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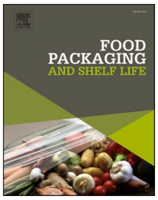

Identification of polymer additives from multilayer milk packaging materials by liquid-solid extraction coupled with GC-MS

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ABSTRACT

Polyethylene-based co-extruded multilayer films are exclusively used in India for packaging of processed dairy commodities, such as, milk, *ghee*, curd, etc. and large variety of chemical compounds, like: processing aids, additives, etc. are added during fabrication to enhance their functionality. Chemical migration of these additives from packaging materials into food could be a potential means of contamination which possess human health risks. In present study, gas chromatography-mass spectrometry (GC-MS) was used for identification of chemical compounds in milk packaging films. Samples were extracted with chloroform: methanol (1:1) and out of 65 detected compounds only 17 are listed in Commission Regulation (EU) No.10/2011. Further, frequently occurring compounds, viz., 2, 4-di-tert-butylphenol, butylated hydroxyl toluene, diethyl phthalate, acetyl tributylcitrate (ATBC), bis (2-ethylhexyl) phthalate, bis (2-ethylhexyl)adipate, 13-docosenamide, Irgafos®168, tris (2,4-di-tert-butylphenyl) phosphate, Irganox®1076 were quantified in multiple reaction monitoring (MRM) mode. ATBC was the most detected compound in concentrations ranging 28.16–91.58 μg mL^{-1}, followed by Irgafos®168 (32.54–60.68 μg mL^{-1}).

1. Introduction

Food packaging plays a crucial role in protecting food against contamination and preserving its inherent taste and quality (Hwang et al., 2019). Lately, polymers are extensively used in food and beverage industries because of numerous benefits including good functionalities, oxygen resistance, low manufacturing costs, etc. (Li et al., 2015). Polymers which are regularly used in food packaging applications include polyamide (PA), polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), etc. In order to attain desired physical and chemical properties in packaging materials, base polymers are often incorporated with chemical additives such as, plasticizers, antioxidants, ultraviolet (UV) absorbers, heat stabilizers, lubricants, etc. during manufacturing (Bhunia, Sablani, Tang & Rasco, 2013). In recent times, multilayer packaging materials with added functionalities are being utilized. They are produced by blending different polymers (containing additives) to form multilayer structure, where each layer performs a specified function (Anukiruthika et al., 2020). Such packaging assemblies in global markets are widely utilized in manufacturing of flexible films and pre-formed pouches. In India, approximately 85% of pasteurized milk is marketed in PE-based multilayer films due to their low cost, easy transportation; good mechanical properties and resistance against UV light (International Life Sciences Institute- India Monograph, 2017).

Despite the advantages that packaging delivers to consumers and food processors, several studies have indicated that food packaging materials are possible source of contamination due to migration of additives into food products (Guerreiroe, de Oliveira, Melo, de Oliveira Lima, & Catharino, 2018; Baner & Piringer, 2008). Migration from packaging material involves leaching of compounds due to absorption or diffusion into the food (Arvanitoyannis & Kotsanopoulos, 2014). These migrating substances might include substances from base polymer materials e.g., additives, starting monomers or non-intentionally added substances (NIAS) like; reaction intermediates, degradation products, process impurities, etc. (Lestido-Cardama et al., 2020). Owing to increased consumer consciousness, migration of chemical additives (MW ≤ 1000 Da) from food contact materials (FCMs) has attracted close

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Abbreviations: GC-MS:, Gas chromatography- Mass spectrometry.
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monitoring by regulatory authorities around the globe. These substances are considerably harmful as they get readily absorbed in the gastro-intestinal tract (GIT) of humans (European Food Safety Authority, 2008) and regular exposure to such chemicals have been associated with several health implications, like: obesity, heart ailments, reproductive and endocrine imbalance, reformed fetal development, etc. (Muncke et al., 2020). Keeping in view the quality and safety of the food products and to safeguard the consumer's health, U.S. Food and Drug Administration (FDA) and European Union (EU) have formulated positive lists of allowed substances to be used during manufacturing of food grade packaging materials. This drive was further strengthened by framing guidelines and regulations for testing of food packaging materials for both overall migration limits and specific migration limits (SMLs) of many substances (Commission Regulation (EU) No.1282/2011 (2011), Code of Federal Regulation (FDA) Title 21 (2012)). Over the years, these legislative outlines were adopted and modified by several other nations. Food Safety and Standards Authority of India, (FSSAI) has also implemented new packaging and labelling regulations in 2019 with a view to address the issue of chemical migration, which were drawn from Bureau of Indian Standards (BIS) in a unified manner (Food Safety Standards Regulations, 2018). These regulations specifically mention standards for packaging materials coming in contact with food indicating the positive lists of constituents for PE, PP and their copolymers (Bureau of Indian Standards IS 16738:2018, 2018) and Nylon-6 polymer (Bureau of Indian Standards, IS 12248:1988 (R2020), 2020). However, it is worth mentioning that the methodology for verifying additives in packaging material is still lacking and thus verification of compliance to above standards is presently not being implemented.

India has come a long way from being deficit in milk from 20 MT in 1970 to the world's largest milk producing country to an estimated production of 198.4 MT in 2019–20 (National Dairy Development Board, 2021), wherein the majority of the market milk (pasteurized milk with varying fat content) is packaged in co-extruded multilayer films. The use of co-extruded blend of linear low-density polyethylene (LLDPE) and low-density polyethylene (LDPE) (LDPE: LLDPE) is the typical packaging film of choice in Indian dairies and has in fact contributed in the development of dairy industry in India. However, no extensive studies assessing the chemical safety of these packaging films have been comprehensively addressed. Hence, in the present study, a methodology has been developed to identify the existing additives and NIAS in PE-based packaging materials (intended for pasteurized milk) being marketed in India. To achieve this, solvent mixture and extraction time were optimized and extracts obtained were further subjected to Gas Chromatograph-Mass Spectrometer (GC-MS) for screening of both additives and NIAS. The prominent chemical compounds were further quantified using GC-MS/MS in multiple reaction monitoring (MRM) mode. Packaging materials were also evaluated for their thickness and composition using micrometer and attenuated total reflectance- Fourier transform infrared (ATR- FTIR) spectroscopy, respectively.

2. Materials and methods

2.1. Reagents and standards

Analytical standards of 2,4-di-tert-butylphenol (DTBP) 99% (CAS: 96–76–4), butylated hydroxytoluene (BHT) 99% (CAS: 128–37–0), diethyl phthalate (DEP) 99.5% (CAS: 84–66–2), Bis (2-ethylhexyl) phthalate (DEHP) 99% (CAS: 117–81–7), octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate (Irganox®1076) 99% (CAS: 2082–79–3) were purchased from Sigma Aldrich (Schnelldorf, Germany). While bis (2-ethylhexyl) adipate (DEHA) 99% (CAS: 103–23–1) and tributyl O-acetylcitrate (ATBC) 99% (CAS: 77–90–7) were procured from Fluka (Steinheim, Germany). 13-Docosenamide, 99% (CAS: 112–84–5), tris (2,4-di-tert-butylphenyl) phosphate (phosphate Irgafos®168), 99% (CAS: 95906–11–9), phenol, 2,4-bis(1,1-dimethylethyl)-, phosphite (3:1); (Irgafos®168) plastic additive 12, European Pharmacopoeia (EP) reference standard, 99% (CAS: 31570–04–4) were sourced from Supelco (Bellefonte, USA).

All chemicals used in study were of analytical grade. Acetonitrile (ACN), n-hexane, methanol, dichloromethane (DCM), n-heptane, chloroform and ethanol were from Merck (Darmstadt, Germany).

Stock solution of DTBP, BHT, and ATBC was prepared in ethanol and for DEP, DEHA, 13-Docosenamide, DEHP, Irgafos®168, phosphate Irgafos®168, Irganox®1076 in n-hexane. Working solutions of all chemical compounds were prepared by dilution with ACN. The solutions and prepared samples were stored under refrigerated conditions in darkness and brought to ambient temperature prior to their respective use.

2.2. Samples

A total of thirty-six food packaging samples of multilayer milk packaging films were procured directly from various Indian dairy industries. Packaging materials comprised of different brands with varying thickness and containment capacities.

2.3. Characterization of milk packaging materials

2.3.1. Film thickness

Digital micrometer (0–25 mm range; Mitutoyo, Japan) was used for thickness measurement of packaging films. Three measurements were taken at different locations for each sample.

2.3.2. Attenuated total reflectance- Fourier transform infrared (ATR-FTIR) characterization of packaging materials

ATR- FTIR Spectrometer (Specac ATR, USA; Shimadzu IR Affinty1, Tokyo, Japan) was used for identification of type of packaging material. The scan was performed on both surfaces of all the packaging samples (food contact and non-food contact side). At first, the sample was cut, wiped (using iso-propanol), allowed to dry and compressed against the optical diamond crystal of ATR using the clamp pressure to cover its entire surface for spectrometric analysis. Spectra were acquired in mid IR region from 4000 cm^{-1} to 450 cm^{-1} in transmittance mode. Resolution was set at 4 cm^{-1} and background scan was obtained after every sample. Transmission bands were recognized using a peak height algorithm within the Shimadzu IR Solution software (Shimadzu Corporation, Kyoto, Japan) and thereafter, equated to bands of polymer types as stated in the literature and attained from unspecific in-built spectral library. At least six matching absorption bands were regarded for identification as no pre-existing specialized database was used in this study.

2.4. Extraction of additives from packaging material

2.4.1. Preparation of samples

Sample packaging film was cut into a definite surface area of 5 × 5 mm^2 and 200 mg of the sample was then weighed in amber coloured borosilicate vial for solid-liquid extraction (SLE) of chemical additives. It was next put in contact with 4.8 mL of chloroform: methanol (1:1) and 0.20 mL of tetradecanamide (internal standard) at 25 °C for 18 h. The extraction solvent and time were optimized as per description under Section 2.4.2. Subsequently, packaging material was removed and the extract was evaporated under gentle N_2 stream to around 0.10 mL, followed by its reconstitution in 1 mL methanol. The aliquot was filtered via 0.45 μm PVDF syringe filters (Pall Acrodisc, Port Washington, New York, USA) followed by auto-injection in GC-MS for further analysis.

