ 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 ₂ O ₂ (up to 3 % (V/V)) or free radical and/or H ₂ O ₂ (5–20 mol) 3 % (V/V) H ₂ O ₂ 25 °C, 60 °C ; Peroxide control 25 °C, 60 °C ; Azobisisobutyronitrile 40 °C, 60 °C (Blessy et al., 2014) 3 % (V/V) H ₂ O ₂ 1 to 3 hours (WHO, 2008) 3 to 30 % (V/V) H ₂ O ₂ (Bardin et al., 2011)	(Waterman et al., 2002b)

Microbiological contamination	<p>Test on 10 mg or mL of product or 10 patches/films/container/...</p> <p>Examination of the product:</p> <ul style="list-style-type: none">- Membrane filtration method- Plate-count methods (pour-plate method or surface-spread method)- Most-probable-number method- 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)- 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)	<p>(Kneifel et al., 2002)</p> <p>Microbial determination methods in pharmaceutical quality control:</p> <ul style="list-style-type: none">- Standard plate count- Most probable number- Direct epifluorescent filter techniques- ATP detection of viable cells- Impedance microbiology direct or indirect- ELISA tests- Immunomagnetic separation- Polymerase chain reaction (PCR)- Microarray and biochip technologies- Phospholipid fatty acid analysis (Nemati et al., 2016)
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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 D₂) went from 25 days at 25 °C to 1 day at 40 °C ($\geq 95\%$ remaining). The stability of cholecalciferol (vitamin D₃) 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 B₁₂, pK_a = 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)).

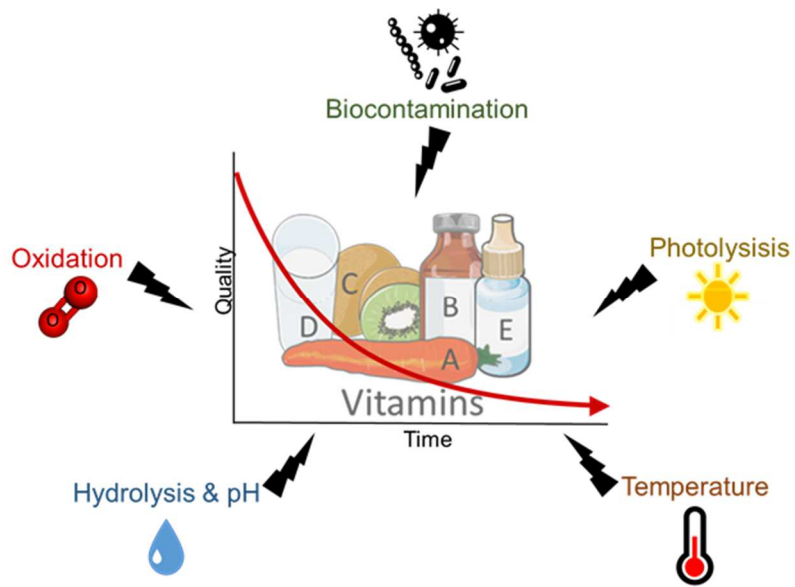
2.2.3. Photolysis

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 B₉), which has double bonds and carbonyl groups is very sensitive to photolysis. Indeed, a degradation of 80 % of a 1.10^{-5} 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 α -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, α -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 B₁, B₂, B₆, and C in neonatal parenteral nutrition using 3 % and 10 % (V/V) of hydrogen peroxide for 6 h at room temperature. Vitamin B₁ showed higher sensitivity to oxidation than vitamins B₂ and B₆ (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)
α -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 ₂) and Cholecalciferol (Vitamin D ₃)	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 ₃)	25, 45, 55 and 65 °C - 1 h			HCl – 70 °C - 5 h	Iodine solution - 1 h	Temperature: isomerization to pre-vitamin D ₃ isomer Iodine: cis/trans isomerization of vitamin D ₃ (trans-vitamin D ₃) and pre-vitamin D ₃ (tachysterol) Acidic: Acid-catalyzed isomerization product		(Mahmoodani et al., 2017)
Cholecalciferol (Vitamin D ₃)	25 and 60 °C – 24 h			0.1 M HCl 0.1 M NaOH	0,3 and 15 % (V/V) H ₂ O ₂	Acidic condition All other conditions	1 h * 24 h * Degradation products: Tachysterol D ₃ , D ₃ Pre-vitamin D ₃ , Trans-vitamin D ₃ , Vitamin D ₃ , Lumisterol D ₃ , Hydroxy vitamin D ₃	(Temova and Roskar, 2016)
Cyanocobalamin (Vitamin B ₁₂)	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 ₃)	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 ₁) Riboflavin (Vitamin B ₂) Pyridoxine (Vitamin B ₆) Ascorbic acid (Vitamin C)	4 and 25 °C - 72 h	With or without photoprotection	Sulfuric acid 10 %	3 and 10 % (V/V) H ₂ O ₂ - 6 h	Residual quantity (%)		(Ribeiro et al., 2011)		
					Vitamin	B ₁	B ₂	B ₆	C
					3 % H ₂ O ₂	74.7	80.6	98.4	
					10 % H ₂ O ₂	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 ₁)	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)

Excipient	Use	Number of registered medicines	Side effects	Administration routes
Sulfite derived	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		
Synthetic Phenolic Antioxidant	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)		
Benzalkonium chloride	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
Benzoic acid and benzoates (<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	
Bronopol	Antibiotic preservative	3 (including 1 topical medicine)	May cause local cutaneous reaction (eczema)	Topical
Chlorocresol	Antibiotic preservative	5 (including 5 topical medicines)	May cause an allergic reaction.	Topical and parenteral
Sorbic acid and salts (<i>E200-203</i>)	Antimicrobial agent	104 (including 12 topical medicines)	May cause local cutaneous reaction (eczema)	Topical
Parahydroxybenzoates and their esters	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		
Organic mercury compounds	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[®] 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 μm 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
Di(2-ethylhexyl) phthalate or DEHP	Plasticizer
Epoxidized soy oil	Plasticizer and stabilizer
Epoxidised linseed oil	Stabilizer
Butylhydroxytoluene	Antioxidant
Ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate]	Antioxidant
Pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]	Antioxidant
Tris(2,4-di-tert-butylphenyl) phosphite	Antioxidant
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6-(1H,3H,5H)-trione	Antioxidant

Name	Use
2,2'-bis(octadecyloxy)-5,5'-spirobi[1,3,2-dioxaphosphinane]	Antioxidant
Diocetadecyl 3,3'-thiodipropionate	Antioxidant
Plastic additive 18	Antioxidant
Oleamide	Slip and anti-block agent
Erucamide	Antiblock agent
Copolymer of dimethyl succinate and (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol	Antioxidant
Tris(2-ethylhexyl) trimellitate	Plasticizer
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 CO₂, O₂, N₂, 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)

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

Antioxidant releaser	Synthetic antioxidants: BHA, BHT, TBHQ (tert-butylhydroquinone) Organic acids: sorbic, ascorbic, citric acid Natural antioxidants: phenolic compounds, ascorbic acid, α -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)
Nanostructuring	Nanoparticles: metal (Ag, Au, Cu), metal oxide (TiO ₂ , 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)

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).

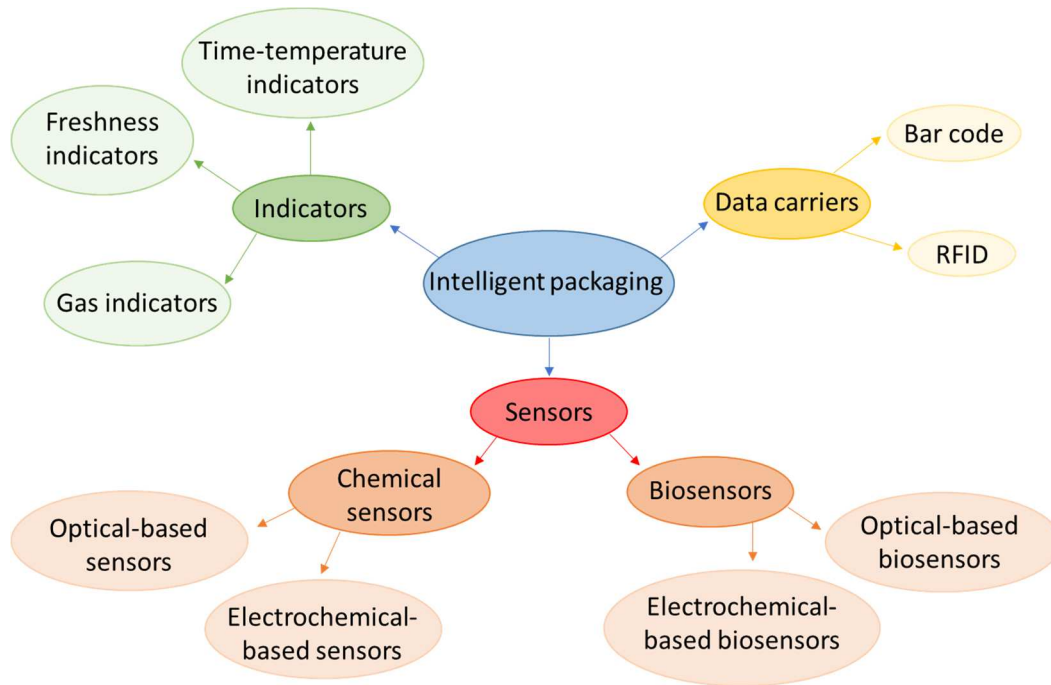


Fig. 2 Different classes of intelligent packaging (Müller and Schmid, 2019); RFID: Radio Frequency Identification

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 (Doderio 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.

