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Review article

Residual solvents in pharmaceutical products: acceptable limits, influences on physicochemical properties, analytical methods and documented values

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Abstract

Residual solvents in pharmaceutical products, known as a potential toxic risk but actually only limited officially by the USP XXIII, have attracted considerable interest during the last years, with demands for international harmonisation of limits. In this sense, the limits proposed by the International Committee for Harmonisation (ICH) will most probably be adopted by the pharmacopoeias of USA, Japan and Europe. Beside the glass transition temperature, several other physicochemical parameters as the dissolution properties, the permeability and the crystallinity of substances have been reported to be affected by residual solvents. For the quantitative and the qualitative analysis of residual solvents, the official methods (USP 23 ⟨467⟩ Organic Volatile Impurities and Eur. Ph. V.3.3.9 chapters) and other gas chromatography methods, especially static and dynamic headspace chromatography, are the most appropriate methods of all those reviewed. The importance of a drying step during the preparation process of pharmaceutical products is underlined by the literature-documented residual solvent values, presented in this article. © 1997 Elsevier Science B.V.

Keywords: Residual solvents; Residual solvent limits; Analytical methods; Gas chromatography; Pharmaceutical products

1. Introduction

Residual solvent (RS) analysis in pharmaceutical products is necessary not only because residual organic solvents represent a potential risk for human health due to their toxicity and their undesirable side effects, but also because they may affect the physicochemical properties of pharmaceutical products and excipients, which in turn could govern the manufacture processes or the preparation conditions. Compared to these two main reasons, which will be treated in more detail below, possible odour or colour changes, caused by RS, can be considered as a minor problem, but which should not be neglected, because of patient compliance.

Few review articles deal with aspects of residual solvent limits and/or determination [1–5], but to our knowledge, none of them encompasses all the aspects of the present review article, which compiles also recently published articles.

1.1. Toxicity and tolerated limits of residual solvents

Based on the toxicity of the individual solvents, RS limits for pharmaceutical products and excipients (summarised in Tables 1–3) have been set by different associations. The toxicity and some physical data on a large number of organic solvents can be found in the

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Table 1
Residual solvent limits set by different associations

IUPAC name	MAK-value (mg/m^3)	S.I.S.F. limit (mg/day) [19]	Limit of Aschifarma [129][a]	Proposed class for the former DDR [18][b]
Acetic acid	25			
Acetone	1200	80		1
Acetonitrile	70		50 ppm/50 μg	
Benzene	carcinogenic	≤20 ppm	100 ppm/100 μg	3
Benzyl chloride		7		
1-Butanol	300	5	1000 ppm/1000 μg	3
2-Butanol	300	5	1000 ppm/1000 μg	2
2-Butanone	590	19		2
Butyl acetate	950			2
Carbon tetrachloride	65			
Chloroform	50	0.2	50 ppm/50 μg	3
Cumene	245			
Cyclohexane	1050	35		1
1,2-Dichloroethane	–			3
1,1-Dichloroethylene	8			
1,2-Dichloroethylene	790			
Dichloromethane	360	12	1000 ppm/1000μg	2
Diethyl ether	1200			
Diisopropyl ether	2100			1
N,*N*-Dimethylacetamide	35			
N,*N*-Dimethylanilin	25	≤20 ppm		
N,*N*-Dimethylformamide	30	1	500 ppm/500μg	
p-Dioxane	180		100 ppm/100 μg	
Ethanol	1900			1
2-Ethoxyethanol	19			
Ethyl acetate	1400	47		1
Formamide	12	1		
Formic acid	9			
Hexane	180			
2-Hexanone	21			3
Isobutyl acetate	950			
Isooctane	2350			
Isopropyl acetate	840			
Methanol	260	9	1000 ppm/1000 μg	3
2-Methoxyethanol	15			
Methyl acetate	610			
3-Methyl-1-butanol	360			
3-Methyl-2-butanone	700			2
4-Methyl-2-pentanone	400	14		3
1-Methyl-1-propanol	300			3
1-Methyl-2-pyrrolidinone	80			
Pentane	2950			
1-Propanol	–			2
2-Propanol	980	33		1
Propyl acetate	840			
Pyridine	15	0.5		3
Tetrahydrofuran	590			2
Toluene	190	12	1000 ppm/1000 μg	2
1,1,1-Trichloroethane	1080			3
Trichloroethylene	270	18		3
Xylene	440			

[a] The first value indicates the allowed residual solvent concentration in pharmaceuticals applied in dosages up to 1 g/day, and the second value indicates the allowed daily intake of residual solvents for all pharmaceuticals applied in dosages higher than 1 g/day.
[b] Class 1 corresponds to the solvents of lowest toxicity and class 3 to those of highest toxicity.
MAK, Maximale Arbeits Konzentration (mean tolerated solvent concentration in the air during an 8 h/day 5 day work-week exposure).
S.I.S.F., Società Italiana die Scienze Farmaceutiche.
DDR, Deutsche Demokratische Republik (German Democratic Republic).

Table 2
Residual solvent limits of USP 23, proposed limits for the Eur. Ph. and limits presented in the ICH guidelines

IUPAC name	USP 23 limit (ppm)	Eur. Ph. proposed limit (ppm) [15]	ICH class[a]/limit/PDE (mg/day) [16]
Acetonitrile		50	2/410 ppm/4.1
Benzene	100	100	1/2 ppm
1-Butanol		500	
Carbon tetrachloride			1/4 ppm
Chlorobenzene			2/360 ppm/3.6
Chloroform	50	50	2/60 ppm/0.6
Cyclohexane			2/3880 ppm/38.8
1,2-Dichloroethane			1/5 ppm
1,1-Dichloroethene			1/8 ppm
1,2-Dichloroethene			2/1870 ppm/18.7
Dichloromethane	500	500	2/600 ppm/6.0
1,2-Dimethoxyethane			2/100 ppm/1.0
N,N-Dimethylacetamide			2/1090 ppm/10.9
N,N-Dimethylformamide		1000	2/880 ppm/8.8
1,4-Dioxane	100	100	2/380 ppm/3.8
2-Ethoxyethanol			2/160 ppm/1.6
Ethyleneglycol			2/310 ppm/3.1
Formamide		1000	2/220 ppm/2.2
Hexane			2/290 ppm/2.9
Methanol		1000	2/3000 ppm/30.0
2-Methoxyethanol		1000	2/50 ppm/0.5
Methyl butyl ketone			2/50 ppm/0.5
Methylcyclohexane			2/1180 ppm/11.8
N-Methylpyrrolidone			2/4840 ppm/48.4
Nitromethane			2/50 ppm/0.5
Pyridine			2/200 ppm/2
Sulfolane			2/160 ppm/1.6
Tetraline			2/100 ppm/1.0
Toluene		1000	2/890 ppm/8.9
1,1,1-Trichloroethane			1/1500 ppm (environmental hazard)
1,1,2-Trichloroethene			2/80 ppm/0.8
Xylene[b]			2/2170 ppm/21.7

[a] The most toxic solvents of class 1 should be avoided.
[b] Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

extensive work of Snyder [6,7] and in [8] presenting the determination of the MAK (Maximale Arbeits Konzentration)-values (mean tolerated solvent concentration in the air during an 8 h/day 5 day work-week exposure). The justification of the limits and toxicity data of the USP OVI (Organic Volatile Impurities), found to have irreversible toxic effects such as carcinogenicity, teratogenicity, mutagenicity and/or severe neurotoxicity [9], were discussed in several articles of the Pharmaceutical Forum Journal [10–14].

Up to now, the USP 23 is the only pharmacopoeia setting limits (chapter ⟨467⟩ Organic Volatile Impurities) for residual solvents in pharmaceutical products (see Table 2). By comparison, the Eur. Pharm. general monograph V.3.3.9 contains just the methods to analyse residual solvents. Limits were proposed in 1990 in Pharmeuropa [15] (Table 2) and recently again in the second draft of the ICH guideline for residual solvents [16], which may soon become official and already serves as guidelines in the European pharmaceutical industry. In the ICH guidelines for residual solvent analysis, the solvents are classified in four groups (see Tables 2 and 3), of which the first one contains the most toxic compounds (5 solvents), known or strongly suspected of being human carcinogens and environmental hazards. These should be avoided, unless strongly justified. For the toxic solvents of class 2 (26 solvents), two options are available for setting the limits. The first one describes a concentration (ppm), calculated from permitted daily exposures (PDE) on the assumption of a daily dose of 10 g administered to the patient. In the second option, a maximum daily intake (mg/day) is defined. Solvents with low toxic potential, which should preferably be used, are included in class 3 (28 solvents, Table 3). Their limits are set at 0.5% without further justification. When solvents of the fourth class are used (10 solvents), the manufacturers should supply justification for residual levels of these solvents, as no adequate toxicological data on which to base PDE were found. The advantages of the ICH

residual solvent limit settings, when compared to the USP 23 ones, are the much more rigorous specifications and limits for the highly toxic class 1 solvents, the more detailed solvent list and especially the limitation of the PDE of class 2 solvents. In USP 23, the residual solvents are only limited by the concentration (ppm), independently of the daily intake of the pharmaceutical preparations.

Amongst the earlier publications on residual solvent limits [17–19] (see Table 1), those of the S.I.S.F. (Società Italiana die Scienze Farmaceutiche) were the first to take into consideration the maximum daily intake of a pharmaceutical product and the duration of a medical treatment. The former DDR (German Democratic Republic) used a classification system comparable to the one of ICH but assigning class 3 to the most toxic solvents. Reviews on monographs and selected examples from several Pharmacopoeias, requiring the analysis of RS are available [2,18]. Stumpf et al. [4] proposed for ethanol, ethyl acetate, heptane, acetone, 2-butanol, methyl ethyl ketone, 2-propanol and methanol in phytochemicals limits as low as 20 ppm and a limit of ≤ 1 ppm for carcinogenic solvents, if they have to be used.

In certain cases, the RS limits set above even don't satisfy the consumers demand because of their strong smell, especially for compounds of the aldehyde, ketone and aromatic types [20,21].

Table 3
Class 3 solvents, proposed in the ICH guidelines to be used in the pharmaceutical industry because of their low toxic potential and the additional solvents of class 4 [16].

