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Analytical procedures for the quality control of pharmaceuticals in terms of residual solvents content – challenges and recent developments

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Abstract

Residual solvents play an important role in the synthesis of drug substances and in product formulations. At the same time they pose a problem and must be removed, because many of them have toxic or environmentally hazardous properties. Therefore, constant monitoring of quality control is needed. In this paper, we present an overview of regulatory and general methods described by various Pharmacopoeias. Next, the most commonly used methodologies for the determination of residual solvents in different pharmaceutical samples are reviewed to demonstrate their limitations, which form the basis for discussion about new methods. Several interesting new alternatives for sample preparation and gas chromatography (GC) separation are presented using examples from recent literature. The techniques described are direct injection, headspace analysis with different modifications and variations, liquid extraction, single-drop microextraction, solid-phase microextraction. Various GC separation techniques are compared and new solutions to improve sensitivity and efficiency are presented.

Keywords: residual solvents; pharmaceutical samples; analytical procedures; sample preparation techniques; headspace analysis; gas chromatography

Abbreviations

ANDAs – Abbreviated New Drug Applications, US Food and Drug Administration
API – Active Pharmaceutical Ingredient
BA – Benzyl Alcohol
B.P. – Boiling Point
CW – Carbowax
DI – Direct Injection (Immersion)
DMA – *N,N*-dimethylacetamide
DMF – *N,N*-dimethylformamide
DMI – 1,3-dimethyl-2-imidazolidinone
DMSO – Dimethylsulfoxide
DSC – Differential Scanning Calorimetry
DVB – Divinylbenzene
ECD – Electron Capture Detector
EHC – Environmental Health Criteria
FDA – US Food and Drug Administration
FET – Full Evaporation Technique
FID – Flame Ionization Detector
FTIR – Fourier Transformation Infrared Spectroscopy
GC – Gas Chromatography
GC-MS – Gas Chromatography coupled with Mass Spectrometer
GCxGC – Two-Dimensional Gas Chromatography
GMP – Good Manufacture Practice
HPLC – High Performance Liquid Chromatography
HS – Headspace Analysis
HS-MS – Headspace Sampler coupled with Mass Spectrometer
ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ils – Ionic Liquids
IMS – Ion Mobility Spectrometry
IRIS – Integrated Risk Information System
LE – Liquid Extraction
LOD – Limit of Detection
LPME – Liquid-Phase Microextraction
LTM – Low Thermal Mass
MHE – Multiple Headspace Extraction
MHS-SDME – Multiple Headspace Single-Drop Microextraction
MLLE – Liquid Microextraction
MS – Mass Spectrometry

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MTBE – Methyl T*ert*-Buthyl Ether
NDAs – New Drug Applications, US Food and Drug Administration
NIR – Near Infrared Spectroscopy
NMP – *N*-methyl-2-pyrrolidinone
PA – Polyacrylate
PAT – Process Analytical Technologies
PDE – Permitted Daily Exposure
PDMS – Polydimethylsiloxane
PTV – Programmed Temperature Vaporization inlet
QA/QC – Quality Assurance/Quality Control
SDME – Single-Drop Microextraction
SPME – Solid-Phase Microextraction
TD – Thermal Desorption
TGA – Thermogravimetric Analysis
TVT – Total Vaporization Technique
WHO – World Health Organization

Contents

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1. Introduction

Pollution of pharmaceuticals can be any component that is not the chemical compound defined as the active substance or an excipient in the drug product. Therefore, the safety of pharmaceuticals does not only depend on toxicological properties of active substances and excipients in the drug product, but partly also upon the pollutants that it may contain. Due to the significant impact of pollutants on the pharmaceutical quality, recommendations concerning contaminants were introduced by the US Food and Drug Administration (New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)) [1]. Moreover, the lack of chemical stability of the active pharmaceutical ingredients may cause formation and emission of volatile compounds, which may affect the stability of drug products and their physicochemical properties, causing negative or even effects [2].

~~Organic solvents are routinely used in the synthesis and process chemistry of drug substances and drug products. These process solvents cannot be completely removed by practicable manufacturing practices such as freeze-drying or drying at high temperature under vacuum. Therefore, they may remain in pharmaceuticals~~. Organic solvents do not possess therapeutic benefits for patients and should be removed in order to meet the requirements of product specifications, good manufacturing practices and appropriate quality - control requirements [3,4]. ~~The concentration levels of residue organic solvents in drug products should be below recommended acceptable levels (safety limits). It is the responsibility of manufacturers to ensure that any solvent present in the final product does not pose a threat to patient health or to the environment [7-9].~~

General methods for the determination of residual solvents in pharmaceuticals are well known and described by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) [5] and various Pharmacopoeias [6-8]. These methods are based primarily on gas chromatography (GC) due to the volatility of organic solvents and the substantial separating capability of capillary columns. Over the last decade, several GC methods have been reported in the literature [9-12]. Unfortunately, they do not meet expectations, mainly due to large time and effort, and, generally, multi-step processes of isolation and preconcentration of analytes. Most of the GC methods tend to have long run times and to be very specific for a limited number of solvents (mainly solvents with similar physicochemical properties) and sample matrices. Efficient and sensitive analytical methodologies need to be developed to significantly increase productivity of an analytical laboratories in the pharmaceutical industry. Fig. 1 presents ‘milestones’ in the

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field of development of analytical methodologies for evaluating the level of residual solvents and identification as well as quantitation of specific analytes.

FIGURE 1

Determination of volatile compounds from the group of organic pollutants has many analytical problems. The main source of problems in the identification of organic solvents is their high volatility and hydrophobic properties, which is directly related to the difficulty in sampling and their preparation for analysis. Moreover, the determination of polar residual solvents in pharmaceutical preparations continues to present an analytical challenge mainly because these compounds are difficult to remove from water or other polar solvents.

In this paper the most commonly used methodologies for the determination of residual solvents in pharmaceutical samples have been reviewed and critically evaluated. Recommended methods are presented and discussed. Challenges and new solutions with examples from recent literature are proposed.

2. Residual solvents

Residual solvents ~~in pharmaceuticals are organic volatile chemicals that could be used or produced during the manufacturing processes of drug substances, drug products and excipients. They~~ play an important role in the production of pharmaceuticals (reaction, separation, purification and drying) and in product formulations (for example: granulation, coating, eye-drop formulation, spray formulation, etc.). At each of these stages, the product can be potentially contaminated by organic solvents. ~~The pharmaceutical industry is one of the largest users of organic solvents per amount of the final product [18].~~ Some of them are used during the synthesis of active substances or during the preparation of pharmaceutical products to increase the process efficiency, improve their stability, purity, solubility and to facilitate crystallization. Therefore, the solvent and its quality may be a critical parameter in the synthesis process [5].

Toxicity is the major and unquestionable reason for control of residual solvent contents. Additionally, most organic solvents are volatile, flammable and hazardous to humans and the environment. They are also the main component of generated waste. Moreover, they pose a risk of inducing phase transformations (e.g. transformation of orthorhombic paracetamol by residual ethanol) and jeopardizing the physicochemical stability of an active substance. For

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example, formic acid, its esters and formaldehyde, a commonly present impurities in excipients, can interact with amino or hydroxyl groups from pharmaceutical compounds and form amides, esters or *N*-methyl derivative [13]. Table 1 presents information on classes of solvents commonly used in the pharmaceutical industry [1,5,13].