To avoid any possible degradation or variation in the contents of extracts, preparation of samples was carried out under low-light settings of laboratory and extracts were further stored in amber sample vials at 4 °C till further analysis.

2.4.2. Optimization of extraction solvent

Based on our previous laboratory experience, literature available and preliminary trials; an array of semi-polar to non-polar solvents viz., ACN, n-hexane, n-heptane, chloroform and their combinations with methanol (1:1) were tested to optimize solvent system for extraction of additives from milk packaging films.

Packaging materials were exposed to solvent mixtures for time period ranging from 1 h to 24 h at room temperature. Further, the interactive effects of solvent system, extraction time on the total ion concentration of additives were statistically studied using Random Block Design (CoStat 6.400 Statistics Software, USA). Hence, chloroform: methanol (1:1) was optimized as the suitable solvent mixture for the SLE studies.

2.5. Toxicity evaluation of additives

Toxicity of recognized compounds was evaluated by using the software Toxtree v2.6.13 (Toxtree, Ideaconsult Ltd., Sofia, Bulgaria) which is a non-proprietary application and determined the Cramer class of a chemical substance and ascertained its relative toxic hazards by applying decision tree approach comprising of 33 broad questions given by Cramer, Ford & Hall (1978). The classification scheme by Cramer (the decision tree) is an acclaimed approach to estimate threshold of toxicological concern (TTC) for a specific chemical substance centered on its chemical structure. Wherein, compounds with simple molecular structures and effective metabolism modes were indexed as *low toxicity-class I*, substances that might submit substantial toxicity or possess receptive functional groups were grouped under *intermediate toxicity-class II* whereas, *high toxicity-class III* was assigned to compounds having chemical structure that document no robust safety impression and might even submit a significant level of toxicity (Galmán GraíñoSendón, López Hernández & Rodríguez-Bernaldo de Quirós, 2018; Garcia Ibarra, Losada & Sendon, 2018). The specifications of identified chemicals in respective group are discussed in Table 1.

2.6. GC-MS analysis for identification and quantification of additives

A Shimadzu TQ 8030 Series triple quadrupole GC-MS (Shimadzu, Tokyo, Japan) equipped with Shimadzu AOC- 20i automatic injector (Shimadzu, Tokyo, Japan) and Shimadzu AOC- 20 s automatic sampler (Shimadzu, Kyoto, Japan) was used to scan chemical migrants. Separation of compounds was carried out on Supelco SLB®– 5 ms Capillary GC Column (30 m × 0.25 mm × 0.25 μm) (Sigma-Aldrich Co. LLC, MO, USA) 5% diphenyl and 95% dimethyl polysiloxane. One microlitre of sample was injected at 280 °C in split ratio of 1: 10. Helium (99.99% purity) was used as a carrier gas with flow rate of 1 mL min^{-1}. Interface and ion source temperatures were set at 240 °C and 230 °C respectively. GC oven temperature was primarily set at 70 °C for 2 min, ramped at a rate of 10 °C min^{-1} until 300 ℃ and held for 20 min at 300 °C. The overall run time of each sample analysis was 45 min. Mass spectra were attained using mass selective detector under electron impact (EI) ionization at a voltage of 70 eV and the MS was programmed in Q3 SCAN acquisition mode with *m/z* range of 45–600. The internal calibration of MS was performed by the autotuning of perfluorotributylamine (PFTBA) via masses 69, 219 and 502 Da. These ions were used to regulate the *m/z* values over the complete range of spectrum. Acquisition and processing of data was done in Shimadzu GCMS solution version 4.11 software (Shimadzu Corporation, Kyoto, Japan). The processed peaks were identified using NIST/EPA/NIH Mass Spectral Library 17. Blank solvent was run prior to all samples, in order to ward off any potential memory effects from previous samples.

To quantify additives regularly used in PE-based packaging materials and based on their frequency of occurrence, ten chemical compounds were selected (Table 2). Accordingly, mixture of analytes (at a concentration of 15 μg mL^{-1}) were injected in spitless mode, oven ramp used was programmed at 70 °C for 2 min, then escalated until 300 °C at 10 °C min^{-1}, with the final holding time of 15 min. Argon gas (grade 5.0) was used in collision-induced dissociation (CID) cell and quantifications were carried out in MRM acquisition mode using the target ions, reference ions 1 and reference ions 2 at detector voltage of 0.2 kV (Presented in Table 2).

Quantification of selected compounds was performed using a calibration line based on different calibration levels and area of response. Calibration lines were constructed by diluting stock solution with a concentration ranging from 1 to 40 μg mL^{-1}. Conditions followed for recognition of analytes were the retention time (RT), occurrence of two MRM transitions, and relative transition intensities. To identify analytes in tandem MS-constructed methods, RT and their relative MRM transition intensities should not differ beyond ± 1% & ± 20%, respectively, with respect to their standards. Samples prepared in Section 2.4.1 were used for detection of chemical additives in milk packaging films and results are expressed in μg mL^{-1}.

2.7. Control of blank concentrations for phthalate analysis

Owing to the problems associated with the phthalate analysis, several preventive steps were taken so as to lessen the blank problems related to the pervasive nature of phthalates in environment. The use of plasticware was avoided throughout the study, including handling samples and making dilutions. Glassware were used instead of plastic material which were carefully rinsed and thermally treated for 4 h at 400 °C and then covered with aluminum foil and kept in clean environment prior to their respective use. Chloroform, methanol and other solvents were tested for background levels of phthalates and every analytical sequence was comprised of two procedural blanks (at beginning and the end of the sequence).

3. Results and discussion

3.1. Physico-chemical characterization

The packaging materials used in this study were measured for their thickness and characterised by ATR-FTIR spectroscopy from food contact and non-food contact sides. Results indicated that thickness of all packaging films with containment volumes 500 mL, 1 L and 6 L varied from range 47–54.67 μm, 53.67–61.33 μm and 97.67–113 μm respectively. Summary of samples studied are provided in supplementary data (Supplementary Data (SD) Table 2–4). It may be noted that thickness of packaging materials increased with the containment capacities. However, in an effort towards safe collection and recycle of plastic waste, globally 127 countries have adopted legislations to regulate thickness threshold of plastic films or bags (United Nations Environment Programme, 2018). Likewise, in India, use of plastic bags with thickness less than 50 μm is banned (Food Safety Standards (Packaging) Regulation, 2018). On contrary to stated regulation, in our study ~ 8% of milk packaging films was found to have thickness below 50 μm.

Further, ATR-FTIR spectra showed that all of the films analyzed were multilayer PE-based blends of linear low-density polyethylene (LLDPE) and low-density polyethylene (LDPE) from both the sides of contact. ATR-FTIR spectra of five samples, (S1, S2, S3, S4 and S5) are shown in Fig. 1. Each sample analysed featured characteristic peaks with strong transmission intensities by virtue of two active functional groups: methyl and methylene at wavenumbers 2915 cm^{-1}, 2845 cm^{-1}, 1467 cm^{-1}, 730 cm^{-1} and 717 cm^{-1} which were further attributed to CH_2 stretch, CH stretch, amorphous CH_2 bend, amorphous CH_2 rock respectively (Jung et al., 2018). An extra band present at 1377 cm^{-1} with strong to medium intensities is attributed to crystalline CH_3 bend vibrations and is suggestive of LDPE and LLDPE blend; which has relatively small proportions of branching on its polymer chains (Mitchell, France, Nordon, Tang & Gibson, 2013). The region at 885 cm^{-1}and 888 cm^{-1} are shown in Fig. 1, using an enlarged scale to present an appreciable difference in weak and medium absorption pattern of butene and octene crystalline

Table 1
Compounds identified in milk packaging materials (n = 36) with their chemical characteristics, frequency of occurrence (n), level of toxicity (TC) according to Cramer rules and uses.