Class 3 solvents	Class 4 solvents
Acetic acid	1,1-Diethoxypropane
Acetone	1,1-Dimethoxymethane
Anisole	2,2-Dimethoxypropane
1-Butanol	Isooctane
2-Butanol	Isopropyl ether
Butyl acetate	Methyl isopropyl ketone
tert-Butylmethyl ether	Methyl tetrahydrofuran
Cumene	Petroleum ether
Dimethyl sulfoxide	Trichloroacetic acid
Ethanol	Trifluoroacetic acid
Ethyl acetate	
Ethyl ether	
Ethyl formate	
Formic acid	
Heptane	
Isobutyl acetate	
Isopropyl acetate	
Methyl acetate	
3-Methyl-1-butanol	
Methyl ethyl ketone	
Methyl isobutyl ketone	
2-Methyl-1-propanol	
Pentane	
1-Pentanol	
1-Propanol	
2-Propanol	
Propyl acetate	
Tetrahydrofuran	

1.2. Influence of RS on physicochemical properties

The results of Hansen [22] and Ellis [23] indicate that solvent evaporation from polymer films is a two-stage process: the first one depends on the solvent's volatility and vapour pressure, limited by the boundary layer phenomenon, and the second one depends on internal diffusion resistance, and therefore is much slower. As to the diffusion coefficient of the solvent, it depends on the molecular branching: linear molecules have a lower volatility but a faster diffusion rate. Molecule side groups hinder the diffusion, as confirmed by Prager and Long [24], who determined the diffusion coefficients of a series of hydrocarbons in poly(isobutylene). Straight hydrocarbons showed the highest diffusion coefficients, followed by the singly branched ones and the lowest were found for double branching. Within each group the diffusion coefficient decreased with increasing molecular size, but molecular branching had much more effect on diffusivity than molecular size. When resins are added in a percentage lowering the glass transition point under a set temperature, solvent evaporation will depend upon diffusion only and therefore be slower during the first stage. The addition of a plasticizer or solvent to a high molecular weight polymer has the same effect as an increase in temperature; in other words a decrease of T_g [25], which leads to an increase of free volume, once above the glass transition temperature. An increase in free volume again is accompanied by an increase in the polymer chain segment motion and a greater flexibility, leading to a greater segmental jump frequency (which is exponentially dependent on the free volume), as well as increased diffusion coefficients for smaller molecules. Film drying by solvent evaporation finally is controlled by internal diffusion [22]. Furthermore, equations for calculating the solvent evaporation rate from polymer films are reviewed by Yoshida [26] taking into consideration the decreasing film thickness and the change of surface concentration during solvent evaporation. Additionally, Newman and Nunn [5] came to the following conclusions for the parameters affecting solvent retention in organic coatings:

- an additional vacuum treatment may have no influence of the drying process, but raising temperature leads to an increased drying rate;
- with an increasing film thickness the solvent retention increases;
- for a homologous series of solvents, retention increases with increasing boiling point, otherwise there is no relation between retention and volatility of a solvent;
- in multicomponent solvent systems, the less volatile solvent is the most retained;

- plasticizers reduce solvent retention, as they reduce the glass transition temperature of the polymer [27], but in certain cases they may have the opposite effect [28];
- raising the drying temperature above T_g leads to a much more rapid solvent loss.

Newman and Nunn [5] also give a list of approximate order of increasing retention for individual RS. The importance of molecular interactions (van der Waals'/hydrogen bonds) between different solvents and between solvents and polymers was pointed out by Murdock and Wirkus [29]. The hardness and solvent retention of polymer films from preheated casting multicomponent solutions were compared to those prepared from non heated solutions. Faulkner et al. [30] and Apicella et al. [31] demonstrated that *o*-chlorotoluene and mesitylene can be eliminated from cast films by contacting with *n*-hexane vapour as well as by conventional thermal annealing. Possibly *n*-hexane plasticized the glassy polymer during sorption, which permitted a back diffusion of the otherwise entrapped solvents. Occluded solvates in rather big crystalline materials (500–600 μm) are mostly as easily removed by heat or vacuum or even simply by exposure to air, as the solvents adsorbed to the surface.

Physicochemical parameters influenced by RS are particle size, dissolution properties [32] and wettability [33]. Ouano [34] has found an increased dissolution rate for poly(methyl methacrylate) (not of pharmaceutical grade), when prebaked at high temperature (160°C), done to faster and higher residual solvent loss, which caused an increased free volume. List and Laun [35] noticed that residual isopropyl alcohol enhanced the water permeability in the Eudragit® L films used as tablet coating for protecting water-sensitive drugs. Therefore the coated tablets have to be stored immediately in a water vapour free atmosphere until the films are dried and the water vapour diffusion rate is reduced to a minimum. The *R*-epimer of bacampicillin precipitate was found to bind residual butyl and ethyl acetates unspecifically by solvation, whereas the *S*-epimer bound them in long tunnels inside the crystals. Additionally the mixture of *R*- and *S*-epimers showed higher solvent retention than the *R*-epimer alone, which could be dried completely [36]. Other possible consequences of RS were examined by Osawa and Aiba [37], by analysing the influence of nature of RS on poly(vinyl chloride) (PVC) during photo-irradiation. Whereas THF, having a plasticizing effect, led to an increased molecular mass, due to crosslinking reactions and the hindering of the formation of conjugated double bonds, residual methylene chloride did not influence the polymer structure during photo-irradiation. Residual methylene chloride present at the beginning of the curing reaction, was shown to influence the T_g of cured resin, due to a retardation in cure kinetics leading to modifications of network structure [38]. Internal stress and T_g in epoxide resin coatings was found to correlate with the RS content, as well as the shrinkage below the T_g. Therefore, higher RS amounts reduce the internal stress of the coatings [39]. For polycarbonate, residual methylene chloride impeded the beta molecular motion similar to the effects of plasticizer, and if present in small amounts only, no crystallisation was induced during storage but when present in a critical amount, crystallisation occurred [40]. The latter effect was also documented for poly(2,6-dimethyl-1,4-phenylene oxide)-polystyrene blends (cast from trichloroethylene), where thermal treatment reduced the RS content and led to crystallinity loss [31].

2. Methods used for residual solvent analysis

2.1. Miscellaneous methods

Up to day various methods have been used to determine RS in pharmaceutical products and excipients, most of which are rather unspecific or have high detection limits and therefore have been almost completely replaced by gas chromatography methods, which will be treated in more detail below. One of the simplest methods for determining the content of volatile residues consists in measuring the weight loss of a sample during heating (gravimetry). However, this method suffers the great disadvantages of being totally non-specific (multicomponent solvent blends cannot be analysed and there will always be a doubt on humidity contamination) and of needing several grams of product to achieve a detection limit of about 0.1% [5,41–43]. Nevertheless, when carried out by thermogravimetry, the limit can be lowered to 100 ppm using only a few milligrams of substance [41].

For preliminary experiments or solvent evaporation studies, the solvent can be mixed with a labelled solvent (normally ^{14}C), allowing the measurement of the radioactivity of the end-product, for determining the RS content. But as polymers absorb beta-rays, the samples have to be redissolved in a scintillation solvent. Therefore, this method is restricted to soluble samples and limited to the determination of maximum two solvents [5,27,29]. For a 100 mg sample quantities down to 0.02% (*m*/*m*) of labelled solvents can be detected [29], when having 200 counts/min/mg of solvent.

In the case of chlorinated solvents, the residual content can be obtained from the chlorine content determinations [42,44] or by the method described by Eisdorfer [45], who analysed residual trichloroethylene in vegetable oils, by separating the solvent by co-distillation with xylene, heating with pyridine and a sodium hydroxide solution, and quantifying the colour produced spectrophotometrically. Quantities down to 0.001% could be measured this way.

Pardun and Vogel [46] analysed residual petroleum concentrations down to 0.01% in extracted oils by stripping the oil with air, which was then passed through a tube filled with a support coated with sulphuric acid and selenium dioxide, which changed colour into yellow/brown in the presence of petroleum. The length of the coloured layer was proportional to the RS content.

Infrared spectroscopy (IR) [37] and Fourier Transform Infrared Spectrometry (FT-IR) [47] were used to determine residual THF, dichloroethane and methylene chloride in polymer samples by measuring the characteristic solvent bands in the spectra. The most common limiting factors in these methods are possible interferences of solvent and matrix peaks and, in the case of IR, the high detection limit (above 100 ppm) and a lack of accuracy at low concentrations [48]. When analysing residual silicone oil in poly(lactic acid) and poly(lactic acid-*co*-glycolic acid) microspheres by IR, Thomasin et al. [49] found a detection limit of 5000 ppm, whereas the detection limit for the same solvent was beneath 100 ppm, when using ^{1}H-NMR (^{1}H nuclear magnetic resonance).

Avdovich et al. [50] determined benzene, toluene, acetone, methyl ethyl ketone and ethyl ether (in a few samples also methylene chloride and ethyl acetate) in cocaine samples by NMR, which allowed a quantification down to 100 ppm, with possibly detection or identification problems in the case of ethyl ether and methyl ethyl ketone at these low levels. However, these detection limits are too high to satisfy the requirements relating to RS determination, especially for the most toxic solvents.

Whenever identification of the vapour composition is unnecessary, because the single RS used is known (as in the case of coated films) the method described by Martin [51], applicable to all solvents responsive to flame ionisation detection systems, can be used. The sample is heated, the vapour phase cycled for a certain time and then transferred to a flame ionisation detector to be quantified. Again the rather high quantitative detection limit of 0.1% (V/m) is the limiting factor of the method.

2.2. Gas chromatography (GC)

The most appropriate method for analysing RS and organic volatile impurities is gas chromatography. Firstly, because of its excellent separation ability, according to the chromatographic conditions and the column and, secondly, because of its low detection limits and the possibility of analysing liquid or solid samples of a complex nature. Whenever direct GC-analysis of a sample is feasible, this should be the method of choice in view of its simplicity and reliability. But often the samples contain non volatile or corrosive substances, which would remain on the column or reduce its lifetime. In these cases, the samples require a separation of the volatile substances before GC analysis, which can be performed by using headspace chromatography (HSC). Generally, two types of headspace techniques are available: static and dynamic procedures, reviewed and compared by several authors [41,52–60].

2.2.1. Static headspace chromatography

In the static headspace procedure, the liquid or solid sample is placed in a vial, closed with a septum and thermostated until a thermodynamic equilibrium between the sample and the gas phase is reached. The time needed to reach this equilibrium depends strongly on the diffusion coefficient, which is at least by 3 orders of magnitude lower in solid samples than in liquids [61]. A known aliquot of the gas phase is then transferred to a gas chromatograph and analysed. This method is preferred when the liquid or solid samples are soluble in solvents such as water, benzyl alcohol, dimethylformamide, dimethylacetamide or dimethylsulfoxide [58,62]. The thermodynamic equilibrium should be reached within a reasonable time and the temperature should be non destructive. If no appropriate solvent can be found for a solid sample, the RS have to evaporate easily or the matrix must be heatable above the T_g. To calculate the RS content the single step HSC method requires the knowledge of the partition coefficient K ($K = C_L/C_G$), representing the concentration ratio of a volatile in the liquid (L) and gas (G) phase at a defined temperature and pressure at equilibrium stage [52,57]. Usually, to avoid the determination of the partition coefficient, model reference systems are examined under exactly the same conditions. The applicability of this procedure is limited to systems with very simple condensed matrices, allowing the simulation of the composition of the matrix. Another possibility is to use the standard addition method, assuming that the standard does not alter significantly the thermodynamic properties of the phases [52,53]. For systems with an unknown partition coefficient, the repeated gas extraction method, firstly proposed by McAuliffe [63], can be used. Kolb called it multiple headspace extraction (MHE) [64,65] and proposed the method for the RS analysis of insoluble samples (certain polymers or printed foils) requiring external calibration. In this method (see Fig. 1a and b), the same sample is extracted several times (at least twice) with a gas to obtain exponentially decreasing peak areas, which allow the calculation of the total RS amount of a sample (provided that the thermodynamic equilibration is always reached). Ioffe and Vitenberg [66] and Vitenberg and Kostkina [67] dealt with the theory and limitations of the repeated gas extraction method, stressing the importance of the partition coefficient and the volume