TABLE 1

Organic solvents usually used in the production process are as follows: the reaction medium, reagent or catalyst of synthesis reaction and an extractant during the extraction process. They can also play a role as entrainers during the process of azeotropic or extractive distillation. The crystallization process is commonly used for purification of the drug substance [14]. It is very important that the properties of formed crystals should be controlled during the crystallization process, i.e. their size and shape which determine the quality of the final product, its stability or dissolution rate. Certain products, crystallized from different classes of solvents or their mixtures demonstrate a variable crystals size and morphologies, as for example: ibuprofen or carboxylic acids [13]. After the crystallization process, residual solvents are located in the pores of the particulate product, and then are removed in the course of drying and homogenization (possibly grinding) process, or recrystallization. The physicochemical properties can have a large impact on the bioavailability of the final drug product [4,5,10]. Consequently, *on-line* process monitoring of solute concentrations can be beneficial to control the level of supersaturation that drives nucleation and crystal growth.

During the formulation of the final product to a form suitable for administration, some organic solvents can be used as its component to fulfill the function of diluents or solubilizers, mainly in semisolid and liquid pharmaceuticals, where water cannot be used [1,9,10]. Organic solvents can also contaminate the drug products during their packaging, storage and transportation [13]. They may also occur as products of various reactions and processes during the shelf-life of the product under its storage conditions. For example, sodium benzoate used in oral liquid pharmaceutical products can potentially generate residual levels of free carcinogenic benzene under heat and acidic conditions [15].

From the viewpoint of factories, the complete removal of residual organic solvents by practical manufacturing techniques (different drying processes) is practically impossible, therefore, their presence in final products is unavoidable [5,11-13]. Residual solvents are significant contamination of pharmaceuticals, because they can cause toxic effects and safety problems, influence on physicochemical properties of the active substance or an excipient in

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the drug product and may affect the products formulation process [2,4,10]. As a result, they may be responsible for the unpleasant odor, color change and may affect the therapeutic effect, safety and stability of the final products [13]. Moreover, they may also accelerate the decomposition process of the product. Therefore, constant monitoring of quality control in pharmaceuticals is needed to ensure patient safety and meet regulatory expectations [3,5,11]. Identification of impurities in pharmaceuticals also allows to use profiles of these contaminants as a 'fingerprint' of the manufacturer. Impurity profiles are a valuable tool for detecting "counterfeit" drugs or illicit substitutions and tracking down their source, and are the subject of interest for forensic laboratories [16].

3. Legislations

~~Organic solvents play a key role in the production of pharmaceuticals, but many of them have toxic or environmentally hazardous properties. Therefore, they should be avoided unless their use can be justified on the basis of risk-benefit assessment [3-5,29].~~ In order to control concentration levels of residual solvents in drug substances, products and excipients, national and international guidelines were introduced [1,2,4,5-8]. In 1997, the ICH classified, in guideline Q3C [5], commonly used organic solvents into four classes in terms of their level of hazard to humans and the environment and to regulate the concentration level of each solvent. So far, the document has been updated five times because of new toxicological data for tetrahydrofuran, *N*-methylpyrrolidone and cumene [5]. Moreover, the World Health Organization (WHO) [3] and other national and international health authorities and institutes introduced a new term (permitted daily exposure, PDE) to define the maximum concentration limits as a pharmaceutically acceptable intake of residual solvents per day [2]. The list presented in the guideline is not exhaustive and one should evaluate the synthesis and manufacturing processes for all possible solvents. Class 1 includes solvents (e.g. benzene, carbon tetrachloride, 1,2-dichloroethane etc.) considered to be the most toxic, which using should be avoided in the production of pharmaceutical products. The absolute limits in the range of 2 – 8 ppm are defined for solvents that are known to be highly toxic and the limit of 1500 ppm is applied for trichloroethane, an environmentally hazardous chemical. Class 2 and 3 of residual solvents are considered a lesser risk. Class 2 solvents (e.g. acetonitrile, chloroform, hexane, 2-methoxyethanol, nitromethane etc.) should be limited in their usage and specifically tested for in products. Class 3 solvents (e.g. acetone, 2-butanol, ethanol, ethyl acetate etc.) require only non-specific testing based on Good Manufacturing Practice (GMP).

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Higher amounts of solvents from Class 3 can be acceptable if manufacturer will prove that the content is realistic with relation to manufacturing capability and good manufacturing practice. Class 4 includes solvents without any information about toxicity, for example: isooctane, petroleum ether, trifluoroacetic acid etc. According to the ICH guideline, solvents from Class 1 must be identified and quantified, solvents from class 2 have individual limits between 50 and 5000 ppm, and solvents from class 3 need to be identified and quantified, when they are found to be more than 0.5 % (*w/w*). Exposure limits in the ICH guideline are established by referring to methodologies and toxicity data described in the Environmental Health Criteria (EHC) monographs and the Integrated Risk Information System (IRIS) [3-5].

The US FDA published their guidance at the end of 1997 and the European Pharmacopoeia included the guideline in the chapter entitled 'Residual solvents' [1,4,8]. Also, countries from the ICH group (United States Pharmacopeia and Japanese Pharmacopoeia) [6,7] and others have adopted requirements for their pharmacopoeias. The guideline set criteria for analytical methods used to identify and quantify residual solvents as well as provide acceptable concentration limits. However, it applies only to existing marketed drug products. It cannot be applied to potential new drug substances, excipients and drug products used during the clinical research stages of development.

4. Analytical methodologies

Manufacturers are free to choose the most appropriate validated analytical procedure for a particular application. The ICH Q3C (R5) [5] guideline adopted by the regulatory bodies of the European Union, Japan and USA set and define general methods for performing residual solvents testing. Procedures for determination are described and detailed in a separate chapter of Pharmacopoeias [6-8]. This general methods may be used:

- ✓ for identification of Class 1 and 2 residual solvents when there is no information about solvents which may be present in the sample;
- ✓ as a limit test for Class 1 and 2 solvents when they are detected in the sample;
- ✓ for quantification of Class 2 solvents when limits are greater than 0.1 % (*w/w*);
- ✓ for quantification of Class 3 solvents when it is required.

