Journal of Pharmaceutical and Biomedical Analysis 155 (2018) 298–305

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Development of an HPLC/UV method for the evaluation of extractables and leachables in plastic: Application to a plastic-packaged calcium gluconate glucoheptonate solution

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ARTICLE INFO

Article history:
Received 3 January 2018
Received in revised form 17 March 2018
Accepted 19 March 2018
Available online 21 March 2018

Keywords:
Content container interaction
Extractable
Leachable
Calcium gluconate glucoheptonate
Safety concern threshold
Analytical evaluation threshold

ABSTRACT

Calcium gluconate glucoheptonate (GGCa) is known to interact with glass containers, leading to the leaching of aluminum from the glass into the solution at toxic level. Therefore, plastic containers seem to be a preferable packaging alternative. Nevertheless, plastics contain potentially toxic additives which could be released into the solution. In order to study content container interaction between GGCa and two plastic containers (polypropylene PP and polyethylene PE containers), an HPLC-PDA method was developed to separate, detect and quantify eleven additives commonly found in plastic materials, with good limit of detection and quantification. This method was then applied to evaluate the compatibility between GGCa and the two plastic containers. After 3 months of storage at 25 °C, none of the eleven additives were detected in GGCa solutions. The safety concern threshold (SCT) and of the analytical evaluation threshold (AET) were evaluated to discriminate the need to identify and qualify unknown peaks.

1. Introduction

Calcium gluconate glucoheptonate (GGCa) is prescribed when calcium supplementation is needed during parenteral nutrition as compounding agent for the preparation of the parenteral formulation. It is well documented that glass-packaged GGCa solutions are the primary source of high levels of aluminum salts in the resulting parenteral nutrition formulation, due to aluminum (Al) release from the glass container [1–4]. This is why recommandations have been made to use plastic packaging for formulating GGCa solutions [5,6]. Plastic turned out to be the material of choice for many pharmaceutical products, as it presents many advantages compared to glass: it is less friable, has a lower cost, is easier to handle and store. The major disadvantage of plastic packaging materials is the necessity to incorporate in the final formulation of the plastic film various additives. These additives, if they are released in the contained product, may potentially be toxic and impact the safety profile of the pharmaceutical product [7].

During the pharmaceutical development, regulatory requirements and guidelines impose to assess the container-content compatibility, particularly as regards leachables and extractables [8,9]. Some expert working groups (mostly PQRI) have proposed a methodology for assessing both extractable and leachable from plastic containers [10–12]. The first step aims at gathering the most updated information on the composition of the plastic materials and its quality control specifications from the provider which is hardly achieved due to confidentiality reasons. The second step consists in performing extraction studies to seek potential presence of the additive extracted from the container material. These tests should be performed using extraction solvents and/or extraction conditions that are more aggressive than the conditions encountered in the actual condition of use [13]. The last step aims at evaluating the leachables which are defined as those chemical substances that migrate from the container material into the final product, under normal storage conditions and within the product shelf life. Leachables are evaluated only in the final product under exaggerated or accelerated conditions [13]. Those content container interaction studies face analytical challenges, as the additives that can be found in almost all of the plastics used in packaging materials have diverse chemical structure and properties (from simple molecules such as Butylated hydroxytoluene (BHT) up to

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https://doi.org/10.1016/j.jpba.2018.03.044
0731-7085/

complex polymers as the Irganox family). Moreover, for many additives no commercial standards are available and those additives can themselves degrade with time into several other degradation products and thus generate unidentifiable peaks on the chromatogram [13,14]. It is then recommended to use multiple analytical methodologies, as it was performed by Jenke et al. (2013) for the evaluation of five plastic materials using combined GC–MS, HPLC–MS and ICP-OES [15]. If extractables/leachables are observed, identification and toxicity evaluation is necessary, which could be time and cost consuming, not to mention that for many additives no toxicological data can be found. It is necessary to define a safety concern threshold (SCT): value below which leachable and/or extractable is not considered for identification and toxicological qualification, and to convert this SCT into an analytical evaluation threshold (AET): level at/or above which a leachable and/or extractable should be reported and considered for potential toxicological assessment [11,10]. These assessments of extractables and leachables are now described in the general chapters ⟨1663⟩ and ⟨1664⟩ of the USP.