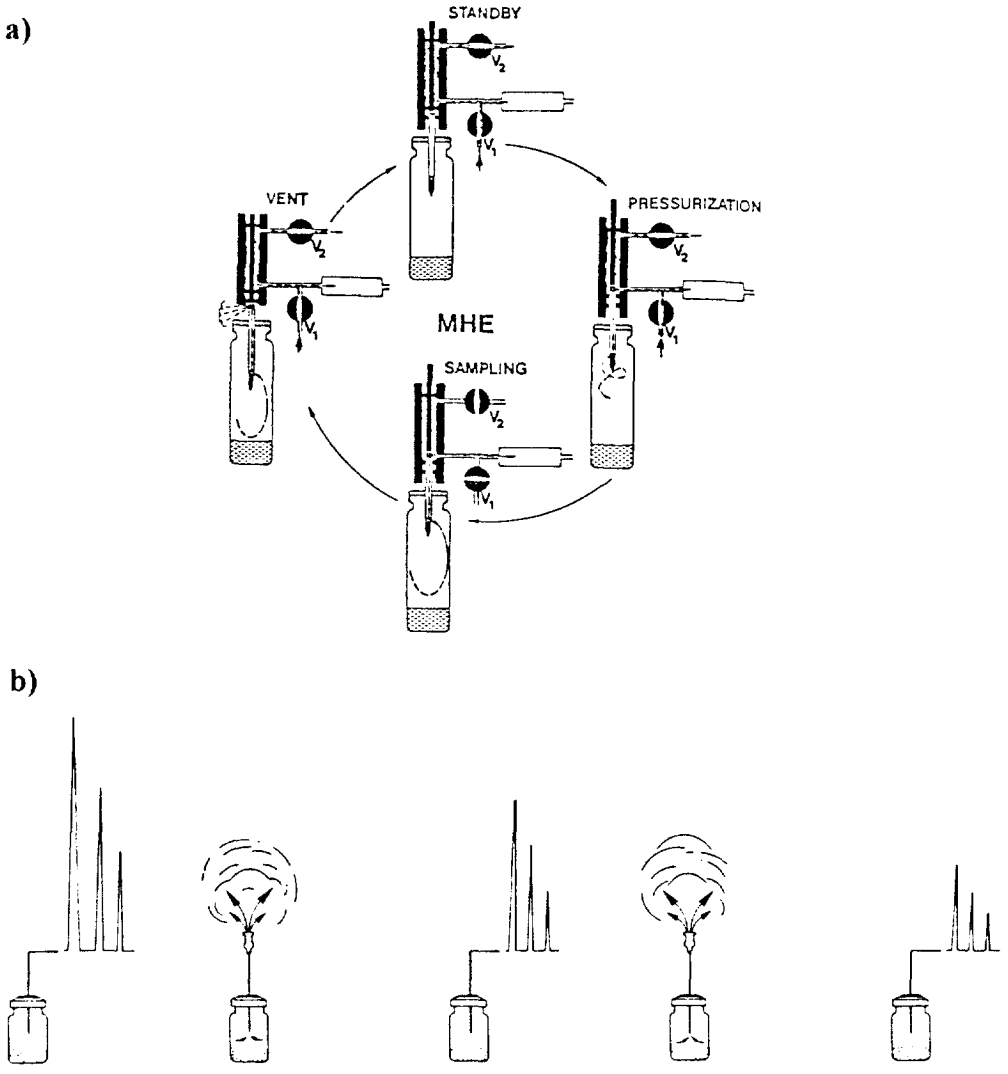

Fig. 1. Multiple static headspace extraction (MHE) of a sample. (a) Working schema of the Perkin-Elmer automatic headspace sampler HS-100 [170]. (b) Visualisation of peak area decreases during MHE application [171].

ratio r ($r = V_g/V_l$, i.e. the ratio of the gas (g) and liquid (l) volumes) of a substance. Based on their conclusions, the ordinary static HSC with direct injection of the gas phase on the column, can be considered as suitable for substances with low partition coefficients (about $K <$ 10–100), leading to high gas concentrations, even when the RS are present in only low concentrations. For substances with a high partition coefficient (also to avoid considerable errors), much more gas is needed to extract the solvent from the sample, requiring some device for its concentration or trapping. Several methods are available for reducing the partition coefficient of volatiles, in particular in aqueous systems, and thus to improve the HSC sensitivity, such as salting-out, pH adjustment or increasing the equilibration temperature of the sample [52,53,55,56,58,60,67,68].

2.2.2. Dynamic headspace chromatography

In dynamic HSC, a continuous flow of gas is swept over the surface of a sample or through the sample to provide maximum surface contact between the gas and liquid phases, conveying the volatiles to a trap where they are accumulated prior to analysis. When compared to the static HSC, several advantages characterize this method:

- it is particularly suited for the determination of very low concentrations of volatiles, as the 'total' amount of a substance is extracted, trapped and analysed at one time, resulting in lower detection limits;

- substances with high partition coefficients ($K > 1000$) can be analysed;
- no equilibrium between the gas and liquid phase is required;
- the sample volume is not restricted and solid samples, which are insoluble or cannot be heated above a transition temperature, can be analysed [54,56–58].

At this point, one has to mention that pre-concentration of the volatile impurities can also be used in static HSC and multiple extraction in dynamic HSC [52,56].

In dynamic HSC, principally three variants of sample stripping and enrichment can be distinguished:

- conservation trapping either in a closed circuit or in an open arrangement;
- equilibration trapping in a closed circuit, originally described by Grob and co-workers [69,70] (the same gas is passed several times in a closed circuit through the sample and the trap before injection) which is specially suited for very low RS concentrations, as only very low carrier gas impurities will be accumulated;
- (pseudo)equilibration trapping.

Drozd [71] presented the principles and theory of quantification of the three methods, and Vitenberg and Ioffe [59] dealt with the basic equations of dynamic HSC under non-equilibrium conditions in an open system (first variant, mentioned above). Additionally, Vitenberg [55] reviewed the methods using equilibration trapping (last variant listed above) in non volatile solvents deposited on a solid support or directly on the tube walls, followed by the thermal desorption of the volatile compounds. In another variant the impurities are absorbed in a layer of a volatile liquid, which can be directly injected into the gas chromatograph. The partition coefficients of the liquids trapping the impurities have to be decreased, when compared to those in the sample matrix.

The simplest way to accumulate volatile impurities consists in freezing them out of the headspace gas by drawing the gas through a loop with a cryogenic trap. Once the impurities are collected, the cooling bath is replaced by a heater and the vaporised concentrate is swept by the carrier gas into the gas chromatograph (see Fig. 2). Unfortunately, when analysing samples with other volatile condensable components, the analysis will be complicated by their excessive accumulation [53]. Other trapping systems include a column filled with a sorbent [52,53,56]. Chromosorb®, Porapak®, Amberlite® XAD resins and Tenax® GC are the most commonly used sorbents and especially the last one because of its thermal stability, in spite of its limited specific surface area. The trap may either be cooled or kept at room temperature. Grob [72] pointed out the advantages of small (dimensions of a piece of capillary column) wall-coated traps for capillary chromatography, permitting instantaneous thermal desorption. Water contamination of the column can be avoided by freezing out the excess of water vapour at a temperature of -15 to -20°C in a first cold trap [73]. To desorb the volatile impurities from the trap, liquid or thermal desorption is used. In the case of liquid desorption, the volatiles are extracted from the sorbent (often thermal unstable sorbents such as Amberlite® XAD resins) with small volumes of an organic solvent, such as methanol, isopropanol, acetone and low-molecular-weight ketones. This method carries the risk of artefact introduction and of masking the peaks of the volatiles by the solvent. In the case of heat resistant volatiles and sorbent material like Tenax® GC, thermal desorption is performed by heating the column rapidly from room temperature to 200–300°C. Some further considerations on trapping methods are reviewed by Vitenberg [55].

Of course, the sensitivity of HSC method not only depends on the partition coefficient of the volatile, the sampling technique and the choice of the trap sorbent material, which influence the extent of extraction, but also on the sample amount, and especially on the detector used [74,75], with the flame ionisation detector

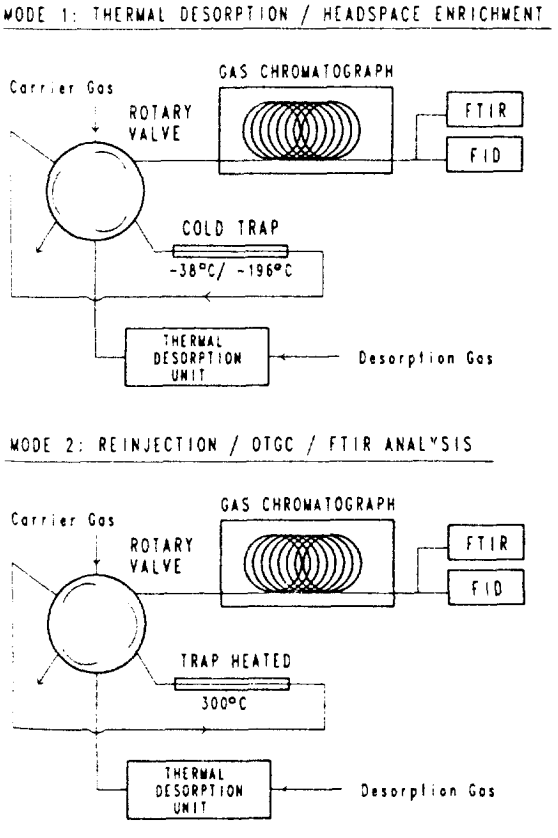

Fig. 2. Schematic description of a dynamic headspace/cold trap reinjection system [166]. Legend: FTIR, Fourier transform infrared spectroscopy; FID, flame ionisation detector; OTGC, open tubular gas chromatography.

Table 4
Summary of detector characteristics [74]

Detector type	Characteristics	Approximative detection limit	Linear range
Flame Ionisation (FID)	Universal (organic compound)	2×10^{-12} g/s	$>10^7$
Thermoionic Emission (TID)	Selective (organic nitrogen and phosphorus)	10^{-13} g/s N 5×10^{-14} g/s P	10^5
Flame Photometric (PID)	Selective (sulphur and phosphorus)	$<10^{-11}$ g/s S $<10^{-12}$ g/s P	$\geq10^3$ $\geq10^4$
^{63}Ni Electron capture (^{63}Ni ECD)	Selective (halogens and other electron capturing groups)	Highly variable, as low as 5×10^{-15} g	10^4
Photoionisation (PID)	Universal	2×10^{-13} g/s	$>10^7$
Thermal Conductivity (TCD)	Universal	4×10^{-10} g/ml (propane)	$>10^5$
Hall Electrolytic conductivity	Selective (halogen, sulphur, nitrogen and esters)	5×10^{-13} g/s Cl $2\text{–}4\times10^{-12}$ g/s N $2\text{–}4\times10^{-12}$ g/s S	10^6 10^4 10^4
Thermal Energy Analyser (TEA)	Selective (nitrosamines)	100 pg (dimethyl nitrosamine)	10^6
Fourier Transform Infrared (FT-IR)	Universal or selective	200 pg–40 ng	10^4
Mass Spectrometer (MS)	Universal or selective	EI: 10–100 pg SIM: $<10^{-12}$ [75]	10^5

N, nitrogen; P, phosphorous; S, sulphur; Cl, chlor; EI, electron ionisation; SIM, selected ion monitoring.