It should be noticed, that a procedure applied quantitatively to control residual solvents in samples must be validated [8]. Typically, they are determined by chromatographic techniques due to their high sensitivity, separation efficiency and the possibility of analyzing liquid or solid samples of a complex nature [9-12,15,17-19]. Direct injection (DI) of samples for GC

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analysis is feasible and should be the method of choice in view of its simplicity and reliability [9,10,18,19]. But non-volatile components or corrosive substances present in the sample can cause the contamination of the GC system and the deterioration of the column and consequently, frequent and time-consuming cleaning is required. Therefore, samples need a separation of the volatile substances before analysis, which can be performed by using headspace sampling (HS) or different extraction techniques [17,18]. HS sampling can prevent from contamination, but it limits analysis to those solvents being evaporated from the HS only and it requires a larger sample load [11,12]. In addition, the analysis time can be longer due to sampler equilibration prior to GC separation. Another sample preparation techniques, for example: solid-phase microextraction (SPME) and single-drop microextraction (SDME), have been developed to overcome the drawbacks of those conventionally used, facilitating rapid and efficient isolation and/or enrichment of analytes as well as eliminating the consumption of toxic organic solvents [9,13,17,18,20-22]. Moreover, standard addition is the most recommended quantitation technique to overcome the matrix effect in analyses [9,10,21]. If only Class 3 solvents are present, a non specific method, such as loss on drying may be used [5]. Moreover, when there is no need to specify the concentration of residual solvents in a sample, but only to check their presence, other analytical techniques can be used, for example: sensors, different thermal analysis techniques or spectroscopic methods [1,6-8]. ~~In Fig. 3, the most popular methodologies for determining residual solvents in pharmaceutical products are presented.~~

~~FIGURE 3~~

The most frequently used method for routine determination of residual solvents in pharmaceutical quality assurance/quality control (QA/QC) is a static headspace sampler coupled with gas chromatography [6-12,17,18]. This general method is recommended by various Pharmacopeias, but at the same time its implementation is a subject of debate in the pharmaceutical industry due to its limited selectivity and sensitivity [23]. For example, formamide, 2-ethoxyethanol, 2-methoxyethanol, ethyelene glycol, *N*-methylpyrrolidone and sulfolane are not readily detected by headspace injection [5,8]. Other appropriate procedures need to be developed for their control. The most important step for successful analysis is the development of a selective, sensitive and stable methodology for determination of compounds with different volatility and polarities. It can be seen as several trends in the determination of residual solvents:

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- determination of a broad spectrum of solvents in a single analytical run (multiresidue methods);
- miniaturization and automation of analytical techniques by application of solventless and solvent-minimized sample preparation techniques, for example: SPME, SDME;
- development of new techniques for fast screening methods, for example: HS sampler coupled with mass spectrometer (MS), flow-modulation GC;
- application of advanced techniques, for example: fast GC, two-dimensional gas chromatography (GC×GC);
- application of environmentally friendly sample diluents, for example: ionic liquids (Ils), binary solvents, water.

The main advantages of these methods are shorter analysis times, minimization of harmful solvents consumption, and typically, the high enrichment factor. The improved sensitivity makes it possible to minimize the amount of the sample needed for the analysis. ~~Ideally, the sample preparation stage should be as simple as possible, because it does not only reduce the time required, but also decreases the possibility of introducing contaminants. Research is continuing into the improvement of existing analytical methods and the development of new ones, which would enable solvents with different physicochemical properties to be reliably and reproducibly determined at the same time in a quick, simple, cheap, effective and environmentally friendly manner.~~

5. Methods recommended by the Pharmacopoeias

For determination of a high content of residual solvents with lower toxicity (greater than 1000 ppm) a loss of weight method can be applied [6-8]. It was the first analytical method published in Pharmacopoeias and is mainly dedicated to Class 3 solvents [10]. For the determination of hazardous solvents (Class 1 and 2), the use of analytical methods is recommended to enable determination of concentrations as low as possible [5].

The loss of weight method is a technique which is simple and easy to perform based on measuring the weight loss of sample during the heating process and can be carried out at a normal pressure or under the vacuum. However, it has many disadvantages, such as poor sensitivity and specificity (multicomponent solvent mixtures cannot be analyzed), high limits of detection and requires a large amount of sample for analysis (about 1 – 2 g). Moreover, atmospheric humidity may affect the results of measurements [10,18]. Therefore, the current

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trend focuses on more sophisticated techniques, which ensure the achievement of meaningful results. For example, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) have been used successfully [9,10,17,18]. Also, spectroscopic and spectrometric methods have proved to be a good alternative demonstrating low detection limits for toxic residual solvents [24]. All of these methods used to determine residual solvents in pharmaceutical products and excipients have been almost completely replaced by GC methods, which have also been approved by various Pharmacopoeias. Analytical procedures based on gas chromatography are the most popular and chemically specific for determination of residual solvents.

The general method for residual solvents determination described in European Pharmacopoeia, 8th edition, defines a general methodology and specifies two complementary procedures (systems) [8], which are presented in Fig. 2. "System A" is recommended for general use to identify unknown solvents and is equivalent to "Methods IV and V" of the U.S. Pharmacopoeia for analysis of volatile organic impurities [6]. "System B" is used for quantification of samples already resolved with a generic method as a confirmation of identity and to solve coelutions.

FIGURE 2

Three procedures are defined for sample preparation depending on the type of matrix. Two of them concern the nature of the solubility of analytes in water. For water-soluble samples, water is recommended as a solvent and for water-insoluble substances *N,N*-dimethylforamide (DMF) is suggested. For samples suspected of containing *N,N*-dimethylacetamide (DMA) and/or DMF, 1,3-dimethyl-2-imidazolidinone (DMI) is proposed as a solvent. After that, 5 mL of solution is transferred to vial and HS analysis is performed. Three different headspace conditions are proposed and their choice depends on the solvent which was selected for sample preparation. In addition, the properties of the residual solvents (high or low boiling) and the type of analyzed material (thermally stable or unstable) should also be taken into account. For final determination, all these methods utilized GC with capillary or wide-bore columns and a flame ionization detector (FID). The procedures (System A and B) vary in terms of the column type (film-coatings and dimensions) and in chromatographic conditions. Moreover, in European Pharmacopoeia as a complement with U.S. Pharmacopoeia, a mass spectrometer (MS) or electron capture detector (ECD) have been additionally proposed as an alternative detector [6-10,18]. As was mentioned before, all

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analytical methodologies used to quantitative determination of residual solvents must be validated. For this reason, manufacturers seek to develop their own methodologies, which would be faster, easier and tailored to their specific type of samples and analytes.

6. Sample preparation techniques

Because of the complex composition of pharmaceutical samples, different and low concentrations of the target analytes, the sample must be adequately prepared for analysis by the use of techniques for efficiently extracting the target compounds and for their cleanup prior to the quantitative determination stage. ~~In addition, pharmaceutical products often contain compounds with similar properties to the analytes, which further complicates the separation and quantitative determination. The choice of the technique depends on the properties of the target analytes, their volatility, polarity, solubility in water and organic solvents.~~ Classification of sample preparation techniques commonly used for determination of residual solvents is presented in Fig. 3.

