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Study of leachable compounds in hospital pharmacy-compounded prefilled syringes, infusion bags and vials

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ABSTRACT

Hospital pharmacy compoundings are crucial for maintaining patient care. They are time- and cost-effective in hospital pharmacy settings because they prevent waste, preparation errors, dosage errors, microbial contamination and breakage due to handling. Unfortunately, the drawbacks of hospital pharmacy compounding include the selection of inappropriate medical devices (MDs) for long-term storage, which could directly impact patients.

In this study, three important hospital pharmaceutical compoundings, vancomycin in prefilled syringes (PFSs) made of polypropylene (PP) material, paediatric parenteral nutrition (PN) in ethylene vinyl acetate (EVA) bags and diluted insulin in cyclic olefin copolymer (COC) vials, were selected for leachate study and risk assessment. These compounds were studied via a semiquantitative screening approach by means of an ultrahigh-performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-HRMS) with postcolumn infusion and an in-house built database. 17 leachable compounds for the PFS, 25 for the PN, and 10 for the vial were identified, and their concentrations were estimated for toxicological assessments.

In conclusion, all MDs used in hospital pharmacy compoundings were observed suitable thanks to risk assessments. However, suitable MDs recommended for long-term storage would remain with polymers like COC, for higher safety when exposed to frail and vulnerable patients like neonates and infants.

Introduction

Prefilled drug products (DPs) are becoming more common in industry. Their goal is to offer a practical approach for patients and caregivers by significantly reducing the number of errors.[1,2] Hospital pharmacies intend to provide compound drugs in batches with the same level of safety to maintain efficient and effective patient treatments. Therefore, hospital pharmacies also produce compounded DPs in response to hospital demands and practices for frail and/or vulnerable patients. This approach requires that more specific active pharmaceutical ingredients (APIs) and concentrations be adapted to hospital practices.[3,4] However, there could also be risk of inappropriate use of medical devices for routine long-term batch production, due to the three factual assertions: lack of knowledge of current polymers and quality in the market for long-term storage, cost constraint to purchase high quality polymer medical devices (MDs) and lack of regulatory framework to facilitate selection of appropriate MDs for hospital pharmacy batch production.

Industrially manufactured prefilled DPs abide by strict regulations issued by authorities before market accessibility.[5,6] Risk assessment via extractables and leachables (E&L) on container closure systems in combination with the drug solution is necessary to evaluate the toxicity and safety exposure of the population. Pharmaceutical industries follow guidelines and recommendations to perform diverse tests and to evaluate risk assessments via decision-making workflows.[7-10] For hospital pharmacies, batches of prefilled drug products are smaller in size and do not possess as long a shelf life as industrially manufactured products. They are subject to product control in accordance

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with the Pharmacopoeia (United States Pharmacopoeia and European Pharmacopoeia) along with national and international authorities (SwissMedic, ANSM, European Medicine Agency, Food & Drug Administration) .[11-13] However, no E&L regulations exist for hospital pharmacy-compounded DPs, which are concerning when they are at high risk due to their route of administration, formulation, type of patient, frequency of administration and long-term shelf life.[14,15]

To cover a broad screening of plastic additives, such as volatile, semivolatile and nonvolatile compounds, as well as trace elements, different analytical platforms are needed.[15] All experiments are conducted to obtain reliable results for new DP release.[7] Presently, more sophisticated analytical methods that surpass the sensitivity of recommended approaches have been proposed. These analytical methods could be applied in a hospital pharmacy setting to assist with the study of additives in batch productions of ready-to-use prefilled drug products (DPs).

Current analytical approaches generally involve chromatographic techniques, i.e., gas chromatography (GC) and liquid chromatography (LC) combined with mass spectrometry (MS) and inductively coupled plasma–mass spectrometry (ICP-MS). Recent advances in ultrahigh-performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-HRMS) and postcolumn infusion (PCI) as well as the development of in-house databases have made identification of plastic additives in hospital pharmacies possible with the highest confidence.[15,16]

During the screening of leachates, identifying and semiquantifying compounds of interest is one aspect, but it is not sufficient on its own. Assessing the risk of these compounds in a DP would give them meaning. Evaluating the toxicological risk of the identified plastic additives using internal databases is extremely advantageous. The toxicology of compounds can be assessed using the permissible daily exposure (PDE), which is a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a considerable amount of time or for a lifetime.[17,18] This exposure threshold requires the no observed adverse effect level (NOAEL), which is a chronic toxicological dose descriptor, the level at which the greatest concentration or amount of a substance have no detectable adverse effects in an exposed population.[19] This toxicological descriptor is divided by a series of uncertainty factor multiplications, which are needed to compensate for the interindividual variation, inherent differences in species, route of administration, and duration of exposure.[17,18,20] In the hospital pharmacy context, the risk assessment of DPs is performed by measuring the exposure, which is the PDE, and the hazards, which are the frequency of administration, duration of treatment and vulnerability of the patient. The quality of the PDE would be obtainable due to recent experimental NOAEL data, but in a hospital pharmacy context, toxicological assessments are not time- or cost-friendly. Thus, evaluating it by estimation could be an attractive solution.[15]

In the present work, a leachable compound study was performed on three hospital pharmacy DPs compounded for long-term storage, i.e., vancomycin at 5 mg/mL conditioned as a prefilled polypropylene (PP) syringe, parenteral nutrition conditioned in an ethylene vinyl acetate (EVA) and lastly, insulin at 1 IU/mL conditioned in a cyclic olefin co-polymer (COC) vial as well as the different sources of water for injection (WFI) used in the compoundings. The study involved the identification and semiquantitation of leachable compounds using a hospital pharmacy-built analytical method via UHPLC-PCI-HRMS and an in-house database. A risk assessment was conducted on all identified plastic-related compounds in terms of toxicology and potential endocrine disruptors. The analyses were performed to evaluate the risk of leachable compounds exposed to patients due to container misappropriation.

Experimental

Reagents and Materials

Bis(2-ethylhexyl)phthalate-3,4,5,6-d_4, bisphenol M, 4,4′-thiobis (2-tert-butyl-5-methylphenol), 2,4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl) phenol and bisphenol A-d_{16} were procured as internal standards from Sigma Aldrich (Gygli, Switzerland). MS-grade water, methanol (MeOH) and acetone were purchased from Biosolve® (Dieuze, France). LC-grade dichloroethane and 25 % ammonium hydroxide (NH_4OH) were purchased from Merck® (Gygli, Switzerland). Since these experiments involved the use of leachable compounds, liquid solvents were obtained in glass containers to avoid plastic additive contamination.

LC–MS Conditions

A Thermo Scientific™ ultrahigh-performance liquid chromatograph Vanquish™ Horizon™ (Thermo Scientific™, MA, USA) was coupled to a Thermo Scientific™ Orbitrap™ Q Exactive mass spectrometer (Thermo Scientific™, MA, USA) equipped with a heated electrospray ionisation (HESI-II) source. The samples were kept at 10 °C during the analyses, and a volume of 10 μL was injected.

