Aarya Publishing House

Available Online at

http://www.aphinfo.com/ijmpbs

October-December 2022

INTERNATIONAL JOURNAL OF MEDICAL, PHARMACEUTICAL AND BIOLOGICAL SCIENCES

eISSN : 2832-787X, pISSN : 2832-7888

Review Article | Volume-2 | Issue-3 | Article ID: 0038

ANALYTICAL APPROACHES FOR EXTRACTABLE AND LEACHABLE FROM PHARMACEUTICAL PRODUCTS : A REVIEW

Chaitanya A. Gulhane[1*], Pragati R.Khokle[1], Ravindra L .Bakal[1], Jagdish V. Manwar[2]

[1]IBSS Dr. Rajendra Institute of Pharmacy, Mardi Road,Amaravti-444603 MS India.
[2]IBSS Dr. Rajendra College of Pharmacy, Mardi Road,Amaravti-444603 MS India.

***Corresponding Author: Email:** chaitanyagulhane60@gmail.com*

Received: 20 October 2022 / Revised: 22 November 2022 / Accepted: 15 December 2022 / Available online: 31 December 2022

ABSTRACT

Plastics used in drug packaging systems and medical equipment are often made up of homologous polymers with additives like antioxidants, plasticizers, and other physicochemical qualities. However, due to the possibility of migration or leaching into the therapeutic product, these additions may have downsides. Leaching can change the chemical composition of a medicine, which can affect its therapeutic efficacy and, in some situations, its organoleptic qualities. Because of their intrinsic toxicological qualities, leachable may potentially be considered a health threat. Analytical characterization (detection, identification, typification/qualification, and quantification) of leachable compounds is required before a drug may be approved by the FDA, and this information must be included in the drug's application dossier. The major goal of this study is to gather and contextualise the analytical procedures for characterising and/or regulating organic leachable from plastic materials in interaction with pharmaceuticals that have been documented. We also discuss the state of the art in the field of leachable, as well as a useful, broad-based compilation of directives and guidelines. Finally, we present an up-to-date collection of leachable investigations using gas and liquid chromatography as separation techniques over the last eight years. Because there is already a large amount of research on inorganic contaminants, we opted to focus our review solely on organic leachable.

Keywords *– Pharmaceuticals, Leaching, Polymer*

1. INTRODUCTION

Ampoules, bags, blisters, bottles, cartridges, inhalers, prefillables syringes, pouches, vials, and their associated plastic packaging systems are among the pharmaceutical packaging systems.Labels, inks, and printing overpouches are examples of secondary components [1]. Simple gadgets to test equipment and implants are all examples of medical devices. Artificial hips/knees, bandages, catheters, coronary stents, medical diagnostic equipment, pacemakers, prosthetic limbs, surgical gloves, and surgical instruments are examples of medical devices [2]. Single-use technologies, such as disposable bioreactors or media and buffer storage bags, are also taken into account, as they have become increasingly popular in bioprocess development and biopharmaceutical manufacture in recent years.

Plasticizers, stabilisers, lubricants, antioxidants, colourants, and other additives are utilised in medication packaging systems and medical devices, and they include additives such as plasticizers, stabilisers, lubricants, antioxidants, colourants, and others [3]. In order to achieve the qualities necessary for a certain purpose, organic and inorganic additives may be introduced [4]. The

addition of additives may change the plastic's physical and chemical qualities, sterilisation, biocompatibility, toxicity, and environmental impact [5]. The nature of additions varies depending on their goals; references [6,7] have a table with thorough information on the different types of additives and their effects on the performance of plastic materials.

Drug items are widely known for interacting with the plastic materials with which they come into contact. Interaction can be divided into five categories [8].

Adsorption occurs when a portion of the medication product is retained or concentrated on a material component's contact surface.

Adsorption: the substance may penetrate the surface and migrate into the material after adsorption.

Permeation: if a substance is absorbed deeper, it may migrate through the material to the noncontact surface and beyond.

Leaching: chemicals from a contact material may transfer or migrate into the medication product.

Extraction is a very extensive migratory process in which a solvent dissolves specific chemical components from the contact material, causing some chemical alteration and, as a result, changing its properties to a great level [9].

In light of the foregoing, the purpose of this work is to gather and contextualise analytical methodologies for identifying and quantifying organic leachables and extractables in order to give systematised analytical information. To begin, we'll go over some basic terms and definitions, such as drug impurities and chemical safety indices. The state of the art on leachables and extractables is then described, followed by a comprehensive set of directives and guidelines, each with a brief summary. We decided not to analyse inorganic leachables because there is already a lot of material on inorganic L&E.