FIGURE 3

At present, the literature focuses mainly on the techniques for the isolation, preconcentration and final determination of analytes, all of which can affect the reliability of the information obtained about a sample. Chemists tend to develop environmentally friendly analytical methodologies that are consistent with the principles of 'Green Chemistry' [20]. ~~These ensure that:~~

- ~~the use of chemical reagents, particularly organic solvents, is eliminated or at least substantially reduced,~~
- ~~the application of highly toxic reagents is eliminated,~~
- ~~coexisting components can be removed efficiently,~~
- ~~the labour- and energy-consumption of processes is reduced,~~
- ~~the procedure can be carried out conveniently and quickly,~~
- ~~the cost of analysis is low,~~
- ~~a broad spectrum of target analytes can be determined in a single analytical run.~~

~~The rapid development of new techniques in analytical chemistry (miniaturization, automation, high-throughput performance, *on-line* coupling with analytical instruments etc.)~~

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~~has meant that the consumption of solvents in the analysis can be very substantially reduced; very often the use of solvents can be eliminated altogether if solvent-free techniques are applied [40].~~

6.1 Dissolution and liquid extraction

The traditional technique of sample preparation for residual solvent determination is direct injection in which sample is dissolved in or extracted with suitable solvent. Good sample diluent should have a high capability for dissolving a large number of samples, high boiling point and good stability. For water-soluble samples and analytes, water is recommended as a diluent [6-8]. Water has the advantage of having no solvent peak when the FID is used. Moreover, it is a clean, stable and inexpensive solvent, but at the same time causes a sample backflash as a result of the large expansion volume of water causing poor injection reproducibility and poor method precision. To overcome this problem a polar organic solvent can be added to the water. A mixture 3:1 (*v/v*) of water and methanol was proposed as a diluent for dissolution of pantoprazole sodium in the form of tablets [19]. DI-GC-MS was used for analysis. The obtained limit of detection for dimethyl sulfate (genotoxic reagent used during the synthesis) was 1 µg mL^{-1}. Matrix effects as interfering peaks from the drug and the diluent were not observed. For other types of pharmaceutical samples dimethylsulfoxide (DMSO), DMF, DMA, benzyl alcohol (BA), hexane and ethylene glycol have been applied as sample diluents [9-11,18]. Using high boiling point solvents has the advantage that the diluent solvent peak will elute later, thus not interfering with the earlier eluting analyte peaks. In cases where a solvent with a low boiling point is used as diluent, only residual solvents having a high boiling point can be determined, so that the peaks do not overlap and their separation is possible [17,20]. Particular attention should be paid when benzyl alcohol is used as a diluent in combination with the DI technique. Interactions inside the GC injection port between solvent and matrix components could cause a number of problems. Benzene was reported to be the product of any interaction involving drug salts and benzyl alcohol inside a heated injection port [10]. Temperature in the injection port must be high enough to ensure complete vaporization of the solvents but low enough to avoid problems of sample reactivity or decomposition.

Direct injection to the GC column of a sample dissolved in an appropriate diluent is useful if residual solvents are determined in a drug substance [19,25,26]. If products such as tablets, gels, syrups are analysed, components of matrix may not be vaporized, or may not dissolve in

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the dissolution media applied. All these problems can be avoided by extensive sample preparation techniques. To overcome the matrix effects and to isolate trace analytes, liquid extraction (LE) can be applied. LE is one of the most common and also one of the oldest extraction techniques. The solvents are usually toluene and methyl *tert*-buthyl ether (MTBE) [18,20]. Though fairly simple and cheap, this technique has a number of drawbacks: it requires relatively large quantities of often toxic solvents, there is a risk of emulsions forming during stirring, and there is the problem of how to dispose of the post-extraction solvents. To achieve the desired preconcentration coefficient, the excess solvent usually has to be evaporated; extract cleanup is often also necessary. To minimize these disadvantages numerous improvements have been made to this method, most of which have involved miniaturizing the process to reduce the amounts of solvents consumed. For example, only 3 mL of MTBE was applied as a solvent for extraction of dimethyl sulfate from active pharmaceutical ingredient (API) intermediate [27]. To reduce the process time and more rapid phase separation after mechanically shaking the mixture was centrifuged at 13000 rpm for 10 min. Approximately 1.5 mL of organic phase was obtained and analyzed by GC-MS. The limit of detection was 0.05 μg mL^{-1} and the linearity range was 0.16 – 9.72 μg mL^{-1}.

6.2 Headspace analysis

Headspace (HS) analysis is a sampling method for determination of residual solvents in pharmaceuticals which is preferred and approved by ICH and various Pharmacopoeias. It is a more suitable technique which avoids many drawbacks of direct injection [12,17,21,28]. Pharmaceutical samples usually contain non-volatile or degradable compounds that can accumulate in the injector liner or the GC column, reduce their lifetime, co-elute with analytes or create interfering peaks from volatiles during thermal degradation. As a result, it can cause deterioration in method performance (recovery, sensitivity, precision, etc.) [9]. In most cases, samples require the separation of volatile residual solvents before analysis. This can be performed by HS analysis. It is an alternative technique, but is rather limited in terms of optimization possibilities with respect to its selectivity [17]. The analysis is conducted when a volume of gas above the pharmaceutical sample is collected and analyzed by GC. HS is desirable because it minimizes potential contamination of the system by avoiding introduction of a large quantity of the sample. It can be performed in two forms: in a static mode and a dynamic mode (in the literature it is also referred to as purge and trap analysis) [18]. These

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techniques have been extensively reviewed in the literature [9,10,16-18,28,29] and are briefly described in Table 2.

TABLE 2

The main advantage of the static mode of HS is easy operation and automation, whereas the dynamic mode of HS has the general advantages of low detection limits and smaller sample volumes required for analysis. While static HS commonly offers straightforward initial sample preparation, analysts often notice differences in instrument response during analysis of complex pharmaceutical samples, depending on their matrices [29]. In the static HS procedure, the sample (liquid or sometimes solid) is placed into a sealed vial and heated until a thermodynamic equilibrium (between the sample and the gas phase) is achieved. Then, a volume of headspace gas is collected and transferred to the gas chromatograph for analysis. Thus, only volatile components are introduced into the GC, resulting in a longer lifetime of the column and the system. The equilibrium should be reached within the shortest possible time and the temperature should be non-destructive [9,10,18,29-31]. This method is mainly dedicated for pharmaceutical samples soluble (or extractable) in solvents. Moreover, the addition of inorganic salt, pH control, an increase in the equilibrium temperature or control of the phase ratio can be used to improve sensitivity.

In a dynamic HS analysis, a stream of inert gas (usually high purity nitrogen) passes through the sample or sweeps over the surface of sample to ensure a maximum surface contact between the phases. Consequently, the solubility of volatile components in the liquid decreases, thus the removal of residual solvents is faster and more efficient. Volatiles from the sample matrix are transported to a trap where analytes are accumulated prior to analysis. The trap is generally a short column containing a sorbent, such as Chromosorb®, Porapak®, XAD® resins or Tenax®, which is the most used sorbent because of its thermal stability, in spite of its limited specific surface area [9,10,17,18]. After that, a thermal desorption cycle of the trap is initiated and the carrier gas transports the analytes into GC for further analysis. Cold trapping (cryofocusing) followed by thermal vaporization is another technique of dynamic mode headspace analysis and is sometimes applied to increase the quality of peak shapes [17]. By freezing out the excess of water vapour in a cold trap, contamination of the chromatographic column by water can be avoided. Dynamic headspace analysis is mainly dedicated for the determination of solvents at very low concentration levels. Because the thermodynamic equilibrium is not necessarily needed and the adsorption of analytes on the trap increased the

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method sensitivity, lower detection limits are obtained. Moreover, the sample volume is not restricted and solid samples, which are insoluble or cannot be heated, can be analyzed. However, this may result in the risk of higher measurement uncertainty. The method efficiency can be enhanced by increasing the temperature or by salting out [32].