(FID) and the mass-spectrometer (MS) being the most widely used in the analysis of volatile impurities. The detection limits of different detectors are listed in Table 4.

2.2.3. Calibration methods

As the liquid and gas phase concentrations in static HSC are related to each other by the partition coefficient and an experimentally-derived proportionality constant, calibration methods have to be used whenever those constants are unknown. Poole [56] and Kolb [76] summarised calibration methods for static HSC. If the sample matrix can be obtained in a pure form, known amounts of the analyte will be added to the matrix and analysed under the same conditions as the sample, provided that the repeatability of the method is good. In case of an unsatisfactory reproducibility, a known amount of a solvent other than the analyte can be added as a standard. If the sample matrix cannot be duplicated, a known amount of the analyte can be added. This version of standard addition method requires two analysis of the sample for calculation, but has the advantage that the influence of the sample matrix on the volatility of the analyte is included in the calibration procedure, assuming that the small amount of analyte added does not change the partition coefficient. The standard addition method can be applied to soluble solid samples or to liquid samples. Multiple static or dynamic HSC, as already mentioned, is preferred for analysing insoluble solid samples or liquid samples of varying matrix compositions (from one sample to the other), such as biological fluids with changing salt concentrations, influencing the partition coefficients of the analytes [77].

When using quantitative dynamic HSC, it is necessary to know the relationship between the initial amounts of the analytes in the sample and the amounts recovered from the trap, which cannot be assumed to reach 100% in any finite time. To calibrate the system, a reference sample will be used. This carries the risk of matrix differences, resulting in different partition coefficients, which may complicate the quantification. As for static HSC, these matrix effects can be eliminated by using repetitive gas-phase sampling [71].

2.3. Official methods

The official methods presently recommended for analysing RS in pharmaceutical products are described in the USP 23 under chapter ⟨467⟩ Organic Volatile Impurities (OVI) and in Eur. Ph. (V.3.3.9). A chronology of the development of the USP chapter till 1990 was presented by Hubert [9]. The first published proposal, for USP XXII, included a list of 7 solvents and limits representing the maximum allowable daily dose [78]. Method I was originally based on the work published by Haky and Stickney [79]. Methods II and III of USP XXII, which dealt with the dynamic HSC, coupled to a FID in case of Method II and to a mass spectrometer in case of Method III, were proposed initially to be subsequently removed in 1993 [80], since in the individual monographs these methods were no longer used for OVI testing. Method V was added in the fifth supplement of USP XXII and Method VI in the eighth supplement of USP XXII. Method IV and the method for methylene chloride in coated tablets are HSC variations of Method V, whereas Method VI describes several columns and chromatographic temperature programs, depending from the individual monograph.

Table 5
Gas chromatographic methods described in USP 23 and Eur. Ph. to analyse residual solvents in pharmaceutical products and excipients

Method	Sample	Standardisation	Column	Detector
USP ⟨467⟩ Method I: Direct GC injection	Dissolved in water or another appropriate solvent	External	30 m × 0.53 mm ID, fused silica, with 5 μm cross-linked G27[a] stationary phase and a 5 m × 0.53 mm ID silica guard column, phenylmethyl siloxane deactivated	FID*
USP ⟨467⟩ Method IV: Static HSC	Dissolved in water containing sodium sulphate and heated for 1 h at 80°C before injection of the headspace	External	As USP ⟨467⟩ Method V	FID
USP ⟨467⟩ Method V: Direct GC injection	As USP ⟨467⟩ Method I	As in USP ⟨467⟩ Method I	30 m × 0.53 mm ID, fused silica with 3 μm G43[b] stationary phase and a 5 m × 0.5 mm ID silica guard column, phenylmethyl siloxane deactivated	FID
USP ⟨467⟩ Method VI: Direct GC injection**	As USP ⟨467⟩ Method I	As in USP ⟨467⟩ Method I	One of 9 columns[c], listed under ⟨467⟩, specified in the monograph	FID
USP ⟨467⟩ Method for methylene chloride in coated tablets	The tablet water extract is heated for 20 min at 85°C before headspace injection	Standard addition	As USP ⟨467⟩ Method V	FID
Eur. Ph. V.3.3.9, System A: Static HSC	Dissolved in water (or another solvent defined in the monograph)	Standard addition	30 m × 0.32 or 0.53 mm ID, fused-silica or wide-bore, with 1.8 or 3 μm crosslinked 6% polycyanopropylphenylsiloxane/94% polydimethylsiloxane	FID (or ECD for chlorinated solvents)
Eur. Ph. V.3.3.9: System B: Static HSC	As in system A	As in System A	30 m × 0.32 or 0.53 mm ID, fused silica or wide-bore, with 0.25 μm polyethylene glycol 20 000 R	FID (or ECD for chlorinated solvents)

* To confirm the identity of a peak in the chromatogram, a mass spectrometer can be used or a second validated column, containing a different stationary phase.
** Method VI presents a collective of chromatographic systems.
[a] 5% Phenyl/95% methylpolysiloxane.
[b] 6% Cyanopropylphenyl/94% dimethylpolysiloxane.
[c] S2, styrene–divinylbenzene copolymer; S3, copolymer of ethylvinylbenzene and divinylbenzene; S4, styrene–divinylbenzene; G14, polyethyleneglycol (M_w 950–1050); G16, polyethylene glycol compound (Polyethylene Glycol Compound 20M or Carbowax 20M; G27, see [a]; G39, polyethylene glycol (M_w 1500).

The methods, which became official in the Eur. Ph. on January 1st 1996, were presented in Pharmeuropa in March 1995 [81] but first discussed in 1993 [82]. The chromatographic conditions of system A correspond to those of Method V of USP 23, but to avoid contamination of the capillary or wide-bore columns, static headspace injection is prescribed as it is in Method IV of the USP. In case of matrix interferences or of possible solvent co-elution, system B has to be used. In contrast to the USP, the Eur. Ph. also recommends the use of an electron capture detector (ECD) for the analysis of halogenated solvents, as certain laboratories experienced difficulties when detecting concentrations lower than 50 ppm with an FID [83], and renounces direct injection methods.

Unfortunately these official methods, summarised in Table 5, are only applicable to soluble samples.

3. Presentation of documented literature data

3.1. Method and instrumental aspects

Results produced by methods other than gas chromatography to determine RS are summarised in Table 6. Unfortunately, the validation of those methods was not carried out in every case.

In contrast, results obtained with the official and non official gas chromatographic methods (summarised in Tables 5 and 7–9) are generally well validated. Cyr et al. [84] compared the resolution capacity of 21 common volatile compounds of the column used in USP Method

Table 6
Miscellaneous methods (other than chromatographic) used to determine residual solvents in pharmaceutical products

Method	Sample	Sample preparation/treatment	Detection limit (ppm)	Residual solvent content (ppm)	Reference
(1) Thermogravimetric analysis	Progesterone-loaded DL-PLA microspheres	(1) 10°C/min, (25–180°C)	n.m.	Methylene chloride: (1) 18000–47000, for (1) and (2)	[42]
(2) Chlorine analysis		(2) n.m.			
Thermogravic analysis	Ethyl cellulose microspheres	5–10 mg, 5°C/min (20–50°C)	n.m.	Methylene chloride: undetectable	[43]
Thermogravic analysis	Eudragit® L films	5°C/min	n.m.	Isopropyl alcohol: 44000	[35]
Chlorine analysis (Schöniger flask combustion method)	^{165}Ho-acetylacetonate-loaded DL-PLA microspheres	n.m.	n.m.	Chloroform: 8000–53000	[44]
Colorimetric method	Vegetable oils (cottonseed and soybean oils)	Co-distillation with xylene, which is heated with pyridine and sodium chloride and analysed spectrophotometrically at 475 nm	Trichloroethylene: 10	Trichlorethylene. 14–740	[45]
Colorimetric method	Extracted oils (soybean oil)	Colorimetric reaction of petroleum with sulphuric acid and selen in tube, after previous extraction by air flow	Petroleum: 100	Petroleum: n.d.–1000	[46]
(1) FT-IR	Acetylsalicylic acid-loaded Eudragit® RS100 microspheres	(1) Dispersed at 1% in KBr, measured at 730 cm^{-1}	(1) n.m.	(1) Methylene chloride: n.d.	[47]
(2) Thin layer chromatography		(2) On a silica plate with *n*-hexane, sprayed with 5% ethanolic solution of phosphomolymdic acid (105°C, 5 min)	(2) Mineral oil: 2 μg	(2) Mineral oil: $\leq$1000	
IR	PVC films	Absorption peaks: 1060 cm^{-1} for tetrahydrofuran, 880 cm^{-1} for dichloroethane	n.m.	n.d.–a few percent	[37]
(1) FT-IR	Drug-free and BSA-loaded DL-PLA and DL-PLGA microspheres	(1) Extract of 100 mg microspheres, absorption peak: 1300–1240 cm^{-1}	(1) Silicone oil DC-200: 5000	(1) n.d.	[49]
(2) ^{1}H-NMR		(2) 20 mg microspheres dissolved in 1 ml deuterated chloroform	(2) Silicone oil DC-200: <100	(2) 2000–5000	
Nuclear magnetic resonance identification	Cocaine	50–200 mg	Benzene: 100, toluene: 150, acetone: 100, ethyl ether: 250, methyl ethyl ketone: 200	Benzene: 100–600, toluene: 800–2300, acetone: 400–11000, ethyl ether: 700– 1200, methyl ethyl ketone: 1600–7700	[50]
FID analysis of headspace	Coatings	1000 cm^2, 140°C, 5 min	$\leq$1000 (various solvents, detectable by FID)	0.002– 0.050 ml/m^2 (solvents not specified)	[51]

n.m., not mentioned in the reference; n.d., not detected.