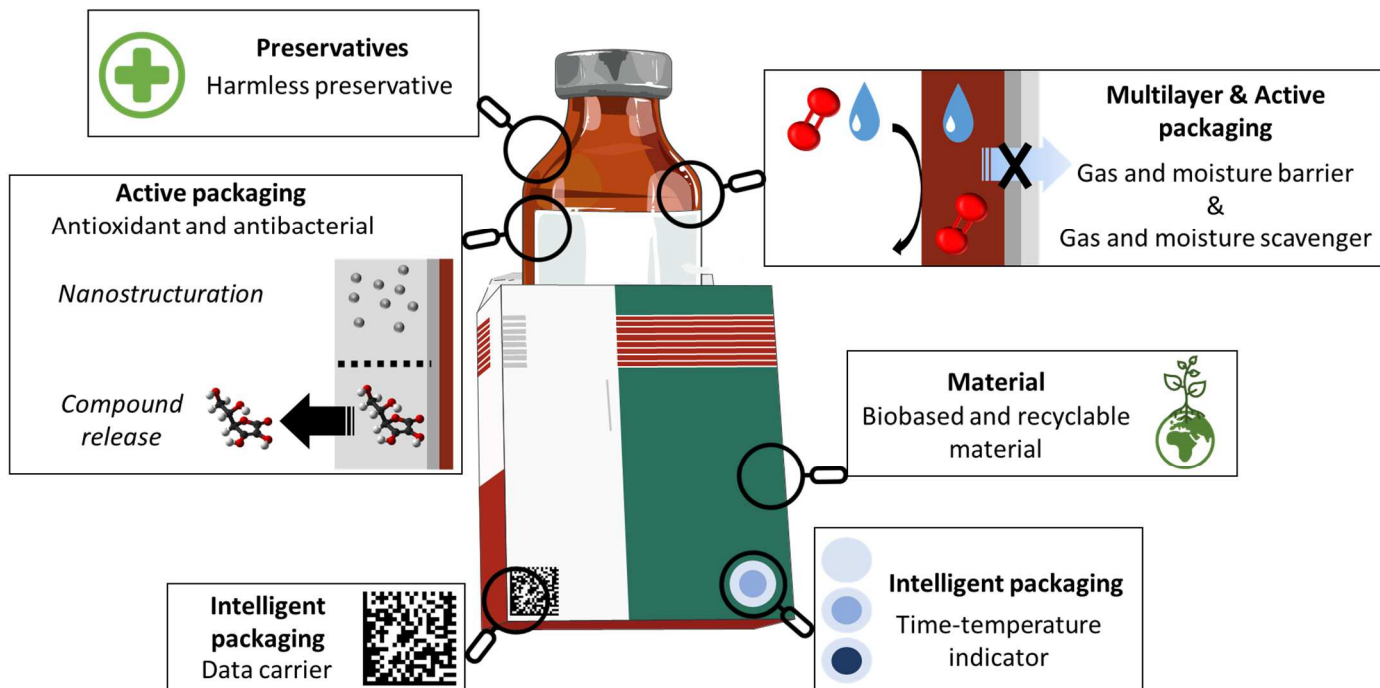


Fig. 3 Theoretical ideal smart pharmaceutical packaging

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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.

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.

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.

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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References

- Adams, A.I.H., Morimoto, L.N., Meneghini, L.Z., Bergold, A.M., 2008. Treatment of invasive fungal infections: stability of voriconazole infusion solutions in PVC bags. *Braz. J. Infect. Dis. Off. Publ. Braz. Soc. Infect. Dis.* 12, 400–404. <https://doi.org/10.1590/s1413-86702008000500011>
- 720 ADRENALINE RENAUDIN 1 mg/ml, solution injectable en ampoule - Résumé des caractéristiques du produit - Base Données Publique Médicam. URL <https://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=69553494&typedoc=R#RcpListeExcipients> (accessed 5.3.22).
- Ahari, H., Soufiani, S.P., 2021. Smart and Active Food Packaging: Insights in Novel Food Packaging. *Front. Microbiol.* 12, 657233. <https://doi.org/10.3389/fmicb.2021.657233>
- 725 Ahmad, I., Ahmed, S., Anwar, Z., Sheraz, M.A., Sikorski, M., 2016. Photostability and Photostabilization of Drugs and Drug Products. *Int. J. Photoenergy* 2016, 1–19. <https://doi.org/10.1155/2016/8135608>
- Ahmad, I., Hussain, W., Fareedi, A., 1992. Photolysis of Cyanocobalamin in Aqueous-Solution. *J. Pharm. Biomed. Anal.* 10, 9–15. [https://doi.org/10.1016/0731-7085\(92\)80004-7](https://doi.org/10.1016/0731-7085(92)80004-7)
- 730 Ahmad, I., Qadeer, K., Zahid, S., Sheraz, M.A., Ismail, T., Hussain, W., Ansari, I.A., 2014. Effect of Ascorbic Acid on the Degradation of Cyanocobalamin and Hydroxocobalamin in Aqueous Solution: A Kinetic Study. *AAPS PharmSciTech* 15, 1324–1333. <https://doi.org/10.1208/s12249-014-0160-5>
- Ahmad, S.S., Yousuf, O., Islam, R.U., Younis, K., 2021. Silver nanoparticles as an active packaging ingredient and its toxicity. *Packag. Technol. Sci.* 34, 653–663. <https://doi.org/10.1002/pts.2603>
- 735 Albini, A., Fasani, E. (Eds.), 1998. Photochemistry of drugs: An overview and practical problems, in: *Special Publications*. Royal Society of Chemistry, Cambridge, pp. 1–73.
- Alfei, S., Marengo, B., Zuccari, G., 2020. Nanotechnology application in food packaging: A plethora of opportunities versus pending risks assessment and public concerns. *Food Res. Int.* 137, 109664. <https://doi.org/10.1016/j.foodres.2020.109664>
- 740 Al-Maqtari, Q.A., Rehman, A., Mahdi, A.A., Al-Ansi, W., Wei, M., Yanyu, Z., Phyo, H.M., Galeboe, O., Yao, W., n.d. Application of essential oils as preservatives in food systems: challenges and future perspectives - a review. *Phytochem. Rev.* <https://doi.org/10.1007/s11101-021-09776-y>
- Alsante, K.M., Ando, A., Brown, R., Ensing, J., Hatajik, T.D., Kong, W., Tsuda, Y., 2007. The role of degradant profiling in active pharmaceutical ingredients and drug products. *Adv. Drug Deliv. Rev.* 59, 29–37. <https://doi.org/10.1016/j.addr.2006.10.006>
- 745 Androutopoulou, C., Christopoulou, S.D., Hahalis, P., Kotsalou, C., Lamari, F.N., Vantarakis, A., 2021. Evaluation of Essential Oils and Extracts of Rose Geranium and Rose Petals as Natural Preservatives in Terms of Toxicity, Antimicrobial, and Antiviral Activity. *Pathogens* 10, 494. <https://doi.org/10.3390/pathogens10040494>
- 750 Antikainen, O., Yliruusi, J., 2003. Determining the compression behaviour of pharmaceutical powders from the force-distance compression profile. *Int. J. Pharm.* 252, 253–261. [https://doi.org/10.1016/S0378-5173\(02\)00665-8](https://doi.org/10.1016/S0378-5173(02)00665-8)
- Anukiruthika, T., Sethupathy, P., Wilson, A., Kashampur, K., Moses, J.A., Anandharamkrishnan, C., 2020. Multilayer packaging: Advances in preparation techniques and emerging food applications. *Compr. Rev. Food Sci. Food Saf.* 19, 1156–1186. <https://doi.org/10.1111/1541-4337.12556>
- 755 Archer, C.B., MacDonald, D.M., 1984. Chlorocresol sensitivity induced by treatment of allergic contact dermatitis with steroid creams. *Contact Dermatitis* 11, 144–145. <https://doi.org/10.1111/j.1600-0536.1984.tb00959.x>
- Asgher, M., Qamar, S.A., Bilal, M., Iqbal, H.M.N., 2020. Bio-based active food packaging materials: Sustainable alternative to conventional petrochemical-based packaging materials. *Food Res. Int.* 137, 109625. <https://doi.org/10.1016/j.foodres.2020.109625>
- 760 Awalgaonkar, G., Beaudry, R., Almenar, E., 2020. Ethylene-removing packaging: Basis for development and latest advances. *Compr. Rev. Food Sci. Food Saf.* 19, 3980–4007. <https://doi.org/10.1111/1541-4337.12636>
- Bahar, A.A., Ren, D., 2013. Antimicrobial Peptides. *Pharmaceuticals* 6, 1543–1575. <https://doi.org/10.3390/ph6121543>