Static HS is one of the most popular technique for residual solvents analysis in pharmaceuticals due to full automation, good precision, accuracy and it is preferred for samples soluble and uniformly distributed in water or organic solvents (dissolution medium) [12,18,28,29-31,33-50]. The matrix and sample dissolving solvents can significantly affect the sensitivity of the HS method due to variable partition coefficients of analytes in different matrices [35]. It was demonstrated, that detection sensitivity can be increased by four times when sample is dissolved in a specific solvent [30]. Water is the most appropriate for water soluble samples [6-8,36,41,43,44], but many drug substances and drug products have low water solubilities, which would limit the sample load [11,12]. Moreover, applying water as a dissolution medium can also lead to lower method precision in comparison with organic solvents, like DMF [28]. In order to improve the dissolution of the samples, mixtures of water with solvents (for example: DMA, DMF, DMSO or sodium phosphate buffer) were proposed [12,19,28,34]. Mixtures are able to solubilise the sample and prove to be the most suitable solutions to obtain good recoveries and to increase method sensitivity [11,12,18,26,30,33,49,50]. It should be noticed, that the HS equilibration temperature cannot be higher than the boiling point of sample diluent, because a large amount of sample may be vaporized, resulting in a hazardously high vial pressure and flood of the sample diluent and analytes to the gas chromatograph [9,17,18]. In the case of water and water-organic mixtures application, the equilibration temperature should be lower than 100 ºC [12,36]. However, many organic solvents may not be fully vaporized at this temperature due to higher boiling points. In order to obtain a good phase distribution and HS equilibration efficiency a longer equilibration time is needed, for example 30 – 90 minutes [28,29,30,33,35]. This significantly extends the time of analysis, which is contrary to the principles of 'Green Chemistry' [20]. Furthermore, a high equilibration temperature can be problematic in antibiotics analysis, because many of them are water insoluble and temperature sensitive [29]. Antibiotics are complex in nature and several other volatile impurity peaks in the chromatogram are expected, which leads to separation and identification difficulties [33].

Organic solvents have higher boiling points than water and provide higher method sensitivity due to better solvent recoveries [11,30,32,33,34,35,37-40,42,46,48]. On the basis of literature data it can be concluded that the following solvents are most frequently used for

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the analysis of pharmaceuticals: BA (b.p. 204 ºC); DMA (b.p. 166 ºC); DMF (b.p. 153 ºC); DMI (b.p. 105 ºC); DMSO (b.p. 189 ºC) [11]. However, BA, DMF and DMA do not exhibit stability at higher temperatures and are susceptible to degradation under the influence of ultrasonic wave energy during sample preparation. The products of these processes may interfere with the analyses of residual solvents [30]. Thus, the use of sonication to dissolve greater quantity of pharmaceutical samples in a matrix medium should be avoided [50]. In order to elude interferences by amines, the HS unit equipped with a sample loop, needle assembly and transfer line made of Silcosteel® was proposed [48]. In addition, residual solvents with very low vapour pressures, such as ethylene glycol, 2-ethoxyethanol, 2-methoxyethanol, formamide, *N*-methylpyrrolidone and sulfolane cannot be readily analysed using the HS method [28]. Other procedures are needed to control these solvents in pharmaceutical samples, especially that they should be limited according to the ICH guideline [5] and the U.S. Pharmacopoeia [6].

In the case of solid samples, the establishment of an equilibrium between the solid phase and the gas phase poses a challenge, due to matrix effects involving the difficulty in homogeneous mixing of residual solvents into the solid samples, such as polymer resins or hard gelatin capsules, which cannot be dissolved in water and common organic solvents [35]. Moreover, preparation of a sample solution requires a large amount of pharmaceutical sample to obtain a concentrated sample solution. For example, 0.5 g of sample needs to be dissolved in a matrix medium to obtain 5 mL of solution. It can be a serious problem in analysis of expensive products, products made for animal studies (such as toxicity testing for pre-clinical work) with a small lot size and their intermediate products [17,30]. Recently, immiscible binary solvents (mixture of 5 mL of decane and 1 mL of HCl) have been proposed as a dissolution medium in the static HS method for determination of residual ethanol in hydroalcoholic sealed hard gelatin capsules [35]. A mixture of ethanol and water is commonly used to seal hard shell capsules by liquid encapsulated and microspray sealing technology. What is important, residual ethanol occurs between the caps and bodies of capsule shells and cannot be measured when capsules remain intact. Therefore, an appropriate capsule dissolving and disintegrating solvent is needed. Organic solvents and water cannot completely dissolve and uniformly distribute the hard gelatin capsule shells which are a mixture of amino acids derived from collagen. For this reason, 0.1 M HCl was chosen to completely disintegrate the capsules. Moreover, additional peaks on the chromatogram were not observed after the sonication of 0.1 M HCl solution. It was noticed, that the ethanol headspace concentrations increased four times when an aliphatic hydrocarbon solvent (decane) was added into the

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sample solution, in comparison with commonly used organic solvents, such as: *N*-methyl-2-pyrrolidinone (NMP), DMA, DMF and DMSO. ~~Ethanol responses in different organic solvents: *N* methyl 2 pyrrolidinone (NMP), DMA, DMF, DMSO and decane are presented in Fig. 6.~~

~~FIGURE 6~~

Ethanol is a polar protic and hydrophilic compound, thus cannot form hydrogen bonds with decane in contrast to other solvents. Moreover, decane was not miscible with the capsule sample solution of 0.1 M HCl, which further improved method sensitivity [35].

~~Ionic liquids~~ Ils have attracted scientific attention due to a unique combination of physicochemical properties and were proposed as dissolution medium for determination of residual solvents in pharmaceuticals [20,51-56]. Especially, low vapor pressure at ambient temperatures makes them an interesting 'green' alternative for many applications, for which the volatility of traditional organic solvents (matrix medium) causes problems [29,52]. In addition, Ils have a wide liquid range, high thermal, chemical stability and extraordinary dissolubility so that the organic solvents are readily dissolved in them and the effect of matrix medium in chromatogram can be avoided, even at higher headspace equilibrium temperatures [53]. Thus, Ils appear to be an ideal matrix medium for HS analysis of pharmaceuticals and several examples from recent literature are presented in Table 3.