S No.	Compounds	IUPAC Name	CAS No.	Chemical Formula	Molecular Mass (g/mol)	RT (min)	TC	n	Uses
1.	benzene, 2,4-diisocyanato-1-methyl-	2,4-diisocyanato-1-methylbenzene	86–91–9	$C_9H_6N_2O_2$	174.2	8.703	III	8	Resins ingredients
2.	quinoline, 1,2-dihydro-2,2,4-trimethyl-	2,2,4-trimethyl-1,2-dihydroquinoline	26,780–96–1	$C_{12}H_{15}N$	173.25	9.049	III	32	Antioxidant/ Stabilizer/ Polymerization inhibitor
3.	1-tridecene	tridec-1-ene	2437–56–1	$C_{13}H_{26}$	182.35	11.123	I	32	Alkane Hydrocarbon
4.	n-tetradecane	tetradecane	629–59–4	$C_{14}H_{30}$	198.39	11.203	I	34	Alkane Hydrocarbon
5.	pyrrole-3 carbonitrile, 5-formyl-2,4-dimethyl-	5-formyl-2,4-dimethyl-1 h-pyrrole-3-carboxylic acid	253,870–02–9	$C_8H_9NO_3$	167.16	12.401	I	7	Raw material/ Intermediate in dyes and pigments
6.	2-(hydroxymethyl) benzimidazole	1 h-benzimidazol-2-ylmethanol	4856–97–7	$C_8H_8N_2O$	148.16	12.46	III	15	Processing intermediates
7.	2,4-di-tert butylphenol	2,4-di-tert-butylphenol	96–76–4	$C_{14}H_{22}O$	206.32	12.754	I	36	Thermal stabiliser/ By-product of antioxidant
8.	1-dodecanol	n-dodecan-1-ol	112–53–8	$C_{12}H_{26}O$	186.34	13.211	I	14	Surfactant, Lubricant/ Fatty Alcohol
9.	phthalimide	isoindole-1,3-dione	85–41–6	$C_8H_5NO_2$	147.13	13.257	III	30	Intermediates in dyes and pigments
10.	pentadecane	pentadecane	629–62–9	$C_{15}H_{32}$	212.41	13.524	I	34	Alkane Hydrocarbon
11.	butylated hydroxytoluene*	2,6-ditert-butyl-4-methylphenol	128–37–0	$C_{15}H_{24}O$	220.35	13.61	II	36	Antioxidant/ Thermal stabilizer in hot-melt adhesives
12.	benzoic acid, 4-ethoxy-, ethyl ester*	ethyl 4-ethoxybenzoate	23,676–09–7	$C_{11}H_{14}O_3$	194.22	13.904	II	13	Polymer modifier/ Fatty acid Derivatives
13.	11-methyltricosane	11-methyltricosane	27,538–41–6	$C_{24}H_{50}$	338.654	14.393	I	14	Hydrocarbon/ Lubricants
14.	dichloroacetic acid, 4-hexadecyl ester	hexadecan-4-yl 2,2-dichloroacetate	74,339–54–1	$C_{18}H_{34}Cl_2O_2$	353.4	14.589	III	12	Adhesives/ Fatty Acid Derivatives
15.	diethyl phthalate	diethyl benzene-1,2-dicarboxylate	84–66–2	$C_{12}H_{14}O_4$	222.24	14.674	I	36	Plasticizer
16.	hexadecane	hexadecane	544–76–3	$C_{16}H_{34}$	226.44	14.845	I	36	Alkane Hydrocarbon
17.	2- carboxy-benzophenone	2-benzoylbenzoic acid	85–52–9	$C_{14}H_{10}O_3$	226.23	15.331	III	20	UV Blocker/ Photoinitiator for UV-curing of inks
18.	2–2'- hydroxy-5-methyl-phenyl benzotriazole*	2-(benzotriazol-2-yl)– 4-methylphenol	2440–22–4	$C_{13}H_{11}N_3O$	222.28	15.78	III	20	Azo dyes (chromophore)/ UV Absorbers and stabilizers
19.	drometrizole*	2-(2 hydroxy-benzotriazol-2-yl)– 4-methylphenol	2440–22–4	$C_{13}H_{11}N_3O$	225.25	15.828	III	20	Azo dyes (chromophore)/ UV Absorbers
20.	heptadecane	heptadecane	629–78–7	$C_{17}H_{36}$	240.47	15.932	I	36	Alkane Hydrocarbon
21.	methyl benzoate	2-methylbenzoic acid	118–90–1	$C_8H_8O_2$	136.15	16.559	I	20	Solvent in printing inks
22.	hexadecyl isopropyl ether	1-propan-2-yloxyhexadecane		$C_{19}H_{40}O$	284.5	16.695	I	36	Solvent base for waxes, dyes and resins
23.	hexyl salicylate	hexyl 2-hydroxybenzoate	6259–76–3	$C_{13}H_{18}O_3$	222.28	17.184	I	32	UV Stabilizer
24.	isopropyl myristate	propan-2-yl tetradecanoate	110–27–0	$C_{17}H_{34}O$	270.5	17.237	I	32	Lubricant
25.	1-tetradecanol	tetradecan-1-ol	112–72–1	$C_{14}H_{30}O$	214.39	17.873	I	22	Ingredient in lubricants, resins/ Processing aid/ Surfactant/ Fatty Alcohol
26.	palmityl alcohol*	hexadecan-1-ol	36,653–82–4	$C_{16}H_{34}O$	242.44	17.913	I	34	Processing aid/ Fatty acyl alcohol
27.	homosalate	3,3,5-trimethylcyclohexyl 2-hydroxybenzoate	118–56–9	$C_{16}H_{22}O$	262.34	18.115	I	28	Antioxidant/ UV stabilizer
28.	7,9-di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione	7,9-ditert-butyl-1-oxaspiro [4.5] deca-6,9-diene-2,8-dione	82,304–66–3	$C_{17}H_{24}O_3$	276.37	18.229	III	34	By-product of antioxidant
29.	n- octadecenoic acid, methyl ester (e)	methyl octadeca-2,4-dienoate	1937–62–8	$C_{19}H_{34}O_2$	294.5	18.303	I	36	Lubricants/ Ink for printing/ Fatty Acid Derivative
30.	diisooctyl phthalate	bis(6-methylheptyl) benzene-1,2-dicarboxylate	27,554–26–3	$C_{24}H_{38}O_4$	390.61	18.676	I	34	Plasticizer
31.	1-heptacosanol	heptacosan-1-ol	2004–39–9	$C_{27}H_{56}O$	396.7	18.98	I	36	Fatty Alcohol/ Lubricant/ Processing aid
32.	behenic acid*	docosanoic acid	112–85–6	$C_{22}H_{44}O_2$	340.58	19.043	I	32	Intermediate/ Fatty Alcohol, Lubricant
33.	eicosane	icosane	112–95–8	$C_{20}H_{42}$	282.55	19.136	I	36	n-alkane (may have its origin from paraffin wax)
34.	isopropyl palmitate	propan-2-yl hexadecanoate	142–91–6	$C_{19}H_{38}O_2$	298.50	19.243	I	32	Lubricant/ Emulsifiers/ Stabilizers, Resins/ Plasticizers/ Fatty Acid Derivatives
35.	sorbitan palmitate*	[(2r)– 2-[(2r,3r,4 s)– 3,4-dihydroxyoxolan-2-yl]– 2-hydroxyethyl] hexadecanoate	26,266–57–9	$C_{22}H_{42}O_6$	402.6	19.451	III	32	Sealants/ Intermediate for detergents, emulsifiers, stabilizers,

(*continued on next page*)

Table 1 (*continued*)

S No.	Compounds	IUPAC Name	CAS No.	Chemical Formula	Molecular Mass (g/ mol)	RT (min)	TC	n	Uses
									resins, plasticizers/ Fatty Alcohol
36.	1-heptacosanol	heptacosan-1-ol	2004–39–9	$C_{27}H_{56}O$	396.74	19.703	I	36	Fatty Alcohol/ Lubricants/ Processing aids
37.	behenic alcohol	docosan-1-ol	661–19–8	$C_{22}H46O$	326.609	19.871	I	32	Intermediate/ Fatty Alcohol/ Lubricant
38.	methyl stearate	methyl n-octadecanoate	112–61–8	$C_{19}H_{38}O_2$	298.5	20.226	I	36	Lubricant/ Thermal stabilizers
39.	oleamide*	(z)-octadec-9-enamide	301–02–0	$C_{18}H_{35}NO$	281.47	20.404	III	36	Slip agent/ Fatty amide
40.	pentafluoropropionic acid, 4-hexadecyl ester	hexadecyl 2,2,3,3,3-pentafluoropropanoate	6222–07–7	$C_{19}H_{33}F_5O_2$	388.51	20.647	III	32	Halogenated acid esters/ Solvents for inks and pigments/ Starting material
41.	1-nonadecane	nonadecane	629–92–5	$C_{19}H_{40}$	268.51	20.841	I	24	Alkene Hydrocarbon
42.	tributyl acetyl citrate*	tributyl 2-(acetyloxy) propane-1,2,3-tricarboxylate	77–90–7	$C_{20}H_{34}O_8$	402.47	21.276	I	36	Plasticizer for both food contact materials and for inks, adhesives
43.	stearamide*	octadecanamide	124–26–5	$C_{18}H_{37}NO$	283.50	21.926	I	32	Lubricants/ Thermal stabilizers
44.	furan, tetrahydro-2,2,4,4-tetramethyl-	2,2,4,4-tetramethyltetrahydrofuran	3358–28–9	$C_8H_{16}O$	128.21	22.235	I	5	Solvent for paints/ Vehicles for pigment dispersions
45.	1,4-benzenediamine, n-(1,3dimethylbutyl)-n'-phenyl-	n-(1,3-dimethylbutyl)-n'-phenylbenzene-1,4-diamine	793–24–8	$C_{18}H_{24}N_2$	268.397	22.41	III	6	Polymer stabilizer/ Antioxidant
46.	bis(2-ethylhexyl) adipate*	hexanedioic acid, bis(2-ethylhexyl) ester	103–23–1	$C_{22}H_{42}O_4$	370.56	22.515	I	36	Adipate plasticizer
47.	tetrapentacontane	tetrapentacontane	5856–66–6	$C_{54}H_{110}$	759.45	22.676	1	32	Alkane Hydrocarbon/ Fatty Acyl/ Lubricants
48.	bis(tridecyl) phthalate	ditridecyl benzene-1,2-dicarboxylate	119–06–2	$C_{34}H_{58}O_4$	530.80	23.401	III	32	Plasticizers
49.	di(2-ethylhexyl) phthalate*	bis(2-ethylhexyl) phthalate	117–81–7	$C_{24}H_{38}O_4$	390.61	23.713	I	36	Plasticizer/ Solvent for paints/ Vehicles for pigment dispersions
50.	2-palmitoylglycerol	1,3-dihydroxypropan-2-yl hexadecanoate	23,470–00–0	$C_{19}H_{38}O_4$	330.5	23.545	I	28	Anti-fogging agent/ Fatty acid Derivatives
51.	n-octadecenamide*	octadec-9-enamide	124–26–5	$C_{18}H_{35}NO$	283.5	24.017	III	28	Slip agent/ Lubricant/ Fatty Acid Derivative
52.	carbonic acid, eicosyl vinyl ester	ethenyl icosyl carbonate		$C_{23}H_{44}O_3$	368.6	24.037	I	16	Starting materials/ Intermediates/ Breakdown Products
53.	n-tetracosanol-1	tetracosan-1-ol	506–51–4	$C_{24}H_{50}O$	354.66	24.129	I	28	Fatty Acyl /Alcohol
54.	octacosanol	octacosan-1-ol	557–61–9	$C_{28}H_{58}O$	410.76	24.347	I	14	Fatty Acyl /Alcohol
55.	octocrylene*	2-ethylhexyl 2-cyano-3,3-diphenylprop-2-enoate	6197–30–4	$C_{24}H_{27}NO_2$	361.50	24.709	III	24	UV filter
56.	4,4'-((p-phenylene) diisopropylidene) diphenol	4-[2-[4-[2-(4-hydroxyphenyl) propan-2-yl]phenyl] propan-2-yl] phenol	2167–51–3	$C_{24}H_{26}O_2$	346.47	24.839	III	24	Monomer/ Oligomer/ Plasticizers
57.	nonadecyl heptafluorobutyrate	nonadecyl heptafluorobutanoate		$C_{23}H_{39}F_7O_2$	480.543	25.202	III	12	Fluorinated monomers/ Antioxidant/ Heat stabilizer
58.	squalene	(6e,10e,14e,18e)– 2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,22-hexaene	111–02–4	$C_{30}H_{50}$	410.70	25.826	I	36	Substituted Hydrocarbon/ Plasticizer and oxygen scavenger
59.	13-docosenamide, (z)-*	docos-13-enamide	112–84–5	$C_{22}H_{43}NO$	337.58	25.994	III	36	Anti-blocking agent/ Slip agent
60.	tricaprylin	2,3-di(octanoyloxy)propyl octanoate	538–23–8	$C_{27}H_{50}O_6$	470.68	26.792	I	16	Slip agent/ Anti-blocking agent
61.	di-isononyl phthalate	nonyl 2-(nonyloxycarbonyl) benzoate	28,553–12–0	$C_{26}H_{42}O_4$	418.6	28.321	I	10	Plasticizer/ Solvent for paints/ Vehicles for pigment dispersions
62.	4,4'-cyclohexylidenebis(2-methylphenol)	4-[1-(4-hydroxy-3-methylphenyl) cyclohexyl]– 2-methylphenol	2362–14–3	$C_{20}H_{24}O_2$	296.4	28.838	III	12	Thermal stabilizer/ Antioxidant
63.	phenol, 2,4-bis(1,1-dimethylethyl)-, phosphite (3:1)*	phenol, 2,4-bis(1,1-dimethylethyl)-, phosphite	31,570–04–4	$C_{42}H_{63}O_3P$	646.92	33.005	III	36	Phenolic Antioxidant
64.	tris(2,4-di-tert-butylphenyl) phosphate	tris[2,4-bis(2-methyl-2-propanyl) phenyl] phosphate	95,906–11–9	$C_{42}H_{63}O_4P$	662.93	37.178	III	36	Oxidized/ Degradation product of antioxidant Irgafos®168
65.	benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)– 4-hydroxy-, octadecyl ester*	octadecyl 3-(3,5-ditert-butyl-4-hydroxyphenyl) propanoate	2082–79–3	$C_{35}H_{62}O_3$	530.9	37.863	II	36	Antioxidant/ General adhesive