Table 7
Applications of direct injection gas chromatographic methods used to analyse residual solvents in pharmaceuticals and related products

Sample	Sample preparation	Column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Ref.
Water and pharmaceutical solutions	300 ml extracted with 2 ml carbon disulphide	Fused silica capillary SE-30	MS (SIM)	Internal: 1-chlorohexane	n.m.	Chloroform: 1.7–5.3, bromodichloromethane: 0.03–0.07, chlorodibromomethane: 0.02–0.03, tribromomethane: 0.01–0.1, tetrachlorethylene: 0.01–0.03, dichloroethylene: 0.01–0.03	[130]
Bacampicillin HCl	1% aqueous solution	Glass, 15% Carbowax® 1500 on Chromosorb WAW	FID	n.m.	n.m.	Butyl acetate and ethyl acetate <1000–70 000	[36]
Piroxicam	200 mg in 2 ml dimethylformamide	SP-2100 with 0.1% CW-1500 on Supercoport® with a precolumn	FID	External	n.m.	n.m. (method to analyse methanol, acetone, dimethylacetamide, ethyl benzene, *m*-xylene, *p*-xylene, *o*-xylene)	[101]
Paracetamol	Microdistillation of 500 mg paracetamol in 5 ml methanol (dioxan determination) or 1-butanol (ethanol determination)	Packed with Porapack® super Q	FID	External	n.m.	Dioxane: n.d.–188, ethanol: 1495–2501	[109]
Topiramate	40 mg dissolved in 4 ml dimethylformamide	DB-wax	FID	Internal: isobutanol	20 for all solvents	Methanol: n.d; ethanol: 900; toluene: 100	[131]
Water-soluble drug raw material (chlordiazepoxide HCl, chlorpromazine HCl, flurazepam HCl, furosemide, naproxen, propranolol HCl, sulfinpyrazone	Dissolved in water (pH-adjustment) and extracted with toluene, *n*-octane or ether	Glass, with Sep-Pak®	FID (MS for identification)	External	20–50	Toluene: n.d.–200–3300, acetone: n.d.–150–5100	[132]
Anti-angina substance	Dissolved in benzyl alcohol	Inox, packed with Porapak® Q	FID	Internal: acetone	*Tert*-butyl methyl ether: 400, toluene: 500	*Tert*-butyl methyl ether: 1500; toluene: n.d.	[41]
Triazolam raw materials	17 mg in 1.7 ml benzyl alcohol	Fused silica, DB-5, coupled with a retention gap	FID	External	n.m.	Methyl ethyl ketone: n.d.–100–750; benzene: n.d.–6–30; propanol: n.d.–80–300; ethyl acetate: n.d.–510; ethanol: n.d.–100	[96]
Different drug substances	≤250 mg in 5 ml solvent	Various columns	TCD	External/standard addition	n.m.	Acetophenone, acetonitrile, 2-propanol, methylcyclopentane (method presentation)	[133]

Table 7 (continued)

Sample	Sample preparation	Column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Ref.
Bulk drug substances (steroids, CNS agents, antibiotics)	10 mg drug dissolved per ml benzyl alcohol	Fused-silica capillary with crosslinked methyl silicone: R_{tx}-1 halfmil or DB-1 Megabore®, with a guard-column	FID	External	Methanol:3; ethanol:3; acetone:4; 2-propanol:4; dichloromethane:11; ethyl acetate:5; tetrahydrofuran:4; *n*-butanol:3; isooctane:4	Acetone: 210–10 760, isooctane: 330, *n*-butanol: 800, diethyl ether: 479–700, ethyl acetate: 5170, methanol: 850, *n*-butyl acetate: 110	[94]
Bulk pharmaceuticals (hypolipidemic, antitumor, antihypertensive, antibiotic and anticonvulsive drugs)	In benzyl alcohol	Glass, packed with 3% OV-101 on Anachrom® Q and the second part with 3% SP1500 on Carbopack® B (80–120 mesh)	FID	External/standard addition method	n.m.	Ethanol: 1900–39000; dimethylformamide: 2300; hexane: 4600; tetrahydrofuran 200; methanol: 400	[79]
Flurbiprofen, flurbiprofen sodium (raw material and tablets)	17 mg in 1.7 ml benzyl alcohol	Fused silica capillary (5% phenyl dimethylpolysiloxane)	FTIR	External	n.m.	n.d. in two samples, ev. acetone: 75 in one sample and ev. traces of benzene and trichloroethylene in another	[97]
Bulk pharmaceuticals	40 mg dissolved in 4 ml benzyl alcohol	Fused silica capillary R_{tx}-5 with a guard column	FID	External	n.m.	n.m.	[91]
Bulk pharmaceuticals	100 mg dissolved in 1 ml benzyl alcohol, dimethylformamide or dimethylsulfoxide or 2 g extracted with 15 ml of the mentioned solvents	Fused silica capillary DB-624	FID	Internal: methylcyclohexane	6–83 for 12 solvents	n.m.	[87]
Captopril tablets and raw material	17 mg dissolved in 1.7 ml water	Capillary DB-5	FID/FT-IR	External	n.m.	Methanol: n.d. 200; ethanol: n.d.-2600; acetone: n.d.-2200, t-butanol: n.d.-90; dichloromethane: n.d.-3700; 2-butanone: n.d.-70; ethyl acetate: n.d.-720; chloroform. n.d.-3150; t-butyl acetate: n.d.-440 per coated tablet	[134]
Semi-solid poly(ortho ester)	0.5 g polymer dissolved in 10 ml acetone	Fused silica capillary, Supelcowax 10	FID	External	n.m.	Cyclohexane: 200 tetrahydrofuran: 1500 methanol: 4100	[135]
Polycarbonates	2 g in 10 ml chloroform	Stainless-steel with 10% 2-ethylhexyl sebacate on Chromosorb® W	FID	Internal: chloroform	n.m.	n.m.	[98]
Ethyl cellulose films	500 mg extracted with 2 ml methanol or tetrahydrofurane	OV-224 glass capillary alkylated with pentafluorobenzyl bromide	n.m.	Internal: isopropanol or 2-butanol	n.m.	Methylene chloride: n.d.–3150, methanol: n.d.–after 8.5 h drying, acetone: n.d. after 8.5 h drying, chloroform: traces-detectable (whatever this means)	[136]
Hydroxypropylmethylcellulosephthalat, ethylcellulose and hydroxypropylmethyl-cellulose film coating material	500 mg tablet or film coating powder dissolved or suspended in 2 ml tetrahydrofuran or methanol, centrifuged	Glass with Porapak® Q	FID	Internal: n-propanol	n.m.	Ethanol: 2200–25 900, acetone: <100–1500, isopropanol: 200–1300, dichloromethane: 300–5700, methanol: <10–400	[108]

Table 7 (continued)

Sample	Sample preparation	Column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Ref.
Ethylcellulose and hydroxypropyl methylcellulose coated tablets	Tablets were submerged in chloroform	Glass with Porapak® R	FID	Internal: isopropyl alcohol	Methanol: 6, methylene chloride: 10	Methanol: 115–312, methylene chloride: 30–74 (per 760 mg tablet)	[137]
Tablets coated with cellulose acetophthalate	Dissolved in dimethylformamide	Glass, packed with Chromosorb® 101 and Chromosorb® 104	FID	External	Isopropanol and ethyl acetate: 70 (= quantification limit)	Isopropanol and ethyl acetate: ≤600–700	[99]
Cisplatin-loaded DL-PLA and DL-PLGA microspheres	22 mg microspheres in 2 ml dimethylformamide	Silanized glass with 20% QF1 absorbed on Chromosorb® P	FID	n.m.	n.m.	Dichloromethane: 30 000 (undried microspheres) and 100 (after 1 year)	[113]
Cisplatin-loaded DL-PLA microspheres, prepared by (o/w) solvent evaporation	22 mg microspheres in 2 ml dimethylformamide	Silanized glass, 20% QF1 adsorbed on Chromosorb® P	FID	n.m.	n.m.	Methylene chloride: 260–37 500	[112]
BSA-loaded and drug-free DL-PLA and DL-PLGA microspheres	100 mg microspheres dissolved in 0.5 ml 1,4-dioxane, centrifuged after addition of 1 ml isooctane	Fused silica capillary with crosslinked methylsilicone (PS 255)	FID	Internal: 2-butoxyethanol	Dichloromethane, ethyl acetate, hexane, octamethylcyclotetra-siloxane: <100	Dichloromethane: <100–43 200, ethyl acetate: 20 700–84 800, hexane: 24 900–55 100, octamethylcyclotetrasiloxane: 5200 13 500	[49]
Salmon calcitonin-loaded DL-PLGA microspheres	Microspheres dissolved in dioxane	GS-Q porous layer open tubular with a pre-column	FID	n.m.	n.m.	Methylene chloride: <10–129	[117]
TRH-loaded DL-PLGA microspheres	450 mg in 5 ml dimethyl sulfoxide	20% polyethylene glycol-1000 on Chromosorb® W-AW DMCS	FID	n.m.	n.m.	Acetonitrile: <20–4100, dichloromethane: <20–3100	[111]
Multilamellar liposomes with a cisplatine der- ivative	Liposomes suspended in saline, centrifuged and supernatant extracted with toluene	Glass packed with 1% SP-1000 on Carbopack® B (60/80)	MS	Internal: tetrachloromethylene	n.m.	40 250 *tert*-Butyl alcohol, 40 chloroform	[138]
Monomeric zinc phthalocyanine-loaded liposomes	4 ml suspended liposomes, extracted with 1 ml methanol on Bond-Elut® C_{18} column	Quartz capillary, HP 5	FID	Internal: chlorobenzene	n.m.	*N*-Methyl pyrrolidone: 40, *tert*-butyl alcohol: 30	[139]

[a] If not otherwise defined.
n.d., not detectable; n.m., not mentioned.

Table 8
Applications of static HSC methods used to analyse residual solvents in pharmaceutical and related products

Sample	Sample preparation before headspace injection	Column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Reference
Water samples with halogenated hydrocarbons	60°C, 30 min	Steel capillary with squalene (direct injection of HS cryogenic or sorbent trapping)	FID	Standard addition	Methylene chloride: 8 and 0.6 μg/l; chloroform: 9.5 and 0.5 μg/l;	Acetone: 0.29 mg/l; ethanol: 0.38 mg/l;	[67]
Blood (ethanol, ambient HSC) waste water	(a) 1 ml liquid sample saturated with K_2CO_3, ambient temperature, 30 min; (h) 10 ml liquid sample, saturated with K_2CO_3, 80°C 4 min/mixing/2 min; (d) direct injection (for comparison)	Capillary fused silica, DB-624, with a guard column	FID	Internal: propanol	Direct inj.(d)-ambient-HSC (a)-heated HSC (h) in methylene chloride: 140-13-3 ppb; chloroform: 530-20-7 ppb; benzene: 56-2-0.6 ppb; trichloroethylene: 580-32-3 ppb; 1,4-dioxan: 640-960-11 ppb; toluene: 20-3-1 ppb	n.m.	[100]
Oils and liquid paraffin	500 mg in 500 mg liquid paraffin, 135°C, 20 min	Stainless steel packed with 15% Apiezon® M on Celite® 545	FID	Internal: methyl caproate	Tetrachloroethylene and trichloroethylene: 0.2 μg	n.m. (method presentation)	[140]
Pharmaceutical substances and excipients	50–300 mg in 1 ml diethylene glycol, 100°C, 15 min	Stainless steel packed with Porapak® Q	FID	External:	2–20	n.m. (method presentation for 21 solvents)	[141]
Pharmaceutical substances and excipients	50 mg and 10 μl dimethylformamide, 105°C, 30 min, MHE: two extraction steps	Fused silica capillary, Supelcowax 10	Integrator SP 4270 Spectra Physics	External	n.m.	n.m. (method presentation)	[142]
(1) Phenobarbital Na,	(1) 200 mg and 5μl of internal standard in benzyl alcohol, 100°C, 20 min	Glass, packed with 0.1% SP 1000 on Carbopack®	FID	(1) Internal: *t*-butanol	Ethanol: 0.02–0.31; acetone: 0.3; methanol: 0.023–0.033; isopropanol: 0.07	(1) Ethanol: 4400	[93]
(2) Lidocaine HCl,	(2) 0.5 g in 1 ml benzyl alcohol, 100°C, 20 min			(2) External		(2) Acetone: 2700	
(3) Ca-Pantothenate,	(3) 150 mg in 1 ml water, 90°C, 20 min			(3) External		(3) Ethanol: 1100	
(4) Methyl nicotinate,	(4) 0.5g as (2)			(4) External		(4) Methanol: 14.4	
(5) Na-Ascorbate,	(5) 200 mg in 1 ml water, 90°C, 20 min			(5) External		(5) Ethanol: 127.1	
(6) Nicotinamide,	(6) 700 mg in 1 ml dimethylformamide, 100°C, 20 min			(6) External		(6) Ethanol: 52.8	
(7) Phenylbutazone	(7) 500 mg in 1 ml benzyl alcohol, 100°C, 20 min			(7) External		7) Methanol: 50.9, ethanol: 14.2, Iso- propanol: 419.4	