2. IMPURITIES

Any component of the new drug product that is not the drug substance or an excipient in the drug product is referred to as an impurity [10]. Impurities may occur during the manufacturing process, due to the lack of stability of drug ingredients, or as a result of excipient incompatibility during drug product production and storage. Organic impurities (volatiles and non-volatiles), inorganic impurities (volatiles and non-volatiles), and residual solvents (volatiles and non-volatiles) are the three types of impurities [11].

Impurities are classified into three categories based on their source: process impurities, degradation impurities, and contamination or foreign impurities [39]. The first two occur during the manufacturing and storage of the drug product, respectively. During processing, storage, or delivery, contamination contaminants are mistakenly introduced into drug goods. Starting materials, reagents, intermediates, catalysers, by-products, residual monomers, residual inorganics, and other materials (e.g., filter aids, charcoal) are all examples of process-related impurities [12]. Compounds originating from the chemical breakdown of the drug ingredient during storage are known as degradation impurities. Degradation product has been defined as an impurity resulting from a chemical change in the drug substance caused by the effect of, for example, light, temperature, pH, water, or reaction with an excipient and/or the immediate container closure system during manufacture and/or storage of the new drug product [13]. Physical degradation, such as clumps of proteinaceous material, can also form them. Unexpected adulterating substances detected in the medication ingredient are known as contamination impurities.

3. INDEXES OF SAFETY

The number of impurities detected in drug substances can pose a safety risk and be a determining factor in the finished product's safety.

To describe exposure limits for toxic chemicals, some indexes were proposed, such as the 'tolerable daily intake' (TDI) –used by the International Program on Chemical Safety (IPCS)– or the 'acceptable daily intake' (ADI) –used by the World Health Organization (WHO) and other national and international health authorities and institutes– [14]. In addition, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) recommended a new specific index for residual solvents called "permitted daily exposure" (PDE) to eliminate misunderstanding caused by different ADI values a similar material. The PDE is defined as the maximum amount of impurity in pharmaceutical items that can be consumed per day [15]. PDE values are calculated from toxicity data using a variety of techniques, some of which are outlined in ICH standards [14,15].

The 'permitted concentration limit' (PCL) of a certain impurity that may be contained in the ‘maximum daily dosage' (MDD) of a drug product can be computed using equation 1 utilizing the maximum recommended daily dose of a drug product and the PDE value.

PDE stands for phenylethyl (mg day)

1000 MDD (g/day) PCL (g/g) PCL (g/g) PCL (g/g) PCL (g/g) PCL (g/…. (1)

The MDD is the total quantity of medicinal product ingested on a daily basis by a patient [15]. Depending on the chemical, PDE values might vary by many orders of magnitude (10–3 – 103) [16]. PDEs of most residual solvents, for example, are usually given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm [14] (for example, if the PDE of methanol is 30 mg/day, and the product mass is 10 g administered daily, the concentration limit will be 3000 g/g or 3 mg/g [14]). The related ICH guidelines [14,15] contain extensive PDE data on residual solvents or elemental impurities, while information on organic impurities is rare. Because the PDE must not be exceeded, impurity control has become a crucial aspect of any drug product's quality control approach. Additional quality assurance procedures must be implemented if the impurity level exceeds the allowable concentration limit.

The 'threshold of toxicological concern' is one safety threshold idea that is commonly used as a chemical risk assessment tool (TTC). When there is little or no chemical-specific toxicity data, this approach can be used to assess potential human health problems in relation to a given chemical; it is based on the structural chemical features of the particular chemical for which exposure levels are being calculated [16]. TTC establishes a practical exposure threshold value for chemical items, including those with uncertain toxicity, by using the following formula: taking into account their chemical structures It was created as a replacement for substance-specific data.

The ICH uses the TTC technique to evaluate mutagenic contaminants present in pharmacological products where no carcinogenicity data is available, employing an excess cancer risk factor of 105 (1 in 100,000) over the course of a lifetime of exposure [16]. Using the TTC approach, the proposed safety threshold for mutagenic impurities ranges from 120 g/day (for short-term treatment of less than one month) to 1.5 g/day (for long-term treatment of more than ten years).