[*] Listed in European Regulation No. 10/2011

Table 2
Selected compounds analysed in MRM mode with their retention times, target ions, reference ions.

Compound Name	SML (mg/kg)	RT (min)	TI (*m/z*)	RI 1 (*m/z*)	RI 2 (*m/z*)	Linear Equation	R^2	LOD (µg/mL)	LOQ (µg/mL)
DTBP	–	12.754	191 > 163.2	191 > 57.1	191 > 131.1	y = 37,639.632x − 10,889.068	0.9995	0.061	0.185
BHT	3	13.61	220 > 205.2	205.2 > 177.2	205.20 > 57.1	y = 24,215.831x − 24,212.275	0.9992	0.035	0.111
DEP	–	14.746	149 > 65.1	149 > 93	177 > 149	y = 153,314.124x − 1,004,949.103	0.9994	0.293	0.887
ATBC	ND	20.444	157 > 139	112 > 84	157 > 111	y = 6895.9x - 13240	0.9995	0.055	0.167
DEHA	18	22.476	129 > 101.1	129 > 111.1	129 > 55.1	y = 29,968.115x + 32,645.862	0.9999	0.122	0.368
DEHP	1.5	23.666	167 > 149.1	149 > 65.1	149 > 93	y = 335,160.598x + 2,758,684.793	0.9991	0.036	0.112
13-Docosenamide	ND	25.608	72 > 55	126 > 81.1	126 > 55.1	y = 18,586.168x − 147,340.724	0.9993	0.188	0.572
Irgafos® 168	ND	32.78	441 > 57.1	441 > 147	147 > 117.1	y = 87,276.567x + 360,351.068	0.9994	0.30	0.878
Phosphate Irgafos® 168	–	36.86	316 > 191.2	316 > 57	191 > 57	y = 2787.1051x − 27,362.379	0.9996	0.126	0.384
Irganox® 1076	6	37.611	515 > 147.2	515 > 57.1	530 > 147.2	y = (9273.384x −38,905.862	0.9997	0.162	0.491

*SML= Specific Migration Limit, RT= Retention Time, TI= Target Ion, RI 1 = Reference Ion 1, RI 2 = Reference Ion 2, R2 = Coefficient of Determination, LOD= Limit of Detection, LOQ= Limit of Quantification, ND= Not Defined, DTBP- phenol, 2,6-bis(1,1-dimethylethyl), BHT- butylated Hydroxytoluene, DEP- diethyl Phthalate, DEHA- hexanedioic acid, bis(2-ethylhexyl) ester, DEHP- bis(2-ethylhexyl) phthalate, 13-D- 13-docosenamide, Irgafos® 168- phenol, 2,4-bis(1,1-dimethylethyl)-, phosphite (3:1), Irgafos®168 phosphate- tris(2,4-di-tert-butylphenyl) phosphate, Irganox® 1076- stearyl 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propionate

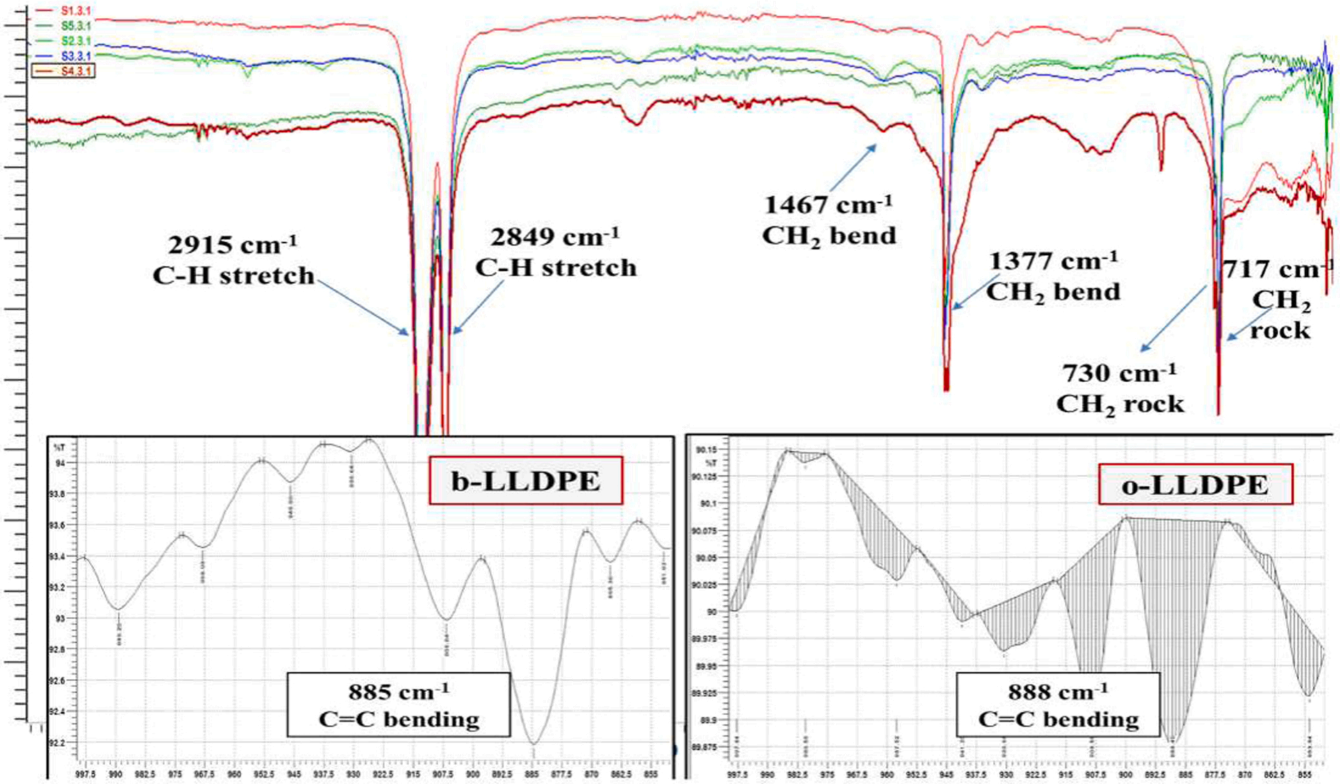

Fig. 1. ATR-FTIR spectra produced from milk packaging films procured as samples, S1, S2, S3, S4, S5 from food-contact side, illustrating the characteristic assignments of low density polyethylene (LDPE) with short chain co-monomers, viz., octene (C-8) and butene (C-4) as linear LDPE.

CH_2 out of plane vibrations (Noda, Dowrey, Haynes & Marcott, 2007). However, LLDPE was then recognised to be present with short-chain alpha-olefins/co-monomers, viz., octene (C-8) or butene (C-4). All major intensities against respective wavenumber are shown in SD Table 1.

3.2. *Solvent interactions with polymer-based chemical additives*

The method of choice for the SLE of chemical compounds from packaging materials was dissolution- precipitation method. The principle of this method is based on the dissolution of a polymer in a solvent, followed by the precipitation of polymeric constituents by the addition of nonsolvent with a different polarity and solubility. (Vandenburg et al., 1997; Ügdüler, Van Geem, Roosen, Delbeke, & De Meester, 2020).