- 765 Bardin, C., Astier, A., Vulto, A., Sewell, G., Vigneron, J., Trittler, R., Daouphars, M., Paul, M., Trojniak, M., Pinguet, F., French Society of Oncology Pharmacy, 2011. Guidelines for the practical stability studies of anticancer drugs: a European consensus conference. *Ann. Pharm. Fr.* 69, 221–231. <https://doi.org/10.1016/j.pharma.2011.07.002>
- Bedale, W., Sindelar, J.J., Milkowski, A.L., 2016. Dietary nitrate and nitrite: Benefits, risks, and evolving perceptions. *Meat Sci.* 120, 85–92. <https://doi.org/10.1016/j.meatsci.2016.03.009>
- 770 Behera, S.S., Ray, R.C., Zdolec, N., 2018. Lactobacillus plantarum with Functional Properties: An Approach to Increase Safety and Shelf-Life of Fermented Foods. *BioMed Res. Int.* 2018, 9361614. <https://doi.org/10.1155/2018/9361614>
- 775 Bellucci, E.R.B., Munekata, P.E.S., Pateiro, M., Lorenzo, J.M., da Silva Barretto, A.C., 2021. Red pitaya extract as natural antioxidant in pork patties with total replacement of animal fat. *Meat Sci.* 171, 108284. <https://doi.org/10.1016/j.meatsci.2020.108284>
- Ben Hsouna, A., Ben Halima, N., Smaoui, S., Hamdi, N., 2017. Citrus lemon essential oil: chemical composition, antioxidant and antimicrobial activities with its preservative effect against *Listeria monocytogenes* inoculated in minced beef meat. *Lipids Health Dis.* 16, 146. <https://doi.org/10.1186/s12944-017-0487-5>
- 780 Bensid, A., El Abed, N., Houicher, A., Regenstein, J.M., Özogul, F., 2020. Antioxidant and antimicrobial preservatives: Properties, mechanism of action and applications in food – a review. *Crit. Rev. Food Sci. Nutr.* 0, 1–17. <https://doi.org/10.1080/10408398.2020.1862046>
- Blessy, M., Patel, R.D., Prajapati, P.N., Agrawal, Y.K., 2014. Development of forced degradation and stability indicating studies of drugs—A review. *J. Pharm. Anal.* 4, 159–165. <https://doi.org/10.1016/j.jpha.2013.09.003>
- 785 Brul, S., Coote, P., 1999. Preservative agents in foods - Mode of action and microbial resistance mechanisms. *Int. J. Food Microbiol.* 50, 1–17. [https://doi.org/10.1016/S0168-1605\(99\)00072-0](https://doi.org/10.1016/S0168-1605(99)00072-0)
- Bryan, N.S., Alexander, D.D., Coughlin, J.R., Milkowski, A.L., Boffetta, P., 2012. Ingested nitrate and nitrite and stomach cancer risk: an updated review. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 50, 3646–3665. <https://doi.org/10.1016/j.fct.2012.07.062>
- 790 Bumbudsanpharoke, N., Ko, S., 2015. Nano-Food Packaging: An Overview of Market, Migration Research, and Safety Regulations. *J. Food Sci.* 80, R910–R923. <https://doi.org/10.1111/1750-3841.12861>
- Burry, J.N., Kirk, J., Reid, J., Turner, T., 1975. Chlorocresol sensitivity. *Contact Dermatitis* 1, 41–42. <https://doi.org/10.1111/j.1600-0536.1975.tb05309.x>
- 795 Caleb, O.J., Mahajan, P.V., Al-Said, F.A.-J., Opara, U.L., 2013. Modified Atmosphere Packaging Technology of Fresh and Fresh-cut Produce and the Microbial Consequences-A Review. *Food Bioprocess Technol.* 6, 303–329. <https://doi.org/10.1007/s11947-012-0932-4>
- Campbell, M.T.D., Jones, D.S., Andrews, G.P., Li, S., 2019. Understanding the physicochemical properties and degradation kinetics of nicotinamide riboside, a promising vitamin B3 nutritional supplement. *Food Nutr. Res.* 63. <https://doi.org/10.29219/fnr.v63.3419>
- 800 Carocho, M., Barreiro, M.F., Morales, P., Ferreira, I.C.F.R., 2014. Adding Molecules to Food, Pros and Cons: A Review on Synthetic and Natural Food Additives. *Compr. Rev. Food Sci. Food Saf.* 13, 377–399. <https://doi.org/10.1111/1541-4337.12065>
- Carocho, M., Morales, P., Ferreira, I.C.F.R., 2018. Antioxidants: Reviewing the chemistry, food applications, legislation and role as preservatives. *Trends Food Sci. Technol.* 71, 107–120. <https://doi.org/10.1016/j.tifs.2017.11.008>
- 805 Cawley, S., McCartney, D., Woodside, J.V., Sweeney, M.R., McDonnell, R., Molloy, A.M., Turner, M.J., 2018. Optimization of folic acid supplementation in the prevention of neural tube defects. *J. Public Health Oxf. Engl.* 40, 827–834. <https://doi.org/10.1093/pubmed/fdx137>
- Chang, Y., 2020. Bacteriophage-Derived Endolysins Applied as Potent Biocontrol Agents to Enhance Food Safety. *Microorganisms* 8, 724. <https://doi.org/10.3390/microorganisms8050724>
- 810 Charnock, C., Finsrud, T., 2007. Combining esters of para-hydroxy benzoic acid (parabens) to achieve increased antimicrobial activity. *J. Clin. Pharm. Ther.* 32, 567–572. <https://doi.org/10.1111/j.1365-2710.2007.00854.x>
- Chauhan, A., HSU, K.-H., 2021. Preservative removal from eye drops. *US11051976B2*.

- 815 Chelliah, R., Wei, S., Daliri, E.B.-M., Rubab, M., Elahi, F., Yeon, S.-J., Jo, K.H., Yan, P., Liu, S., Oh, D.H., 2021. Development of Nanosensors Based Intelligent Packaging Systems: Food Quality and Medicine. *Nanomaterials* 11, 1515. <https://doi.org/10.3390/nano11061515>
- Chennell, P., Yessaad, M., Abd El Kader, F., Jouannet, M., Wasiak, M., Bouattour, Y., Sautou, V., 2020. Do Ophthalmic Solutions of Amphotericin B Solubilised in 2-Hydroxypropyl-gamma-Cyclodextrins Possess an Extended Physicochemical Stability? *Pharmaceutics* 12, 786. <https://doi.org/10.3390/pharmaceutics12090786>
- 820 Chibane, L.B., Degraeve, P., Ferhout, H., Bouajila, J., Oulahal, N., 2019. Plant antimicrobial polyphenols as potential natural food preservatives. *J. Sci. Food Agric.* 99, 1457–1474. <https://doi.org/10.1002/jsfa.9357>
- Chisenga, S.M., Tolesa, G.N., Workneh, T.S., 2020. Biodegradable Food Packaging Materials and Prospects of the Fourth Industrial Revolution for Tomato Fruit and Product Handling. *Int. J. Food Sci.* 2020, 8879101. <https://doi.org/10.1155/2020/8879101>
- 825 Choe, E., Huang, R.M., Min, D.B., 2005. Chemical reactions and stability of riboflavin in foods. *J. Food Sci.* 70, R28–R36. <https://doi.org/10.1111/j.1365-2621.2005.tb09055.x>
- Cleveland, J., Montville, T.J., Nes, I.F., Chikindas, M.L., 2001. Bacteriocins: safe, natural antimicrobials for food preservation. *Int. J. Food Microbiol.* 71, 1–20. [https://doi.org/10.1016/S0168-1605\(01\)00560-8](https://doi.org/10.1016/S0168-1605(01)00560-8)
- Commission Regulation (EC) No 2073/2005 on microbiological criteria for foodstuffs, 2005. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005R2073&from=EN> (accessed 17.5.21).
- 830 Commission Regulation (EC) No 450/2009 on active and intelligent materials and articles intended to come into contact with food, 2009. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0450&from=EN> (accessed 27.10.21).
- Committee for medicinal products for human use (CHMP), 2007a. European Medicines Agency - Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-excipients-dossier-application-marketing-authorisation-medicinal-product-revision-2_en.pdf (accessed 11.02.22).
- 835 Committee for Medicinal Products for Human Use (CHMP), 2015. Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use. 2015. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-methyl-propylparaben-excipients-human-medicinal-products-oral-use_en.pdf (accessed 11.02.22).
- 840 Committee for Medicinal Products for Human use (CHMP), Committee for Medicinal Products for Veterinary use (CVMP), 2019. Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-sterilisation-medicinal-product-active-substance-excipient-primary-container_en.pdf (accessed 11.02.22).
- 845 Darbre, P.D., Harvey, P.W., 2008. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. *J. Appl. Toxicol.* 28, 561–578. <https://doi.org/10.1002/jat.1358>
- de Alvarenga Junior, B.R., Carneiro, R.L., 2019. Chemometrics Approaches in Forced Degradation Studies of Pharmaceutical Drugs. *Molecules* 24, 3804. <https://doi.org/10.3390/molecules24203804>
- 850 de Azeredo, H.M.C., 2013. Antimicrobial nanostructures in food packaging. *Trends Food Sci. Technol.* 30, 56–69. <https://doi.org/10.1016/j.tifs.2012.11.006>
- Dey, A., Neogi, S., 2019. Oxygen scavengers for food packaging applications: A review. *Trends Food Sci. Technol.* 90, 26–34. <https://doi.org/10.1016/j.tifs.2019.05.013>
- 855 D’Huart, E., Vigneron, J., Gindre, I., Lider, P., Demoré, B., 2018. First international database of research teams in stability and compatibility of medications: An additional function in the Stabilis® database. *Ann. Pharm. Fr.* 76, 436–443. <https://doi.org/10.1016/j.pharma.2018.08.001>
- Di Maio, L., Marra, F., Bedane, T.F., Incarnato, L., Saguy, S., 2017. Oxygen Transfer in Co-Extruded Multilayer Active Films for Food Packaging. *Aiche J.* 63, 5215–5221. <https://doi.org/10.1002/aic.15844>
- 860 Diniz do Nascimento, L., Moraes, A.A.B. de, Costa, K.S. da, Pereira Galúcio, J.M., Taube, P.S., Costa, C.M.L., Neves Cruz, J., de Aguiar Andrade, E.H., Faria, L.J.G. de, 2020. Bioactive Natural Compounds and Antioxidant Activity of Essential Oils from Spice Plants: New Findings and Potential Applications. *Biomolecules* 10, E988. <https://doi.org/10.3390/biom10070988>

- Directive 2001/83/EC on the Community code relating to medicinal products for human use, 2001. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=en> (accessed 21.05.21).
- 865 Dodero, A., Escher, A., Bertucci, S., Castellano, M., Lova, P., 2021. Intelligent Packaging for Real-Time Monitoring of Food-Quality: Current and Future Developments. *Appl. Sci.-Basel* 11, 3532. <https://doi.org/10.3390/app11083532>
- Dominguez, R., Barba, F.J., Gomez, B., Putnik, P., Kovacevic, D.B., Pateiro, M., Santos, E.M., Lorenzo, J.M., 2018. Active packaging films with natural antioxidants to be used in meat industry: A review. *Food Res. Int.* 113, 93–101. <https://doi.org/10.1016/j.foodres.2018.06.073>
- 870 Dong, M., Huynh-Ba, K., 2020. Stability Studies and Testing of Pharmaceuticals - An Overview. *LCGC N. Am., LCGC North America-06-01-2020* 38, 325–336.
- Dong, M., Meinerz, N.M., Walker, K.D., Garcea, R.L., Randolph, T.W., 2021. Thermostability of a trivalent, capsomere-based vaccine for human papillomavirus infection. *Eur. J. Pharm. Biopharm.* 168, 131–138. <https://doi.org/10.1016/j.ejpb.2021.08.008>
- 875 Drago, E., Campardelli, R., Pettinato, M., Perego, P., 2020. Innovations in Smart Packaging Concepts for Food: An Extensive Review. *Foods* 9, 1628. <https://doi.org/10.3390/foods9111628>
- Duncan, S.E., Chang, H.-H., 2012. Implications of Light Energy on Food Quality and Packaging Selection, in: Henry, J. (Ed.), *Advances in Food and Nutrition Research*, Vol 67. Elsevier Academic Press Inc, San Diego, pp. 25–73. <https://doi.org/10.1016/B978-0-12-394598-3.00002-2>
- 880 Duncan, S.E., Webster, J.B., 2009. Sensory impacts of food-packaging interactions. *Adv. Food Nutr. Res.* 56, 17–64. [https://doi.org/10.1016/S1043-4526\(08\)00602-5](https://doi.org/10.1016/S1043-4526(08)00602-5)
- EFSA, E.F.S., 2009. Guidelines on submission of a dossier for safety evaluation by the EFSA of active or intelligent substances present in active and intelligent materials and articles intended to come into contact with food. EFSA J. 7, 1208. <https://doi.org/10.2903/j.efsa.2009.1208>
- 885 EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Bampidis, V., Azimonti, G., de Lourdes Bastos, M., Christensen, H., Dusemund, B., Kos Durjava, M., Kouba, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Sanz, Y., Villa, R.E., Woutersen, R., Aquilina, G., Bories, G., Gropp, J., Nebbia, C., Innocenti, M.L., 2020. Safety and efficacy of propyl gallate for all animal species. *EFSA J.* 18, e06069. <https://doi.org/10.2903/j.efsa.2020.6069>
- 890 EFSA Panel on Biological Hazards (BIOHAZ), Koutsoumanis, K., Allende, A., Alvarez-Ordóñez, A., Bolton, D., Bover-Cid, S., Chemaly, M., Davies, R., De Cesare, A., Herman, L., Nauta, M., Peixe, L., Ru, G., Simmons, M., Skandamis, P., Suffredini, E., Jacxsens, L., Skjerdal, T., Da Silva Felicio, M.T., Hempen, M., Messens, W., Lindqvist, R., 2020. Guidance on date marking and related food information: part 1 (date marking). *EFSA J.* 18, e06306. <https://doi.org/10.2903/j.efsa.2020.6306>
- 895 EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2012. Statement on the safety assessment of the exposure to butylated hydroxyanisole E 320 (BHA) by applying a new exposure assessment methodology. *EFSA J.* 10, 2759. <https://doi.org/10.2903/j.efsa.2012.2759>
- 900 EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2011. Scientific Opinion on the re-evaluation of butylated hydroxyanisole – BHA (E 320) as a food additive. *EFSA J.* 9, 2392. <https://doi.org/10.2903/j.efsa.2011.2392>
- 905 Eldien, D.E., El Moghazy, G.M., Fahmy, H.N., 2020. Studies on Some Plant Extracts as Antimicrobials and Food Preservatives. *J. Microbiol. Biotechnol. Food Sci.* 9, 790–798. <https://doi.org/10.15414/jmbfs.2020.9.4.790-798>
- EMA, CHMP, 2019. Annex to the European Commission guideline on ‘Excipients in the labelling and package leaflet of medicinal products for human use’ (SANTE-2017-11668) https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en.pdf (accessed 1.7.21).
- 910 EMA, Committee for Human Medicinal Products (CHMP), 2017a. Benzyl alcohol and benzoic acid group used as excipients. https://www.ema.europa.eu/en/documents/report/benzyl-alcohol-benzoic-acid-group-used-excipients-report-published-support-questions-answers-benzyl/chmp/508188/2013-t_en.pdf (accessed 7.10.21).