Few methods have been published and they often present a lack of sensitivity and/or target only one class of additives. Norwood et al.'s review (2009) illustrates the analytical complexity of extractable/leachable studies [16]. Petrusevski et al. (2016) have proposed an HPLC-PDA-APCI MS method capable to detect and quantify nine plastic additives, including polymeric hindered amine light stabilizers, with successful resolution and good sensitivity [17]. The European Pharmacopoeia proposes three methods of HPLC-PDA capable to detect all the potential additives found in polypropylene (PP) and polyethylene (PE) materials, but these methods are time consuming and the limit of detection is coherent with the expected level of these additives in the plastic material but not coherent with any potential toxicity in the final product. Based on these limitations, it is worth considering developing powerful methods that can detect leachable products, potentially present at a toxic level, in pharmaceutical final product contained in plastic packaging material.

This work has been initiated with the aim of developing a simple, sensitive and resolutive method capable to separate and quantify eleven chemical additives within a wide range of hydrophobicity. This method, once validated, has been applied to evaluate the compatibility between the two infusion bags tested and GGCa solution regarding the detected additives.

2. Experimentals

2.1. Chemical and reagents

Acetonitrile – HPLC grade (Sigma Aldrich, Germany) and purified water (obtained from Milliport in-house water purification system) were used.

System suitability mixture used for method development was composed of the following additives: Butylhydroxytoluene (BHT) (Sigma Aldrich, Germany), Hostanox O3 (Substance of reference, European pharmacopée), Irganox 1010 (Sigma Aldrich, Germany), Irganox 1330 (Sigma Aldrich, Germany), Irganox 1076 (Sigma Aldrich, Germany), Irgafos 168 (Sigma Aldrich, Germany), Irganox 3114 (Substance of reference, European pharmacopée), Bisphenol A (Sigma Aldrich, Germany), Bisphenol M (Sigma Aldrich, Germany), Irganox 415 (TCI Europe, France), and Diphenylamine (Sigma Aldrich, Germany).

Stock solutions of each additive were prepared by dissolving approximately 10 mg of additive in 10 mL methanol. These solutions were mixed to prepare system suitability solution with additive concentrations range from 10 mg/L and 100 mg/L. Dilutions were made with mobile phase (90/10 acetonitrile/purified water).

Table 1
Gradient condition.

Time (min)	ACN (%)	Water (%)
0	50	50
3	70	30
10	80	20
15–25	95	5
25–30	50	50

Extraction studies were carried out with HPLC grade acetonitrile and ultra-pure water. 140 g of calcium gluconate (Zhejiang Ruibang Laboratoires, China) were mixed with 65.50 g of calcium glucoheptonate (Givaudan Lavirotte, France) in two liters of ultra-pure water to obtain the solution of calcium gluconate glucoheptonate. The solution was filtered (through a 0,22 μm filter) and used for extractable and leachable studies detailed in the following paragraphs.

2.2. Containers

Solutions were introduced into 250 mL polyethylene (PE) and polypropylene (PP) infusion bags. Both kind of infusion bags were kindly provided by our two potential future industrial partners. The infusion bags are classic ones and are both already used for others pharmaceutical products on the market.

2.3. Instrumentation

The development and optimization of the analytical method was performed with a Dionex ultimate 3000 HPLC equipment hyphenated with a UV/Vis diode-array detector. Instrument control and results processing was performed using Dionex Chromeleon 6.8 software. Chromatographic separation was optimised using a Luna phenyl hexyl (Phenomenex) column; 150 × 4,6 mm; 3 μm. The final chromatographic conditions were as follows: mobile phase made of water and acetonitrile in gradient mode (gradient presented Table 1), a flow rate of 1 mL/min, injection volume of 20 μL and UV detection at 220 nm, with a UV scale between 220 and 280 nm.