Table 8 (continued)

Sample	Sample preparation before headspace injection	Column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Reference
Antacid, cephalosporin, tetracycline	(1 g) in 5 ml, 80°C, 30 min (liquid samples), 26 mn (with shaking) for solid samples in water	Capillary, DB-Wax	FID/ECD	External and standard addition	Solvents listed in USP XXII: 0.1–6.7	n.m. (method presentation)	[143]
Iohexol and iopentol (X-ray contrast media)	1.75 g in 7 ml water, 90°C, 15 min	Fused silica capillary, DB-624	FID	Internal: 2-pentanol/ standard addition	Methanol: 5 μg/ml; 2-propanol: 0.5 μg/ml; 2-butanol: 0.5 μg/ml; 2-methoxy-1-ethanol: 10 μg/ml	n.m. (method presentation)	[144]
Streptomycin sulphate, meth- acycline HCl	1 g streptomycin sulphate or 0.3 g methacycline HCl 10 ml in 10 ml 1M sodium hydroxide solution, 60°C, 60 min	Stainless steel, with polystyrene	FID	External	n.m.	Triethylamine in streptomycin sulphate: 3540–3710; in methacycline HCl; 1170–1250	[145]
Human menopausal gonadotrophin, human chorionic gonadotrophin	20 mg in 10 ml 2M sodium chloride solution, 5 min ultrasound, 70°C, 30 min	Fused silica capillary, with Pora Pora PLOT® Q	FID	External	Ethanol: 20 ppb, acetone: 8 ppb, diethyl ether: 0.5 ppb	Ethanol: 6.67–16.0, acetone: 0.16–6.52, diethyl ether: 0.6–14.2 ppb	[146]
Piroxicam	200 mg in 2 ml benzyl alcohol, 130°C, 15 min	SP-2100 with 0.1% CW-1500 on Supelcoport®	FID	External	n.m.	n.m. (method presentation for methanol, acetone, dimethylformamide, dimethylacetamide, ethyl benzene, *m*-, *p*-, *o*-xylene)	[101]
Vigabatrin	500 mg in 10 ml water, 60°C, 30 min	Capillary, Supelco SPB-1	FID	Internal: 1,2-dichloroethane and 1-propanol	n.m.	n.m. (method evaluation)	[147]
Acidic, basic and neutral drug substances, soluble in dimethylformamide	100 mg dissolved in 1 ml dimethylformamide, 60°C, 15 min	Capillary, Supelco Nukol® (acid modified, bonded polyethylene glycol)	FID	Standard addition method (13 solvents)	n.m.	n.m. (method presentation)	[148]
Anti-anginous substance	(1) 200 mg in 1 ml diethyl glycol, 100°C, 14 min	Fused silica, methyl silicone (DB1) or polyethylene glycol 20 M (DBWAX)	n.m.	(1) Internal standard;	(1) *Tert*-butyl methyl ether and toluene: 2;	(1) *Tert*-butyl methyl ether: 1370, toluene: 53	[41]
	(2) 200 mg			(2) MHE (5 extractions)	(2) *Tert*-butyl methyl ether: 1, toluene: 0.5	(2) *Tert*-butyl methyl ether: 2189, toluene: 85	
Sulfamethazine	0.2 g in 0.5 ml dimethylacetamide, 105°C, 15 min	Capillary, Rtx-200 (= G6)	MS	Internal: 2-pentanone and standard addition	Acetone: 0.4 (scanning mode); for 9 other solvents: 2–20 ppb (SIM)	Acetone: 0.2–1.0	[62]
Spironolactone	100 mg, heated to the molten state	Capillary, SPB-1 (Supelco)	FT-IR	n.m.	n.m.	Benzene: in one sample of 13 < detection limit of GC-FT-IR	[149]

Table 8 (continued)

Sample	Sample preparation before headspace injection	Column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Reference
Steroid hormones	2–10 mg, 175°C, 30 (-45) s (in some cases two step MHE)	Glass coil, with Porapak® Q	FID	External		n.d. for some samples; ethyl acetate: 160–660, ethanol: 180–620, methyl ethyl ketone: 1050, acetone: 120–2020, methanol: 150–620	[150]
Polymer-coated cellophane	2 ft^2, 155°C, 30 min, under vacuum	Aluminium filled with 10% Carbowax® 20 M on Anakrom® ABS 70/80 mesh	n.m.	External: tetrahydrofuran and toluene in *n*-hexane	n.m.	n.m. (method presentation)	[151]
Polypropylene, polythene or cellophane films, coated with saran or combined in laminaes	250 cm^2+3 μl int. standard, 100°C, >90 min	Silicone oil with UCON® HB2000 (polyalkylene glycol) on Chromosorb W	FID	Internal: butyl acetate or butyl propionate	n.m.	Toluene: 127 and 12 mg/m^{-2}, ethyl acetate: 135 mg/m^{-2}	[152]
Cast films	150–180°C, 10 min, under vacuum	20% PEG 400 on Celite®	FID	External	n.m.	n.m. (method presentation)	[153]
PLGA films	10–25 mg dissolved in 3 ml dimethylformamide, 60°C, 30 min	n.m.	FID	Internal: ethyl acetate	Acetone: 10 ppm	Acetone: n.d.-0.75%	[154]
Polycarbonates	2 g in 9.9 ml 1,4-dioxane, 60°C, 60 min	Stainless steel, with 10% 2-ethylhexyl debacate on Chromosorb® W	FID	Internal standard: dichloromethane	n.m.	n.m.	[98]
Flexible packaging materials	100 cm^2, 115°C, 15 min	Stainless-steel packed with 15% diisodecyl phthalate and 3% polythene on Chromosorb® W or 8% Carbowax® 1540 on HMDS Chromosorb® W	FID	External	n.m.	n.m. (method presentation)	[21]
Gentamycin and gentamycin sulphate in DL-PLA blends	15 mg of antibiotic-polymer blend in 0.5 g N-methyl pyrrolidone, 70°C, 60 min	n.m.	FID	n.m.	Acetone: n.d.–4500	n.m.	[155]
Packaging material	10 cm^2+10 μl dimethylformamide, 120°C, 60 min; MHE: two extraction steps	Fused silica capillary, Supelcowax® 10	Integrator 4270, FA.spectra-Physiscs	External: 19 solvents	n.m.	n.m. (chromatograms of different foils and packaging material are shown)	[92]
Packaging foils	100 cm^2, 60°C, 30 min	Carbowax® 1540 on Chromosorb® W	FID	External: cyclohexane	n.m	Ethylacetate: 26.5 mg/m^2, methyl ethyl ketone: 23.5 mg/m^2 isopropanol: 23 mg/m^2, ethanol: n.d.–1 mg/m^2, toluene: 6.5 mg/m^2	[156]
Eudragit® L100-55 films	5 mg in 1 ml 0.5% (*m*/*V*) triethanolamine in water, 80°C, 10 min	Capillary	FID	Internal: n-propanol	n.m.	Isopropanol: n.d.-10%	[107]

Table 8 (continued)

Sample	Sample preparation before headspace injection	Column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Reference
Copolymers and a terpolymer (composed of vinyl acetate crotonic acid and higher vinyl ester)	500 mg, 110°C, 150 min	20% decyl phthalate on Gas Chrom® Q	(1)FID/PID	Standard addition	n.m.	Acetaldehyde: 10, methyl acetate: 10–40 ppm, vinyl acetate: n.d.–15, ethyl acetate: n.d.–50, benzene: 10–50	[120]
Tetracosactide-loaded and drug-free PLA/PLGA microspheres	50–60 mg microspheres, 110°C, 30 min	Fused silica capillary, DB-624	MS	External, MHE (4 extraction steps)	Methanol: 1.5 methylene chloride: 0.5	Methanol: 2.5–40, methylene chloride: n.d.–5283, chloroform: 934–6000	[110]
Tetanus toxoid-loaded DL-PLGA microspheres	n.m.	n.m.	FID	n.m.	Methylene chloride: <30	n.m.	[157]
Progesterone-loaded microspheres (PHB, PHBV9, PHBV24)	5–50 mg microspheres, 60°C	Stainless steel, 10% FFAP on Chromosorb®	ECD	External	Methylene chloride: 2.5 ng; chloroform: 0.5 ng	Methylene chloride: n.d. 58.41; chloroform: n.d.	[158]
Progesterone-loaded PHB, PHBV9 and PHBV24) microspheres	5–50 mg microspheres	Stainless steel, 10% FFAP on Chromosorb®	ECD	n.m.	Methylene chloride: 2.5 ng	PHBV24 microspheres: 3.7–5.8; PHB9 microspheres: 30; PHB microspheres: 3 4 and when heated 30 min at 40°C	[115]
Nitroglycerine-containing transdermal system	About 25 mg, 120°C, 90 min	Fused silica capillary, OV 1701	FID	External	n.m.	Petroleum spirit 80–110: 11 400 and 11 600	[159]

[a] If not otherwise defined.
DL-PLGA, DL-poly(lactic-*co*-glycolic acid).
DL-PLA, DL-poly(lactic acid).
PHB, poly(β-hydroxybutyrate).
PHBV9, poly(β-hydroxybutyrate-β-hydroxyvalerate) with 9% hydroxyvalerate.
PHBV24, poly(V-hydroxybutyrate-β-hydroxyvalerate) with 24% hydroxyvalerate.
n.d., not detectable.
n.m., not mentioned.