However, to attain exhaustive extraction of all chemical additives present in packaging film, combination of chloroform and methanol (1:1) was statistically screened as a suitable solvent/ nonsolvent system based on their ability to better extract the chemical additives from the polymer matrix. Chromatograms of solvent mixtures are provided in SD Fig. 1. Chloroform and methanol as extracting solvents have been extensively used by several workers to extract additives like hindered amine light stabilizers (HALS), primary & secondary antioxidants (AOs), UV stabilizers, fatty acid type lubricants, etc. from polyolefins using different other types of solvent-based extraction techniques, such as, Soxhlet, ultrasonic and microwave assisted extraction, etc. (Wims & Swarin, 1975; Sevini & Marcato, 1983; Vilaplanang , Karlsson, Ribes-Greus, Ivarsson & Karlsson, 2008; Yamada & Yaso, 2015; Ügdüler et al., 2020). It has also been reported that non-polar solvents like: chloroform, toluene and xylene with methanol are ideal to exhaustively extract additives from polymers (such as polyolefins or polystyrene) as they have their solubility parameters close to polyolefins (Francuskiewicz, 1994; Vandenburg et al., 1997; Vandenburg et al., 1998; Vandenburg et al., 1999). Hence, the dissolving solvent can better fuse with the polymer matrix and promote its extreme swelling at modest temperature and thereafter, promote the diffusion of extraneous compounds into solvents (Robertson, 2012; Bhunia et al., 2013; Braun, 2013; Dorey, Pahl, Uettwiller, Priebe & Hauk, 2018).

3.3. Non-targeted GC-MS screening

GC–MS scanning was carried out to identify the additives and NIAS present in milk packaging films. Sixty-five compounds were identified from packaging samples, including hydrocarbons, plasticizers, lubricants and fatty acids, etc. Fig. 2 is a representative GC-MS chromatogram of packaging sample no. 14. Screened compounds were tentatively recognized by their repetitive RT, mass spectra from different sample extractives and also with similarity index matches during library search.

Toxicological evidences of these chemicals in addition to their identification and quantification are essential to promote human safety and well-being (Su, Vera & Nerín, 2020). However, Cramer Rules were applied to predict toxicity of identified compounds. Chemicals on the basis of their molecular structures and their established toxicity in humans and animals are described as *low toxicity-class I*, *intermediate toxicity-class II* and *high toxicity-class III* (European Food Safety Authority, 2008; Lestido-Cardama et al., 2020). In the study, out of 65 chemical compounds only 39 compounds belong to toxicity-class I; majority of which are lubricants or fatty acid derivatives. Whereas, three and twenty-three compounds fit in class II and class III respectively. The specifications of identified chemicals in respective chemical and toxic groups are illustrated in Table 1 and discussed below.

3.3.1. Plasticizers

Plasticizers are typical organic compounds added to polymers to improve extensibility, softness, flexibility, etc. (Carlos, de Jager & Begley, 2018). Seven different kinds of plasticizers were detected in our study, with phthalates as most dominant. Among them, DEP, DEHP, ATBC and DEHA were found in all samples. Whereas, di-isooctyl phthalate (DIOP) was present in 34 samples and di-tridecyl phthalate (DTDP) (n = 32), di-isononyl phthalate (DINP) (n = 12) were also ascertained. DEHP, DINP, DEP are most noted and extensively studied phthalates in PE packaging materials (Garcia Ibarra et al., 2018) while, ATBC is widely used as a phthalate-substitute plasticizer (Lestido-Cardama et al., 2020). 2-propenoic acid, pentadecyl ester, fatty acid derivative used as extenders and secondary plasticizer was also found in 25 samples. Scientific findings of several workers (Fankhauser-Noti & Grob, 2006; Del Carlo et al., 2008; Amiridou & Voutsa, 2011; Gallart-Ayala, Núñez & Lucci 2013, 2013; Pellegrino Vidal, Ibañez & Escandar, 2016; Montevecchi, Masino, Zanasi & Antonelli, 2017) have shown presence and migration of similar class of plasticizers from food packages (films, bags, bottles) into solvents/ simulants or food items of different nature, such as milk, minced meat and poultry, beverages, edible fats and oils, bottled water, etc. and hence, has contributed to putative food toxicity and gained worldwide concern for human health, ecological risk. Out of all plasticizers reported in the study, only DIOP belongs to class III as per Cramer rules, whereas DEP, DTDP, DINP, DEHA, DEHP and ATBC are classified under class I, which are known to be less toxic.

3.3.2. Antioxidants

Polymers tend to breakdown upon reaction with free radicals, produced during polymer production or on exposure to UV radiation, ozone, heat, etc. (Al-Malaika, 1998; Bhunia et al., 2013). However, to impart oxidative stability AOs are often added (Thomas, Dexter & King, 2002) as primary AOs (mainly phenolic-based) and secondary AOs (phosphites or thioesters) (Dopico-García , López-Vilariñó & González-Rodríguez, 2007). In our study, Irgafos®168 and Irganox®1076 were found in all 36 samples. Igranox®1076 is sterically hindered phenolic AO whereas, Irgafos®168 is phosphite-based AO which additionally performs light and heat stabilization during polymer processing (Cherta et al., 2015). Its oxidized form, tris (2,

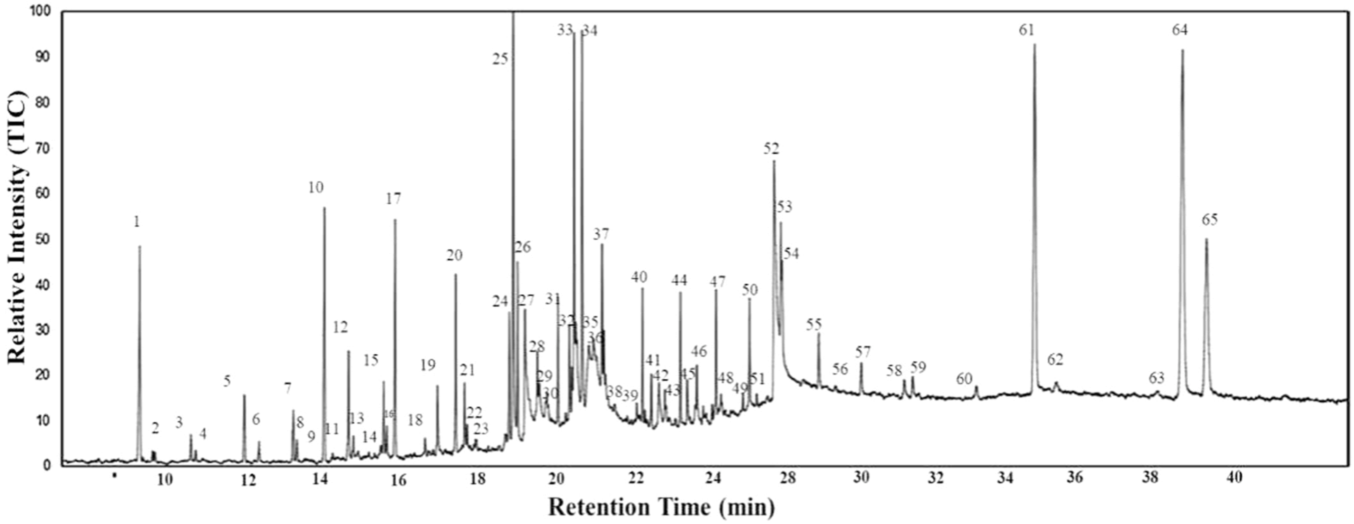

Fig. 2. GC-MS chromatogram of chemical additives extracted using chloroform: methanol fromsample S14. Each number on the peaks represents chemicals listed in Table 1.

4-di-tert-butylphenyl) phosphate or phosphate Igrafos®168 as NIAS; was found in all packaging samples. This can be attributed to oxidation of phosphite (in Irgafos®168) to phosphate (as phosphate Irgafos®168) during polymer processing (Liu & Mabury, 2019). Another NIAS, DTBP was also detected in all samples. Sparkman, Penton & Kitson (2011) have reported it as a common breakdown product from Irganox®1076 or Irgafos®168. 7,9-ditert-butyl-1-oxaspiro[4.5]-deca-6,9-diene-2, 8-dione an additional NIAS as a breakdown product originating from Igrafos®168 and Igranox®1076 (Lestido-Cardama et al., 2020) appeared in 34 samples, which is similar to those detailed by Chatonnet, Boutou & Plana (2014) and Galmán et al. (2018). Ketoamine-based AO, quinoline, 1,2-dihydro-2,2,4-trimethyl (TMQ) was found in 32 samples, which otherwise is used as polymerization inhibitor has also been recorded by Abd El-Ghaffar, Shaffei & Abdelwahab (2014) in polyolefin-based packaging materials. Another sterically hindered amine stabilizer; 1, 4-benzenediamine, N-(1, 3-dimethylbutyl)-N'-phenyl (6PPD) was found in ten percent (n = 6) of the samples analyzed. Migration potential of Irganox®1076 and Irgafos®168 in polyolefins is well established (Bhunia et al., 2013). In the stated profiling of packaging materials, majority of sterically hindered AOs viz., Irganox®1076, Irgafos®168, 6PPD, etc. are present and as per Cramer rules, Irgafos®168, TMQ and 6PPD are highly toxic- class III compounds. Whereas, other AOs, such as Irganox®1076, BHT, Homosalate are counted as less toxic because they fall under class II but all of these AOs are registered substances under REACH-ECHA and do not have any bioaccumulation potential. While degradation products or NIAS from AOs, viz., phosphate Igrafos®168, DTBP, 7,9-ditert-butyl-1-oxaspiro[4.5]-deca-6, 9-diene-2,8-dione are class III compounds under Cramer rules may adversely affect human health upon repeated exposure to moderate-to-high oral doses (European Chemicals Agency (ECHA), 2021).

3.3.3. Lubricants

Polymers above their melting point tend to be viscous or sticky and lubricants are added as functional additives to lower the frictional forces (Hahladakis, Velis, Weber, Iacovidou, & Purnell, 2018). Based on their process performance, they can be grouped as internal lubricants and external lubricants. Fatty alcohols-based internal lubricants, which are popularly used as processing aids, such as, 1-heptacosanol (n = 35), 1-tetracosanol (n = 28) and palmityl alcohol (n = 34) appeared frequently in many samples. Whereas, external amide lubricants, viz., isopropyl myristate, sorbitan palmitate, methyl stearate, behenic alcohol, tetrapentacontane and stearamide were screened in 32 samples each and these long-chain saturated fatty acids (myristate, palmitate & stearate) and hydrocarbons (C-12 to C-30) were also outlined in the studies done by Singh, Saengerlaub, Wani & Langowski (2012) and Rani et al. (2015). Other fatty alcohols viz., 1-tetradecanol, 1-dodecanol and 11-methyltricosane were found in few samples. In our profiling both external and internal lubricants were identified in more than eighty percent of the samples which is similar to those reported by Lahimer, Ayed, Horriche, & Belgaied (2017), Garcia Ibarra et al. (2018) and Galmán Graíño et al. (2018). Hazard assessment studies by ECHA (2021) have indicated that majority of screened lubricants are non-hazardous as they are actively metabolized and excreted from human body. On the similar note, Cramer analysis illustrates that lubricants listed in our study fall under class I, except for sorbitan palmitate which is class III immunotoxin.