Plastic additives were separated on a Waters™ Acquity™ BEH Phenyl column (100 × 2.1 mm, 1.7 μm) (Waters™, Milford, MA, USA) and the corresponding VanGuard™ precolumn. The flow rate and column temperature were 0.2 mL/min and 60 °C, respectively. Solvent A (pure water) and solvent B (pure MeOH) served as the mobile phases. The gradient profile was as follows: a linear increase from 70 % B to 85 % B in 6 min, followed by an increase to 95 % B in 4 min. There was a further increase to 100 % B in 2 min, holding at 100 % B for 4 min, before returning to 70 % B in 0.1 min and re-equilibrating the column for 9 min.

For the HESI-II parameters, the sheath gas and auxiliary gas flow rates were 30 and 5 arbitrary units, respectively. The capillary temperature was 275 °C, and the auxiliary heater temperature was 290 °C. Analytes were scanned at both polarities, with a positive ion spray voltage of 3 kV and a negative ion spray voltage of 2.7 kV.

The acquisition program was parallel-reaction monitoring (PRM) at a mass resolution of 17,500 at an AGC target of 2×10^5 using a maximum filling time of 50 ms for the C-trap. The normalised collision energy was set to 10 %. All chromatograms were obtained using a *m/z* tolerance of 5 ppm. An isolation window of 1 *m/z* was used without an isolation offset or a multiplexing count. Mass calibration was performed once a week at both polarities using the Pierce™ Velos ESI Ion Calibration standard mixture (Thermo Scientific™, MA, USA). For positive ion calibration, the mixture contained n-butylamine, caffeine, MRFA (a peptide of Met-Arg-Ala acetate salt) and Ultramark™ 1621, and for negative ion calibration, it contained sodium dodecyl sulfate, sodium taurocholate and Ultramark™ 1621. A MS Tune 2.8 (Thermo Scientific™, MA, USA) was used to control the instrument, and a Chromeleon™ 7.2.7 (MA, USA) was used to acquire the data.

Development and Challenges of the Analytical Method

A semiquantitative screening method was developed to profile leachable, specifically non-volatile, compounds in hospital pharmacy compoundings prepared for frail and vulnerable patients. This method facilitates the identification of compounds based on their retention time, mass error calculation, and MS isotopic pattern, unique to each compound. These tasks are supported by an internally developed database known as DELTA (Database for Extractables and Leachables Trace Assessment), which includes a list of 205 compounds with chromatographic and mass spectral data for identification. Chromatographic separation of these compounds is crucial and

was achieved for most of the compounds included in the database. However, some compounds, including isomers and those with higher polarity and similar structures, posed challenges and relied on the selective power of the MS. The development and challenges of this method are discussed in detail in the reports previously published by our research group.[15,16]

Postcolumn Infusion (PCI)

A Chemyx® Fusion 100T syringe pump (TX, USA), and 10 mL of microsyringe (Hamilton, Nevada, USA) containing 2 % ammonium hydroxide in methanol infused at a flow rate of 2 μL per minute were utilized. The solution was pumped into the MS source via a stainless-steel T-piece. After each acquisition, the source was meticulously cleaned with 50 % water−methanol to remove traces of ammonium hydroxide.

Standard Solution Preparation

A stock solution of all internal standards at 100 μg/mL was prepared by accurately weighing 10 mg of each compound and dissolving it in 100 mL of MeOH. The stock solution was then diluted with MeOH to reach a concentration of 100 ng/mL as the working solution. To prepare the blank sample, it was again diluted 100 × in a final volume of 10 mL to reach a final concentration of 1 ng/mL. Samples of interest were spiked before sample preparation with internal standards (IS) at the same concentration (1 ng/mL).

The model of the scale used to prepare all standard solutions is a Mettler Toledo® XPR225 (Bussigny, Switzerland). Although its minimum weight recommended according to USP is 21 mg and since the analytical method is semiquantitative by nature, an error range between 50 % and 200 % is already accounted for in the method.

A stock solution containing 30 compounds was used for the system suitability test (SST) to verify the robustness of the analytical methodology, ensuring it can analyze various concentrations of these compounds in the actual contact solution. the selection of these compounds aligns with those detailed in our previous publication.[15]

Internal Standard Solution Preparation

Stock solutions of internal standards (IS) (4,4′-sulfanediylbis[5-methyl-2-(2-methyl-2-propanyl)phenol], 4,4′-(1,3-phenylenedi-2,2-propanediyl)diphenol, bis(2-ethylhexyl)phthalate-3,4,5,6-d4, 2,4-ditert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol and bisphenol A-d16) at 100 μg/mL were prepared by weighing 10 mg of each compound and dissolving them in 100 mL of MeOH. The stock solution was then diluted with H2O/MeOH (1:1) to reach a concentration of 100 ng/mL, which was used as the working solution. A blank solution and the sample, containing 10 mL, were spiked with 250 μL of the working solution before sample preparation by an ultrasound-assisted dispersive liquid–liquid microextraction method (UA-DLLME).

Sample Preparation by UA-DLLME

Sample preparation was performed via an ultrasound-assisted dispersive liquid–liquid microextraction method (UA-DLLME) .[16] Prefilled plastic packaging samples (10 mL) were transferred to 15 mL glass centrifuge tubes. A premixed solution consisting of 2 mL of acetone (ACT) and 0.35 mL of 1,2-dichloroethane was then rapidly injected into the sample via a 2.5 mL Hamilton® glass syringe. A microemulsion was formed in the aqueous solution. The samples were sonicated in an ultrasonic bath (Branson Ultrasonics, Connecticut, USA) for 5 min and then centrifuged for 5 min at 3500 × *g*. After centrifugation, the sediment phase was extracted into small LC glass vials by using a 1 mL Hamilton® glass syringe. A second extraction was performed by injecting 0.35 mL of 1,2-dichroethane into the samples. The samples underwent ultrasonication followed by centrifugation before extraction of the 1,2-dichloroethane sediment phase, which was transferred to the same LC vial. A final extraction, identical to the second extraction, was then achieved. The sedimented phase was collected and transferred into the same LC vial. The collected microextractions were then evaporated with nitrogen gas, reconstituted with 0.2 mL of H_2O:MeOH (1:1) and vortexed before injection for analysis. The reconstituted samples possessed a fifty-fold enrichment factor.

Profiling of Leachables in Water-for-Injection

WFI is a universal diluent for nearly all pharmaceutical DPs and should be of the highest standard in accordance with standards such as the USP and EP.[21,22] Two different WFIs were used in the production of the hospital pharmacy compounding candidates via two different approaches, i.e., distillation (vapor compression distillation and multiple still distillation) and industrially manufactured WFI stored in infusion bags. Each WFI was sampled and prepared in the same way as the compounded DPs, and the concentrations of the additives were normalised with a logarithmic mathematical function to enable a better visual profile.

To add precision, the concentration of the distilled WFI used as a diluting agent was modified to fit the reality of the compounded DPs, i.e., for vancomycin PP prefilled syringe (PFS), no dilution of WFI was required since it was a reconstitution from powder form; for EVA parenteral nutrition (PN), the additive from the industrially packaged WFI was diluted 10x; and for the insulin COC vial, the dilution of the distilled WFI was negligible and therefore was not considered, similar to the situation of vancomycin PP PFS.