- 915 EMA, Committee for Human Medicinal Products (CHMP), 2017b. Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use. https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-benzoic-acid-benzoates-used-excipients-medicinal-products-human-use_en.pdf (accessed 7.10.21).
- 920 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Chapter 3: Premises and Equipment, https://ec.europa.eu/health/system/files/2016-11/chapter_3_0.pdf (accessed 2.10.22)
- 925 European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC), Andersson, N., Arena, M., Auteri, D., Barmaz, S., Grignard, E., Kienzler, A., Lepper, P., Lostia, A.M., Munn, S., Parra Morte, J.M., Pellizzato, F., Tarazona, J., Terron, A., Van der Linden, S., 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA J. 16, e05311. <https://doi.org/10.2903/j.efsa.2018.5311>
- European Pharmacopoeia 1434, Herbal drug preparations, 2010. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/1434E.pdf> (accessed 8.3.22).
- 930 European Pharmacopoeia 2034, Substances for pharmaceutical use, 2021. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/2034E.pdf> (accessed 5.2.21).
- European Pharmacopoeia 20612, Microbiological examination of non-sterile products: microbial enumeration tests, 2021. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/20612E.pdf> (accessed 25.8.21).
- 935 European Pharmacopoeia 20613, Microbiological examination of non-sterile products: test for specified micro-organisms, 2021. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/20613E.pdf> (accessed 25.8.21).
- 940 European Pharmacopoeia 20801, Methods in pharmacognosy, 2008. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/20800E.pdf> (accessed 14.10.21).
- European Pharmacopoeia 20812, Essential oils in herbal drugs, 2019. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/20812E.pdf> (accessed 14.10.21).
- 945 European Pharmacopoeia 30202, Plastic containers and closures for pharmaceutical use, 2022. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/30202E.pdf> (accessed 2.5.22).
- European Pharmacopoeia 50102, Biological indicators and related microbial preparations used in the manufacture of sterile products, 2017. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/50102E.pdf> (accessed 25.8.21).
- 950 European Pharmacopoeia 50208, Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, 2011. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/50208E.pdf> (accessed 5.2.21).
- 955 European Pharmacopoeia 90003, Plastic containers for aqueous solutions for infusion, 2008. <https://pheur.edqm.eu/internal/549d043d78dc47a48e22e914112921c9/10-7/10-7/page/90003E.pdf> (accessed 11.1.21).
- Evstatiev, R., Cervenka, A., Austerlitz, T., Deim, G., Baumgartner, M., Beer, A., Krnjic, A., Gmainer, C., Lang, M., Frick, A., Schachner, H., Khare, V., Gasche, C., 2021. The food additive EDTA aggravates colitis and colon carcinogenesis in mouse models. *Sci. Rep.* 11, 5188. <https://doi.org/10.1038/s41598-021-84571-5>
- 960 Falleh, H., Ben Jemaa, M., Saada, M., Ksouri, R., 2020. Essential oils: A promising eco-friendly food preservative. *Food Chem.* 330, 127268. <https://doi.org/10.1016/j.foodchem.2020.127268>
- Farrar, A.J., Farrar, F.C., 2020. Clinical Aromatherapy. *Nurs. Clin. North Am.* 55, 489–504. <https://doi.org/10.1016/j.cnur.2020.06.015>
- 965 Firouz, M.S., Mohi-Alden, K., Omid, M., 2021. A critical review on intelligent and active packaging in the food industry: Research and development. *Food Res. Int.* 141, 110113. <https://doi.org/10.1016/j.foodres.2021.110113>

- Freitas, J.P., Brandão, F.M., 1986. Contact urticaria to chlorocresol. *Contact Dermatitis* 15, 252. <https://doi.org/10.1111/j.1600-0536.1986.tb01353.x>
- 970 Gaikwad, K.K., Singh, S., Ajji, A., 2019. Moisture absorbers for food packaging applications. *Environ. Chem. Lett.* 17, 609–628. <https://doi.org/10.1007/s10311-018-0810-z>
- Gaikwad, K.K., Singh, S., Lee, Y.S., 2018. Oxygen scavenging films in food packaging. *Environ. Chem. Lett.* 16, 523–538. <https://doi.org/10.1007/s10311-018-0705-z>
- Gaikwad, K.K., Singh, S., Negi, Y.S., 2020. Ethylene scavengers for active packaging of fresh food produce. *Environ. Chem. Lett.* 18, 269–284. <https://doi.org/10.1007/s10311-019-00938-1>
- 975 George, T., Brady, M.F., 2022. Ethylenediaminetetraacetic Acid (EDTA), in: *StatPearls*. StatPearls Publishing, Treasure Island (FL).
- Gharsallaoui, A., Oulahal, N., Joly, C., Degraeve, P., 2016. Nisin as a Food Preservative: Part 1: Physicochemical Properties, Antimicrobial Activity, and Main Uses. *Crit. Rev. Food Sci. Nutr.* 56, 1262–1274. <https://doi.org/10.1080/10408398.2013.763765>
- 980 Ghidelli, C., Pérez-Gago, M.B., 2018. Recent advances in modified atmosphere packaging and edible coatings to maintain quality of fresh-cut fruits and vegetables. *Crit. Rev. Food Sci. Nutr.* 58, 662–679. <https://doi.org/10.1080/10408398.2016.1211087>
- Giese, B., Klaessig, F., Park, B., Kaegi, R., Steinfeldt, M., Wigger, H., von Gleich, A., Gottschalk, F., 2018. Risks, Release and Concentrations of Engineered Nanomaterial in the Environment. *Sci. Rep.* 8, 1565. <https://doi.org/10.1038/s41598-018-19275-4>
- 985 Glass, B.D., Novák, C., Brown, M.E., 2004. The thermal and photostability of solid pharmaceuticals 24.
- Gonyon, T., Tomaso, A.E., Kotha, P., Owen, H., Patel, D., Carter, P.W., Cronin, J., Green, J.-B.D., 2013. Interactions between Parenteral Lipid Emulsions and Container Surfaces. *PDA J. Pharm. Sci. Technol.* 67, 247–254. <https://doi.org/10.5731/pdajpst.2013.00918>
- 990 Goodman, D.L., McDonnell, J.T., Nelson, H.S., Vaughan, T.R., Weber, R.W., 1990. Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). *J. Allergy Clin. Immunol.* 86, 570–575. [https://doi.org/10.1016/s0091-6749\(05\)80214-3](https://doi.org/10.1016/s0091-6749(05)80214-3)
- Grady, L., Thakker, K., 1980. Stability of Solid Drugs - Degradation of Ergocalciferol (vitamin-D2) and Cholecalciferol (vitamin-D3) at High Humidities and Elevated-Temperatures. *J. Pharm. Sci.* 69, 1099–1102. <https://doi.org/10.1002/jps.2600690932>
- 995 Grimm, W., 1998. Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV. *Drug Dev. Ind. Pharm.* 24, 313–325. <https://doi.org/10.3109/03639049809085626>
- Grimm, W., 1986. Stability Testing in Industry for Worldwide Marketing. *Drug Dev. Ind. Pharm.* 12, 1259–1292. <https://doi.org/10.3109/03639048609065859>
- 000 Guo, J., Lovegrove, J.A., Givens, D.I., 2018. 25(OH)D-3-enriched or fortified foods are more efficient at tackling inadequate vitamin D status than vitamin D-3. *Proc. Nutr. Soc.* 77, 282–291. <https://doi.org/10.1017/S0029665117004062>
- Guo, M., Sun, X., Chen, J., Cai, T., 2021. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. *Acta Pharm. Sin. B, Hot Topic Reviews in Drug Delivery* 11, 2537–2564. <https://doi.org/10.1016/j.apsb.2021.03.030>
- 005 Habermeyer, M., Roth, A., Guth, S., Diel, P., Engel, K.-H., Epe, B., Fürst, P., Heinz, V., Humpf, H.-U., Joost, H.-G., Knorr, D., de Kok, T., Kulling, S., Lampen, A., Marko, D., Rechkemmer, G., Rietjens, I., Stadler, R.H., Vieths, S., Vogel, R., Steinberg, P., Eisenbrand, G., 2015. Nitrate and nitrite in the diet: how to assess their benefit and risk for human health. *Mol. Nutr. Food Res.* 59, 106–128. <https://doi.org/10.1002/mnfr.201400286>
- 010 Hancock, B.W., Naysmith, A., 1975. Hypersensitivity to chlorocresol-preserved heparin. *Br. Med. J.* 3, 746–747. <https://doi.org/10.1136/bmj.3.5986.746-a>
- Haned, Z., Moulay, S., Lacorte, S., 2018. Migration of plasticizers from poly(vinyl chloride) and multilayer infusion bags using selective extraction and GC-MS. *J. Pharm. Biomed. Anal.* 156, 80–87. <https://doi.org/10.1016/j.jpba.2018.04.011>
- 015