2.4. Content container interaction study

2.4.1. Estimation of the safety concern threshold (SCT) and the analytical evaluation threshold (AET)

The SCT and the AET are calculated according to PQRI recommendations [11]. GGCa solution is used for parenteral administration, and can be used for chronic use. Therefore, the SCT of 1,5 μg/day is applicable [10]. The estimated AET is then calculated with the Formula (1) [12]. The final AET, which take into account the analytical uncertainty, is calculated with the Formula (2). The uncertainty factor corresponds to the relative standard deviation (%RSD) of the response factors in the database, or corresponds to a factor of 50%, whichever is greater.

$$Estimated AET(\mu g/mL) = SCT(\mu g/day)/daily dose volume(mL/day) \quad (1)$$

$$Final AET(\mu g/mL) = Estimated AET(\mu g/mL) - \text{“}uncertainty factor\text{”} \quad (2)$$

For a chronical parenteral product, a SCT of 1,5 μg/day should be applied as it is assumed to be an acceptable threshold for risk of carcinogenicity. ICH M7 is in agreement with this threshold limit. The AET is calculated in function of the daily dose volume. In the case of GGCa, the daily dose volume is function of Calcium supplementation. In the worst case it can be estimated at 36 mL/day. Taking into account this daily dose, and that the volume inside the infusion bags of the solution is 50 mL in this study (250 mL in the final product), the estimated AET is 0,2 μg/mL.

Table 2
Extractable study conditions.

	3 days			7 days			10 days		
	25 °C	40 °C	60 °C	25 °C	40 °C	60 °C	25 °C	40 °C	60 °C
ACN	X			X			X		
ACN/Water	X	X		X	X		X	X	
Water	X	X	X	X	X	X	X	X	X

2.4.2. Study of extractables

Extractable studies were conducted in three solvents (100% ACN, ACN/Water 50/50%, Water 100%). As the pharmaceutical formulation is the API diluted in water, with neutral pH, 100% water is estimated to be close to the formulation. The two other solvents increase the ability of potential additives to migrate into solvent. 50 mL of each solvent have been distributed in PP and PE infusion bags. Infusion bags were placed under three temperatures up to 10 days depending on the ability of the solvent to extract plastic additives. When vehicle tested was closer to pharmaceutical formulation, thermal stress and times of study were increased. Operating conditions are presented in Table 2.

2.4.3. Study of leachables

Six PP infusion bags and six PE infusion bags were filled with 50 mL of GGCa solution. Half were stored at 25 °C and half were stored at 40 °C. A leachable analysis of the GGCa solution was performed initially and after 1, 2 and 3 months stored at 25 °C and 40 °C.

3. Results and discussion

3.1. Choice of additives

The exact composition of the packaging materials is often a confidential information (even if a confidentiality agreement is signed), and it is practically impossible to know the exact number and name or structure of the additives present in the plastic material which might migrate in the pharmaceutical product. These interaction studies should be included at an early stage of pharmaceutical form development in order to select the container with the lower risk of interaction. Additives evaluated in this study were selected regarding to their commercial availability, and with regard to the European Pharmacopeia monographies for PP and PE. The 11 additives (Butylhydroxytoluene, Hostanox O3, Irganox 1010, Irganox 1330, Irganox 1076, Irgafos 168, Irganox 3114, Bisphenol A, Bisphenol M, Irganox 415, Diphenylamine), presented in Table 3 , were included in this study.

3.2. Development and validation of HPLC conditions

Most of the methods published in the literature or described in the European pharmacopoeia use octadecyl stationary phase. Three different types of HPLC-PDA method are detailed in the European Pharmacopoeia with increasing order of organic phase used in order to cover a wide range of hydrophobicity of the molecules separated. It is well established that increasing length and porosity of this stationary phase with optimization of a gradient could lead to successful separation. However, acceptable resolution and retention on this column for all these additives were not obtained due to the wide polarity range of the additives studied. Therefore, a phenylhexyl stationary phase, on which л-л and hydrophobic interactions can occur between stationary phase and molecules, was selected. Both the difference of hydrophobicity and aromaticity of the components increase retention of those additives on the chromatographic column. The optimization of the method was then made by testing various mobile phase, with isocratic or gradient mode. Best sensitivity of detection was obtained at 220 nm.