Prefilled Plastic Drug Packaging Used for Leachable Compound Profiling

Three different prefilled drug packaging systems were selected for the E&L risk assessment using a nonvolatile screening approach and are prepared solely for hospital medical practice:

A Becton and Dickinson and Brothers® (BD, New Jersey, USA) Plastipak™ 10 mL syringe used as a centralised intravenous additive service (CIVAS) prefilled drug product was purchased from the University Hospital of Geneva Pharmacy (Geneva, Switzerland). The plunger and barrel are constructed of PP, and the syringe plunger head is constructed of bromobutyl isoprene rubber (BIIR) using silicone oil as a lubricant. The active drug solution was 5 mg/mL vancomycin in sodium chloride and water for injection (pH 5.6). This prefilled syringe is used to treat *methicillin-resistant Staphylococcus aureus (MRSA)* infection in neonates and children.[23] The syringe is stored at refrigerated temperatures between 2 and 8 °C for a duration of 6 months.[24] The study was performed 6 months after its production, on three separate batches. For each batch, three syringes were used for the analyses.

The SLB Médical® intravenous (IV) bag PN (SLB, Génas, France) is produced in batches by the Lausanne University Hospital Pharmacy named Aliped. The structure of the IV bag is a single layer of EVA. The contents of the product solution in this bag were 7 % amino acids (17 amino acids), 9.8 % glucose, 0.29 % sodium chloride, 0.15 % potassium chloride, 0.15 % calcium glubionate and 0.4 % magnesium sulfate. The pH of the solution was between 5.5 and 6.5. This solution is administered to paediatric patients postoperatively to increase caloric intake and treat malnourished paediatric patients.[25] The IV bag is stored at refrigerated temperatures between 2 and 8 °C for 12 months. The study was performed 12 months after its production, on three separate batches. For each batch, three EVA bags were used for the analyses.

Aseptic Technologies vial (Gembloux, Belgium) is used as a prefilled drug product container compounded in the University Hospital of Geneva Pharmacy as diluted insulin for paediatric patients. The main body is constructed of COC material and the stopper is constructed of thermoplastic elastomer (TPE). The product was a dilution of NovoRapid® 100 IU/mL from Novo Nordisk® (Copenhagen, Danemark) to prepare UltraRapid® insulin at 1 IU/mL, using saline solution (NaCl 0.9 %). They are administered to paediatric patients who are diagnosed with hyperglycaemia and hyperkaliemia. The product container is stored at a refrigerated temperature between 2 and 8 °C for 12 months and is stable at room temperature for 1 month.[26,27] The study was performed 12 months after its production, on two separate batches instead of three due to time-related issues. For each batch, three syringes were used for the analyses.

Results and Discussion

Quality of High-Risk Drug Products

A container closure system (CCS), as per FDA's guidance to industries and EMA's guideline on plastic immediate packaging materials, must be suitable for its intended use, i.e., it should serve as a means of protection for drug solutions against different physical and chemical phenomena to prevent its degradation.[5,6] This system should include primary and secondary packaging, which protects the solution against light, oxidation, microbial contamination and solvent evaporation. Moreover, the packaging must also be compatible with the drug solution, i.e., there should not be any content–container interaction among the material of the container, the active substance and the excipient(s), which can cause a non-negligible change in the overall product. Such examples could be a change in pH, colour, adsorption or absorption between the material and the drug solution. This interaction could affect the efficacy of the overall drug product. Furthermore, the drug solution that is stored in the CCS should not affect its performance, such as its ease of use, patient compliance and drug delivery. Any leachable compounds should be assessed in terms of toxicological exposure for the treated patient population via a risk assessment.

In hospital pharmacies, drug products are prepared in response to hospital practices and needs (for which no resources are available on the market). Due to the selection of inappropriate medical devices in the preparation of long-term batch preparation of prefilled DPs, this could potentially lead to safety concerns, especially when the users of these products are a specific small subset of the general population, such as frail and vulnerable patients.[3,4] No explicit E&L regulations or guidelines exist for hospital pharmacy-compounded drug products.[14]

Vancomycin Prefilled Syringe Evaluation

Vancomycin is a hospital pharmacy-compounded DP used to treat MRSA infections. This DP is filled in primary packaging made mostly of PP. It is administered via the parenteral IV route in neonates and children. The drug solution does not have a complex formulation and is stored for up to 6 months in a refrigerated area between 2 and 8 °C. The treatment involved the administration of 10 mL 4 times a day for more than a month. A clinical assessment would be mandatory to determine if further treatment is needed. There is a case of container misuse; in other words, an administration-purposed syringe was employed for long-term storage. Therefore, it could be considered a high-risk drug product that is recommended for leachate study and risk assessment. Figure S1. in the supplementary material, helped assess the components of the compounded DP.

Vancomycin is a hydrophilic macromolecule of more than 1449 daltons with multiple aromatic groups, as well as oxygen- and nitrogen-related functional groups. In this drug product, the excipient is simply physiological serum, which results in a slight ionic background.

The primary packaging is composed of two materials: PP, of which the barrel is formed, the plunger rod and the syringe needleless cap, and butyl rubber, of which the plungerhead is formed. PP is a semi-crystalline material, possibly composed of an isotactic or syndiotactic structure, with minimal porosity, which means that gas permeation is limited and that the butyl rubber is an elastomer enrobed in medical grade silicone oil, which serves as a slip agent. The component of greatest risk concern is the butyl rubber plungerhead (elastomer) as well as the barrel. The whole inside of the syringe is enrobed with a silicone-based lubricant.

This container was selected because of its historical context, and vancomycin has been compounded in PP syringes since 1995.[24] Up to this date, an administration-purposed syringe was employed to store this drug product, instead of a more appropriate syringe for long-term storage. Therefore, it could be an incentive to investigate the migration of plastic-related compounds from the medical device into the current drug solution with the help of the highlighted analytical method.

Moreover, the presence of the label, graduation ink marks and needleless cap contact have not been assessed on the surface of the syringe, which could promote the transfer of more risk-related compounds via the penetration of label-related compounds. These components could possess traces of adhesives, ink and varnish derivatives.

Total Parenteral Nutrition Evaluation

For the second drug product, PN is a hospital pharmacy-compounded drug product. PN is filled in primary packaging constructed EVA, which is administered intravenously to paediatric patients and is not composed of a complex formulation. PN is stored for one year in a refrigerated area between 2 and 8 °C. At least 100 mL of parenteral nutrition is administered twice a day until recovery. There could be a case of container misuse due to the presence of a single-layered IV bag. As a result, PN could qualify as a high-risk drug product for leachate study and risk assessment.

DP contains a mixture of salt, glucose and amino acids. There are approximately 4 different salts (sodium, potassium, calcium and magnesium), glucose and 17 different types of amino acids containing lateral chains of different natures (polar, apolar, and neutral) .[25] Overall, this mixture creates a highly ionic background.

EVA has consistently served as the material of choice for storing parenteral nutrition and has been a steady replacement for polyvinyl chloride (PVC).[28] In terms of material evaluation, EVA is an amorphous polymer, which means that it is porous in nature. This IV bag possesses elastomeric or flexible properties. As a single-layered IV bag, the solution inside could be more susceptible to gas permeation, which could induce possible physical–chemical phenomena such as photo-oxidation and hydrolysis. Therefore, it was added as an incentive to perform an investigation on possible migration of leachable compounds in the compounded drug product. Single-layered bag are most recommended for short-term storage, which in this case was used for long-term storage.