TABLE 3

Based on the literature data, it can be concluded, that selection of the most appropriate ionic liquid for HS analysis of pharmaceutical samples still remained at "trying-comparing-screening" step, because of the relatively low availability of physical property data [51-56]. More advanced properties, such as solvation and polarity, measured by various techniques are needed. For example, calculated decomposition temperature of 1-butyl-3-methylimidazolium hexafluorophosphate is 370 °C, but during the experiment it started to decompose at 180 °C [53]. Until more precise data on the properties of ionic liquids are available, the study of development of ionic liquids as a matrix medium for sample preparation will continue based mainly on empirical experimentation [55]. Another problem with the application of Ils is their purity related to volatile remnants from the synthesis. At higher headspace equilibrium temperatures, within the range of 160 to 200 °C, many interfering peaks on chromatograms

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were observed. This may be also associated with premature thermal decomposition of Ils. Moreover, the influence of background signals from the ionic liquid matrix on the separation efficiency was examined [56]. Six commonly used Ils in HS analysis were tested under different conditions: involving no treatment, sparging the liquid with heat, vacuum and purging the headspace vial with nitrogen. These three different methods were applied for each ionic liquid to reduce the amount of volatile species detected above them. The headspace above untreated Ils was found to contain a significant number of impurities, which were solvents (such as acetone, methanol, methylene chloride) and reagents (tetradecene, imidazole) used in the manufacture of Ils. The calculated solvent concentrations were in the range of 3 to 8700 ng mL^{-1} of vapor. The background detected above the sparged Ils was the cleanest, even simpler than that detected above most conventional solvents. The residual solvent concentrations were less than 10 ppm. Based on the results, it can be concluded that Ils routinely need to be purified prior to use to be useful as a matrix medium for HS analysis. Sparging with high purity nitrogen is effective but inconvenient. Higher purity Ils need to be available or simpler methods of purification need to be developed. Moreover, they must also effective dissolve analytes and matrix components such as derivatives of cellulose or fatty acid salts, which still pose a challenge [29,56]. In order to overcome the drawbacks of Ils, liquid paraffin has been recently proposed as a new matrix medium for the determination of high boiling point residual solvents such as: DMF, DMA, DMSO and BA [57]. Liquid paraffin in high purity is easy to obtain, relatively cheap and proved to be suitable for routine analysis of particular sample types. The obtained limits of detection were below 1 µg/vial for each compound, which indicates a drastically improved sensitivity compared to the Pharmacopoeia method, which has not ensured their determination at 1/20 of respective official limit concentrations, as is prescribed in the European Pharmacopoeia [8]. Moreover, interfering peaks from the matrix medium were not observed on chromatograms at HS temperatures below 100 °C, but the application range of liquid paraffin is rather small regarding to general residual solvents analysis due to limited analyte or sample compatibility.

Static HS analysis can be carried out in different variants. One of the modified versions, in which the equilibrium time and partition coefficients are not know, is the multiple headspace extraction (MHE) [9,18]. It relies on gas extraction repeated many times from a sample, followed by summing the peak areas from each step. The total concentration of the residual solvent in the sample, which decreases exponentially, is determined based on the external calibration curve [10,18]. This technique is mainly used for determination of solvents in solid samples, but it can be also applied to liquid samples, particularly when the partition

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coefficient of residual solvents is favorable and relative to the liquid phase. The method requires more time to carry it out than to optimize the classic HS version, which makes it unpopular. Another interesting development of static HS is based on evaporation of all volatile compounds from a very small amount of sample at a sufficiently high equilibration temperature. As a result, all volatiles are in the gas phase and there is no longer an equilibrium, thus matrix effects are eliminated and the concentration in the gas phase is linearly related to the sample size [17,28,29]. However, in practice matrix constituents are not always completely volatile and may remain in the vial interacting with analytes. Therefore, it is recommended that a recovery test should be performed. [58]. In the case when a sealed vial containing the sample (a few milligrams or microliters) is heated to 20 °C above the melting point of the matrix or the desolvation temperature, the method is named full evaporation technique (FET). When the vial is heated to 20 °C above the boiling point of the matrix, the method is named total vaporization technique (TVT) [59]. In this concept, all compounds (including analytes, sample matrix and dilution medium) are transferred to the gaseous phase of the vial. Therefore, since there is no condensed phase left in the vial, the choice of the dissolution medium no longer influences the sensitivity [9,18,58,59]. It should be noted, when the full evaporation is established further increasing the equilibration temperature will not increase the sensitivity. In addition, the evaporation technique can be performed directly from the powdered solid sample, overcoming matrix effects, or a dissolved sample in an appropriate dissolution medium. The volume of the sample introduced for a TVT is limited (between 10 µL and 20 µL) [59] by the increase of pressure in the vial at the high equilibration temperature, which is one of its benefits and further development is expected in this area. Especially, it can be quite interesting in analysis of expensive products.

In order to overcome the complex matrix interferences and improve the accuracy and precision of GC analysis, the internal standard can be added [20,22,49]. The internal standard efficiently compensates for the variables occurring during sample extraction as well as injection, especially when a complex sample preparation procedure is involved [60]. A standard addition method may be used, provided that the standard will not change significantly the thermodynamic properties of the phases [10]. In FET and TVT sampling, the addition of an internal standard is necessary to overcome the uncertainty of the dilution effect induced by small variations of the vial volume [59]. Moreover, in determination of broad spectrum of solvents in a single analytical run, several internal standards can be applied. But at the same time it involves a greater number of parameters to be optimized and controlled. The development of such a complex analytical methodology requires an appropriate

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optimization procedure. The use of chemometric tools is very helpful and they have been increasingly applied to processes optimization, especially over the past few years [21,61]. Recently, the experimental design and the multiple responses optimization techniques have been successfully used in the development of analytical methodology for the determination of 31 residual solvents in metronidazole and betamethasone samples [61]. Chemometric tools proved to be effective in achieving the fast and satisfactory optimization of chromatographic conditions.

Many factors of HS analysis have a significant influence on the quantitative determination of residual solvents and their optimization can be a critical to the development of an accurate methodology. For these reasons, new solutions for sample preparation are needed.

6.3 ~~Liquid-phase microextraction~~ Single-drop microextraction

~~Liquid-phase microextraction (LPME)~~ Single-drop microextraction (SDME) is an attempt to solve the problems of classical LE by minimizing the consumption of solvents. It requires only tiny amounts of organic solvents, of the order of a few microlitres, which eliminates the need for extract cleanup prior to qualitative and quantitative determination. ~~The method is straightforward, quick and inexpensive. It is based on the partition of analytes between the sample solution and the small quantity of organic solvent.~~ There are two types of performing of SDME sampling: direct mode and headspace analysis (HS-SDME), which is similar to traditional HS sampling where the volatile compounds are isolated from the vapours above the sample sealed in the vial, thus avoiding interferences from the matrix [20]. A HS-SDME technique coupled with the GC method was proposed in 2006 for extraction and determination of residual solvents in pharmaceutical products of hydroxycarbamide [22]. ~~While the extraction medium is in the form of a drop, this type of LPME technique is named single-drop microextraction (SDME) and thereby makes it practically a solvent-free method. Analyte isolation and preconcentration takes place in a single step. Around 1 – 3 µL of solvent is drawn into a microsyringe (5 – 10 µL) – for the extraction of residual solvents this is usually DMSO or 1-octanol. Then the needle penetrates the membrane (rubber septum in the screw cap) of the vial containing the sample. In order to form a droplet, the syringe is fixed in such a way that the needle tip with the solvent drop is situated in accordance with the requirements of headspace analysis. When the extraction is completed, the microdroplet is drawn back into the syringe needle and injected into a GC for further analysis.~~