The method was evaluated for its linearity, repeatability and limits of detection (LOD) and quantification (LOQ). An average response factor was calculated in order to estimate the amount of unidentified additives. All of the results are shown Table 5. Linearity was tested by injecting the component of the system suitability mix at trace levels (0.5–10 ppm) and evaluating each individual correlation factor (R^2). The linearity is excellent for all of the tested molecules (R value >0,99). LOD and LOQ for each additive were estimated based on the S/N ratio produced by injecting 20 µL of the system suitability mix at 0.5 ppm. Repeatability was tested with the injection of system suitability mix 3 times. Resolution between peaks is 1,4 minimum, which is sufficient for trace detection of additives. The chromatogram of the system suitability mix of the eleven additives is presented Fig. 1.

3.3. Application to the evaluation of content container interaction between GGCa solution and PP or PE plastic containers

3.3.1. Calculation of the final AET

The estimated AET is 0,2 µg/mL. An uncertainty factor of 50% should be applied, because it is greater than the%RSD of the response factors (49,5%, Table 4). So the final AET is 0,1 µg/mL. For known additives, all of the LOD are below this final AET, which indicate the good sensibility of the developed method.

As it is recommended by the PQRI group [11], the SCT and the AET should be calculated in order to evaluate the necessity of identifying and performing a toxicological risk assessment on the extractables or leachables that could be detected during extractable and leachable studies.

3.3.2. Evaluation of the extractables

As there are no directive for extraction studies, these experiments were designed with regards to the aim of the study. Because GGCa is made of aqueous solvent, extraction studies were done under thermal stress with different solutions containing various amount of water and acetonitrile. The results of the extractables study are presented Tables 5 and 6. For unknown peaks, the concentration is estimated using a surrogate standard (Hostanox O3, as its response factor is closed to the average response factor)

3.3.2.1. ACN 100% at 25 °C up to 10 days. In PP containers, the identified extractible in the 100% acetonitrile conditions were the Irganox 415, 1010, 1330 and 1076, BHT, and Irgafos 168. Nine other unknown extractibles were observed in this condition. In PE containers, only Irganox 415 and 1076 were identified as possible extractables. Five other non-identified extractables were also observed in this condition. For majority of the extractables, the amounts detected increased with time whereas for some of them, their residual amount seemed to decrease with time (Irgafos 168, X8), probably due to their own degradation in unknown entities.

3.3.2.2. 50% acetonitrile/50% water at 25 °C and 40 °C up to 10 days. In PP containers, only two identified extractables were present in the 50% acetonitrile/50% water condition: Irganox 1010 and 1330. Irganox 1010 was present in the same amount as with 100% acetonitrile conditions. The concentration of Irganox 1330 was 5–6 time less than in 100% acetonitrile conditions, and increased with time at 25 °C (1,27 ppm after 3 days, 1,82 ppm after 10 days), but decreased with time at 40 °C (1,23 ppm after 3 days, 0,17 ppm after 10 days). Degradation of Irganox 1330 might happen at 40 °C, but this degradation seems to have no impact on BHT level, the main degradation product. Four unknown molecules were observed in PP containers, including two already observed in 100% acetonitrile condition (X3, X10) and two new (X2 and X9). X1, X5, X6, X7 and

Table 3
Description of the different additives studied.