Moreover, the transfer of compounds from one side to the other side is also possible. The presence of the label and graduation ink could allow compounds to traverse the material over time. Since the bag tends to fold when stored on the shelves, the folding mechanism could result in more surface interactions with the solution. The IV bag solution does not possess official secondary packaging, but it is stored in the absence of light in a refrigerated area, and when removed, it is wrapped in a light protective bag to be sent to medical wards. Figure S2 in the supplementary section helps assess each component of the compounded DP.

Insulin Vial Evaluation

In total, 1 IU/mL Insulin UltraRapid® was used for hospital preparation in a container constructed of COC. This drug is administered to neonates and infants in cases of hyperglycaemia and hyperkaliemia. It is performed parenterally and is frequently administered for glucose monitoring. The DP is stored for 12 months in a refrigerated area between 2 and 8 °C. There is no case of container misappropriation since the COC vial is meant for long-term storage. Therefore, the risk assessment of this quality material should cover this type of solution for the general population, but neonates represent a specific and frail population that should be considered a subset of the general population. Moreover, although the drug product is heavily diluted, the protein as well as its excipients could still possibly interact with their surroundings.[29] Therefore, this product should be subjected to leachate study and risk assessment.

After numerous incidents involving insulin with other polymer materials, COC was deemed one of the optimal storage container materials compatible with this product.[29] In terms of the material, COC is amorphous in nature, similar to EVA, but possesses strong and stiff mechanics, comparable to those of PVC. Their hard physical form is likely due to being a syndiotactic structure. Due to their low leachability, industries certify these materials as being compatible with long-term storage. These materials possess very good physical and chemical resistance, ensuring product stability over a long period. The vial component body is constructed of COC, and the stopper is constructed of a butyl rubber elastomer. The reason for their assessment as hospital pharmacies is their application to neonates, which could pose an added risk. Such a mechanism of container–content interaction could be promoted due to possible supersaturation and blooming. One explanation is the presence of a liquid film on the underside of the rubber stopper seal caused by evaporation or transportation. Over time, this phenomenon may cause the diffusion of additives (organic compounds and metal elements) into a small volume, which could cause aggregation and particle formation. Once this is formed, it may be irreversible because the particles no longer dissolve when in contact with the total volume of the DP. Moreover, this phenomenon could also promote another phenomenon—blooming—the formation of crystals of additives due to different conditions —i.e., low solubility of additives in the polymer, high diffusion of additives through the polymer, and dosing of the additive solubility into the polymer close to the solubility of the additive in the polymer —and low-temperature conditions may accelerate the blooming process.

Moreover, a label risk assessment should also be performed to determine whether compound transfer into the solution is likely to occur. No protective secondary packaging is available for this product. According to the recommendation, it is important to store it in the absence of light. Figure S3 in the supplementary section helps assess each component of the compounded DP.

Study of Leachables in Hospital Pharmacy Compoundings

WFI Profiling

Each WFI was sampled and prepared in the same way as the compounded DPs, and the concentrations of the additives were normalised with a logarithmic mathematical function to enable a better visual profile, as presented in Fig. 1.

Both vancomycin and insulin were prepared using distilled WFI from hospital pharmacies. WFI production by distillation is not commonly employed in many hospitals because the installation is not cost-effective and requires significant maintenance. The validation of such a process would also be time-consuming and labour-intensive.[30] The hospital distillation process can be performed by either vapour compression (VC) or multiple effect stills (MES). Both methods are efficient at purifying water by removing the most unnecessary ions and microorganisms. An advantage of distilled WFI is minimal contact with plastic-related materials, especially when filtration by membranes and WFI storage are not applied to plastic-related materials.[31] The distillation approach is very much used by industry to obtain WFI, as recognised by pharmacopoeias such as the USP and EP. As a result, the WFI profile remains near baseline, with only one compound, BHT, at an ultralow concentration, which could originate from the tubing system that introduces WFI into the production zone (Fig. 1). Many industries and even hospitals employ polyvinylidene fluoride (PVDF)-based materials as WFI conduit pipes.[32,33] These materials are also more often used by pharmaceutical companies instead of stainless steel (SS 304) because the polymer material is a nonreactive fluoropolymer.[32] The PVDF pipes contained 100 % resin and therefore contained no additives.[32-33] However, antioxidants such as BHT can sometimes be present in the resin to prevent unnecessary oxidation at small concentrations and can be leached depending on the quality of the material. These results revealed that the BHT

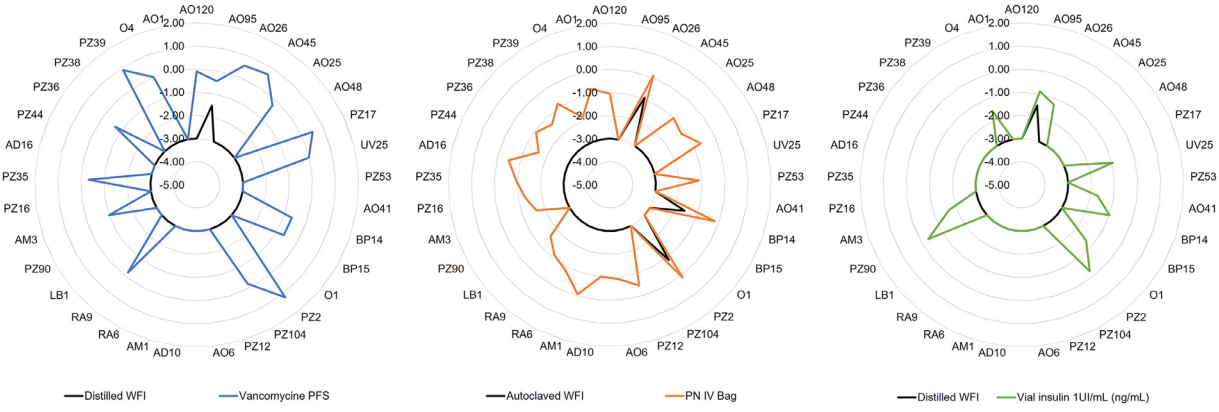

Figure 1. WFI profiling to pinpoint the source of plastic-related compound contamination in all three compounded candidates. All compounds were coded according to their categories, which are as follows: AO120 (2,6-di-tert-butyl-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one), AO95 (2,6-di-tert-butyl-p-cresol), AO26 (3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoic acid), AO45 (3-(3-5-di-tert-butyl-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-yl)propanoic acid), AO25 (3,5-di-tert-butyl-4-hydroxybenzaldehyde), AO48 (3,5-Di-tert-butyl-4-hydroxybenzyl alcohol), PZ17 (Acetyl tributyl citrate), UV25 (Benzotriazole), PZ53 (Bis(2-propylheptyl) phthalate), AO41 (Bis[2,4-bis(2-methyl-2-propanyl)phenyl] hydrogen phosphate), BP14 (Bisphenol A), BP15 (Bisphenol A (2,3-dihydroxypropyl) glycidyl ether), O1 (Caprolactam), PZ2 (Di-(2-ethylhexyl) adipate), PZ104 (Di-(2-ethylhexyl) sebacate), PZ12 (Diphenylamine), AO6 (Hostanox O3), AD10 (methacrylic acid), AM1 (Methylparaben), RA6 (N,N-Dibutylformamide), RA9 (N-butylformamide), LB1 (Oleamide), PZ90 (Phthalic anhydride), AM3 (Propylparaben), PZ16 (Tributyl citrate), PZ35 (Tributyl phosphate), AD16 (Triethyleneglycol dimethacrylate), PZ44 (Tri-p-cresyl phosphate), PZ36 (Triphenyl phosphate), PZ38 (Tris (2-butoxyethyl) phosphate), PZ39 (Tris (2-chloro-1-methylethyl) phosphate), O4 (N-Vinyl caprolactam), AO1 (Irganox 1010).

concentration was ultralow (30 pg/mL), as shown in Fig. 1. The distilled WFI purification approach was almost exempt of plastic-related compounds, which could be used in the production of hospital pharmacy-compounded DPs. Therefore, distilled WFI would be a necessary production method approach for all hospital pharmacies that intend to promote large catalogues of compounds using WFI.