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SDME is easy to apply and does not require sophisticated equipment. But at the same time it requires the optimization of many parameters affecting performance of extraction, including the following: extraction solvent, drop volume, shape of needle tip, extraction time, thermostating temperature, sample amount and headspace volume. This process can be a time-consuming and challenging task at times. A proper choice of the extraction medium is fundamental for obtaining an optimal extraction procedure. There are many solvents with different polarities that can be applied (for the extraction of residual solvents this is usually DMSO or 1-octanol) but the relatively high vapour pressure and a low boiling point of some solvents limited their use in SDME [18]. The amount of analyte extracted to the drop of organic solvent is strictly related to its volume. With larger drops, analyte preconcentration is better and extraction is more efficient. It should be noted that a larger drop, which is injected into the chromatographic system, may cause band broadening in capillary GC. Moreover, drops larger than 3 μL are less stable and the reproducibility of results with such drops is poorer [17,18,22]. On the other hand, too small of drop volume may affect the precision of sampling and insufficient isolation of analytes from the matrix. Moreover, magnetic stirring and addition of inorganic salt can accelerate extraction efficiency, thus reducing the time needed for reaching of thermodynamic equilibrium between the solid (or liquid) and gaseous phases. The stirring time and speed must be selected such that the solvent drop does not become detached from the needle. In order to perform microextraction directly from the solid drug samples and eliminate dissolving step, a multiple headspace single-drop microextraction (MHS-SDME) was proposed [21]. This method combines the SDME and MHE techniques, thereby eliminating possible memory effects as a fresh drop of solvent is used for each extraction. The obtained results indicate that MHS-SDME coupled with GC is very promising and useful in the determination of residual solvents in solid drug products with high precision.

6.4 Solid-phase microextraction

Solid-phase microextraction (SPME), similarly to dynamic headspace analysis, has the advantage of concentrating the analytes, thus lower limits of detection are achieved. It is a sensitive, universal and solvent-free technique. In addition, SPME is simply applied in sample preparation and can be automated routinely [62]. It is based on the adsorption of analytes on a fibre coated with a suitable stationary phase, exposed from a microsyringe [9,17,18]. The sensitivity of this technique depends primarily on the partition coefficient between the sample and the fibre stationary phase. Commonly, fused silica fibres are used [20]. The stationary

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phase is placed in contact with the sample matrix for predetermined time to establish a concentration equilibrium of volatile analytes. A longer exposure of fibres does not lead to accumulation of additional analytes. After that, adsorbed analytes are usually transferred to the injection port of GC, where their thermal desorption and subsequent determination takes place. The efficacy of preconcentration mainly depends on the type of stationary phase and its thickness [62]. Moreover, the following parameters of the process are also important and can influence the extraction efficiency: sample amount, extraction temperature and vial volume, addition of inorganic salt, the pH of the solution and sample stirring. The materials used for coating fibres include: polydimethylsiloxane (PDMS), polyacrylate (PA) and also mixtures of polydimethylsiloxane and polydivinylbenzene (PDMS-DVB) and Carbowax and polydivinylbenzene (CW-DVB) [63-66].

Depending on where the fibre is situated in relation to the sample, SPME can be divided into direct immersion (DI-SPME) and headspace (HS-SPME) types. ~~In the first version, analytes are transported directly from the liquid sample solution to the extracting phase. In the second mode, volatile analytes are extracted after their transfer to the headspace phase above the sample. Thus, the fibre coating is protected from damage by high molecular mass and non-volatile interferences present in the sample.~~ HS-SPME coupled with GC is usually used for determination of residual solvents in pharmaceutical samples. The advantage of this method is that the limited capacity of the adsorbent precludes column overloading. In addition, although it is not accepted by various pharmacopoeias, it provides a promising alternative to HS-GC due to the simplicity of execution and greater sensitivity.

Furthermore, the HS mode of SPME can be performed in additional two systems, as regards different volumes of headspace gas removed with the fibre. If only a small volume of headspace gas is removed from the sample matrix, the technique is named gas-tight SPME [23]. When a larger volume of headspace gas is removed with SPME fibre, the technique is named “headspace” SPME. Both of these techniques were applied and compared with the static HS analysis [67]. The obtained results of detection limits are presented in Table 4.

TABLE 4

Gas-tight SPME was found to be the most sensitive method, especially when very volatile substances are determined (such as alcohols, aldehydes, ketones or some hydrocarbons). However, the HS-SPME exhibited better method precision. Of all developed versions of the SPME method, HS-SPME is the only practically feasible variation that can be employed,

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because the extraction must be performed from a relatively concentrated drug solution, which eliminates the use of immersion, "in-tube" SPME or stir-bar techniques [17,20,67].

Both SPME and SDME are alternatives to traditional extraction methods. Their superiority over classical LE emerges from their rapidity, their consumption of minimal amounts of organic solvent and the possibility of determining compounds present in low concentrations. Moreover, the method is difficult to optimize and selectivity is poor in the case of residual solvents extracted from samples with a complex matrix composition (such as antibiotics). In addition, the extraction efficiency of SPME may change with the growing number of injections, which limits its application in routine analysis of pharmaceutical products.

There are many widely used novel and improved techniques that require the use of minimal amounts of solvent, if any at all. But it is hard to state definitively which of them is the most appropriate for extracting residual solvents from pharmaceutical samples, because each one has its specific advantages and disadvantages. The summary of characteristics of sample preparation techniques used in procedures for determining residual solvents in pharmaceuticals is presented in Table 5.

TABLE 5

7. Detection, identification and quantitation of analytes

The most commonly used technique for the determination of residual solvents is conventional GC, but high performance liquid chromatography (HPLC) is also practicable [18,45]. GC is a natural choice because organic solvents have relatively low boiling points and are generally thermally stable. For GC separation step, capillary (narrow-bore) and wide-bore columns are applied. The most commonly used stationary phases of capillary columns are based on the polysiloxanes and polyethylene glycols. While they have been applied coelution of solvents with similar physicochemical properties was reported [28]. Therefore, they are used alternatively to verify identity. To achieve the satisfactory separation, the GC methods tend to have long run times because of the use of long capillary columns (up to 100 m) and slow temperature gradients (up to 60 minutes). Moreover, an additional time is required to cool the column from the final temperature of the temperature programme to its initial conditions. Nevertheless, in analyses of specific samples, most of the chromatographic run time is not useful since in most pharmaceuticals only a few solvents are present.

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In most cases, chromatographic techniques are used in combination with suitable detectors. For analysis, when residual solvents present in the sample are known or suspected, an universal FID is recommended. For detection of halogenated residual solvents, ECD can be applied. In situations when solvents are unknown and an additional level of identification capability is needed, MS is preferable. The choice of detectors for GC analysis is very rich, but for residual solvents determinations, FID and MS detectors are the most appropriate, which is confirmed by literature data [11,12,19,21,22,23,25-27,28,30,33,34,35,37-39,40-48,50,51-53,57-59,60,65,66].

Information about examples of analytical procedures for determining residual solvents in different types of pharmaceutical samples are presented in Table 6.

TABLE 6

Based on the review of literature data presented in Table 6, it can be concluded that no single universal methodology is applicable to all kinds of solvent samples, which constitutes a further challenge to analysts. Most of them meet the requirements of legal regulations but at the same time they do not meet the expectations of the pharmaceutical industry, because of the high cost of analyses, need for specialized equipment, problems with optimization, complexity of multi-step procedures and thus increased time consumption. Still the most frequently used method for the determination of residual solvents is static HS coupled with GC. Currently, in order to decrease the analysis time significantly, while maintaining complete separation, instrument modification is necessary.