4. LEACHABLES

Compounds that leach into the formulation from elastomeric or plastic components of the medicinal product container closure system were originally designated as leachables [17]. Leachables are currently defined as organic and inorganic chemical entities that migrate from a packaging/delivery system, packaging component, or packaging material of construction into an associated drug product under normal storage and use conditions or during accelerated drug product stability studies in the United States Pharmacopeia (USP) [18]. These are the definitions for packaging-related leachables. Other materials, such as glass or metal components, can also leach leachables, though to a smaller degree than chemically organic compounds. Foreign contaminants

from production systems, container-closure systems, medical equipment, and delivery systems could all be classed as leachables [19,20].

4.1. Extractables

Extractables are organic and inorganic chemical entities that can be released under laboratory conditions from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction. A leachable compound arises as a result of direct contact with the drug product or gas diffusion in normal manufacture, storage, or usage conditions; nevertheless, extractables are extracted from a material under laboratory conditions utilising a specific extraction research. The total laboratory process necessary to generate extractables profile(s) of certain pharmaceutical packaging/delivery systems, packaging components, or building materials is the subject of this study [21]. While extraction studies are primarily concerned with the drug contact material, leachables investigations are concerned with the drug product. Extraction studies are carried out to learn more about the materials that come into contact with a pharmaceutical product. The purpose of acquiring qualitative profiles, quantitative profiles, predictive modelling, and/or actual exposure conditions can influence the extraction conditions and analysis procedures used. All of the above aims can be combined in a complete extraction research [22]. Furthermore, the extractable assessment helps to better understand the sources of leachables and how to limit or minimise their impacts during the medication development/manufacturing process. In this way, the appendix of reference [23] has detailed information regarding various extractables related with various types of plastics such as PVC, PP, PE, and others. As a result, extractables are potentially leachable. This indicates that the leachables reported in a specific medicine dosage form may have been previously identified in a proper extraction investigation. Leachables should consequently be a subset of extractables, according to this theory. In practise, however, leachables investigations can uncover compounds that were previously undetectable during an extraction research.

4.2 Risk management for safety

Risk assessment is a method for arranging data in order to support a risk decision made as part of a risk management process. It entails identifying hazards as well as analysing and evaluating the risks associated with exposure to such hazards [24], with risk being linked to the impact of uncertainty on objectives [25]. It is necessary to obtain particular information on the clinical use of the drug product in order to appropriately assess the safety risk posed by leachables in order to determine the 'human daily intake' (HDI), which is expressed as the mass of a particular leachable per day, or any other limit depending on subjects relevant to the medication product's dosage parameters.

To this purpose, the Product Quality Research Institute (PQRI) introduced the "safety concern threshold" (SCT), which is similar to HDI and is defined as the dose below which a leachable poses insignificant safety concerns from carcinogenic and noncarcinogenic harmful effects [22,23].

SCTL (g L/day) = CL (g L/g product) MDD (g product/day) SCTL (g L/day) = CL (g L/g product) MDD (g product/day) …. (2)

SCT for noncancer effects (general toxicity) are based on toxicokinetics and toxicodynamics data (absorption, distribution, metabolism, excretion) and can be compared to the Cramer classification tree, which is based mostly on chemical structures [25]. The toxicological data for each leachable, as defined by the PDEL (explained earlier in this section), and the matching SCTL are linked in the 'margin of safety' (MoS), which is calculated using equation 3.

MoSL = SCTL (g L/day) PDEL (g L/day) PDEL (g L/day) (3)

If the MoSL is more than one, the leachable is regarded safe and unlikely to cause harm; if not, the leachable is considered a safety risk and the source of a potentially hazardous situation [2].

5. ANALYTICAL TECHNIQUES TO LEACHABLES FROM POLYMERIC MATERIALS

Reference [24] contains a wealth of information on various leachable source materials. However, in this part, only plastic drug contact materials will be considered because, as previously stated, they are the primary producers of leachables.

Trace organic analysis principles can be used to the problem of characterising both L&E profiles. The overall procedure is divided into four steps [14,16]:

a) Information. Improve knowledge of the nature of the drug contact materials (potential analytes and matrix) that will be analysed.

b) Fractionation and extraction Remove the analyte combination from the matrix (packaging system or medical device) and sort it into chemical families if necessary. Additionally, create the extract or fraction in accordance with the requirements of the analytical procedures that will be used later and the information that will be obtained from the analysis.

c) Separation. For consecutive measurements, separate the various analytes. If suitably selective analytical sensors/detectors are available for the next phase, as is usually the case with inorganic L&E, this step could be skipped.

d) Measurement. Use analytical measuring techniques that can generate chemically specific information (structural, qualitative, and/or quantitative) for each analyte.