3.3.4. Heat and light stabilizers

Stabilizers are intentionally added substances (IAS) to increase overall stability of polymers against processing effects (Li et al., 2015) whereas, light stabilizers guard plastics from breakdown on exposure to sun, UV, etc. (Grigsby, Bridson & Schrade, 2014). In our study UV stabilizers, such as, 2-carboxy-benzophenone (n = 20), 2–2'-hydroxy-5-methyl-phenyl benzotriazole (n = 19), hexyl salicylate (n = 33) and octocrylene (n = 24) were reported, alike the analysis of Qiu, Ruan & Li (2020) and Kwon et al. (2018). Benzophenone and benzotriazole based-UV stabilizers (BUVSs) have also been reported in food packaging materials by Bumbudsanpharoke & Ko (2015). However, these polymer additives are established carcinogens and their use is forbidden in United States and EU countries and as per Cramer rules belong to class III highly toxic category. Octocrylene, is used to produce benzophenone in retro-aldol condensation reaction, was also detected in 24 samples. It was detected in all benzophenone-containing samples and contributes to highly toxic-class III category (Downs et al., 2016. Hexyl salicylate (n = 32) used for photo-stabilization of polymers, falls under class I of Cramer rules (Yousif & Haddad, 2013).

3.3.5. Hydrocarbons

Hydrocarbons as polymeric units are further grouped as saturated alkanes, unsaturated alkenes and aromatic hydrocarbons (Bilal & Iqbal, 2019). In our samples screening, several n-alkanes and n-alkenes with chain length ranging between C-15 to C-50 were found, viz., eicosane (n = 36), pentadecane (n = 34), hexadecane (n = 36), heptadecane (n = 36), 1-nonadecane (n = 36), 11-methyltricosane (n = 32), tetrapentaoctane (n = 32) and 1-tridecene (n = 32) which are similar to those noted by Sampaio et al. (2021) and Purcaro, Barp & Moret (2016). These short chain hydrocarbons (SCHs) from packaging polymers have been described by Qian et al. (2018) as IAS because they are known to originate from paraffin wax, which commonly works as an external lubricant in polymers. Squalene, branched naphthalene SCH is used as processing aid, was detected in all samples as reported by Lestido-Cardama et al. (2020) and Galmán Graíño et al. (2018). Hydrocarbon derivative, hexadecyl isopropyl ether appeared in all scanned samples and peaks of aromatic hydrocarbon derivative; benzene, 2, 4-diisocyanato-1-methyl- (n = 7), phthalimide (n = 30) were also spotted. Rani et al. (2015) has documented similar derivatives as NIAS because they are by-products formed during polymerization reactions. However, out of all the screened hydrocarbons and its derivatives only the aromatic hydrocarbon derivative, viz., benzene, 2, 4-diisocyanato-1-methyl- and phthalimide are class III highly toxic compounds which are known to affect the GIT, respiratory, and central nervous systems in humans. While, other hydrocarbons were examined to be class I compounds as per Cramer rules (ECHA, 2021).

FCMs are prevailing source of SCHs and earlier studies have investigated cases of human exposure due to their undue migration from packaging materials into simulants and food commodities (Sampaio et al., 2021; Purcaro et al., 2016). However, recurring detection of high levels of SCHs in packaging materials resulted in adoption of recommendation EU 2017/84 on surveillance for SCHs in food and FCMs by EU Commission (Commission Recommendation (EU) No 2017/84 (2017)). But till date, no SMLs are prescribed for emerging hydrocarbons (European Food Safety Authority (EFSA), 2008).

3.3.6. Slip agents

Slip additives are widely used in polyolefins to decrease film's resistance to sliding over itself or on the parts of converting equipment. They are directly added to the molten polymer (during extrusion) and migrate or bloom to the polymer surface where they create a microcrystalline structure. Based on their ability to migrate rapidly or slowly on the surface of the packaging films (upon cooling), slip agents are categorized as, primary amides and secondary amides (Höfer, 2012). Four different primary amides from unsaturated long chain fatty acids were observed, viz. 13-docosenamide (n = 36), stearamide (n = 9) and oleamide (n = 36), tricaprylin (n = 36). 13-docosenamide and oleamide were found in packaging wrappers and reported by Briscoe, Pogosion & Tabor (1974), Rani et al. (2015) and Galmán Graíño et al. (2018) as the most effective slip agents for polyolefin. Whereas, secondary amides having twice the molecular weight of primary amides were not detected in our study (Keck-Antoine et al., 2010).

Stearamide, tricaprylin are Cramer class I chemicals and several biochemical studies have shown that they get enzymatically metabolized (Guerreiro et al., 2018; Cooper & Tice, 1995). Whereas, oleamide and 13-docosenamide as per Cramer rules belong to class III highly toxic compounds and tend to affect nervous and immune systems (ECHA, 2021) but in EU regulations these compounds are presented without any SMLs.

3.3.7. Unreacted starting and intermediate substances

Starting materials such as, monomers and added intermediates are used as precursors for polymer synthesis and unreacted/ residual substances from these reactions have a tendency to migrate into foods (Bhunia et al., 2013; Hahladakis et al., 2018) and hence, specified as NIAS (Domeño et al., 2017). 4,4'-((p-Phenylene) diisopropylidene) diphenol (bisphenol P) a monomer, sometimes used as substituted plasticizer was found in 24 samples. Fatty acid derivatives and carboxylic acid-based substances which are used in production of co-polymers for printing inks, sealants, adhesives, etc. such as, 2-propenoic acid, pentadecyl ester, an acrylate-rooted intermediates ($n = 25$) and 9-octadecenoic acid, methyl ester ($n = 36$), methyl palmitate ($n = 34$), pyrrole-3-carbonitrile, 5-formyl-2,4-dimethyl ($n = 7$) were detected in studied samples. Another compound, pentafluoro-propionic acid, 4-hexadecyl ester was also noted in 12 samples. It is used as solvents for other starting materials like, stabilizers, emulsifiers, etc. Lastly, permitted packaging inks, methyl benzoate and drometrizole were also detected in 20 samples each. Such unreacted substances have commonly been reported in studies compiled by Bhunia et al. (2013), Rani et al. (2015), Garcia Ibarra et al. (2018) and Hahladakis et al. (2018).

Although as per Cramer analysis all of the reported starting and intermediate compounds in the study belong to Class 1 category except for pentafluoro-propionic acid, 4-hexadecyl ester (class III) but these substances pose grave risks to human health when their amount in food passes a stated limit (EU 10/ 2011). However, restrictions and specifications of such chemical compounds for their use in food packaging materials are monitored and revised by regulatory agencies around the world.

3.3.8. Other processing aids

This section includes substances which could not be placed in any of the above categories. Dichloroacetic acid, 4-hexadecyl ester, an adhesive from chloroacetic acid derivatives (Code of Federal Regulation, Title 21, 2011) was found in 12 samples. Polymer modifier, benzoic acid, 4-ethoxy, ethyl ester was reported in 13 samples and 2-(hydroxymethyl) benzimidazole ($n = 15$) which is popularly used in polymers and biofilms for its anti-microbial activity, was also reported. Such processing aids from packaging materials were documented in similar investigations by Lahimer et al. (2017), Garcia Ibarra et al. (2018) and Sampaio et al. (2021). However, Cramer rules suggested that all of these compounds are highly toxic (class III) and are known to cause reproductive damage, induce unwanted allergic reactions, etc. (ECHA, 2021).

Based on the compiled toxicological data and risk assessment studies, EU Regulation No. 10/2011 stipulates permitted substances in plastic food packaging along with their SMLs (Commission Regulation (EU) No 1282/(2011)). However, this study illustrates that only 17 out of 65 identified compounds (listed in the Table 1) appear as authorized substances for the manufacture of FCMs as per EU Regulation No. 10/ 2011.

3.4. GC-MS/ MS optimization

Furthermore, for quantification of 10 frequently occurring compounds in packaging films, a GC-MS/MS method was developed and validated. To develop the procedure with high sensitivity and selectivity, parameters of MS/MS were optimized and MRM transitions were estimated using GC-MS solution 4.2 with smart MRM and MRM Optimization Tool. (Shimadzu Corporation, Kyoto, Japan). However, the two most suitable MRM transitions determined on the basis of intensity and abundance were selected for further separation of analytes.

3.4.1. Method Validation

The method developed was validated with regard to linearity, recovery, repeatability, limits of detection (LOD) and limits of quantification (LOQ). The linearity of established method was assessed by using standard solutions of known concentrations. The calibration curves comprised of five concentrations ranging from 1 to 40 μg mL^{-1}. Table 3 displays the calculated determination coefficient (R^2) with linear equation. The R^2 obtained in study exhibited good linearity with values > 0.99, denoting calibration yields less than 5% variability error in all subsequent analysis.

LODs and LOQs were calculated as per guidelines of American Chemical Society, ACS (American Chemical Society, 1980) and were assessed as lowermost concentration, which gave a signal-to-noise beyond three (fraction between peak area of target ion for each analyte and peak area of noise) and ten (fraction between peak area of target ion for each analyte and peak area of noise), respectively. Table 3 shows LODs and LOQs of different chemical additives. The method displays good sensitivity with LOQ equal to or lowers than 0.111 μg mL^{-1}, while LOD obtained was equal or lower than 0.035 μg $mL^{-1}$of solvent used for extraction of additives from milk packaging films as described in Section 2.4.1. Relative recovery experiments were performed for trueness assessment of developed analytical method, using six replicate analyses (in three consecutive days) spiked at different levels. Recoveries varied between 80% and 120%. The precision, as relative standard deviations (RSD %), was measured with regards to repeatability. For intra-day precision, six sample replicates were analysed on three successive days. The values attained for repeatability (RSD $< 10\%$) were also conclusive. (SD Table 5).