8. Recent developments in the field of determination of solvent residues

In order to improve the efficiency of analyses, method sensitivity and reduce the GC separation time, several alternatives were proposed in the recent literature, including:

- the use of shorter capillary columns with narrower bores (stationary phase layer about 0.1 – 1 μm) and fast temperature programming, known as a fast gas chromatography (fast GC) [44,47,48];
- the use of two capillary columns with different stationary phases and separation mechanisms, proposed as: parallel dual-column system connected with ‘Y’ splitter [43], flow-modulation gas chromatography [68] and two-dimensional gas chromatography (GCxGC) [69];

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- the use of hydrogen as an alternative carrier gas to helium, thus higher linear velocities can be achieved [18];
- the use of specially developed technologies of heating of capillary columns allowing very high temperature programme rates (up to 1800 °C/min), for example: low thermal mass (LTM) oven [46] and the EZ Flash GC technology (uses resistive heating) [48];
- the use of higher sample injection split ratio (within the range of 1:5-20, in some cases up to 1:100) [11,48];
- the use of the programmed temperature vaporizer inlet (PTV) to inject the samples into the GC column [36,60];
- the use of the methodology without sample pretreatment step, for example: the thermal desorption (TD) technique coupled with GC-MS [70], where residual solvents desorbed from sample by heating were cryofocused at the head of the column prior to GC analysis;
- the use of the nonseparative method for quantitative analysis, for example: the HS-MS method, based on direct coupling of headspace sampler with a mass spectrometer without chromatographic separation [44].

One of alternatives of instrument modifications to improve sensitivity, keeping the simple headspace instrumentation, is the use of the PTV inlet to inject the samples into the GC column. This injector is equipped with a heating and cooling system. By using liners packed with selective adsorption material (mostly Tenax), the analytes can be trapped in the liner. Thus, no sample pretreatment is required and analysis can be performed directly from a solid pharmaceutical sample. In addition, the analytical procedure is simpler and can be automated. Moreover, the creation of artifacts or errors associated with the sample preparation step is minimized. A traditional HS autosampler in combination with fast GC equipped with a PTV and MS detector was applied for the determination of Class 1 residual solvents in drug samples [36]. Different injection techniques were compared: classical split-hot injection, classical splitless-hot injection and solvent vent injection. All experiments were carried out in the PTV inlet. ~~The obtained window of the chromatograms (scan mode) of the most abundant extracted ion for three residual solvents: 1,1-dichloroethene (a), 1,1,1-trichloroethane (b) and benzene (c) with the three injection modes is presented in Fig. 7.~~

~~FIGURE 7~~

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In all three cases, the solvent vent injection technique gave better results. Important benefits of using this type of injection instead of classical-hot injection, such as better peak shapes and better signal-to-noise ratios, were found. Thus limits of detection at the low ppt level were obtained. It should be also noted, that the method showed good precision and accuracy.

Another alternative of instrument modifications, in order to reduce analysis time up to only 3 minutes, is a nonseparative method based on direct coupling of the HS sampler with the mass spectrometer (HS-MS) [44]. First, identification of 20 residual solvents presented in the samples was performed using HS-fast GC/MS. Then, information obtained from low-resolution chromatograms visualized by using contour plots with time and mass/charge ratio axes, and established specific zones for each studied solvent. Quantitative analysis of 27 different pharmaceutical products was performed without chromatographic separation. The proposed methodology proved to be sensitive and sufficient to determine residual solvents according to the ICH requirements. Moreover, no treatment of the sample was required.

An interesting development for fast determination of volatile impurities is the use of an electronic nose technology. E-noses are based on an array of nonselective or selective (based on functional group chemistry) sensors coupled to a pneumatic sampling system [17,71]. The whole set of signals given by the sensor array provides a fingerprint of the analyzed vapor. To compare different fingerprints, a multivariate data analysis is used. Even if the sensitivity of these devices is much weaker than the GC methodologies, their development is important for impurities monitoring in process analytical technologies (PAT) [2,4,17]. For determination of residual volatile impurities after the cleaning of manufacturing equipment the ion mobility spectrometry (IMS) is used [72]. The separation is based on the gas phase ion mobility at atmospheric pressure, which is related to the geometry (structure and size) of the ions. Thus, IMS can be highly specific and selective.

9. Conclusions

Organic solvents routinely used in the manufacture of pharmaceuticals pose a problem and must be removed. Nowadays, pharmaceutical companies try to exchange toxic solvents by more friendly ones with similar properties or look for some new innovations. Substances such as water, supercritical fluids and Ils are taken into consideration as a new alternatives. However, implementation of new technologies into practice is still in development stage due

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to the lack of complete understanding of the basic principles and properties, and the high costs of specialized equipment.

Static HS coupled with GC is the most frequently used methodology for the determination of residual solvents due to the full automation, good precision, accuracy and is preferred for samples soluble and uniformly distributed in dissolution medium. Several interesting new alternatives have been developed in the last few years to support HS analysis. All of them improve the method sensitivity through increasing the instrument response factor, decreasing solution-vapor partition coefficient or increasing the activity coefficient. This can be achieved by the instrument modifications, modified versions of HS and the use of new dissolution medium, such as: mixtures of water and organic solvents or mixtures of different organic solvents, binary solvents and Ils. Instrumental methods include use of the PTV inlet or direct coupling of HS with MS. Research is continuing into the improvement of existing methods and the development of new ones, which would allow determination in a quick, simple, cheap, effective and environmentally friendly manner. This can be also achieved by automation of microextraction techniques and coupling with GC. Currently, automated sampling systems of SPME and SDME are available from major instrument manufacturers. They offer high sensitivity and reproducibility, without many of problems or expense of HS sampling system.

One of the most important trends in the development of methods and low-cost tools for QC/QA of pharmaceuticals, according to the Process Analytical Technology (PAT) concept, is the introduction of different types of sensors and techniques, such as: IMS techniques, electronic nose technology and NIR-based chemical/physical sensors. They provide *on-line* monitoring of volatile impurities during the manufacturing process, thus analysis time is significantly reduced. Moreover, they are automated, efficient, cost-effective and do not require large sample volumes for analysis. Further studies and developments are expected in this area.

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List of figure captions and table headers

1) Fig. 1 'Milestones' in the field of development of analytical methodologies for evaluation the level of residual solvents and identification as well as quantitation of specific analytes

2) Table 1 Examples of classes of solvents commonly used in the pharmaceutical industry [1,5,13]

3) Fig. 2 Procedures for identification and control of residual solvents [8]

4) Fig. 3 Sample preparation techniques commonly used for determination of residual solvents

5) Table 2 Comparison of HS sampling for analysis of pharmaceutical samples

6) Table 3 Ionic liquids (ILs) proposed as matrix medium for headspace analysis of residual solvents in pharmaceuticals

7) Table 4 Comparison of limits of detection [ng mL^{-1}] for residual solvents obtained by using various HS techniques [67]

8) Table5 Characteristics of sample preparation techniques used in procedures for determining residual solvents in pharmaceuticals

9) Table 6 Methodologies for the determination of residual solvents in pharmaceuticals

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