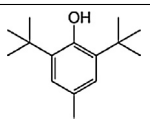
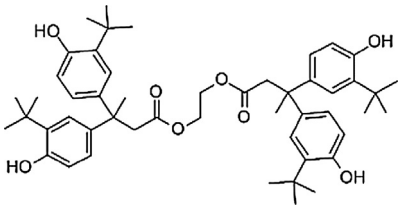
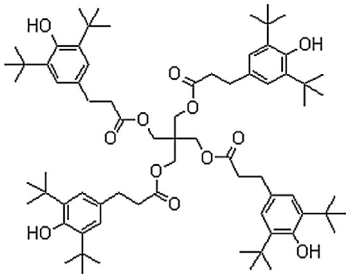
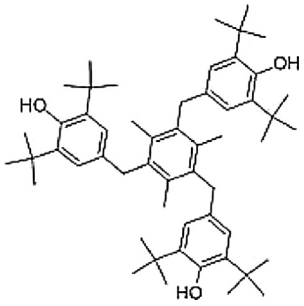
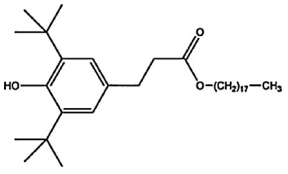
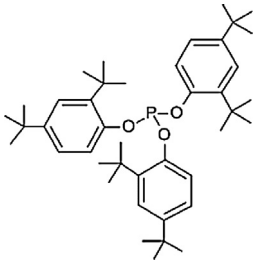
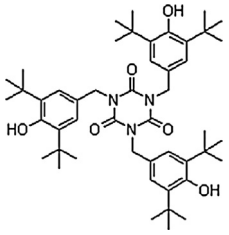
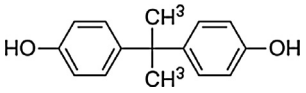
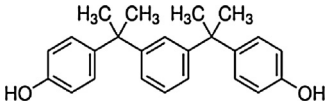
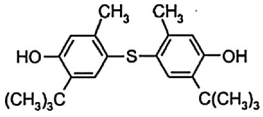
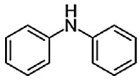
Name of additive	Chemical family	Use	Log P*	Structure
Butylhydroxytoluene (BHT) N° CAS 128-37-0 Additif 07	Phenol	Antioxidant	5,30	
Hostanox O3 N° CAS 32509-66-3 Additif 08	Ester	Antioxidant	13,1	
Irganox 1010 N° CAS 6683-19-8 Additif 09	Ester	Antioxidant	19,4	
Irganox 1330 N° CAS 1709-70-2 Additif 10	Phenol	Antioxidant	17,7	
Irganox 1076 N° CAS 2082-79-3 Additif 11	Ester	Antioxidant	13,8	
Irgafos 168	Phosphate	Antioxidant	15,5	

Table 3 (*Continued*)

Name of additive	Chemical family	Use	Log P*	Structure
N° CAS 31570-04-4 Additif 12				
Irganox 3114	Triazine	Antioxidant	12,8	
N° CAS 27676-62-6 Additif 13				
Bisphenol A	Phenol	Antioxidant	3,3	
N° CAS 80-05-7				
Bisphenol M	Phenol	Antioxidant	6,1	
N° CAS 13595-25-0				
Irganox 415	Thioether	Antioxidant	7,4	
N° CAS 96-69-5				
Diphénylamine	Amine	Stabilizing, ink, manufacture of rubber	3,5	
N° CAS 122-39-4				

* Log P values come from PubChem database.