The remaining DP (EVA PN IV bag) was compounded and filled with the industrially packaged WFI. This WFI was processed industrially, underwent distillation and membrane filtration and was filled in a coextruded polypropylene (CEPP) bag that underwent heat sterilisation before its presence on the open market. WFI packaged in CEPP bags is a convenient and cost-friendly option when the hospital or hospital pharmacy does not have a WFI production facility. As a result, fenozan acid (AO26), di-ethylhexyl adipate (PZ2) and bisphenol A (BPA; BP14) were obtained from the industrially packaged WFI bag used to prepare the PN (Fig. 1). Fortunately, only 10 % of this WFI was used to make the end product. Fenozan likely originated from larger and more complex antioxidants, such as Irganox 1010 and Irganox 1076. These compounds possess many Fenozan monomers, which are linked through esterification, increasing their lipophilicity. This allows them to mix well in the crystallin part of the polymer (reducing leaching tendencies). However, when heat sterilisation is applied to the polymer, the heat and pressure, intended to kill microorganisms, could destabilise the polymer structure as well as the additives, causing the hydrolysis of ester bonds and consequently releasing Fenozan.[34,35] It is common for any packaging constructed of PP to undergo heat sterilisation. DEHA is also a common plasticiser found in almost all polymers and is currently an inexpensive replacement for DEHP. BPA is detected among the other additives. This is a nonintentionally added substance (NIAS), i.e., this compound is not a listed ingredient in the polymer material and could be added due to industrial in-process contamination, which could be transferred from the tubing during the polymer moulding phase. BPA is sometimes observed and remains inconsistent from batch to batch, and its concentration remains low.[15]

In summary, plastic-related compound profiling was performed on WFI. The distilled WFI would be most recommended for the compounding of hospital pharmacy DPs due to the near absence of additives. However, industrially packaged WFI is not a poor option for hospital pharmacy compounding because it could be considered a cost-effective alternative to onsite water purification via distillation. As observed, WFI stored in heat-sterilised CEPP IV bags could leach additives that have already been assessed for public safety by industry. However, it is important to consider that the end users are neonates and infants, and extra precautions are required to improve the safety of these patients when using industrially manufactured WFI. Fig. 1 shows the leachable profile of the WFI used to compound the three drug products. The WFI profiling results are shown in Table S1 in the supplementary materials.

Compounded Drug Product Profiling

The three hospital pharmacy-prepared DPs were analysed in terms of the presence and concentration of plastic-related compounds. The results are presented in Fig. 2. Three batches of each product were analysed, and semiquantitative average results were obtained. The semiquantitation of compounds serves as an estimation of concentration for toxicology assessment based on industrial E&L practices.[7] Compilation of chromatograms and examples of mass spectra issued from the study of leachable compounds in all three hospital compoundings are present in supplementary materials (Fig. S4-S15).

Vancomycin PFS was analysed, and 17 leachable compounds were identified and semiquantified. These compounds were categorised into 5 antioxidants, 4 plasticisers, 1 UV stabiliser (a benzotriazole derivative), 1 rubber-related compound, 1 antimicrobial compound and 5 NIAS compounds (4 industrial in-process contaminants and 1 label-related compound). PN IV Bag was subjected to an identical analytical procedure, and 25 compounds were identified and semiquantified. The 25 compounds were categorised into 6 antioxidants, 6 plasticisers, 0 visible UV stabiliser compounds, 2 rubber-related

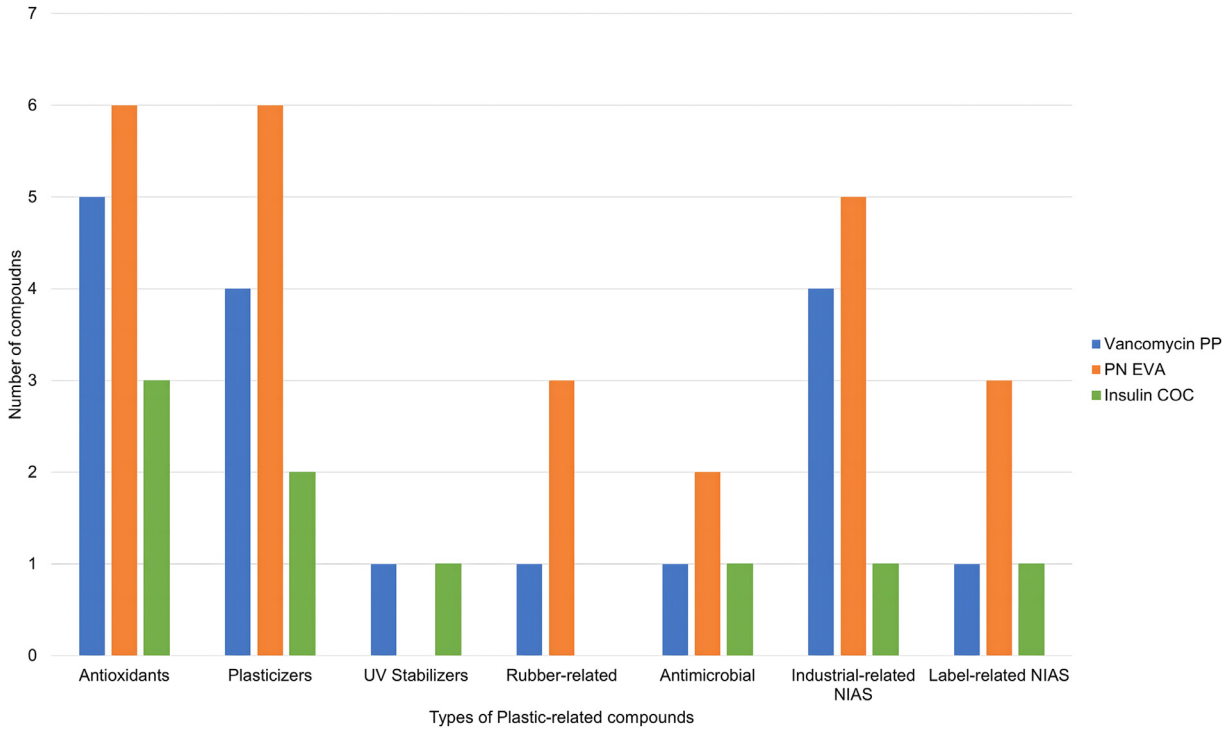

Figure 2. Histogram showing the number of compounds per additive category detected in different hospital pharmacy-prepared drug products.

compounds, 1 lubricant compound, 2 antimicrobial compounds and 8 NIAS compounds (5 industrial in-process contaminants and 3 label-related compounds). Insulin in COC vials was subjected to E&L analysis, 10 compounds were identified, and their concentrations were estimated. This list consists of 3 antioxidants, 2 plasticisers, 1 UV stabiliser, 0 rubber-related compounds, 1 paraben-related compound and 3 NIASs (2 industrial in-process contaminants and 1 label-related compound). Fig. 2 describes the number of additives identified, categorised by functional groups, and detected in each compounded DP. In the supplementary information, Table S2 compiles all chromatographic and mass spectrometric data from all three hospital pharmacy compoundings, and Table S3 includes their semiquantitative results.