Table 9
Applications of dynamic HSC method used to analyse residual solvents in pharmaceutical products and excipients

Sample	Sample preparation	Trap/column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Reference
Water samples	0.5–2 l, 30°C, 60–120 min, 1.0–2.5 ml/min GF	Pure wood charcoal: extraction with 5–15 μl carbon disulphide or 10–100 μl methylene chloride/ column not specified	n.m.	Internal: C6, C10, C14 and C18 1-chloroalkanes	n.m.	n.m. (method presentation)	[70]
Water samples	1 ml, 18 ml/min GF	Cold trap/fused silica capillary DB-624	MS	n.m.	n.m.	n.m. (method presentation)	[88]
Water samples	5 ml, 11 min 40 ml/min GF	Tenax® GC (1/3) and silica gel (1/3) and coconut charcoal (1/3)/glass capillary VOCOL	PID/ECD	Internal: fluorobenzene (PID) and 2-bromo-1-chloropropane (ECD) (and 1-chloro-2-flurobenzene)	58 substances: 0.01–0.1 (except bromomethane, dibromomethane, bromoform and 1,2-dibromo-3-chloropropane)	(Example and method presentation)	[90]
Water samples with Carbowax® 400	40°C, 35 ml/min GF	Tenax® GC (30–60 mesh)/stainless steel, 15% Carbowax® 20 M on Chromosorb® G	FID	External/MHE	n.m.	n.m. (method presentation)	[71]
Water samples (analysis of volatile halocarbons and aromatics)	50 ml, 15 min 40 ml/min GF	Stainless steel with Tenax® GC connected to a cryotrap/capillary SPB-1 Supelco	FID	Internal: fluorobenzene	n.m.	n.m. (method presentation)	[160]
(1) Water samples (2) Pharmaceutical powder	(1) 5 ml, 11 min, 40 ml/min GF (2) preheat 3 min, 10 min, 50 ml/min GF	Stainless steel, with Tenax® TA/fused silica capillary CPSil 8CB	FID	MHE	n.m.	(1) 1,2,4-Trichlorobenze (spiked samples) (2) Toluene	[161]
Anti-anginous substance	5 mg, 90°C, 30 min, 14 ml/min GF	Tenax®, cryogenic/ glass, % SP 1500 on Carbopack® B	n.m.	n.m.	*Tert*-butyl methyl ether and toluene: 0.04	*Tert*-butyl methyl ether: 1538 (1709 after after two analysis); toluene: 79 (83 after two analysis)	[41]
Pharmaceutical samples (not specified)	100 mg, addition of 1 μl internal standard, 100°C, 15 min, 30 ml/min GF	Tenax®/fused silica capillary SE-54	FID	Internal: benzene	n.m.	Toluene: about 100 (method presentation)	[162]
Polypropylene	30 mg, 95–170°C, 5–25 min, 50–500 μm film thickness	Deactivated fused silica cold trap with glass beads/capillary SE-54	FID	n.m.	n.m.	Hexane, tridecane, 2,6-di-*tert*-butyl-4-methylphenol (method presentation)	[61]
Polypropylene-polyethylene copolymer	50–120°C (14°C/min, 5 min), 20 ml/min GF	Cryogenic: in a fused silica capillary/pre-column: capillary CP-WAX 52 B/column: capillary CP-Sil 8 CB	FID/MS	n.m.	n.m.	n.m. (method presentation)	[163]

Table 9 (continued)

Sample	Sample preparation	Trap/column	Detector	Standardisation method	Detection limit (ppm)[a]	Residual solvent content (ppm)[a]	Reference
PVC-bags PP/PE copolymers	120°C, 20 min, 25 ml/min GF	Cold trap filled with glass beads/fused silica capillary SE 54	MS	(External standardisation possible)	n.m.	n.m. (method presentation, a few substances found listed)	[164])
(1) Polyethylene, Polypropylene	(2) 17–17.5 mg micronized, 20°C–95°C within 30 s, held 5 min, 20 ml/min GF	Cold trap filled with glass beads/capillary SE-54	MS	Internal: (n.m.)/MHE	n.m.	(1) 2-Methyl-1-propanol: 240; 3-methylpentane: 82; 2,4-Dimethyl-1-pentanol: 440; decanal: 5.9; Methyltridecene: 151; 2,6-di-*tert*-butyl-4-methylphenol: 26, (2) Decene: 18; tetradecene: 103; 2,4-di-*tert*-butylphenol: 16; 2,6-di-*tert*-butyl-4-methylphenol: 782; dodecyl propionate: 23	[165]
Polymer matrices	30–200 mg/100–230°C, 5–30 min	Cold trap with soda glass beads/fused silica capillary with SE-54	FID	n.m.	n.m.	n.m. (method presentation)	[166]
Polymer matrices	1 mg, 100–250°C, 15 min (600–1000°C, 20 s for the pyrolysis)	Fused silica capillary with SE-54	MS	n.m.	n.m.	n.m. (method presentation)	[167]
(1) Coated tablets (2) Suppositories	35/50 mg, 120°C, 10 min,	Tenax®/inox, Porapak® Q	FID	(1) n.m. (2) External	(1) n.m. (2) Cyclohexanone	(1) n.m. (2) Cyclohexanone: 200–300	[168]
Coated films	215°C, 4 cm^2/min GF,	Solid sample put into the injection port and residual solvents swept away by the gas flow/column packed with 10% UCC-4982 on Chromosorb® W	FID	External	n.m.	1,1,2-Trichloroethane	[169]
L-PLA microspheres	10–50 mg in 1 ml NaOH	Tenax® TA	(FID)	Internal	n.m.	Methylene chloride: 20–1500	[118]

[a] If not defined otherwise.

GF, gas flow; n.d., not detectable; n.m., not mentioned.

I (DB-5, designated as G27 in USP) with a DB-Wax (polyethylene glycol) column. They found a false positive result for chloroform in a ranitidin sample, with the DB-5 column. Chen et al. [85] were the first to propose the use of a DB-624 (G43) column for OVI analysis, as 22 common organic solvents could be separated, with however the risk of the peak of *n*-butanol and trichloroethylene overlapping. Dennis et al. [86] isolated up to 33 solvents when using the same column combined with a static headspace sampling, and reported possible co-elution of isobutanol and benzene. Among the other authors using DB-624 columns, Smith and Waters [87] found that when using a direct injection method, ethanol and diethyl ether, dichloromethane and *tert*-butanol, THF and chloroform and cyclohexane and carbon tetrachloride formed overlapping peaks which could not be resolved. Pankow [88] separated 27 solvents of a water sample when using a dynamic headspace injection. Billot and Pitard [89] used Taguchi design experiments to optimise the separation of 26 solvents using CP Sil 5CB (polydimethylsiloxane), CP Sil 8CB (G27), CP Sil 13CB (G43) and CP Wax 52CB (polyethylene glycol) fused silica capillary columns. Best results were obtained on a CP-Sil 13CB (G43) column with 24 solvents separated and two (isopropanol and diethyl ether) co-eluted. The retention times of 34 solvents for the G6 stationary phase of USP are given in [62]. A dynamic HSC system, using a capillary VOCOL (G43) column coupled to a PID (photoionisation detector) series mounted with a ECD, for analysing 58 solvents in a water sample was described by Shou-Yien Ho [90] and the results of the PID and the ECD were compared. Whereas ECD responds to more solvents than PID and is suited for the analysis of halogenated substances, PID (a non destructive detector) is suited for the analysis of unsaturated compounds, such as aromatics. Only *m*-and *p*-xylene on the one hand and 1,2,3-trimethylbenzene and 2-chlorotoluene on the other hand could not be separated. When using the stationary phase G27 of USP, Kersten [91] noticed co-elution for 2-propanol, acetonitrile and acetone, and for methyl ethyl ketone and *n*-hexane. No resolution could be obtained by Herlitz et al. [92] for methanol and *i*-propyl acetate, and methyl-*i*-butyl-ketone and *i*-butyl acetate when analysing 22 solvents with a Supelcowax® 10 (polyethylene glycol) column. Good solvent resolution was documented for the 24 solvents analysed with a Carbopack® column, coated with SP 1000 (polyethylene glycol modified with nitroterephthalic acid) [93]. 27 solvents were separated with a methyl silicone stationary phase (RTx-1® halfmil or DB-1® Megabore), showing co-elution of ethyl acetate, hexane and chloroform, *n*-butanol and benzene, isooctane and dioxane [94]. The method selected by Haky and Stickney [79] using a column filled with 3% OV-101 (poly(dimethylsiloxane)) on Anachrom® Q and 3% SP1500 on Carbopack® B showed co-elution for acetone and dichloromethane, two frequently used solvents. The advantages, such as lower baseline interferences, good long-term stability and less peak tailing, of a glass capillary columns, when compared to packed columns, were reported [95].

As can be seen in Tables 7–9, FID is the most widely used detector. To overcome the identification problem of a RS in a sample one can proceed as proposed by the official methods or identify the solvents by using an FT-IR detector [96,97].

When comparing direct injection GC and static HSC, Di Pasquale et al. [98] found higher sensitivity for static HSC, owing to the possibility of injecting in the column a sample of higher volume and purity. The figures for RS in coated tablets [99] were lower when using thermogravic analysis, compared to GC, but still precise enough for a first approximation. Four GC systems were compared for the analysis of residual toluene and *tert*-butyl methyl ether in an anti-anginous drug [99]. Dynamic HSC showed the lowest detection limit with 0.04 ppm, followed by multiple extraction HSC (0.5–1 ppm), then static HSC (2 ppm) and finally 400–500 ppm for direct injection GC, which did not allow the detection of toluene in the tablets, in contrast to other methods (53–85 ppm). Comparable results were found in the analysis of six solvents in water samples [100]. GC led to the highest detection limits (several hundred ppb), static HSC to limits of 2–32 ppb with the exception of 1,4-dioxane (960 ppb compared to 640 ppb with direct GC) and to 0.6–11 ppb detection limits, when the water samples were heated to 80°C before static HSC. The precision of direct GC and static HSC were in the same range, as also documented elsewhere [101]. When analysing halogenated solvents in water samples by static HSC, detection sensitivity could be further increased by an order of magnitude, by using a preliminary concentration of impurities in the equilibrium vapour with a cryogenic trap [67]. Hagman and Jacobsson [61] examined the effects of process parameters in dynamic HSC. An increase in stripping gas flow rate by 100% had approximately the same effect as doubling the desorption time. But if the flow rate is too high, reproducibility of recovery will be reduced. A temperature increase of the polymer sample of 10°C led to a 1.5 times higher solvent vapour pressure and the thinner the polymer sample was, the higher the recoveries were. Gas phase concentration in static HSC was found to double for every 20°C rise in temperature [62]. The extraction of methyl methacrylate monomer from poly(methyl methacrylate) raised from 2.4 to 130.4 mg/kg when heated from 80 to 140°C (T_g of the polymer: 110°C) [102]. In the same work, dimethylacetamide (DMA) was shown to be a good sample solvent when compared to dimethylsulfoxide (DMSO) because of its high boiling point (166°C), its purity

(DMSO contains dimethylsulfide and dimethyldisulfide as impurities) and its solubilising properties. Additionally, DMA was found to be an excellent solvent for the analysis of polar RS such as methanol, ethanol and isopropanol, when compared to water, which led to peak broadening for these solvents and was rather recommended for the analysis of non polar solvents. Bergren and Foust [103] reported poor reproducibility for direct injection of aqueous samples, especially at higher injection temperatures and compared the peak area response of the USP OVIs for aqueous, benzyl alcohol and DMF solutions, and pointed out to the need of adapting injection temperature [104]. Clark et al. [105] also noted poor precision for nonpolar solvents, such as trichloroethane and chloroform, when water was used as solvent. Therefore, they proposed the use of water just in the case of a sample not soluble in an organic solvent, in combination with HSC, and DMSO or DMA in all other cases. Solvents like benzyl alcohol, containing high levels of impurities (methanol, toluene and other oxidation products [85]), or methanol [104], generating excessive tailing on the chromatograms, should be avoided. Other impurities met in solvents have been listed by Debeart [106].