- Hannon, J.C., Kerry, J.P., Cruz-Romero, M., Azlin-Hasim, S., Morris, M., Cummins, E., 2016. Assessment of the migration potential of nanosilver from nanoparticle-coated low-density polyethylene food packaging into food simulants. *Food Addit. Contam. Part -Chem. Anal. Control Expo. Risk Assess.* 33, 167–178. <https://doi.org/10.1080/19440049.2015.1114184>
- 020 Heimbach, J., Rieth, S., Mohamedshah, F., Slesinski, R., Samuel-Fernando, P., Sheehan, T., Dickmann, R., Borzelleca, J., 2000. Safety assessment of iron EDTA [sodium iron (Fe³⁺) ethylenediaminetetraacetic acid]: Summary of toxicological, fortification and exposure data. *Food Chem. Toxicol.* 38, 99–111. [https://doi.org/10.1016/S0278-6915\(99\)00125-8](https://doi.org/10.1016/S0278-6915(99)00125-8)
- Heinemann, L., Braune, K., Carter, A., Zayani, A., Krämer, L.A., 2021. Insulin Storage: A Critical Reappraisal. *J. Diabetes Sci. Technol.* 15, 147–159. <https://doi.org/10.1177/1932296819900258>
- 025 Hiatt, A.N., Taylor, L.S., Mauer, L.J., 2010. Influence of Simultaneous Variations in Temperature and Relative Humidity on Chemical Stability of Two Vitamin C Forms and Implications for Shelf Life Models. *J. Agric. Food Chem.* 58, 3532–3540. <https://doi.org/10.1021/jf903342f>
- Hirshfield, I.N., Terzulli, S., O’Byrne, C., 2003. Weak Organic Acids: A Panoply of Effects on Bacteria. *Sci. Prog.* 86, 245–270. <https://doi.org/10.3184/003685003783238626>
- 030 Hong, L.G., Yuhana, N.Y., Zawawi, E.Z.E., Hong, L.G., Yuhana, N.Y., Zawawi, E.Z.E., 2021. Review of bioplastics as food packaging materials. *AIMS Mater. Sci.* 8, 166–184. <https://doi.org/10.3934/matserci.2021012>
- Hovorka, S.W., Schoneich, C., 2001. Oxidative degradation of pharmaceuticals: Theory, mechanisms and inhibition. *J. Pharm. Sci.* 90, 253–269. [https://doi.org/10.1002/1520-6017\(200103\)90:3<253::AID-JPS1>3.0.CO;2-W](https://doi.org/10.1002/1520-6017(200103)90:3<253::AID-JPS1>3.0.CO;2-W)
- 035 ICH Q1A(R2), Stability testing of new drug substances and products, 2003. <https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf> (accessed 3.9.20).
- ICH Q1B, Photostability Testing of New Active Substances and Medicinal Products, 1996. <https://database.ich.org/sites/default/files/Q1B%20Guideline.pdf> (accessed 3.9.20).
- ICH Q1D, Bracketing and matrixing designs for stability testing of new drug substances and products, 2002. <https://database.ich.org/sites/default/files/Q1D%20Guideline.pdf> (accessed 26.4.22).
- 040 ICH Q5C, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, 1995. <https://database.ich.org/sites/default/files/Q5C%20Guideline.pdf> (accessed 30.9.21).
- ICH Q6A, Specifications: Test procedures and acceptance criteria for new drug substances and new drug products : Chemical substances, 1999. <https://database.ich.org/sites/default/files/Q6A%20Guideline.pdf> (accessed 8.2.21).
- 045 ICH Q6B, Specifications : Test procedures and acceptance criteria for biotechnological/biological products, 1999. <https://database.ich.org/sites/default/files/Q6B%20Guideline.pdf> (accessed 8.2.21).
- Iudicello, A., Genovese, F., Strusi, V., Dominici, M., Ruozi, B., 2021. Development and Validation of a New Storage Procedure to Extend the In-Use Stability of Azacitidine in Pharmaceutical Formulations. *Pharmaceuticals* 14, 943. <https://doi.org/10.3390/ph14090943>
- 050 Isaac, J., Scheinman, P.L., 2017. Benzalkonium Chloride: An Irritant and Sensitizer. *Dermat. Contact Atopic Occup. Drug* 28, 346–352. <https://doi.org/10.1097/DER.0000000000000316>
- Jahani, M., Bazzaz, B.S.F., Akaberi, M., Rajabi, O., Hadizadeh, F., 2022. Recent Progresses in Analytical Perspectives of Degradation Studies and Impurity Profiling in Pharmaceutical Developments: An Updated Review. *Crit. Rev. Anal. Chem.* <https://doi.org/10.1080/10408347.2021.2008226>
- 055 Jain, K., Singh, J., Jain, A., Khera, T., 2020. A Case Report of Nonalcoholic Gayet-Wernicke Encephalopathy: Don’t Miss Thiamine. *AA Pract.* 14, e01230. <https://doi.org/10.1213/XAA.0000000000001230>
- Jamrógiewicz, M., Pieńkowska, K., 2019. Recent breakthroughs in the stability testing of pharmaceutical compounds. *TrAC Trends Anal. Chem.* 111, 118–127. <https://doi.org/10.1016/j.trac.2018.12.007>
- 060 Janjarasskul, T., Krochta, J.M., 2010. Edible packaging materials. *Annu. Rev. Food Sci. Technol.* 1, 415–448. <https://doi.org/10.1146/annurev.food.080708.100836>
- Jariyasakoolroj, P., Leelaphiwat, P., Harnkarnsujarit, N., 2020. Advances in research and development of bioplastic for food packaging. *J. Sci. Food Agric.* 100, 5032–5045. <https://doi.org/10.1002/jsfa.9497>
- 065 Jelic, D., 2021. Thermal Stability of Amorphous Solid Dispersions. *Molecules* 26, 238. <https://doi.org/10.3390/molecules26010238>

- Jing, C.-L., Huang, R.-H., Su, Y., Li, Y.-Q., Zhang, C.-S., 2019. Variation in Chemical Composition and Biological Activities of Flos Chrysanthemi indici Essential Oil under Different Extraction Methods. *Biomolecules* 9, 518. <https://doi.org/10.3390/biom9100518>
- 070 Johnson, W., Bergfeld, W.F., Belsito, D.V., Hill, R.A., Klaassen, C.D., Liebler, D.C., Marks, J.G., Shank, R.C., Slaga, T.J., Snyder, P.W., Andersen, F.A., 2017. Safety Assessment of Benzyl Alcohol, Benzoic Acid and its Salts, and Benzyl Benzoate. *Int. J. Toxicol.* 36, 5S-30S. <https://doi.org/10.1177/1091581817728996>
- Kalogianni, A.I., Lazou, T., Bossis, I., Gelasakis, A.I., 2020. Natural Phenolic Compounds for the Control of Oxidation, Bacterial Spoilage, and Foodborne Pathogens in Meat. *Foods Basel Switz.* 9. <https://doi.org/10.3390/foods9060794>
- 075 Kalpana, S., Priyadarshini, S.R., Maria Leena, M., Moses, J.A., Anandharamakrishnan, C., 2019. Intelligent packaging: Trends and applications in food systems. *Trends Food Sci. Technol.* 93, 145–157. <https://doi.org/10.1016/j.tifs.2019.09.008>
- Karkman, A., Do, T.T., Walsh, F., Virta, M.P.J., 2018. Antibiotic-Resistance Genes in Waste Water. *Trends Microbiol.* 26, 220–228. <https://doi.org/10.1016/j.tim.2017.09.005>
- 080 Kireche, M., Peiffer, J.-L., Antonios, D., Fabre, I., Giménez-Arnau, E., Pallardy, M., Lepoittevin, J.-P., Ourlin, J.-C., 2011. Evidence for chemical and cellular reactivities of the formaldehyde releaser bronopol, independent of formaldehyde release. *Chem. Res. Toxicol.* 24, 2115–2128. <https://doi.org/10.1021/tx2002542>
- Kneifel, W., Czech, E., Kopp, B., 2002. Microbial contamination of medicinal plants - A review. *Planta Med.* 68, 5–15. <https://doi.org/10.1055/s-2002-20060>
- 085 Kopecký, A., Benda, F., Němčanský, J., 2018. Xerosis in Patient with Vitamin A Deficiency - a Case Report. *Ceska Slov. Oftalmol. Cas. Ceske Oftalmol. Spolecnosti Slov. Oftalmol. Spolecnosti* 73, 222–224.
- Kranke, B., SzolarPlatzer, C., Aberer, W., 1996. Reactions to formaldehyde and formaldehyde releasers in a standard series. *Contact Dermatitis* 35, 192–193. <https://doi.org/10.1111/j.1600-0536.1996.tb02354.x>
- 090 Kuai, L., Liu, F., Chiou, B.-S., Avena-Bustillos, R.J., McHugh, T.H., Zhong, F., 2021. Controlled release of antioxidants from active food packaging: A review. *Food Hydrocoll.* 120, 106992. <https://doi.org/10.1016/j.foodhyd.2021.106992>
- Kucuk, M., Caner, C., 2005. Effect of packaging materials and storage conditions on sunflower oil quality. *J. Food Lipids* 12, 222–231. <https://doi.org/10.1111/j.1745-4522.2005.00019.x>
- 095 Kuorwel, K.K., Cran, M.J., Orbell, J.D., Buddhadasa, S., Bigger, S.W., 2015. Review of Mechanical Properties, Migration, and Potential Applications in Active Food Packaging Systems Containing Nanoclays and Nanosilver. *Compr. Rev. Food Sci. Food Saf.* 14, 411–430. <https://doi.org/10.1111/1541-4337.12139>
- Kuswandi, B., Asih, N.P.N., Pratoko, D.K., Kristiningrum, N., Moradi, M., 2020. Edible pH sensor based on immobilized red cabbage anthocyanins into bacterial cellulose membrane for intelligent food packaging. *Packag. Technol. Sci.* 33, 321–332. <https://doi.org/10.1002/pts.2507>
- 100 Lavelli, V., D’Incecco, P., Pellegrino, L., 2021. Vitamin D Incorporation in Foods: Formulation Strategies, Stability, and Bioaccessibility as Affected by the Food Matrix. *Foods Basel Switz.* 10, 1989. <https://doi.org/10.3390/foods10091989>
- 105 Lawson, S., Lewis, P., Peacock, G., Brown, S., 2019. Comparative Stability of Oral Vitamin K Liquids Stored in Refrigerated Amber Plastic Syringes. *J. Pharm. Technol.* 35, 105–109. <https://doi.org/10.1177/8755122519838848>
- Le Pichon, J.-B., Riordan, S.M., Watchko, J., Shapiro, S.M., 2017. The Neurological Sequelae of Neonatal Hyperbilirubinemia: Definitions, Diagnosis and Treatment of the Kernicterus Spectrum Disorders (KSDs). *Curr. Pediatr. Rev.* 13, 199–209. <https://doi.org/10.2174/1573396313666170815100214>
- 110 Lennersten, M., Lingnert, H., 1998. Influence of different packaging materials on lipid oxidation in potato crisps exposed to fluorescent light. *Food Sci. Technol.-Lebensm.-Wiss. Technol.* 31, 162–168.
- Ling, T.C., Hight, A.S., 2000. Irritant reactions to an antiseptic bath emollient. *J. Dermatol. Treat.* 11, 263–267. <https://doi.org/10.1080/09546630050517216>
- Lips, P., van Schoor, N.M., 2011. The effect of vitamin D on bone and osteoporosis. *Best Pract. Res. Clin. Endocrinol. Metab.* 25, 585–591. <https://doi.org/10.1016/j.beem.2011.05.002>