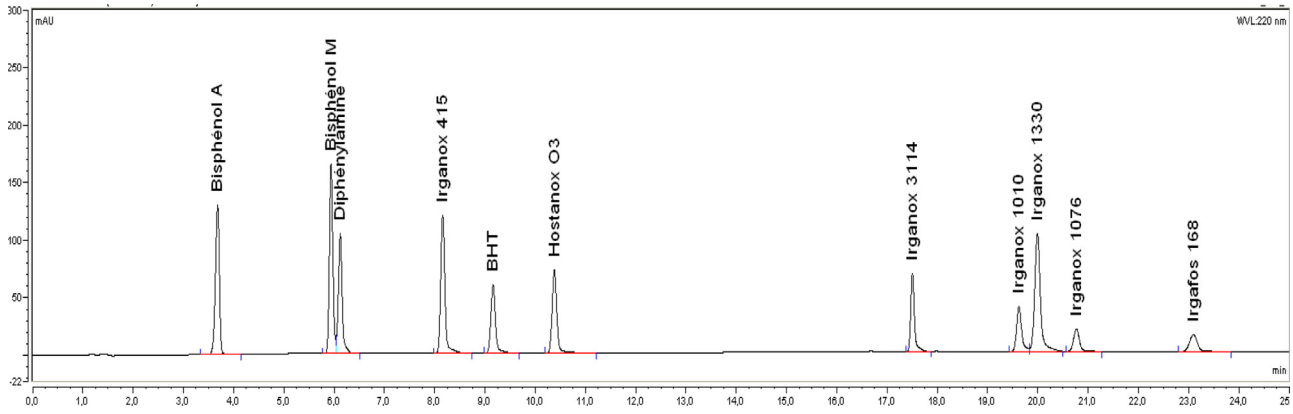


Fig. 1. Chromatogram of the system suitability mix of the 11 additives (concentration of 5 ppm).

Table 4
Method performance, as determined by several validation parameters.

	Retention time (min)	Linearity (R value)	LOD (ppm)	LOQ (ppm)	Repeatability (%RSD)	Response factor (λ = 220 nm)
Bisphénol A	3,69	0,9995	0,05	0,14	0,10	2380
Bisphénol M	5,95	0,9993	0,03	0,09	2,74	2692
Diphénylamine	6,13	0,9996	0,05	0,15	3,63	1845
Irganox 415	8,17	0,9996	0,01	0,04	0,73	2375
BHT	9,16	0,9995	0,01	0,02	0,33	1279
Hostanox O3	10,38	0,9995	0,01	0,04	0,06	1579
Irganox 1010	17,46	0,9992	0,03	0,09	0,28	1156
Irganox 1330	19,45	1,0	0,01	0,03	0,65	0,945
Irganox 3114	19,59	0,9996	0,03	0,09	0,59	2740
Irganox 1076	20,52	0,9918	0,04	0,12	2,02	0,550
Irgafos 168	22,66	0,9967	0,07	0,21	0,83	0,565
Average						1646 (RSD = 49,5%)

Table 5
Evaluation of the extractables in PP and PE containers with 100% acetonitrile.

	PP containers			PE containers		
	3 days, 25 °C	7 days, 25 °C	10 days, 25 °C	3 days, 25 °C	7 days, 25 °C	10 days, 25 °C
	Concentration of known additives(ppm)					
Bisphénol A	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Bisphénol M	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diphénylamine	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Irganox 415	<LOD	<LOQ	<LOQ	<LOQ	0,09	0,04
BHT	0,26	0,26	0,34	<LOD	<LOD	<LOD
Hostanox O3	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Irganox 1010	< LOD	0,09	0,09	<LOD	<LOD	<LOD
Irganox 1330	6,56	8,65	9,99	<LOD	<LOD	<LOD
Irganox 3114	< LOD	<LOD	< LOD	<LOD	<LOD	<LOD
Irganox 1076	15,00	20,11	22,62	0,30	0,27	0,27
Irgafos 168	1,49	1,03	0,93	<LOD	<LOD	<LOD
	Concentration of unknown additives (ppm)					
X1 (tr 3,16)	0,17	0,19	0,19	0,17	0,14	0,14
X3 (tr 7,27)	0,11	0,14	0,19	NO	NO	NO
X4 (tr 7,73)	NO	NO	NO	0,96	1,31	1,53
X5 (tr 10,91)	0,21	0,22	0,19	0,27	0,24	NO
X6 (tr 11,25)	0,39	0,38	0,39	NO	NO	NO
X7 (tr 12,09)	0,24	0,33	0,24	2,16	2,19	2,45
X8 (tr 12,39)	0,68	3,32	1,04	0,62	0,65	2,67
X10 (tr 14,48)	0,09	0,14	0,19	NO	NO	NO
X11 (tr 15,07)	0,11	0,14	0,14	NO	NO	NO
X12 (tr 21,5)	0,11	0,17	0,21	NO	NO	NO

NO: not observed.

Table 6
Evaluation of the extractables in PP and PE containers with solvent mixture of 50% acetonitrile and 50% water.