3.2. Residual solvents in pharmaceutical products

When examining the results of RS determination of the pharmaceutical products and samples presented in Tables 6–9, the need of such determinations in the pharmaceutical industry becomes obvious, since in many cases the allowable limits have been exceeded. Luckily, these solvents can be reduced in most cases to a reasonable level by drying. The success of this drying step depends strongly on the temperature chosen, the polymer porosity and the solvent affinity. Thus, Gutierrez-Rocca and McGinity [107] found accelerated isopropyl alcohol evaporation in an acrylic resin when raising the temperature to 60°C (see Fig. 3) and noticed an important influence of the plasticizer on the final RS content. For samples containing less than 10% of plasticizer, the RS content was still about 2% even after 12 days of drying at 60°C, whereas in the 20% plasticizer-containing sample the RS was undetectable. Additionally higher humidity conditions were found to accelerate the removal of solvents, as water can plasticize films, especially those that are hydrophilic. The results of Patt and Hartmann [108] indicate that a raise of temperature from RT to 30°C led to lower RS concentrations, but as this temperature was still below the T_g, it was of very limited efficacy. Therefore, once lowered to a certain RS concentration, additional drying under the same conditions was rather useless. Interesting observations have been made by Barthelemy et al. [109], when drying aqueous and organic paracetamol solutions. Progressive drying always led to lower RS than drastic drying, in ventilated oven and under vacuum. In the latter case a superficial 'crust', hindering the solvent escape, seemed to be formed.

By comparing the results of RS analysis of the polylactic acid (PLA)/poly-lactic-*co*-glycolic acid (PLGA) microspheres presented in Tables 6–9 the following conclusions can be made: when porous microspheres were obtained, drying at room temperature for several days under vacuum was sufficient to lower the residual methylene chloride and methanol to satisfactory values [110], as well as heating close to the T_g to remove acetonitrile or methylene chloride, which led to undetectable levels [111]. In contrast, drying for 20 h at room temperature was not sufficient for the microspheres prepared by solvent evaporation, leading to values of about 3% [42]. Spenlehauer et al. [112] noticed that the physicochemical nature of cisplatin, which crystallised in the PLA matrix, led to greater microsphere porosity, and consequently to lower residual methylene chloride, when increasing the drug content. During the storage for 1 year at 37°C, the residual methylene chloride content of the microspheres fell from 3 to 0.01% and was shown to have no influence on polymer degradation [113]. Moreover O'Hagan et al. [114] did not detect any methylene chloride (detection limit 10 ppm) in their microspheres prepared by solvent evaporation, this demonstrating the influence of the preparation method on the RS content. Gangrade and Price [115] also found for PHB (poly(β-hydroxybutyrate)) and PHBV (poly(β - hydroxybutyrate - β - hydroxyvalerate)) microspheres that a more compact matrix retained higher amounts of methylene chloride and that a more concentrated polymer organic solution used

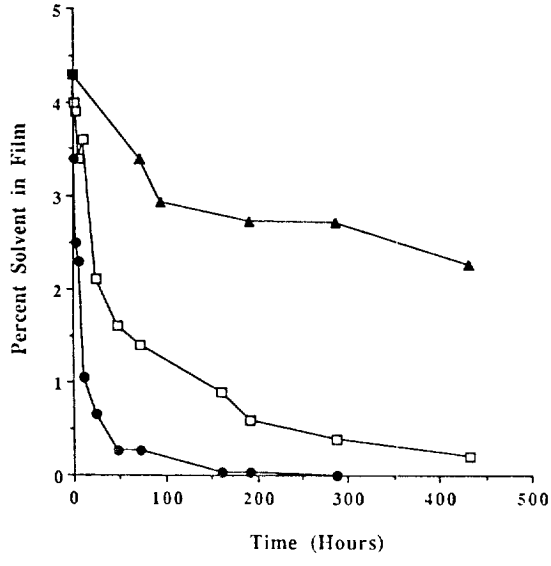

Fig. 3. Influence of drying time and temperature on the residual levels of isopropyl alcohol remaining in Eudragit® L 100-55 films containing 20% triethyl citrate as a plasticizer [107]. Legend: (●) 60°C, (□) 40°C, (▲) 23°C.

during the microsphere preparation (solvent evaporation method) led to much higher RS. Additionally, PHBV9 (9 mol% hydroxyvalerate) retained more methylene chloride than PHB and PHBV24 (24 mol% hydroxyvalerate). Li et al. found in their recently published work [116] that an increase in the ratio dispersed phase/continuous phase (1/100 to 1/10) led to a diminished residual methylene chloride content (760 ppm to < 10 ppm) in DL-PLGA microspheres, prepared by the solvent evaporation method. Some further explanations for those varying residual solvent contents in DL-PLGA microspheres prepared by the (w/o)w solvent evaporation method were presented by Jeyanthi et al. [117]. If the temperature was gradually raised from 15 to 40°C during the solvent removal, the residual methylene chloride was beneath 10 ppm, whereas it was at 21 ppm and 129 ppm when removed by the dilution of the external aqueous phase (dilution factor 1.5 and 2.5). From the work of Ruchatz et al. [118], drying of the microspheres (prepared by ASES) in supercritical carbon dioxide can also be considered as an efficient drying method, specially suited for heat sensitive drugs as temperatures of about 40°C are used. The coacervation method, which was described by Lewis [119], claimed to be a producing process of microspheres with a low RS content, resulted in residual methylene chloride and residual heptane contents of up to 0.1% and 1%. Those values are still to be considered as exceeding the allowable limits. Thomasin et al. [49] reduced the dichloromethane content in BSA loaded and drug free DL-PLA and DL-PLGA microspheres, prepared by the coacervation process, from 0.046–0.67% down to 0.04–< 0.01% by drying them at 40°C under reduced pressure. For ethyl acetate, silicone oil and octamethylcyclotetrasiloxane, drying at 40°C led to values not lower than a third of the initial residual solvent content (see also Tables 6 and 7). However, they demonstrated that increasing the drying temperature resulted in lower residual solvent levels, while a diminution of the drying pressure had no significant effect. Additionally, the low molecular weight DL-PLA microspheres were found to retain less residual solvent when compared to high molecular DL-PLA, as well as when compared to microspheres composed of DL-PLGA of the same molecular weight.

Further examples of RS analysis, not mentioned in any table of this review, such as the detection of methylene chloride in pills, hydrocarbons in crude oil, or toluene in printed foils were published together with examples of ethylene oxide residue analysis in sterilised medical material or polymer monomer analysis by Kolb and co-workers [64,65], using MHE. Also Goetz et al. [120] presented, together with the RS analysis of a polymer, several examples of trace analysis of volatile compounds by static HSC (1,4-dioxan in shampoos containing ethoxylated surfactants, hydrogen sulfide analysis using PID) and dynamic HSC (residual monomer analysis of polymers, residual ethylene oxide analysis of polypropylene). Residual acetone/ethanol (0.052–0.569%) was found in coated tablets by Osterwald [121] after drying for 18 h at room temperature and at a slightly lower concentration, when dried at 31°C, using direct injection GC. A GC method for analysing methanol, methylene chloride and diethylamine impurities in γ-aminobutyric acid derivatives was presented by Shmuilovich et al. [122] (no quantitative results given). Relatively harmless RS like ethanol and ethyl acetate in a range of 0.5–1.6% were found in flucloxacilin sodium from the purification process, using static HSC [123]. A concentration of 2.1% of residual methylene chloride was found by Thoma and Schlütterman [124] in microspheres prepared by solvent-evaporation method and 0.3% when prepared by spray drying, using GC (method not described). The fact that evaporation of organic solvents from polymer systems is a two-stage process, as discussed in the Introduction (Section 1), can also be seen from the work of Fuchs and Zeller [125], where the influence of vacuum-fluidised-bed drier on the residual ethanol, isopropanol and acetone content were studied.

Additionally, water sample analysis methods (Tables 7–9) were also selected because of their possible adaptation to water-soluble pharmaceutical products.

4. Conclusions

Whenever organic solvents are used in the production of pharmaceutical products, especially in the last processing steps, the content of RS in the final product should be analysed. Acceptability seems to be best judged following the ICH RS limit guidelines [16], which may be soon adopted by the Eur. Pharm. and probably USP and JP, and which classifies the solvents into four groups. In class 1 are included the most toxic solvents (benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene and 1,1,1-trichloroethane) which, unless strongly justified, should be avoided. For the toxic solvents of class 2, the limits are expressed as concentrations (ppm) and additionally, in the case of known daily drug intake, by the very important 'permitted daily exposure' (PDE), which is missing in the USP 23. The class 3 includes the solvents with low toxic potential for which the general limit is set at 0.5%. The class 4 includes solvents for which no adequate toxicological data was found. But up to now, official residual solvent limits are only given in the USP 23 chapter ⟨467⟩ Organic Volatile Impurities.

A reasonable drying step should be included in the preparation to guarantee low residual solvents. This may consist in heating to or even above the T_g, if permitted by the drug stability, and possibly under

vacuum, or in the case of heat sensitive drugs just under vacuum at lower temperatures, which however has the disadvantage of a slower and possibly incomplete solvent evaporation. For the residual solvent analysis of soluble samples, the official GC methods of USP or the one proposed for the Eur. Ph. give precise results with good residual solvent separation. Possibly, one or some of the chromatography parameters may need to be changed. The GC method should be selected in the following order: direct injection GC > static HSC > dynamic HSC, as direct GC is the most simple one. If the residual solvents have low partition coefficients but the sample a deleterious effect on the GC column, static HSC is recommended. In the case of solid samples, not soluble in a suitable solvent, multiple HSC can be used or dynamic GC. The latter is the method of choice for RS with high partition coefficients or for the analysis of very low concentrations/quantities. The addition of a standard should be used for calibration purposes whenever possible, as leading to the most precise results and because it is not influenced by the matrix, and external standardisation should only be used in the case of insoluble solid samples.

Beside pharmaceutical products, also foodstuff [126,127] as well as environmental samples and materials [128] contain residual solvents, which may act on man too.

Even though no world-wide accepted harmonisation guidelines for limiting residual solvent exist at the moment, it can be anticipated that the FDA (USA), the MHW (Japan) the CPMP (Europe), and the representatives from the pharmaceutical industry from the three regions will come to an agreement in the near future on this subject [16].

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