- 115 Liu, L., Wang, J.-R., Mei, X., 2022. Enhancing the stability of active pharmaceutical ingredients by the cocrystal strategy. *CrystEngComm* 24, 2002–2022. <https://doi.org/10.1039/d1ce01327k>
- Lopez-Gomez, A., Cerdan-Cartagena, F., Suardiaz-Muro, J., Boluda-Aguilar, M., Esther Hernandez-Hernandez, M., Angeles Lopez-Serrano, M., Lopez-Coronado, J., 2015. Radiofrequency Identification and Surface Acoustic Wave Technologies for Developing the Food Intelligent Packaging Concept. *Food Eng. Rev.* 7, 11–32. <https://doi.org/10.1007/s12393-014-9102-y>
- 120 Luveris 75 UI poudre et solvant pour solution injectable - Résumé des caractéristiques du produit. Base Données Publique Médicam. https://ec.europa.eu/health/documents/community-register/2022/20220131154662/anx_154662_fr.pdf (accessed 2.11.22).
- Mabey, W., Mill, T., 1978. Critical-Review of Hydrolysis of Organic-Compounds in Water Under Environmental-Conditions. *J. Phys. Chem. Ref. Data* 7, 383–415. <https://doi.org/10.1063/1.555572>
- 125 Mahajan, R., Templeton, A., Harman, A., Reed, R.A., Chern, R.T., 2005. The effect of inert atmospheric packaging on oxidative degradation in formulated granules. *Pharm. Res.* 22, 128–140. <https://doi.org/10.1007/s11095-004-9018-y>
- Mahmoodani, F., Perera, C.O., Fedrizzi, B., Abernethy, G., Chen, H., 2017. Degradation studies of cholecalciferol (vitamin D3) using HPLC-DAD, UHPLC-MS/MS and chemical derivatization. *Food Chem.* 219, 373–381. <https://doi.org/10.1016/j.foodchem.2016.09.146>
- 130 Maibach, H.I., 1977. Dermal sensitization potential of 2-bromo-2-nitropropane-1,3-diol (Bronopol). *Contact Dermatitis* 3, 99. <https://doi.org/10.1111/j.1600-0536.1977.tb03608.x>
- McEney-Stonelake, M., Silvestri, D.L., 2014. Contact Allergens in Oral Antihistamines. *Dermatitis* 25, 83–88. <https://doi.org/10.1097/DER.0000000000000028>
- 135 Mohamed, S.A.A., El-Sakhawy, M., El-Sakhawy, M.A.-M., 2020. Polysaccharides, Protein and Lipid -Based Natural Edible Films in Food Packaging: A Review. *Carbohydr. Polym.* 238, 116178. <https://doi.org/10.1016/j.carbpol.2020.116178>
- MOPRAL 20 mg, gélule gastro-résistante - Résumé des caractéristiques du produit. Base Données Publique Médicam. <https://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=64103828&typedoc=R> (accessed 11.17.21).
- 140 Müller, P., Schmid, M., 2019. Intelligent Packaging in the Food Sector: A Brief Overview. *Foods* 8, 16. <https://doi.org/10.3390/foods8010016>
- Munyaka, A.W., Makule, E.E., Oey, I., Van Loey, A., Hendrickx, M., 2010. Thermal Stability of L-Ascorbic Acid and Ascorbic Acid Oxidase in Broccoli (*Brassica oleracea* var. *italica*). *J. Food Sci.* 75, C336–C340. <https://doi.org/10.1111/j.1750-3841.2010.01573.x>
- 145 MYOVIEW 230 microgrammes, trousse radiopharmaceutique - Résumé des caractéristiques du produit. Base Données Publique Médicam. <https://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=61360340&typedoc=R> (accessed 8.20.21).
- 150 Naghmouchi, K., Belguesmia, Y., Bendali, F., Spano, G., Seal, B.S., Drider, D., 2020. *Lactobacillus fermentum*: a bacterial species with potential for food preservation and biomedical applications. *Crit. Rev. Food Sci. Nutr.* 60, 3387–3399. <https://doi.org/10.1080/10408398.2019.1688250>
- Nair, B., 2001. Final report on the safety assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. *Int. J. Toxicol.* 20 Suppl 3, 23–50. <https://doi.org/10.1080/10915810152630729>
- 155 Negi, P.S., 2012. Plant extracts for the control of bacterial growth: Efficacy, stability and safety issues for food application. *Int. J. Food Microbiol.* 156, 7–17. <https://doi.org/10.1016/j.ijfoodmicro.2012.03.006>
- Nemati, M., Hamidi, A., Dizaj, S.M., Javaherzadeh, V., Lotfipour, F., 2016. An Overview on Novel Microbial Determination Methods in Pharmaceutical and Food Quality Control. *Adv. Pharm. Bull.* 6, 301–308. <https://doi.org/10.15171/apb.2016.042>
- 160 Nestic, A., Cabrera-Barjas, G., Dimitrijevic-Brankovic, S., Davidovic, S., Radovanovic, N., Delattre, C., 2020. Prospect of Polysaccharide-Based Materials as Advanced Food Packaging. *Molecules* 25, 135. <https://doi.org/10.3390/molecules25010135>
- Nguyen, V.H., Le, M.N., Nguyen, H.B., Ha, K.O., Pham, T.H.V., Nguyen, T.H., Dao, N.S.H., Nguyen, V.G., Nguyen, D.L., Trinh, N.T., 2021. Propyl Gallate. *Molbank* 2021, M1201. <https://doi.org/10.3390/M1201>

- 165 Nowak, C., K Cheung, J., M Dellatore, S., Katiyar, A., Bhat, R., Sun, J., Ponniah, G., Neill, A., Mason, B., Beck, A.,
Liu, H., 2017. Forced degradation of recombinant monoclonal antibodies: A practical guide. *mAbs* 9, 1217–
1230. <https://doi.org/10.1080/19420862.2017.1368602>
- Nur Hanani, Z.A., Roos, Y.H., Kerry, J.P., 2014. Use and application of gelatin as potential biodegradable packaging
170 materials for food products. *Int. J. Biol. Macromol.* 71, 94–102.
<https://doi.org/10.1016/j.ijbiomac.2014.04.027>
- Off, M.K., Steindal, A.E., Porojnicu, A.C., Juzeniene, A., Vorobey, A., Johnsson, A., Moan, J., 2005. Ultraviolet
photodegradation of folic acid. *J. Photochem. Photobiol. B* 80, 47–55.
<https://doi.org/10.1016/j.jphotobiol.2005.03.001>
- Ogienko, A.G., Drebuschak, V.A., Bogdanova, E.G., Yunoshev, A.S., Ogienko, A.A., Boldyreva, E.V., Manakov,
175 A.Y., 2017. Thermodynamic aspects of freeze-drying A case study of an “organic solvent-water” system. *J.*
Therm. Anal. Calorim. 127, 1593–1604. <https://doi.org/10.1007/s10973-016-6003-8>
- Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food
(AFC) related to para hydroxybenzoates (E 214–219), 2004. . *EFSA J.* 2, 83.
<https://doi.org/10.2903/j.efsa.2004.83>
- 180 Ottaway, P.B., 2010. Stability of vitamins during food processing and storage, in: Skibsted, L.H., Risbo, J., Andersen,
M.L. (Eds.), *Chemical Deterioration and Physical Instability of Food and Beverages*. Woodhead Publ Ltd,
Cambridge, pp. 539–560.
- Pandey, A.K., Kumar, P., Singh, P., Tripathi, N.N., Bajpai, V.K., 2017. Essential Oils: Sources of Antimicrobials and
Food Preservatives. *Front. Microbiol.* 7, 2161. <https://doi.org/10.3389/fmicb.2016.02161>
- 185 Pandya, J.K., DeBonee, M., Corradini, M.G., Camire, M.E., McClements, D.J., Kinchla, A.J., 2019. Development of
vitamin E-enriched functional foods: stability of tocotrienols in food systems. *Int. J. Food Sci. Technol.* 54,
3196–3204. <https://doi.org/10.1111/ijfs.14296>
- Parke, D.V., Lewis, D.F., 1992. Safety aspects of food preservatives. *Food Addit. Contam.* 9, 561–577.
<https://doi.org/10.1080/02652039209374110>
- 190 Prakash, B., Media, A., Mishra, P.K., Dubey, N.K., 2015. Plant essential oils as food preservatives to control moulds,
mycotoxin contamination and oxidative deterioration of agri-food commodities - Potentials and challenges.
Food Control 47, 381–391. <https://doi.org/10.1016/j.foodcont.2014.07.023>
- Proposal for a Directive of the European Parliament and of the Council amending Directive 95/2/EC on food additives
195 other than colours and sweeteners and Directive 94/35/EC on sweeteners for use in foodstuffs /*
COM/2004/0650 final, n.d.
- Ramsey, J.T., Shropshire, B.C., Nagy, T.R., Chambers, K.D., Li, Y., Korach, K.S., 2020. Essential Oils and Health.
Yale J. Biol. Med. 93, 291–305.
- Rashwan, A.K., Karim, N., Xu, Y., Xie, J., Cui, H., Mozafari, M.R., Chen, W., 2021. Potential micro-/nano-
200 encapsulation systems for improving stability and bioavailability of anthocyanins: An updated review. *Crit.*
Rev. Food Sci. Nutr. <https://doi.org/10.1080/10408398.2021.1987858>
- Regulation (EC) No 1333/2008 on food additives, 2008., OJ L. [https://eur-lex.europa.eu/legal-
content/EN/TXT/PDF/?uri=CELEX:32008R1333&from=EN](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1333&from=EN) (accessed 30.6.21).
- Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food and repealing
205 Directives 80/590/EEC and 89/109/EEC, 2004., OJ L. [https://eur-lex.europa.eu/legal-
content/EN/TXT/PDF/?uri=CELEX:32004R1935&from=EN](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R1935&from=EN) (accessed 30.6.21).
- Regulation (EU) No 1169/2011 on the provision of food information to consumers, 2011., OJ L. [https://eur-
lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN) (accessed 28.5.21).
- Ribeiro, D.O., Pinto, D.C., Lima, L.M.T.R., Volpato, N.M., Cabral, L.M., de Sousa, V.P., 2011. Chemical stability
study of vitamins thiamine, riboflavin, pyridoxine and ascorbic acid in parenteral nutrition for neonatal use.
210 *Nutr. J.* 10, 47. <https://doi.org/10.1186/1475-2891-10-47>
- Ribeiro-Santos, R., Andrade, M., de Melo, N.R., Sanches-Silva, A., 2017. Use of essential oils in active food
packaging: Recent advances and future trends. *Trends Food Sci. Technol.* 61, 132–140.
<https://doi.org/10.1016/j.tifs.2016.11.021>