All three drug products appear to contain large amounts of antioxidant leachables. The role of antioxidants is to protect the polymer against oxidative substances. The identified products are mostly degradants of primary antioxidants, which are sterically hindered phenols that react with free radicals to form inactive products. These compounds are BHT-related compounds that include BHT and fenozan.[34,35] Like what was identified in CEPP IV Bag (see Section 3.2), these compounds could be derived from complex compounds, such as Irganox 1010, 1076, 1330 and 3114, which are constructed from subsets of these identified compounds. It is rare for complex compounds to be extracted into aqueous solutions. Polymer materials, such as PP, are semicrystalline in nature. Highly lipophilic antioxidants, such as Irganox 1010 and Hostanox O3, are anchored in the crystalline part of the polymer and therefore are less susceptible to leaching. However, this situation is different for amorphic materials such as EVA. These very lipophilic compounds do not anchor well into the plastic matrix and sometimes leach into their surroundings. Moreover, since amorphic polymers such as EVA tend to be porous, the phenomenon of oxidation can also occur, as explained by the number of oxidised antioxidant degradants. Although the COC material is amorphous in nature, the copolymers are randomly arranged with no measurable degree of crystallinity, which promotes chain stiffening and bulkiness, similar to those of PVC. Their excellent optical clarity, similar to that of glass materials, stems from their exceptional purity and absence of chromophores in COC resins. Due to its overall structure, COC material has low permeability to oxygen and water vapour.[36] As observed, there were no oxidised forms of antioxidant degradants. Apart from hindered phenols, a secondary phosphite antioxidant degradant was identified in the insulin COC vial. This compound originates from Irgafos 168, which is a common complex antioxidant used in combination with primary phenolic antioxidants for optimal performance in the protection of polymers. The presence of this degradant is known to inhibit cell growth even at low concentrations.[37]

The concentration of antioxidants leached from each drug product is expected to increase in quantity in the PP syringe, not because of its physical structure but because of its current quality. The vancomycin drug solution was added to a misappropriated container that was originally meant for administration rather than for storage. It would have been fine for a short period, but after 6 months of storage, this situation could explain the higher concentration in this drug product. For the EVA IV bag, it is unusual to obtain many leachates for this kind of matrix solution. A single layer bag was used for this application. A multilayered bag could have modified the outcome of the leachate profiling but would restrict gas permeation, therefore reducing the amount of oxidised forms of antioxidants as well as the number of NIASs from the label and the graduation scale. The insulin COC vial was the most appropriate container due to the low number of leachates retrieved. No signs of supersaturation or blooming on the underside of the rubber septum were observed, as there were no signs of particle formation in the solution.

A good variety of plasticisers, such as citrate, adipate, phthalate, sebacate and phosphate, are found in all three drug solutions. Each polymer contains a unique blend of plasticisers at various concentrations to enhance performance. They are added to the polymer after its extrusion and are linked to the polymer strands via van der Waals bonding, enabling more free space that prevents them from stacking and leading to greater polymer flexibility. Due to the presence of weak bonds, these compounds can easily leach into any aqueous solution.[38] In the past, it was common to find DEHP, but now that it is known for its potential for container–content interactions and diverse toxic effects, it is very common to find DEHA in most polymers. In long-term syringes, it is unusual to find a considerable amount of DEHA.

For UV stabilisers, only benzotriazole, which is a degradant or the main functional group of UV stabilisers, was identified. These compounds are usually detected in small concentrations, which explains the concentration of benzotriazole in some of the drug products. Their role is to protect the polymer against photodegradation. Similarly, antimicrobials such as traces of methylparaben and propylparaben were identified in some of the drug products. Like UV stabilisers, they are commonly present in minute concentrations, which explains their small amount in the screening results for drug products.

For lubricants, it is common to use silicone and/or oleamide as plunger slip agents. Compared with the PP syringes and the EVA IV bag, the COC vials did not appear to contain detectable rubber-related compounds. The quality of the butyl rubber from the COC vial is even better than that of the butyl rubber from the plunger head of the vancomycin syringe. The other two containers release rubber cross-linker compounds such as formamide derivatives.

Nonintentionally added substances (NIASs) are compounds that were never intended to be in the polymer material mix.[39] There are two types of NIASs: industrial-related compounds and label-related compounds. The former is due to contamination caused by in-process tubing during the manufacturing of the polymer, and the latter is due to the transfer of compounds from the label through the polymer material into the drug solution.[15] Labels on polymer containers are not expected to migrate through the polymer and contaminate the solution. Therefore, it is necessary to assess these compounds for potential contamination risks. On a label, substances originating from the ink, the label material and the glue solvent must be considered since they can be lipophilic chemical entities that can be adsorbed. The usual industrial-related compounds are BPA, BADGE derivatives, caprolactam and some phosphate-based flame retardants. BPA is used as a starting block for the polycarbonate and BADGE resins. These three drug containers are not constructed of these materials; therefore, they are never intended to release such compounds. Like in the CEPP IV bag, BPA could derive from industrial in-process contamination during the polymer moulding phase. Caprolactam is a monomer of nylon 6 or polycaprolactam, which is the same as bisphenol A and its derivatives.[40] Flame retardants should normally be absent in primary packaging.[15] It is important to distinguish phosphate-based flame retardants from phosphate-based plasticisers, which tend to resemble and sometimes possess two functions (a flame retardant or plasticiser). Therefore, as an overall review, the drug products that appeared to have the most industrial-related compounds were the PFS and EVA IV bags, whereas the COC vial was observed to contain nearly no leachable compounds. This finding is to be expected since the quality of the material of both PP and EVA are never meant for long-term storage, which contributed to 4 times more compounds leaching out than COC vials.

For label-related compounds, the EVA IV bag seemed to be most susceptible to this type of compound, especially for single-layered compounds. Since it is amorphous in nature, the bag is also porous, enabling better transfer of glue solvent-related compounds such as acrylate derivatives and ink-related compounds such as vinyl-caprolactam.[15] Compared with the EVA IV bag, the vancomycin solution was found to contain only one label-related compound, vinyl

caprolactam, and was much less abundant. This finding could be attributed to the semicrystalline structure of PP, which restricts the permeation of these compounds through the polymer. As already observed, COC vials remain the optimal vials with the least number of compounds at considerably low concentrations. The next step is to assess the risk exposure of patients to these compounds.