An outstanding and highly recommended book that discusses step-by-step the determination of antioxidants in plastic materials and their migration into solution [19] provides an example of the application technique.

5.1 Extraction

Extraction is a technique for isolating possible leachables from the rest of the mixture. Extraction, in this sense, refers to a controlled laboratory operation whose goal is to determine what compounds are leached from a test material to what quantity under operational conditions. The extraction is, without a doubt, the first step towards a good characterization of leachables.

An extraction can be done in a variety of methods, but it's critical that the method used matches the study's objectives. Reflux, soxhlet, maceration in a sealed vessel, ultrasound- or microwave-assisted extraction, pressurised liquid extraction, or headspace vaporisation, which could be coupled to a solid-phase adsorption and subsequent thermal desorption system, are the most popular extraction processes.

The Product Quality Research Institute's (PQRI) Leachables and Extractables Working Group has recommended some experimental protocols for controlled extraction studies from various types of plastic material [4,5], in which specific analytical conditions that should be considered in a standard are laid out; these protocols have also been gathered in several chapters of the handbook broadly quoted in this tutorial [21].

For leachable separation in medical devices, four major types of extraction techniques have been identified [12]:

- Simulated-use extraction: assessing leachable levels from packaging/delivery systems or medical devices to which the user is exposed during ordinary use to simulate product use.
- Exaggerated extraction refers to any extraction that is designed to release a higher amount of a chemical constituent than would be produced under simulated use settings.
- Exhaustive extraction occurs when the amount of leachables discovered in a subsequent extraction is less than 10% of that detected in the initial extraction, or when there is no analytically significant rise in the cumulative leachable material levels observed.
- accelerated extraction: extraction that allows for the measurement of leachables released from a device or material under conditions that cause the compounds to leach faster into the extraction vehicle.

The extraction temperature fluctuates depending on the expected conditions to provide a suitable exaggeration of the expected use conditions. For example, an extraction temperature of 40 oC is advised for plastic components and systems used to manufacture pharmaceutical medicinal products to speed up, but not change, the extraction process for an extraction time of 1-21 days [21]In addition, in extraction studies, some recommended temperatures/times for medical equipment include [22,23]

- (371)°C for (1202) hours
- (371) oC for 72 hours
- (502) oC for (722) hours
- (702) oC for (242) hours
- (10.1) h at (121.2) oC

5.2 Analytical procedures for measurements

The growing use of drug contact plastics in the pharmaceutical sector for packaging, delivery systems, and medical devices has resulted in a wide range of possible organic leachables of various kinds. This means that no single method can provide a credible, comprehensive analytical assessment. To make the analytical method as simple as possible, the typical leachables are divided into many categories based on their chemical properties, allowing each group to be defined using a specific analytical technique as part of a broad, non-targeted strategy. The most basic approach divides the population into fve groups [24,25]: (1) volatile, (2) semi-volatile, and (3) non-volatile organic compounds, (4) elemental entities, primarily metal cations, and (5) inorganic anions and low-molecular weight organic acids, which are measured using gas chromatography-mass spectrometry (GC/MS) with or without headspace (HS) sampling, reversed-phase liquid chromatography (usually equipped with a fist UV-adsorption detector), and reversed-phase liquid chromaton chromatography, inductively coupled plasma (such as optical spectroscopy mode or coupled to mass spectrometry), and inductively coupled plasma (such as optical spectroscopy mode or coupled to mass spectrometry). From the last few decades, mass spectrometry (MS) and associated analytical techniques have played an increasingly important role in the identification and quantification of leachables [22,13]

Additional analytical techniques, such as total organic carbon (TOC) or non-volatile residue (NVR) analysis, can be employed separately or in combination to estimate the amount of leachable material present and verify that important leachable constituents are not overlooked. For aqueous formulations, TOC analysis may offer an estimate of total leachables.

The first step in doing a proper leachables control is to select an analytical technique. The next crucial decision is to choose the most appropriate analytical method, which will have an impact on the assessment's success or failure. To guarantee that each individual leachable chemical is correctly described, i.e. detected and hopefully recognised, typified/qualified, and quantified, fit-for-purpose analytical procedures should be used [25].