	PP containers			PE containers		
	3 days, 25 °C/40 °C	7 days, 25 °C/40 °C	10 days, 25 °C/40 °C	3 days, 25 °C/40 °C	7 days, 25 °C/40 °C	10 days, 25 °C/40 °C
	Concentration (ppm)					
Bisphenol A	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Bisphenol M	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Diphenylamine	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Irganox 415	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BHT	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Hostanox O3	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Irganox 1010	0,13/0,13	<LOD/0,11	<LOD/<LOQ	<LOD	<LOD	<LOD
Irganox 1330	1,27/1,23	1,61/0,53	1,82/0,17	< LOD	<LOD	<LOD
Irganox 3114	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Irganox 1076	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Irgafos 168	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
	Concentration (ppm)					
X2 (tr 5,48)	0,69/NO	0,77/NO	0,22/NO	NO	NO	NO
X3 (tr 7,27)	0,13/NO	0,05/NO	0,09/NO	NO	NO	NO
X4 (tr 7,73)	NO	NO	NO	0,33/2,40	0,47/4,50	0,57/4,69
X9 (tr 12,43)	0,49/1,29	0,96/1,17	1,37/0,58	0,16/0,13	0,17/0,13	0,14/0,13
X10 (tr 14,48)	0,08/0,12	0,09/0,30	0,13/0,30	NO	NO	NO

NO: not observed.

X8 extracted under 100% acetonitrile were not observed in the 50% water/50%acetonitrile condition. In PE containers, none of the 11 additives were identified, and only two unknown molecules were observed in this condition (X4 and X9), with X9 presents in fewer amounts in PE than in PP.

3.3.2.3. Water 100% at 25 °C, 40 °C and 60 °C up to 10 days. No trace amount of known additives were found after in either PP or PE bags filled with 100% of water even under the strongest condition at 60 °C up to 10 days (Fig. 2), this result could be linked with the log P of the additives. Minor unknown peaks were revealed between 1 and 3 min with concentration below 0,1 μg/mL which is negligible regarding to the final AET.

Extractables studies are made to evaluate and to identify the potential leachable products. Therefore, forced conditions are used: in general, polar solvents and elevated temperatures. In this study, the amount of known additives and unknown molecules decreased with regard to the polarity of solvent employed for the experiment. This is in agreement with the LogP values of the additives (Table 3). We observed that some extractable product concentrations are prone to decrease with corresponding increase in temperature, probably linked to their degradation. Therefore we suggest that several temperatures should be used during these studies. The use of different conditions allows to observed more additives. With regard to the fewer amount of known additives and unknown molecules in any conditions, PE infusion bag is supposed to generate less interaction. In order to appreciate predictability of these experiments both plastics were evaluate during the leachable product studies.

3.3.3. Evaluation of the leachables

Leachable studies were performed on PE and PP infusion bags filled with 50 mL of GGCa and stored at 25 and 40 °C for 3 months.

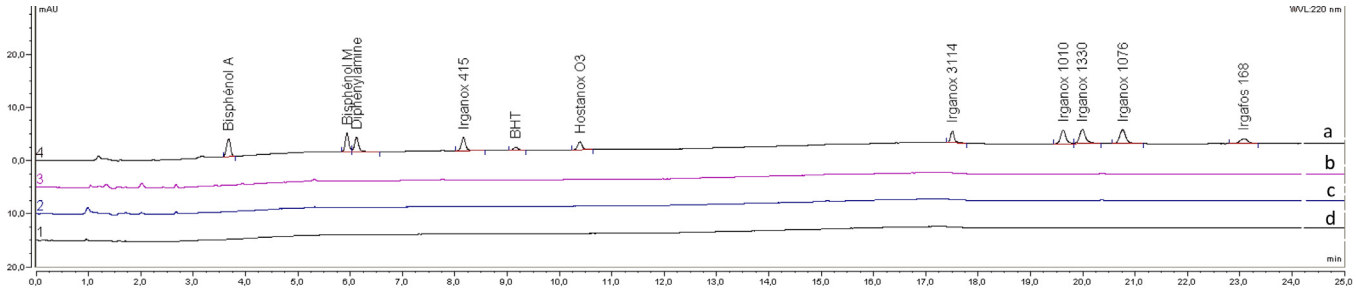


Fig. 2. Chromatograms of (a) system suitability mix at 0,5 ppm, (b) PP containers filled with 100% of water and stressed at 60 °C for 10 days, (c) PE containers filled with 100% of water and stressed at 60 °C for 10 days, (d) mobile phase.