Toxicological Assessment

Toxicology assessment of identified and semiquantified compounds observed in drug products can be based on a series of risk assessment steps, such as permissible dose exposure (PDE), and potential endocrine disruptors have been investigated.[15,17-20]

The formula for permissible dose exposure (PDE) was used.

$$\text{PDE [ng/day]} = \frac{\text{Estimated NOAEL [ng/kg bw/day]}}{\text{T1} \times \text{T2} \times \text{T3} \times \text{T4}} \times \text{Body Weight [kg]} \quad (1)$$

Maximum daily dose (MDD) was calculated as follows:

$$\text{MDD [mL/day]} = \text{Total Volume [mL]} \times \text{Number of daily Administration [1/day]} \quad (2)$$

The formula for total daily exposure (TDE) was used.

$$\text{TDE [ng/day]} = \text{Semiquantified concentration [ng/mL]} \times \text{MDD [mL/day]} \quad (3)$$

For the first step, the PDE threshold must be compared with the total daily exposure (TDE). The estimated PDE must be multiplied by the concerned weight of the patient to obtain the unit ng per day, as illustrated in Eq. (1). The weights used were 1.8 kg for preterm neonates, 3 kg for full-term neonates and 10 kg for toddlers. These values are taken as average weights for each population as a means to perform a generalised comparison. Before obtaining the TDE, the maximum daily dose (MDD), which consists of multiplying the total administered volume by the number of daily administrations (Eq. (1)), is needed. The acquired semiquantified concentration was then multiplied by the total volume of the drug product and the frequency of administration to determine the MDD. Both the MDD and weighted PDE were mathematically transformed via a logarithm function to achieve simplified visual differentiation.[15,17-20] Fig. 3 shows the leachable profiles of all three drug products in accordance with their MDD. Table S4 shows the toxicological data obtained from all three hospital pharmacy compoundings, including TDE, PDE and potential endocrine disruptors.

All information was acquired through in silico predictions (extrapolation) via the EPA T.E.S.T database.[41] Understanding the toxicology of the identified compounds is a quick approach. This knowledge adds an extra layer of protection for specific patients, such as neonates and children, who are significantly more vulnerable. However, any compounds identified as positive through predictions should be verified with concrete experimental data. If there are no existing data for a specific compound, a toxicology analysis should be conducted. Typically, experimental data will have higher thresholds than their in silico counterparts.

The estimated PDE was calculated as described in Eq. (1) by using the generalised average weights of the patients of interest. First, vancomycin PFS was subjected to a toxicological assessment. In this compounded DP, 17 leachable compounds were identified and semiquantified. As a result, 2 of the 17 compounds surpassed their estimated PDE threshold: the first was tris(2-chloro-1-methylthyl) phosphate (TCPP) (PZ39), which is an industrial-related NIAS, and the second was 3,5-di-tert-butyl-4-hydroxybenzaldehyde (BHT-CHO) (AO45), which is an oxidised BHT-related compound. The remaining compounds are at least 0.5 to 1 order of magnitude from their PDE threshold, which results in a moderate margin of safety. Therefore, these two compounds need to be re-evaluated in terms of toxicology by searching for their experimental data to calculate a more precise PDE. According to another database, EPA's CompTox, the experimental NOAEL of TCPP obtained from subchronic exposure to rats is 125 mg kg^{-1} bw/day; therefore, when calculated for PDE, 37,500 ng/day was obtained for a neonate weighing 3 kg.[42] For BHT-CHO, no experimental NOAEL existed; therefore, a read-across NOAEL of BHT was used. The obtained value was 10 mg kg^{-1} bw/day, with which the PDE value was 3000 ng/day. Therefore, these threshold values seemed to be far from their TDE and thus were deemed not a risk for the patient. For the other DPs, the PN EVA IV bag released 25 leachable compounds, the highest number of additives compared to the other two DPs. However, none of the compounds surpassed their PDE thresholds. The COC vial containing insulin exhibited the release of the fewest number of compounds and the lowest concentrations, all of which were significantly below their PDE thresholds, as illustrated in Fig. 3. This outcome was expected since the COC material is by far optimal for long-term storage.

The search for potential endocrine disruptor compounds (EDCs) in these different DPs was then assessed. Nine potential EDCs were identified for vancomycin PFS in PP (2,6-di-tert-butyl-p-cresol, acetyl tributyl citrate, benzotriazole, bisphenol A, di(2-ethylhexyl) adipate, propylparaben, tributyl phosphate, triphenyl phosphate, tris(2-chloro-1-methylethyl)phosphate), 11 in PN IV bag in EVA (acetyl tributyl citrate, bis(2-propylheptyl) phthalate, bisphenol A, di(2-ethylhexyl) adipate, methylparaben, propylparaben, tributyl citrate, tributyl phosphate, tri-p-cresyl phosphate, triphenyl phosphate, tris(2-butoxyethyl) phosphate, tris(2-chloro-1-methylethyl)phosphate) and 4 in the insulin vial in COC (benzotriazole, bisphenol A, di(2-ethylhexyl) adipate, propylparaben) via several sites (EDlist and DEDuCT) .[43,44] Plasticisers constitute the category regrouping the greatest number of EDCs, comprising phthalates, adipates, phosphates and citrates. Some NIAS phosphates from the category of flame retardants were also observed in the Vancomycin PFS and the PN EVA IV Bag. Supposedly, they are leached into the solution due to long-term contact with the material.

The amount of potential EDCs in the vancomycin PFS and PN IV bags was significant, especially in comparison with that in the COC vial. EDCs work best at ultralow concentrations, which could be most disturbing since the end patients are neonates and children. Their receptors are most sensitive in their developmental phase, which makes them the most vulnerable.[45] Fig. 4 shows the different EDCs present in all three compounded drug products.

From an analytical point of view, the screening method allowing identification with the highest level of confidence could represent a somewhat limited profiling of the extensive array of plastic additive compounds. Indeed, for now, the database in this study comprises approximately 200 toxicologically relevant nonvolatile compounds. However, annotations for unknown analytes could not be performed. Moreover, it is important to include the profiling of volatile, semi-volatile compound screening and trace elements. As for more impacting compounds which require further precise studying, an absolute quantitative method can be developed and validated to quantify these compounds. Consequently, further research is essential to deepen our understanding of EDCs and their impact on the health of premature patients. It is crucial to develop strategies to mitigate these risks and ensure the safety of medical treatments for this sensitive patient population.

In terms of toxicology, the PDE was assessed for each compound detected in all compounded DPs and compared with their estimated concentrations. Additives found in all DPs were considered at safe levels, below their PDE. Therefore, all containers were safe to use,

Figure 3. Leachable profiling of all hospital pharmacy-compounded drug products demonstrated using PDE in terms of TDE according to their maximum daily dose (MDD). All compounds were coded according to their categories, which are as follows: AO120 (2,6-di-tert-butyl-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one), AO95 (2,6-di-tert-butyl-p-cresol), AO26 (3-(3,5-di-tert-butyl-4-hydroxyphenyl)propanoic acid), AO45 (3-(3-5-di-tert-butyl-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-yl)propanoic acid), AO25 (3,5-di-tert-butyl-4-hydroxybenzaldehyde), AO48 (3,5-Di-tert-butyl-4-hydroxybenzyl alcohol), PZ17 (Acetyl tributyl citrate), UV25 (Benzotriazole), PZ53 (Bis(2-propylheptyl) phthalate), AO41 (Bis [2,4-bis(2-methyl-2-propanyl)phenyl] hydrogen phosphate), BP14 (Bisphenol A), BP15 (Bisphenol A (2,3-dihydroxypropyl) glycidyl ether), O1 (Caprolactam), PZ2 (Di-(2-ethylhexyl) adipate), PZ104 (Di-(2-ethylhexyl) sebacate), PZ12 (Diphenylamine), AO6 (Hostanox O3), AD10 (methacrylic acid), AM1 (Methylparaben), RA6 (N,N-Dibutylformamide), RA9 (N-butylformamide), LB1 (Oleamide), PZ90 (Phthalic anhydride), AM3 (Propylparaben), PZ16 (Tributyl citrate), PZ35 (Tributyl phosphate), AD16 (Triethyleneglycol dimethacrylate), PZ44 (Tri-p-cresyl phosphate), PZ36 (Triphenyl phosphate), PZ38 (Tris (2-butoxyethyl) phosphate), PZ39 (Tris (2-chloro-1-methylethyl) phosphate), O4 (N-Vinyl caprolactam), AO1 (Irganox 1010).