5.3 Identification

Analytical identification is defined as the process of attributing an analyte (analytical signal) to a single chemical molecule or a group/class of chemical compounds based on properties/features that are similar [18]. This is usually accomplished by comparing a sample property to that of a reference standard (e.g., spectrum, chromatographic behaviour, chemical reactivity) [7]. The majority of identification tests are spectroscopic in nature and may be compound-specific. As a result, leachable identification analysis should be as specific as possible, and it can be done using a variety of chromatographic techniques and detection systems. The scope of the chosen test techniques is sometimes insufficient, allowing extracted components to go undetected [23].

The identity of several leachables can frequently be established by comparing results to appropriate analytical standards. Additionally, identification entails more than just acquiring a chemical formula. If the components are not commercially available, such as degrading chemicals or reaction by-products from polymer manufacturing, it may not be possible. Due to the enormous variety of closely related isomers and oligomers, leachables such as oligomers of base polymers or slogans may not always be correctly detected. A generic categorisation could be used in this scenario. In ref., a clear decision tree for identifying and qualifying leachables is shown. When possible, authentic materials should be analysed to establish the presence of organic leachables. If the actual material's retention time and measured mass spectrum match those of the fake,

Unidentified organic leachables must be labelled as such. It is still possible to report an organic leachable as tentatively or certainly identified if it cannot be confirmed. The following are possible classifications for identification test results: Confirmed: adequate data (molecular mass, fragmentation pattern, MS/UV spectra matching with online databases, and retention with standard) are available. Confident: enough data to rule out the structures that are most closely related (molecular mass and MS fragmentation pattern). □ Only appropriate facts to deduce the possible substance or combination of compounds is considered tentative (molecular mass and partial elucidation of fragmentation patterns). It's vital to emphasise at this point that the amount of assurance in identifying any individual leachable is dependent on the intended use. The entity in charge of the leachable study must decide on the level of identification that will be used.

5.4 Calibration /Quantitation

The intensity of an instrumental signal from the desired leachable in comparison to an appropriate analytical reference is used to calculate L&E. Individual leachables (or extractables) must therefore be isolated (either directly using chromatography or indirectly using selective detection) and each one must generate a measurement intensity value that is functionally dependent on the amount of the leachable in a given extract or medicinal product. For the quantification of leachables, various methodologies could be used. We defined two possible approaches: formal quantitation and proper quantitation. The test solution is quantified using an external calibration curve made up of standard solutions of each target chemical at various concentrations, including the concentration detected in the test solution.

Semi-quantitative or ad hoc quantification. When there are no commercially accessible standards, this method uses a surrogate, which is a standard with a similar chemical structure or behaviour. Internal surrogates can only be used if the surrogate has never been used in the test solution before. For 38 leachable and eight internal surrogate candidates, this technique was employed to produce a database of GC-FID and GCMSresponse variables. More recently, the behaviour of semi-volatile organic compounds was studied using an analytical approach that combined solid phase extraction with GC-MS, yielding a comprehensive database of both relative response factors (RRF) and relative retention durations (RRT) for 154 possible organic leachables. Another fascinating study looked at the variation in RRF and found it to be rather interesting.

5.5.Validation: analytical evaluation threshold

The analytical methods for L&E are essentially the same as those for other trace organic analysis methods, and any of the existing validation guidance offered by recognised bodies or authorities, particularly those focused on organic contaminant control, such as those from the UNODC or the EU Directorate General for Health and Food Safety, may be appropriate.

However, validation requirements for leachable analytical procedures may be considered unique, owing to the usage of a specified analytical limit known as the 'analytical evaluation threshold' (AET). The AET is defined as the threshold at or beyond which a leachable should be described and reported for toxicological assessment, as advocated by the PQRI. The AET is a drug –

product – specific analytical threshold that is directly converted from the toxicological SCT (or HDI or TCT) to a container or canister unit of the supplied dosage form of a drug product or a prescribed medical device. The AETL is determined from the SCT and the dosage, represented as the number of doses per day, for a certain leachable, L.

AETL (µg L/specimen) =SCTL (µg day) /Dosage (doses/day)× Content (doses/specimen (4) …

Then the dosage is indicated as daily intake, in g of drug product per day, (for example, for this equation may also be expressed in equation (5).

AETL (µg L/specimen) =SCTL (µg Lday)/Intake (g drug/day)× Content (g drug/specimen) (5)..