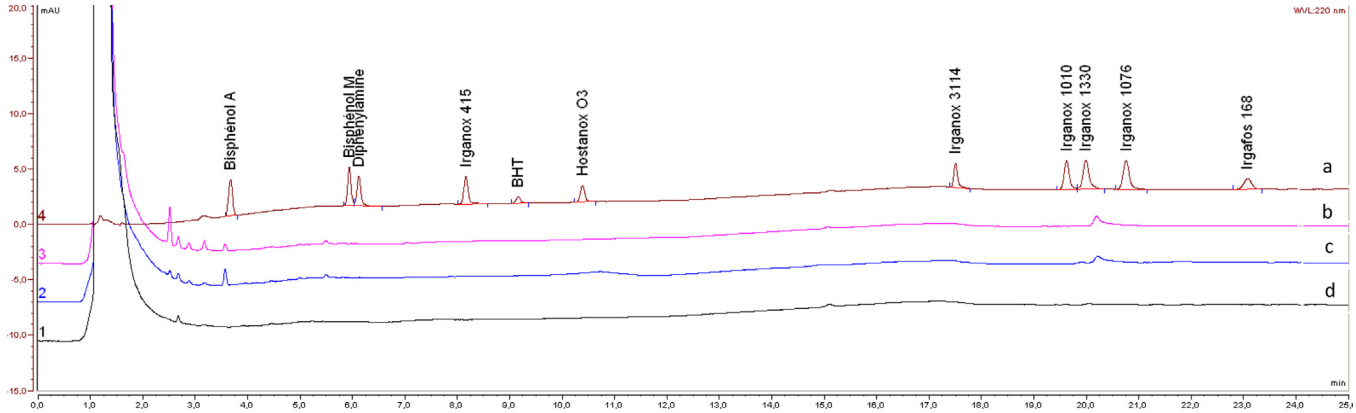


Fig. 3. Chromatograms of (a) system suitability mix at 0,5 ppm, (b) gluconate glucoheptonate solution after 3 months in PP containers at 25 °C, (c) gluconate glucoheptonate solution after 3 months in PE containers at 25 °C and (d) gluconate glucoheptonate solution after 3 months in glass containers at 25 °C (used as control).

Gluconate/glucoheptonate peak is quickly eluted (retention time: 1,3 min) as they have no interaction with the stationary phase. Traces of known degradation products of this counter ion were found at trace amount and are not represented in the results. After 1, 2 and 3 months in PE containers, none of the known leachable was identified, and minor unknown peaks were revealed between 2 and 5 min, with a concentration <0,1 μg/mL which is negligible regarding to the final AET. The same observation was made after 1 and 2 months in PP containers, but after 3 months at 25 °C, one unknown peak with a concentration over the final AET was observed. The amount of this unknown additive was decreasing with temperature (0,27 μg/mL at 25 °C; 0,13 μg/mL at 40 °C), which could be linked with its degradation, and could explain that it was not seen during extractables studies. Results of the 3 months analysis are presented Fig. 3. As previously explained, the concentration of unknown peaks is estimated using a surrogate standard (Hostanox O3).

From these results, PE container is a preferable choice for our product. In this plastic container, no peak over the final AET is observed, therefore it is not necessary to identify and qualify those impurities.

4. Conclusion

This study focused on developing a simple HPLC/PDA method capable to determine eleven common plastic additives used for the formulation of plastic packaging materials. The method allowed their detection at low concentrations and in a relative short time-analysis. The method was applied to evaluate two different plastic containers in contact with Calcium gluconate glucoheptonate solution and made it possible to determine the plastic container that is the most compatible regarding possible leachable whithin those eleven additives.

Declarations of interest

None.

Acknowledgements

We thank Estelle Surget for her help in data acquisition and Jean-Hugues Trouvin for his helpful comments and reviewing of the present work.

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