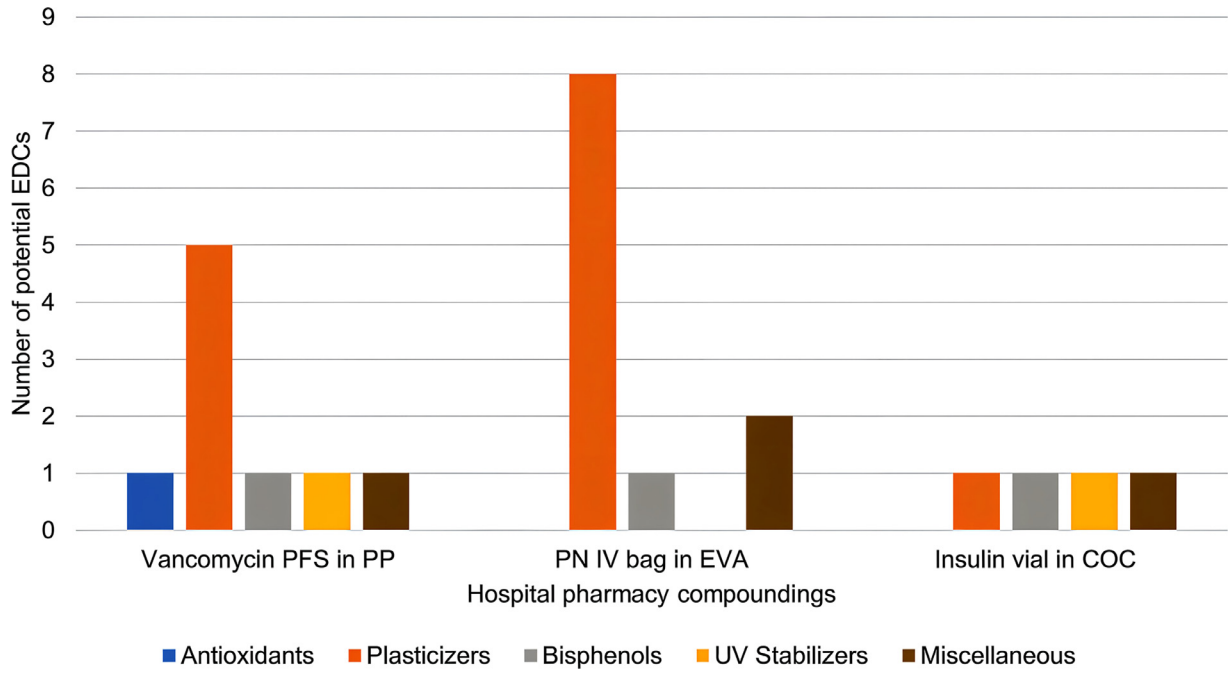

Figure 4. Histogram showing the number of EDCs per category of additive found in different drug products compounded in hospital pharmacies.

especially those that were meant for administrative purposes rather than storage. These syringes/IV bags used for the filling of vancomycin/parenteral nutrition could be viable options instead of expensive COC packaging. The recommended container materials for hospital pharmacy compounding are COC, cyclic olefin polymers (COPs) and high-quality PP (a less expensive alternative), which exhibit the optimal leachable profile in terms of number, concentration and toxicological risks. The EVA IV bag could be considered, but the DP did not show optimal results because the single-layer EVA bag was not favourable for long-term storage. On the other hand, a triple-layered bag would be the most appropriate, with either PA or low-density polyethylene (LDPE) as the outer and inner layers. This would serve as a protective layer against physical-chemical phenomena such as oxidation. For security reasons, it is recommended that high-quality containers be stored and that hospital pharmacies employ such a scheme; for that to happen, industry and hospital pharmacies could collaborate to identify a cheaper alternative that makes hospital pharmacies compounding friendly.

Although they are detected below their PDE, DPs such as the vancomycin PFS and PN IV bag should present results comparable to those of their COC counterparts. The PDE of each compound was calculated using extrapolated data, and all positive predictions were re-evaluated via experimental data because of the lack of reliability, which is closely linked to the database's training set. Its disadvantage is the potential for underestimation and overestimation of values. Nevertheless, any extrapolated data could constitute a quick, easy and inexpensive approach for early evaluation. The PDE estimation could add an extra safety margin for more vulnerable and frail patients, such as neonates and children. Potential EDCs were also assessed in these DPs. Unfortunately, no threshold value limit has been established, and only identification is possible.

Conclusion

Three hospital pharmacy batch preparation were selected for a leachable compound study to be evaluated in terms of risk to patients. Compounds were screened and quantified via a semiquantitative system with a UHPLC-PCI-HRMS platform. As a result, vancomycin PFS and PN EVA IV bags released a considerable amount of plastic additives as compared to insulin COC vial which was observed to release a small number of compounds at ultra-low concentrations. This finding clearly highlights the optimal potential of the COC material for use in long-term storage in comparison to the inappropriate use of MDs for long-term storage (Vancomycin PFS and PN IV bag). In terms of toxicology, the insulin COC vial was deemed to have the best risk assessment profile, followed by the PN EVA IV bag, despite having the highest number of leachates. The least favourable profile was that of vancomycin PFS due to the higher concentration of the leachable compounds. Moreover, potential endocrine disrupting effects were highlighted, no elimination threshold limits were set, and only compounds were identified. As mentioned in the last section, the vial with the least EDC was the insulin COC vial, and the vial with the most EDC was the PN EVA IV bag.

Overall, all DPs were deemed safe because of their positive risk assessments. This finding shows that administration-purposed containers could be a viable option instead of storage-purpose containers. Ideally, long-term compounded drug products in a hospital pharmacy setting should be encouraged. However, due to the high costs and maintenance associated with procuring filling equipment, the use of containers designed for administration may continue. The optimal and best suited DP for long-term use was the insulin COC vial, as observed with the least amount of leachable compounds found at low concentrations. The other two primary packaging are not suitable for long-term storage, especially in industry. However, they could still be employed for compounding in hospital pharmacies depending on the degree of risk for the patient. Container-content interaction-related practices are not regulated in hospital pharmacies and could be leveraged to select an approach that best suits the needs of hospital pharmacies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

William Bello: Conceptualization, Investigation, Methodology, Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Julian Pezzatti:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Serge Rudaz:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Farshid Sadeghipour:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xphs.2024.08.004.

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