If SCT is not determined for the considered leachable, values between 0.15 and 1.5 µg/day could be used (see section 3.3). AETL is typically expressed in mass leachable (usually µg)contained in each dosage form, canister or medical device containing the drug product. This may be easily expressed as a concentration of leachable, AET-CONCL, in the drug product[28] by equation (6) and (7):

- for liquid dosage forms:

  AET_COCL (µg L/ml specimen) =AETL (µg L specimen)/volume (ml/specimen)(6)

- for solid dosage forms:

  AET_CONCL (µg L/g specimen) =AETL (µg L specimen)/mass (g/specimen)(7)…

In the references, some examples of AET computations for various dose forms are detailed. In addition, in reference, you may find an instructive example set of leachable results for a fictional sample container closure (AET = 10 g/g). The AET is unique to each product. It specifies the least amount of leachable in a drug product that must be recognised and measured; as a result, it can be utilised as a target value for analytical technique development and validation. This is especially true when it comes to the quantification limit (and, by extension, the detection limit). To ensure that the analytical method detects, identifies, and quantifies the AET, a proposal would be that the quantification limit be equal to or less than half of the AET.

After reaching this point, the authors propose separating the two main purposes of analytical methods for L&E control: I type-S methods, which are aimed at ensuring the safety of the chemicals by verifying that each leachable's concentration is below its AET; and (ii) type-D methods, which are aimed at determining the concentration of each leachable. Both methods rely on quantification, but the validation requirements must be tailored to the primary goal.

6. RECENT ANALYTICAL BACKGROUND FOR ORGANIC L&E: THE LAST EIGHT YEARS

As noted in earlier sections, multiple studies of the analytical control of L&E have been conducted in recent years utilising various analytical techniques. Furthermore, as previously noted, there is a wealth of information about inorganic L&E, and the analytical methods used to determine them, notably elemental metal entities, are well established. In addition, a universal, conclusive method for determining leachable (and extractable) metals in pharmaceutical goods using ICP-MS has been presented. Analytical work on organic L&E is also in progress. References include a review of both LC and Chromatographic methods for organic L&E up to 2003. More recently, a tutorial shows how to use thermal desorption GC-MS to profile packaging materials for possible extractables, and another describes how to use thermal desorption GC-MS to characterise packaging materials for prospective extractables.