- 215 Rincon-Lopez, J., Almanza-Arjona, Y.C., Riascos, A.P., Rojas-Aguirre, Y., 2021. Technological evolution of cyclodextrins in the pharmaceutical field. *J. Drug Deliv. Sci. Technol.* 61, 102156. <https://doi.org/10.1016/j.jddst.2020.102156>
- Risher, J.F., Murray, E.H., Prince, G.R., 2002. Organic mercury compounds: human exposure and its relevance to public health. *Toxicol. Ind. Health* 18, 109–160. <https://doi.org/10.1191/0748233702th138oa>
- 220 Roberts, M.S., Cossum, P.A., Galbraith, A.J., Boyd, G.W., 1980. The availability of nitroglycerin from parenteral solutions. *J. Pharm. Pharmacol.* 32, 237–244. <https://doi.org/10.1111/j.2042-7158.1980.tb12905.x>
- Rodil, R., Benito Quintana, J., Cela, R., 2012. Oxidation of synthetic phenolic antioxidants during water chlorination. *J. Hazard. Mater.* 199, 73–81. <https://doi.org/10.1016/j.jhazmat.2011.10.058>
- 225 Sabliov, C.M., Fronczek, C., Astete, C.E., Khachatryan, M., Khachatryan, L., Leonardi, C., 2009. Effects of Temperature and UV Light on Degradation of α -Tocopherol in Free and Dissolved Form. *J. Am. Oil Chem. Soc.* 86, 895–902. <https://doi.org/10.1007/s11746-009-1411-6>
- Sadeghi, K., Lee, Y., Seo, J., 2021. Ethylene Scavenging Systems in Packaging of Fresh Produce: A Review. *Food Rev. Int.* 37, 155–176. <https://doi.org/10.1080/87559129.2019.1695836>
- 230 Sakai, T., Hirai, D., Kimura, S.-I., Iwao, Y., Itai, S., 2018. Effects of tablet formulation and subsequent film coating on the supersaturated dissolution behavior of amorphous solid dispersions. *Int. J. Pharm.* 540, 171–177. <https://doi.org/10.1016/j.ijpharm.2018.02.013>
- Sanjeev, K., Ramesh, M.N., 2006. Low oxygen and inert gas processing of foods. *Crit. Rev. Food Sci. Nutr.* 46, 423–451. <https://doi.org/10.1080/10408390500215670>
- 235 Santos, J.C.P., Sousa, R.C.S., Otoni, C.G., Moraes, A.R.F., Souza, V.G.L., Medeiros, E.A.A., Espitia, P.J.P., Pires, A.C.S., Coimbra, J.S.R., Soares, N.F.F., 2018. Nisin and other antimicrobial peptides: Production, mechanisms of action, and application in active food packaging. *Innov. Food Sci. Emerg. Technol.* 48, 179–194. <https://doi.org/10.1016/j.ifset.2018.06.008>
- Santos-Sanchez, N.F., Salas-Coronado, R., Valadez-Blanco, R., Hernandez-Carlos, B., Guadarrama-Mendoza, P.C., 2017. Natural Antioxidant Extracts as Food Preservatives. *Acta Sci. Pol.-Technol. Aliment.* 16, 361–370. <https://doi.org/10.17306/J.AFS.2017.0530>
- 240 Sautou, V., 2013. Guide méthodologique des études de stabilité des préparations. SFPC GERPAC. https://www.gerpac.eu/IMG/pdf/guide_de_stabilite_vf_avril2013.pdf (accessed 30.9.21).
- Saw, N.K., Hindmarsh, J.R., 2005. Acute irritant reaction to an antiseptic bath emollient. *Postgrad. Med. J.* 81, 131–132. <https://doi.org/10.1136/pgmj.2003.018564>
- 245 Schnuch, A., Lessmann, H., Geier, J., Uter, W., 2011. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. *Br. J. Dermatol.* 164, 1316–1325. <https://doi.org/10.1111/j.1365-2133.2011.10253.x>
- Scientific Committee on Consumer Safety SCCS - Opinion on Butylated Hydroxytoluene (BHT), 2021.
- Sengupta, P., Chatterjee, B., Tekade, R.K., 2018. Current regulatory requirements and practical approaches for stability analysis of pharmaceutical products: A comprehensive review. *Int. J. Pharm.* 543, 328–344. <https://doi.org/10.1016/j.ijpharm.2018.04.007>
- 250 Shahidi, F., Zhong, Y., 2010. Novel antioxidants in food quality preservation and health promotion. *Eur. J. Lipid Sci. Technol.* 112, 930–940. <https://doi.org/10.1002/ejlt.201000044>
- Sharma, S., Barkauskaite, S., Jaiswal, A.K., Jaiswal, S., 2021. Essential oils as additives in active food packaging. *Food Chem.* 343, 128403. <https://doi.org/10.1016/j.foodchem.2020.128403>
- 255 Shintani, H., 2015. Validation Studies for Microbial Contamination and Control of Contaminants. *Biocontrol Sci.* 20, 161–170. <https://doi.org/10.4265/bio.20.161>
- Shwaiki, L.N., Lynch, K.M., Arendt, E.K., 2021. Future of antimicrobial peptides derived from plants in food application-A focus on synthetic peptides. *Trends Food Sci. Technol.* 112, 312–324. <https://doi.org/10.1016/j.tifs.2021.04.010>
- 260 Silva, M.M., Lidon, F.C., 2016. An overview on applications and side effects of antioxidant food additives. *Emir. J. Food Agric.* 28, 823–832. <https://doi.org/10.9755/ejfa.2016-07-806>
- Simon, N., Sperber, C., Voigtlaender, C., Born, J., Gilbert, D.F., Seyferth, S., Lee, G., Kappes, B., Friedrich, O., 2020. Improved stability of polyclonal antibodies: A case study with lyophilization-conserved antibodies raised