The presented work is the foremost attempt at using GC–MS/MS for the analysis of extractives from multilayer milk packaging films. Particularly, the method offers advantages with enhanced sensitivity and selectivity (in comparison to other GC-based methods).

3.4.2. Quantification of selected chemical compounds

Ten chemical compounds including, plasticizers (DEP, ATBC, DEHA, DEHP), AOs (BHT, Irgafos®168, Irganox®1076) and a slip agent (13-docosenamide) and degradation products/ NIAS (2, 4-Di-tert-butylphenol, phosphate Irgafos®168) were quantified using GC-MS/MS with different optimized CEs. The average concentrations of selective additives obtained from 36 packaging samples are listed in Table 3. Amongst the four plasticizers, ATBC was reported in the highest concentration range of 28.16–91.58 μg mL^{-1}. ATBC concentrations varied from 0.9 to 38.3 μg mL^{-1} in the cap gaskets of jarred bottles, commercial wraps and other FCMs (Carlos et al., 2018) and 166–229 ng g^{-1} in plastic kitchen wrap films. (Nara, Nishiyama, Natsugari, Takeshita & Takahashi, 2009). Several investigators have also documented the presence of ABTC in different food items, such as, skim milk (27.9 mg/ kg), corn snacks (0–7.09 ng g^{-1}), cookies (0.557 ng g^{-1}) and cakes (2.33 ng g^{-1}) (Nara et al., 2009; Garcia Ibarra et al., 2018).

DEHA was found also in heavy concentration, ranging from 17.02 to 57.74 μg mL^{-1}in all samples. The similar levels of DEHA (1.2–429 μg mL^{-1}) were reported in wide range of food-grade plastics by more than ten researchers in their studies as compiled by the International Agency for Research on Cancer (IARC, 1987). Carlos et al. (2018) have also reported the presence of DEHA in commercial plastic wraps (14.1–20.2 μg mL^{-1}) and soda bottles (39.6 μg mL^{-1}). Our results are in accordance with the stated values of ATBC and DEHA in packaging materials by Lajqi, Kerolli-Mustafa, Malollari, & Lajqi (2015) as well. However, active detection in FCMs and migration of ATBC and DEHA into food reflects that the manufacturers are replacing phthalate plasticizers with non-phthalate alternatives.

Other phthalate-based plasticizers, viz. DEP and DEHP were also found in all samples, in such an order that the minute levels were reported and the highest values as 6.58 and 7.55 μg mL^{-1} for DEP and DEHP, respectively. Qian et al. (2018) have likewise stated the presence of DEHP at low concentrations (0.244–0.294 μg mL^{-1}). However, values

Table 3
Concentrations of selected chemical additives from packaging samples.

S No.	DTBP (μg/mL)	BHT (μg/mL)	DEP (μg/mL)	ATBC (μg/mL)	DEHA (μg/mL)	DEHP (μg/mL)	13-D (μg/mL)	Irgafos®168 (μg/mL)	Irgafos®168 phosphate (μg/mL)	Irganox® 1076 (μg/mL)
1.	< LOQ	8.56 ± 0.08	5.4 ± 0.26	46.45 ± 0.36	17.32 ± 0.42	< LOQ	1.81 ± 0.02	42.44 ± 0.21	< LOQ	< LOQ
2.	1.302 ± 0.38	7.41 ± 0.44	6.51 ± 0.28	28.16 ± 0.18	24.3 ± 0.2	< LOQ	3.91 ± 0.13	33.19 ± 0.04	17.31 ± 0.124	1.27 ± 0.14
3.	0.414 ± 0.28	5.57 ± 0.15	6.6 ± 0.08	51.67 ± 0.33	43.45 ± 0.42	< LOQ	2.76 ± 0.16	33.17 ± 0.05	ND	< LOQ
4.	1.32 ± 0.08	9.68 ± 0.19	6.77 ± 0.06	67.63 ± 0.38	50.6 ± 0.21	< LOQ	10.17 ± 0.12	32.54 ± 0.4	< LOQ	< LOQ
5.	1.493 ± 0.06	8.17 ± 0.11	6.42 ± 0.22	51.34 ± 0.14	40.42 ± 0.2	< LOQ	3.14 ± 0.18	55.32 ± 0.2	24.3 ± 0.341	1.38 ± 0.37
6.	1.542 ± 0.31	8.3 ± 0.1	7.43 ± 0.17	37.64 ± 0.26	49.4 ± 0.16	< LOQ	2.62 ± 0.16	42.45 ± 1.2	ND	< LOQ
7.	< LOQ	8.137 ± 0.16	5.4 ± 0.14	45.44 ± 0.25	47.24 ± 0.2	< LOQ	1.68 ± 0.2	45.63 ± 0.41	< LOQ	< LOQ
8.	1.27 ± 0.37	7.62 ± 0.22	6.51 ± 0.24	31.73 ± 0.1	42.62 ± 0.01	< LOQ	6.31 ± 0.03	34.41 ± 0.2	43.45 ± 0.11	1.71 ± 0.14
9.	0.781 ± 0.18	7.36 ± 0.21	6.853 ± 0.1	50.6 ± 0.5	42.25 ± 0.21	< LOQ	1.91 ± 0.1	47.75 ± 0.31	< LOQ	< LOQ
10.	1.3 ± 0.02	8.42 ± 0.06	6.6 ± 0.37	66.46 ± 0.06	26.6 ± 0.46	< LOQ	8.11 ± 1.23	35.2 ± 0.22	< LOQ	< LOQ
11.	1.4 ± 0.08	8.48 ± 0.21	7.02 ± 0.91	50.72 ± 0.22	46.71 ± 0.34	< LOQ	3.79 ± 0.02	54.42 ± 0.56	50.6 ± 0.04	1.6 ± 0.35
12.	1.38 ± 0.11	8.61 ± 0.26	6.89 ± 0.16	39.22 ± 0.3	46.29 ± 0.41	< LOQ	2.41 ± 0.2	36.83 ± 0.23	ND	< LOQ
13.	1.22 ± 0.32	9.51 ± 0.1	6.43 ± 0.4	78.1 ± 0.56	31.98 ± 0.62	2.38 ± 0.12	2.41 ± 0.1	44.38 ± 1.82	< LOQ	0.82 ± 0.14
14.	1.46 ± 0.38	8.043 ± 0.11	7.4 ± 0.56	68.1 ± 1.33	34.53 ± 0.65	2.41 ± 0.1	10.73 ± 0.1	34.14 ± 0.61	40.42 ± 0.671	1.71 ± 0.21
15.	0.85 ± 0.2	6.61 ± 0.22	7.01 ± 0.12	80.74 ± 2.24	46.2 ± 2.34	< LOQ	6.61 ± 0.16	36.2 ± 0.8	ND	0.82 ± 0.05
16.	1.73 ± 0.23	10.58 ± 0.73	7.2 ± 0.36	76.84 ± 0.4	33.06 ± 2.14	< LOQ	7.6 ± 0.51	43.2 ± 0.52	< LOQ	4.42 ± 0.2
17.	1.44 ± 0.13	8.58 ± 0.2	6.98 ± 0.29	66.06 ± 2.1	35.4 ± 1.87	< LOQ	7.13 ± 0.01	51.81 ± 0.89	49.4 ± 0.034	4.47 ± 0.34
18.	1.68 ± 0.42	9.51 ± 0.21	7.54 ± 0.44	84.6 ± 1.64	44.92 ± 0.58	< LOQ	21.91 ± 1.16	43.96 ± 0.85	ND	4.31 ± 0.08
19.	1.34 ± 0.43	8.67 ± 0.28	5.46 ± 0.43	77.9 ± 0.01	54.03 ± 3.8	< LOQ	2.53 ± 0.21	48.1 ± 1.18	< LOQ	1.14 ± 0.11
20	1.54 ± 0.14	7.93 ± 0.04	6.89 ± 0.1	70.01 ± 1.4	46.64 ± 3.28	< LOQ	5.73 ± 2.61	49.26 ± 1.1	47.24 ± 0.016	2.21 ± 0.1
21.	0.61 ± 0.13	12.66 ± 0.16	7.32 ± 0.41	85.8 ± 1.73	41.3 ± 1.5	< LOQ	5.67 ± 0.01	51.38 ± 1	< LOQ	1.44 ± 0.61
22.	1.6 ± 0.13	9.04 ± 0.38	6.68 ± 0.05	77.28 ± 2.3	51.78 ± 0.81	< LOQ	13.3 ± 1.78	44.13 ± 1.1	< LOQ	4.63 ± 0.06
23.	1.51 ± 0.06	10.86 ± 1	7.1 ± 0.1	70.32 ± 1.83	51.88 ± 2.24	< LOQ	9.94 ± 0.2	54.24 ± 2.31	42.25 ± 0.131	4.3 ± 0.08
24	1.5 ± 0.26	9.78 ± 0.31	7.6 ± 0.23	88.84 ± 0.36	49.93 ± 1.2	< LOQ	14.88 ± 0.44	35.98 ± 1.08	ND	3.81 ± 0.3
25.	1.47 ± 0.13	9.64 ± 0.16	6.78 ± 0.2	87.01 ± 1.51	41.78 ± 2.2	2.45 ± 0.08	12.51 ± 0.23	44.67 ± 1.42	ND	4.42 ± 0.21
26.	1.85 ± 0.08	8.4 ± 0.22	7.52 ± 0.16	74.34 ± 4.24	29.04 ± 2.66	5.71 ± 0.1	54.48 ± 3.96	36.03 ± 2.64	42.62 ± 0.011	8.78 ± 0.14
27.	0.71 ± 0.18	7.38 ± 0.24	7.1 ± 0.1	85.23 ± 4.71	51.04 ± 1	< LOQ	12.88 ± 2.36	37.92 ± 1.53	ND	5.61 ± 0.54
28.	1.63 ± 0.06	10.41 ± 0.18	7.54 ± 0.42	91.58 ± 1.1	52.7 ± 1.54	< LOQ	37.15 ± 1.81	54.98 ± 1.06	< LOQ	13.83 ± 1.64
29.	1.72 ± 0.26	9.5 ± 0.22	6.67 ± 0.14	79.54 ± 1.26	52 ± 0.5	< LOQ	55.91 ± 0.67	48.68 ± 3.21	26.6 ± 0.012	11.85 ± 2.25
30.	1.51 ± 0.08	10.45 ± 0.8	7.32 ± 0.04	78.5 ± 1.44	54.87 ± 1.28	< LOQ	25.32 ± 0.69	43.29 ± 3.4	< LOQ	6.18 ± 0.06
31.	1.42 ± 0.05	9.5 ± 0.23	6.67 ± 0.2	77.21 ± 3.72	52.03 ± 0.66	< LOQ	39.36 ± 0.92	49.86 ± 1.48	ND	4.32 ± 0.18
32.	1.81 ± 0.12	8.85 ± 0.14	7.63 ± 0.44	88.1 ± 1.3	56 ± 1.31	< LOQ	37.98 ± 1.4	60.68 ± 1.54	46.71 ± 0.128	8.62 ± 0.18
33.	0.91 ± 0.11	9.61 ± 0.2	7.5 ± 0.58	90.13 ± 1.6	40.83 ± 0.8	< LOQ	14.2 ± 2.32	44.44 ± 0.96	ND	5.36 ± 0.3
34.	1.68 ± 0.2	10.31 ± 0.36	6.45 ± 0.01	76.62 ± 3.24	29.08 ± 2.63	< LOQ	30.02 ± 0.2	49.8 ± 0.4	ND	14.73 ± 2.9
35.	1.78 ± 0.28	9.71 ± 0.08	7.82 ± 0.22	74.51 ± 1.48	56.73 ± 0.92	2.85 ± 0.2	42.56 ± 1.06	51.78 ± 0.94	46.29 ± 0.11	11.76 ± 2.43
36.	1.65 ± 0.26	10.13 ± 0.06	7.2 ± 0.1	81.38 ± 0.85	52.98 ± 2.1	< LOQ	26.67 ± 1.68	35.7 ± 1.54	< LOQ	4.96 ± 0.1