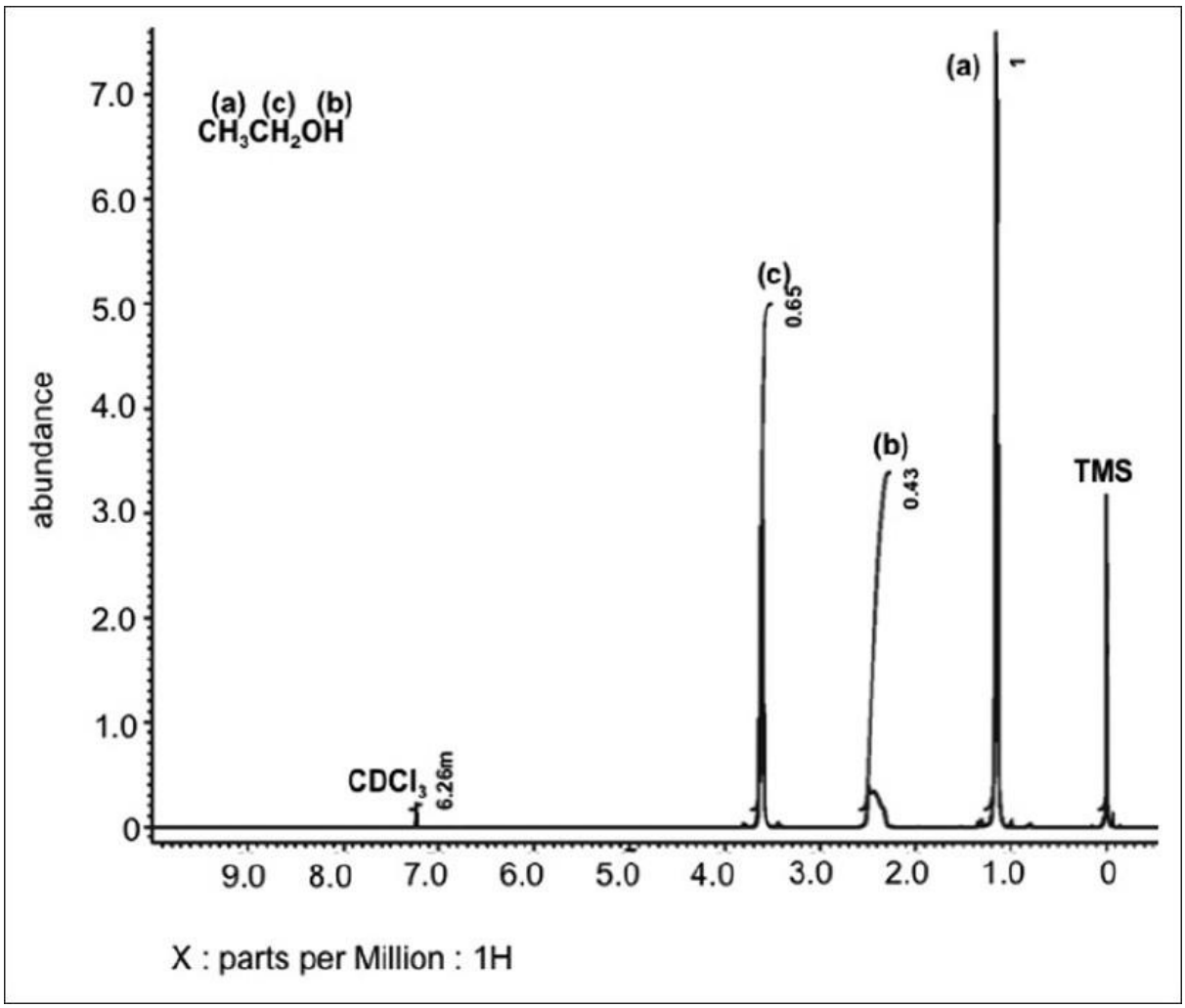

Fig.1: Ethanol containing impurity by leaching of plastic.

7. CONCLUSION

Up to 2008, a comprehensive study looked at all of the reported LC methods utilised in L&E investigations. Using these earlier reviews as a starting point, we present an updated collection of studies on chromatographic analysis of L&E published in recent years. PVs are used to store and dispense homoeopathic medicine, and they leak out various plastic components and additional substances. The purity of the HE procedure from the supplier was confirmed using proton NMR spectroscopy because it was employed as a solvent in the current experiments. The spectral graph of homoeopathic grade ethanol produced by H1 NMR spectroscopy revealed clear chemical shape values for ethanol at 1.1 ppm level, namely (Triplet. CH3), 2.4 ppm (Singlet, OH), and 3.6 (Quadrate,, CH2), indicating that the ethanol employed in this study is of high quality.

REFERENCES

1. ISO 10993-13:2010, Biological Evaluation of Medical Devices: Part 13: Identification and Quantification of Degradation Products from Polymeric Medical Devices, International Organization for Standardization, Geneva, 2010.

2. E.N. Peters, Plastics: thermoplastics, thermosets and elastomers, in: M. Kutz (Ed.), Handbook of Material Selection, John Wiley & Sons, New York, 2002, ch 11, pp. 335355. https://doi.org/10.1002/9780470172551.ch11.

3. USP 41 <661.1>, Plastic Packaging Systems for Pharmaceutical Uses, United States Pharmacopeia, Rockville, 2017.

4. L.W. McKeen, Plastics used in medical devices, in: K. Modjarrad, S. Ebnesajjad (Eds.), Handbook of Polymer Applications in Medicine and Medical Devices, Elsevier, Amsterdam, 2014, ch. 3, pp. 21-53. https://doi.org/10.1016/B978-0-323-22805-3.00003-7.

5. CPMP/QWP/4359/03, Guideline on Plastic Immediate Packaging Materials, European Medicines Agency, London, 2005.

6. J. Brandsch, O, Piringer, Characteristics of plastic materials, in: O.G. Piringer, A,L. Baner (Eds.), Plastics Packaging – Interactions with Food and Pharmaceuticals, second ed., Wiley-VCH Verlag, Weinheim, 2008, ch. 2, pp. 15-62. https://doi.org/10.1002/9783527621422.ch2.

7. M. Bolgar, J. Hubbal, J. Groeger, S. Meronek, Handbook for the Chemical Analysis of Plastic and Polymer Additives, second ed., CRC Press, Boca Raton, 2016.

8. USP 41 <661>, Plastic Packaging Systems and their Materials of Construction, United States Pharmacopeia, Rockville, 2017.

9. J. Pospíšil, S. Nešpurek, Polymer additives, in: O.G. Piringer, A,L. Baner (Eds.), Plastics Packaging – Interactions with Food and Pharmaceuticals, second ed., Wiley-VCH Verlag, Weinheim, 2008, ch. 3, pp. 63-88. https://doi.org/10.1002/9783527621422.ch3.