- against epitopes from the malaria parasite *Plasmodium falciparum*. *Eur. J. Pharm. Sci.* 142, 105086. <https://doi.org/10.1016/j.ejps.2019.105086>
- 265 Singh, P., Wani, A.A., Karim, A.A., Langowski, H.-C., 2012. The use of carbon dioxide in the processing and packaging of milk and dairy products: A review. *Int. J. Dairy Technol.* 65, 161–177. <https://doi.org/10.1111/j.1471-0307.2011.00744.x>
- 270 Sławińska, A., Fornal, E., Radzki, W., Skrzypczak, K., Zalewska-Korona, M., Michalak-Majewska, M., Parfieniuk, E., Stachniuk, A., 2016. Study on vitamin D₂ stability in dried mushrooms during drying and storage. *Food Chem.* 199, 203–209. <https://doi.org/10.1016/j.foodchem.2015.11.131>
- Socha, D.S., DeSouza, S.I., Flagg, A., Sekeres, M., Rogers, H.J., 2020. Severe megaloblastic anemia: Vitamin deficiency and other causes. *Cleve. Clin. J. Med.* 87, 153–164. <https://doi.org/10.3949/ccjm.87a.19072>
- Sofos, J.N., Busta, F.F., 1981. Antimicrobial Activity of Sorbate. *J. Food Prot.* 44, 614–622. <https://doi.org/10.4315/0362-028X-44.8.614>
- 275 Song, X., Shi, L., Liu, S., Hou, C., Zhu, K., Cheng, Q., Mei, L., 2022. Development of Microcapsule Bioactive Paper Loaded with Chinese Fir Essential Oil to Improve the Quality of Strawberries. *Coatings* 12, 254. <https://doi.org/10.3390/coatings12020254>
- 280 Sothornvit, R., 2019. Nanostructured materials for food packaging systems: new functional properties. *Curr. Opin. Food Sci., Food Chemistry and Biochemistry • Food Bioprocessing* 25, 82–87. <https://doi.org/10.1016/j.cofs.2019.03.001>
- Stawny, M., Gostyńska, A., Olijarczyk, R., Jelińska, A., Ogrodowczyk, M., 2020. Stability of high-dose thiamine in parenteral nutrition for treatment of patients with Wernicke's encephalopathy. *Clin. Nutr. Edinb. Scotl.* 39, 2929–2932. <https://doi.org/10.1016/j.clnu.2019.12.003>
- 285 Summers, Q.A., Nesbit, M.R., Levin, R., Holgate, S.T., 1991. A non-bronchoconstrictor, bacteriostatic preservative for nebuliser solutions. *Br. J. Clin. Pharmacol.* 31, 204–206. <https://doi.org/10.1111/j.1365-2125.1991.tb05517.x>
- Sun, C., Cao, J., Wang, Y., Huang, L., Chen, J., Wu, J., Zhang, H., Chen, Y., Sun, Chongde, 2022. Preparation and characterization of pectin-based edible coating agent encapsulating carvacrol/HP beta CD inclusion complex for inhibiting fungi. *Food Hydrocoll.* 125, 107374. <https://doi.org/10.1016/j.foodhyd.2021.107374>
- 290 Sun, Y., Zhang, M., Adhikari, B., Devahastin, S., Wang, H., 2022. Double-layer indicator films aided by BP-ANN-enabled freshness detection on packaged meat products. *Food Packag. Shelf Life* 31, 100808. <https://doi.org/10.1016/j.fpsl.2021.100808>
- Tamizi, E., Jouyban, A., 2016. Forced degradation studies of biopharmaceuticals: Selection of stress conditions. *Eur. J. Pharm. Biopharm.* 98, 26–46. <https://doi.org/10.1016/j.ejpb.2015.10.016>
- 295 Temova, Z., Roskar, R., 2016. Stability-Indicating HPLC-UV Method for Vitamin D-3 Determination in Solutions, Nutritional Supplements and Pharmaceuticals. *J. Chromatogr. Sci.* 54, 1180–1186. <https://doi.org/10.1093/chromsci/bmw048>
- [dataset] Thériaque <https://www.theriaque.org/>
- 300 Thery, T., Lynch, K.M., Arendt, E.K., 2019. Natural Antifungal Peptides/Proteins as Model for Novel Food Preservatives. *Compr. Rev. Food Sci. Food Saf.* 18, 1327–1360. <https://doi.org/10.1111/1541-4337.12480>
- Topuz, F., Uyar, T., 2020. Antioxidant, antibacterial and antifungal electrospun nanofibers for food packaging applications. *Food Res. Int.* 130, 108927. <https://doi.org/10.1016/j.foodres.2019.108927>
- 305 Trajkovska Petkoska, A., Daniloski, D., D'Cunha, N.M., Naumovski, N., Broach, A.T., 2021. Edible packaging: Sustainable solutions and novel trends in food packaging. *Food Res. Int. Ott. Ont* 140, 109981. <https://doi.org/10.1016/j.foodres.2020.109981>
- Treleano, A., Wolz, G., Brandsch, R., Welle, F., 2009. Investigation into the sorption of nitroglycerin and diazepam into PVC tubes and alternative tube materials during application. *Int. J. Pharm.* 369, 30–37. <https://doi.org/10.1016/j.ijpharm.2008.10.024>
- 310 Urbanaviciute, I., Liaudanskas, M., Bobinas, C., Sarkinas, A., Rezgiene, A., Viskelis, P., 2020. Japanese Quince (*Chaenomeles japonica*) as a Potential Source of Phenols: Optimization of the Extraction Parameters and Assessment of Antiradical and Antimicrobial Activities. *Foods* 9, 1132. <https://doi.org/10.3390/foods9081132>

- 315 Vallverdu-Queralt, A., Regueiro, J., Rinaldi Alvarenga, J.F., Martinez-Huelamo, M., Leal, L.N., Lamuela-Raventos, R.M., 2015. Characterization of the phenolic and antioxidant profiles of selected culinary herbs and spices: caraway, turmeric, dill, marjoram and nutmeg. *Food Sci. Technol.* 35, 189–195. <https://doi.org/10.1590/1678-457X.6580>
- Vally, H., Misso, N.L.A., Madan, V., 2009. Clinical effects of sulphite additives. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* 39, 1643–1651. <https://doi.org/10.1111/j.1365-2222.2009.03362.x>
- Vasile, C., Baican, M., 2021. Progresses in Food Packaging, Food Quality, and Safety-Controlled-Release Antioxidant and/or Antimicrobial Packaging. *Molecules* 26, 1263. <https://doi.org/10.3390/molecules26051263>
- 320 Veien, N.K., Hattel, T., Laurberg, G., 1996. Oral challenge with parabens in paraben-sensitive patients. *Contact Dermatitis* 34, 433–433. <https://doi.org/10.1111/j.1600-0536.1996.tb02252.x>
- Vena, G.A., Foti, C., Angelini, G., 1994. Sulfite contact allergy. *Contact Dermatitis* 31, 172–175. <https://doi.org/10.1111/j.1600-0536.1994.tb01959.x>
- 325 Vieira, M., Bessa, L.J., Rosario Martins, M., Arantes, S., Teixeira, A.P.S., Mendes, A., da Costa, P.M., Belo, A.D.F., 2017. Chemical Composition, Antibacterial, Antibiofilm and Synergistic Properties of Essential Oils from *Eucalyptus globulus* LABILL. and Seven Mediterranean Aromatic Plants. *Chem. Biodivers.* 14, e1700006. <https://doi.org/10.1002/cbdv.201700006>
- Vogel, J., Weiss, V., Oischinger, J., Daschner, R., Meiller, M., 2016. Treatment of nanomaterial-containing waste in thermal waste treatment facilities. *Gefahrstoffe Reinhalt. Luft* 76, 331–337.
- 330 Walker, S.E., Iazzetta, J., Law, S., Kanji, S., Bolduc, B., Lamontagne, F., Adhikari, N.K.J., 2019. Administration of Intravenous Ascorbic Acid-Practical Considerations for Clinicians. *Nutrients* 11. <https://doi.org/10.3390/nu11091994>
- Wang, H., Qian, J., Ding, F., 2018. Emerging Chitosan-Based Films for Food Packaging Applications. *J. Agric. Food Chem.* 66, 395–413. <https://doi.org/10.1021/acs.jafc.7b04528>
- 335 Wang, S., Liu, X., Yang, M., Zhang, Y., Xiang, K., Tang, R., 2015. Review of Time Temperature Indicators as Quality Monitors in Food Packaging. *Packag. Technol. Sci.* 28, 839–867. <https://doi.org/10.1002/pts.2148>
- Waterman, K.C., Adami, R.C., 2005a. Accelerated aging: Prediction of chemical stability of pharmaceuticals. *Int. J. Pharm.* 293, 101–125. <https://doi.org/10.1016/j.ijpharm.2004.12.013>
- 340 Waterman, K.C., Adami, R.C., Alsante, K.M., Antipas, A.S., Arenson, D.R., Carrier, R., Hong, J., Landis, M.S., Lombardo, F., Shah, J.C., Shalae, E., Smith, S.W., Wang, H., 2002a. Hydrolysis in Pharmaceutical Formulations. *Pharm. Dev. Technol.* 7, 113–146. <https://doi.org/10.1081/PDT-120003494>
- Waterman, K.C., Adami, R.C., Alsante, K.M., Hong, J., Landis, M.S., Lombardo, F., Roberts, C.J., 2002b. Stabilization of Pharmaceuticals to Oxidative Degradation. *Pharm. Dev. Technol.* 7, 1–32. <https://doi.org/10.1081/PDT-120002237>
- 345 Wentworth, A.B., Yiannias, J.A., Davis, M.D.P., Killian, J.M., 2016. Benzalkonium Chloride: A Known Irritant and Novel Allergen. *Dermat. Contact Atopic Occup. Drug* 27, 14–20. <https://doi.org/10.1097/DER.0000000000000160>
- WHO Expert Committee on specifications for pharmaceutical preparations, 2008. *Rev. Inst. Med. Trop. São Paulo* 50, 144–144. <https://doi.org/10.1590/S0036-46652008000300013>
- 350 WHO guidelines, Annex 10 on stability testing of active pharmaceutical ingredients and finished pharmaceutical products, 2018. <https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1010-annex10-who-stability-testing-of-active-pharmaceutical-ingredients.pdf> (accessed 2.11.22).
- 355 Wilson, M.D., Stanley, R.A., Eyles, A., Ross, T., 2019. Innovative processes and technologies for modified atmosphere packaging of fresh and fresh-cut fruits and vegetables. *Crit. Rev. Food Sci. Nutr.* 59, 411–422. <https://doi.org/10.1080/10408398.2017.1375892>
- Wu, D., Zhang, M., Chen, H., Bhandari, B., 2021. Freshness monitoring technology of fish products in intelligent packaging. *Crit. Rev. Food Sci. Nutr.* 61, 1279–1292. <https://doi.org/10.1080/10408398.2020.1757615>
- 360 Xu, X., Liu, A., Hu, S., Ares, I., Martínez-Larrañaga, M.-R., Wang, X., Martínez, M., Anadón, A., Martínez, M.-A., 2021. Synthetic phenolic antioxidants: Metabolism, hazards and mechanism of action. *Food Chem.* 353, 129488. <https://doi.org/10.1016/j.foodchem.2021.129488>

- Yan, Y., Li, Y., Zhang, Z., Wang, X., Niu, Y., Zhang, S., Xu, W., Ren, C., 2021. Advances of peptides for antibacterial applications. *Colloids Surf. B-Biointerfaces* 202, 111682. <https://doi.org/10.1016/j.colsurfb.2021.111682>
- 365 Yang, X., Song, W., Liu, N., Sun, Z., Liu, R., Liu, Q.S., Zhou, Q., Jiang, G., 2018. Synthetic Phenolic Antioxidants Cause Perturbation in Steroidogenesis in Vitro and in Vivo. *Environ. Sci. Technol.* 52, 850–858. <https://doi.org/10.1021/acs.est.7b05057>
- 370 Yildirim, S., Röcker, B., Pettersen, M.K., Nilsen-Nygaard, J., Ayhan, Z., Rutkaite, R., Radusin, T., Suminska, P., Marcos, B., Coma, V., 2018. Active Packaging Applications for Food. *Compr. Rev. Food Sci. Food Saf.* 17, 165–199. <https://doi.org/10.1111/1541-4337.12322>
- Zhang, C., Li, Y., Wang, P., Zhang, H., 2020. Electrospinning of nanofibers: Potentials and perspectives for active food packaging. *Compr. Rev. Food Sci. Food Saf.* 19, 479–502. <https://doi.org/10.1111/1541-4337.12536>
- 375 Zhang, F., Zhang, M., Chen, Y., Ouyang, J., Wang, Yan, Yang, H., Luo, X., Zhang, D., Lu, Y., Yu, H., Wang, Yipeng, 2021. Antimicrobial, anti-biofilm properties of three naturally occurring antimicrobial peptides against spoilage bacteria, and their synergistic effect with chemical preservatives in food storage. *Food Control* 123, 107729. <https://doi.org/10.1016/j.foodcont.2020.107729>

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