Results are presented as Mean ± SD (n = 3)
*DTBP= phenol, 2,6-bis(1,1-dimethylethyl) BHT= butylated Hydroxytoluene, DEP= diethyl Phthalate, DEHA= hexanedioic acid, bis(2-ethylhexyl) ester, DEHP= bis (2-ethylhexyl) phthalate, 13-D= 13-docosenamide, Irgafos® 168 = phenol, 2,4-bis(1,1-dimethylethyl)-, phosphite (3:1), Irgafos® 168 phosphate= tris(2,4-di-tert-butylphenyl) phosphate, Irganox® 1076 = stearyl 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propionate. < LOQ= lesser than limit of quantification, ND= Not detected.

from our study also fall in the comparable ranges of 0.5–53 μg mL^{-1} for DEP and 2.0–4.0 μg mL^{-1} for DEHP in milk-based packaging materials studied by Castle, Mercer, Startin & Gilbert (1988), Lin, Chen, Zhu & Wang (2015), Qian et al. (2018) and Ayamba, Agyekum, Derick & Speldewinde (2020). Whereas, Carlos et al. (2018) have documented much higher concentration of DEHP in PET soda bottles (40.9 μg mL^{-1}), beer bottles (42.9 – 46.1 μg mL^{-1}) and lacquered lids of jarred bottles (35.5 – 38 μg mL^{-1}). Fierens et al. (2012) reported the presence of DEP and DEHP in snacks with concentrations ranging from not detectable to 308.0 ng g^{-1}, and 5.3 ng g^{-1} respectively; while Gao, Gu & Wei (2011) studied the concentrations of DEP and DEHP in cakes and cookies, in the range of 0.35–1.97 ng g^{-1} and 45.7–750 ng g^{-1} respectively; which are lower than those detected in the packaging materials as some fraction of the initial concentrations of these plasticizers have migrated into different food items, depending upon the time and temperature of contact, fat content of food, etc.

AOs, viz., BHT, Irgafos®168 and Irganox®1076 which are also used as stabilizers were found in all samples. The levels of BHT in analysed samples varied from 7.76 to 18.75 μg mL^{-1}. It is a small sized AO which tend to migrate rapidly and completely from packaging materials (Lestido-Cardama et al., 2020) and the similar trend of BHT (1.4–32 μg mL^{-1}) was observed by Dopico-Garica et al. (2007) in commercial polyolefin-based films. While Irganox®1076 was found at levels below LOQ in nine samples and the highest concentration recorded was at 12.764 μg mL^{-1}. Studies by Forooghi, Ahmadi, Farhoodi, & Mortazavian (2022) have also reported the presence of Irganox® 1076 at levels as low as not detected to 0.17 μg mL^{-1} but Beldi, Pastorelli, Franchini, & Simoneau (2012) described its levels from 0.13 to 52.6 μg g^{-1} in different food items. Lastly, Irgafos®168 was the most abundant AO detected, with an average range 32.82–59.58 μg mL^{-1}. These concentrations of Irgafos®168 obtained are in concordance with the stated levels of 0.05–300 μg mL^{-1} in the polyolefin-based packaging materials, as reported between by Dopico-García et al. (2007), Ritter, Michel, Schmid & Samuel (2005), Gillet, Vitrac & Desobry (2011), Galotto, Torres, Guarda, Moraga & Romero (2011) and Carrero, Oliva, Navascués, Borrull, & Galià (2015).

Other quantified compounds were the breakdown products/ NIAS of Irgafos®168; namely, DTBP and phosphate Irgafos®168 which are commonly reported as NIAS. DTBP was reported in all samples with the concentration range from 1.51 to 1.77 μg mL^{-1}. This value was less than the reported values 2.431–45.554 μg mL^{-1} in FCMs by Qian et al. (2018). Whereas, phosphate Irgafos®168 was detected (below its LOQ) in only half of the samples. Such low concentrations of both compounds are dissimilar to those stated by Dopico-García et al. (2007), Lahimer et al. (2017), Yan, Hu, Wang, & Jiang (2018) and Blázquez-Blázquez, Cerrada, Benavente, & Pérez (2020) as these compounds in the respective studies by investigators were produced under the impact of sunlight or UV exposure, microwave heating, etc. However, in our study the packaging materials during sample processing were not exposed to any of such harsh settings which in turn, resulted in no alteration of Irgafos®168 concentrations and the presence of small amount of breakdown products can be owed to initial stress oxidation during polymer processing steps due to high temperature and presence of copper-based catalysts within the reaction vessels (Djouani, Richaud, Fayolle, & Verdu, 2011; Blázquez-Blázquez et al., 2020).

Lastly, the levels of frequently reported 13- docosenamide, used as a slip agent in packaging films were also determined. The concentration varied from 1.8 to 41.81 μg mL^{-1} in the samples which largely complies with the values (2.1–50.47 μg mL^{-1}) reported by Cooper et al. (1995), O'Brien, Goodson, & Cooper (1999), Zeddam and Belhaneche-Bensemra (2010) and Garcia Ibarra et al. (2018).

4. Conclusions

The present study reports a simple and robust SLE procedure for non-targeted profiling of IAS (such as plasticizers, slip agents, antioxidants, etc.) and NIAS (intermediate materials from printing inks or dyes, degradation products from antioxidants, such as, carbonic acid, eicosyl vinyl ester; 7,9-di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione; tris(2,4-di-tert-butylphenyl) phosphate etc.) present in the multilayer co-extruded packaging films used for milk. Several other reaction intermediates and by-products of processing additives, such as, 2-(hydroxymethyl) benzimidazole, phthalimide, 2, 4-di-tert butylphenol, etc. were also reported in the study. These NIAS can cause undesirable flavours and toxicity in the food. Consequently, to address the potential health risk, GC-MS with EI ionization is a valuable tool for determination of potent migrants in packaging materials. The presented methodology can be helpful for quality control and regulatory purposes as it could serve as an option that permits regular analysis of unknown contaminants from FCMs. This method exhibits good sensitivity and potential to constructively separate and identify the ingredients of packaging films. Existing commercial libraries are beneficial but extensive use of GC-MS has allowed the comparison of data with other publications. At the same time, it is noteworthy that most of detected compounds are not included in the positive list of monomers and additives which are permitted to be used in plastic food contact materials; and neither in registered list of the European Printing Ink Association, EuPIA (EuPIA, 2019).

Further, GC–MS/MS analytical protocol was formulated to quantify 10frequently reported chemical compounds in the PE-based packaging films. The introduced method was effectively validated i.e., it is appropriate for quantification of even minute amounts of plasticizers (DEHP, DEP, ATBC), slip agents (13-docosenamide) and AOs (BHT, Irgafos®168, Irganox® 1076) or their degradation products/ NIAS (such as, DTBP, phosphate Irgafos®168). The proposed procedure demonstrated satisfactory ranges for both accuracy and repeatability, and low LODs and LOQs verified high sensitivity of the process. The developed protocol could be a less expensive and more eco-friendly method, due to small volume of solvents and samples required for sample preparation and can also be modified for further analysis of chemical compounds with similar physicochemical properties. Analytical outcomes could be considered in the upcoming exposure assessment of different chemical compounds from food packaging materials into milk. It is additionally suggested that GC-MS coupled with high-resolution mass spectrometry techniques like, orbitrap or time of flight could also be employed as hybrid instruments for the analysis of unpredicted NIAS to allow more precise mass determinations along with their structural details and fragmentation patterns for accurate identification.

CRediT authorship contribution statement

Nishi Singh: Conducted the research and preparation of manuscript. **Bimlesh Mann:** concept development, management of research, financial support and suprivisor, manuscript edited. **Rajan Sharma:** management of research, financial support and manuscript edited. **Ajay Verma:** statistical analysis. **Narender Raju Panjagari:** experiments planning, manuscript edited. **Kamal Gandhi:** experiments planning, provided the resources for the research, manuscript edited.

Data Availability

Data will be made available on request.

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Conflict of interest

Authors state that there are no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.fpsl.2022.100975.

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