10. J.N. Hahladakis, C.A. Velis, R. Weber, E. Iacovidou, P. Purnell, An overview of chemical additives present in plastics: migration, release, fate and environmental impact during their use, disposal and recycling, J. Hazard. Mater. 244 (2018) 179-199. https://doi.org/10.1016/j.jhazmat.2017.10.014.

11. M.A. Ruberto, D. Paskiet, K. Miller, Chemical and physical attributes of plastics and elastomers: impact on the extractables profile of container closure systems, in: D.J. Ball, D.L. Norwood, C.L.M. Stults, L.M. Nagao (Eds.), Leachables and Extractables Handbook – Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products, John Wiley & Sons, Hoboken, 2012, ch. 10, pp. 185-215. https://doi.org/10.1002/9781118147672.ch11.

12. Ph Eur 9.3, ch. 3.1.13: Plastic Additives, European Pharmacopeia, Strasbourg, 2017.

13. E.J. Smith, D.M. Paskiet, The management of extractables and leachables in pharmaceutical products, in: S. Nema, J.D. Ludwing (Eds.), Pharmaceutical Dosage Forms Parenteral Formulations. Vol 3: Regulations, Validation and the Future, third ed., Informa Healthcare, New York, 2010, pp. 175-221. https://doi.org/10.3109/9781420086485-11.

14. R. Franz, A. Störmer, Migration of plastic constituents, in: O.G. Piringer, A,L. Baner (Eds.), Plastics Packaging – Interactions with Food and Pharmaceuticals, second ed., Wiley-VCH Verlag, Weinheim, 2008, ch. 11, pp- 349-416. https://doi.org/10.1002/9783527621422.ch11.

15. O.G. Piringer, A,L. Baner, Plastics packaging – Interactions with food and pharmaceuticals, second ed., Wiley-VCH Verlag, Weinheim, 2008.

16. K.A. Barnes, C.R. Sinclair, D.H. Watson, Chemical migration and food contact materials, Woodhead Publishing, Cambridge / CRC Press, Boca Raton, 2007.

17. T.R. Crompton, Additive migration from plastics into foods – A guide for analytical chemists, Smithers Rapra Technology, Shawbury, 2007.

18. EUR: 24105 EN, Guidelines for performance criteria and validation procedures of analytical methods used in controls of food contact materials, Joint Research Centre, European Commission, Luxembourg, 2009.

19. EFSA Technical Report 2017:EN-1224, Administrative guidance for the preparation of applications for the safety assessment of substances to be used in plastic food contact materials, European Food Safety Authority (EFSA) Supporting Publications 14(5), 2017.

20. O-W. Lau, S-K. Wong, Contamination in food from packaging material, J. Chromatogr. A 882 (2000) 255-270. https://doi.org/10.1016/S0021-9673(00)00356-3.

21. 21.K. Bhunia, S.S. Sablani, J. Tang, B. Rasco, Migration of chemical compounds from packaging polymers during microwave, conventional heat treatment, and storage, Compr. Rev. Food Sci. Food Saf. 12 (2013) 523-545. https://doi.org/10.1111/1541-4337.12028.

22. 22.R. Sendón García, A. Sanches Silva, I. Cooper, R. Franz, P. Paseiro Losada, Revision of analytical strategies to evaluate different migrants from food packaging materials, Trends Food Sci. Technol. 17 (2006) 354-366. https://doi.org/10.1016/j.tifs.2006.01.005.

23. 23.Y. Sanchis, V. Yusà, C. Coscollà, Analytical strategies for organic food packaging contaminants, J. Chromatogr. A 1490 (2017) 22-46. https://doi.org/10.1016/j.chroma.2017.01.076.

24. 24.D. Paskiet, E.L. Lippert, B.D. Mitchell, D. Zurbriggen, Inorganic leachables, in: D.J. Ball, D.L. Norwood, C.L.M. Stults, L.M. Nagao (Eds.), Leachables and Extractables Handbook – Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products, John Wiley & Sons, Hoboken, 2012, ch. 20, pp. 549-571. https://doi.org/10.1002/9781118147672.ch20.

25. 25.D. Jenke, C. Rivera, T. Mortensen, P. Amin, M. Chacko, T. Tran, J. Chum, A Compilation of metals and trace elements extracted from materials relevant to pharmaceutical applications such as packaging systems and devices, PDA J. Pharm. Sci. Tecnol. 67 (2013) 354-375. https://doi.org/10.5731/pdajpst.2013.00927.