16

Residual Solvents in Products

16.1 RESIDUAL SOLVENTS IN VARIOUS PRODUCTS

George Wypych
ChemTec Laboratories, Inc., Toronto, Canada

There are physical and chemical barriers that control solvent removal from solid-solvent systems. The most basic relation is given by the following equation:

$$W = \frac{P_1}{K_w} \qquad [16.1.1]$$

where:

W	equilibrium fraction of residual solvent
P_1	partial pressure of solvent in vapor phase
K_w	Henry's law constant

Both the partial pressure and Henry's law constant depend on temperature, pressure, and solvent properties. This relationship does not consider interaction between solute and solvent. In the case of polymers, the Flory-Huggins theory gives a simplified relationship for low concentrations of solvent:

$$\ln\frac{P_1}{P_1^0} = \ln\phi_1 + 1 + \chi \qquad [16.1.2]$$

where:

P_1^0	vapor pressure of pure solvent
ϕ_1	volume fraction of solvent
χ	Flory-Huggins interaction parameter

Vapor pressures of some solvents can be found in the referenced monograph.[1]

The weight fraction of residual solvent at equilibrium can be calculated from the following equation, which accounts for polymer-solvent interaction:

$$W = \frac{P_1}{P_1^0}\frac{\rho_1}{\rho_2}\exp-(1+\chi) \qquad [16.1.3]$$

where:

ρ_1	density of solvent
ρ_2	density of polymer

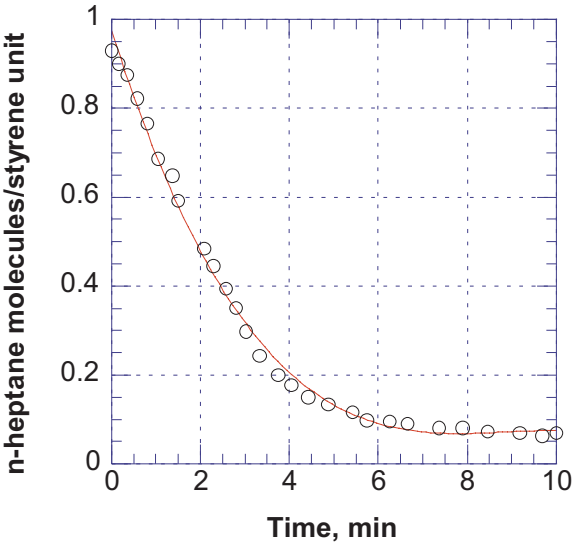

Figure 16.1.1. Number of n-heptane molecules per one mer of polystyrene vs. drying time. [Data from L A Errede, P J Henrich, J N Schrolpfer, *J. Appl. Polym. Sci.*, **54**, 649 (1994).]

The last equation does not give the real values of residual solvents because equilibrium is not attained in real drying processes and the prediction of different interactions by the interaction parameter is too simplistic. The real values are substantially higher and the real barriers of solvent removal more complex. These are discussed below.

In real systems, several phenomena take place. These include chemical interaction between the functional groups of polymer and the solvent. These are mostly related to hydrogen bond formation. The crystalline structure of polymer is responsible for the modification of the diffusion process. Solvent properties determine diffusion. Polymer properties are responsible for the macromechanism of solvent removal from a highly viscous polymer. In addition, some real systems make use of stripping solvents which are designed to help in removal of trace quantities of solvents by use of stripping solvent displacing process solvent. These various factors interplay and determine the result. Figure 16.1.1 shows the number of residual solvent molecules per one mer of polystyrene. It is evident that solvent removal has zero-kinetics until its concentration is decreased to about 0.2 molecules of solvent per mer. It is also true that some solvent remains after drying. Even after 24 h drying, 0.06% solvent remains.

These data indicate that there is a different mechanism of removing residual solvent. It is not clear if this is because of interactions, a change in the glass transition temperature, or a change in crystallinity. So far the partial effects of these influences cannot be separated. It is confirmed by experiment that in the last stages of drying, glass transition temperature of polymer changes rapidly. Also, the degree of crystallinity of the polymer increases during drying.[3,4] From studies on polyaniline, it is known that its conductivity depends on the concentration of adsorbed molecules of water.[5] Water interacts by hydrogen bonding with the polymer chain. The activation energy of hydrogen bonding is very low at 3-5 kcal/mol. Drying at 120°C reduced the amount of water molecules from 0.75 to 0.3 molecules per aniline unit. This change in water concentration drastically alters electrical conductivity which decreases by three orders of magnitude. Drying for two hours at 120°C did not result in complete removal of water. Given that the activation energy of hydrogen bonding is very low, the process of interaction is probably not the main barrier to removal of residual moisture. Also the relationship between conductivity and number of molecules of water is linear in the range from 0.15 to 0.75 molecules of water per aniline unit which means that there is no drastic change in the mechanism by which water participates in increasing the conductivity of polyaniline. Its conductivity simply depends on the distance between neighboring adsorbed molecules of water which apparently participate in the charge migration.

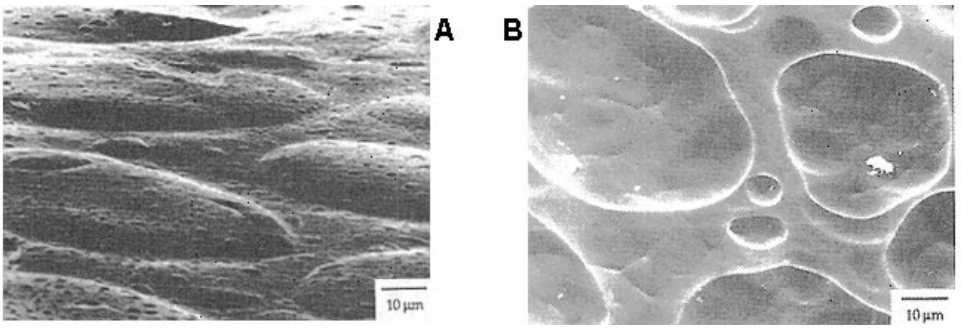

Figure 16.1.2. Blister formation in polyethylene containing originally 4000 ppm hexane. a - lateral surface 2.2 s after extrusion, b - cross-section after 28 s. [Adapted, by permission from R J Albalak, Z Tadmor, Y Talmon, *AIChE J.*, **36**, 1313 (1990).]

SEM studies contribute to an understanding of a major obstacle to residual solvent removal. Figure 16.1.2 shows two photographs of polyethylene strands extruded from a melt which initially contained 4000 ppm hexane. After a short period of time following the extrusion, blisters form which remain in the material and become enlarged until they break and release solvent. This blistering mechanism, determines the rate of residual solvent removal from the material. The rate of removal depends on bubble nucleation, temperature, and polymer rheological properties.[6]

Observing such mechanisms makes it easy to understand the principle involved in stripping solvents which became popular in recent inventions.[7-9] Stripping solvents were used to improve the taste and odor properties and the oxidative thermal stability of thermoplastic ethylene polymers.[7] Volatile components, such as products of degradation, solvent and monomer contribute to taste problems and odor formation. Striping solvents used include highly volatile hydrocarbons (ethylene, propylene, isobutane), inert gases, and supercritical fluids. An addition of at least 0.1% stripping solvent reduces volatiles from the typical levels of between 300-950 ppm to 45 ppm with even as low as 10 ppm possible. A stripping solvent helps in the generation of bubbles and their subsequent breaking by which both the stripping and the residual solvent are removed. In cosmetics and pharmaceutical formulations traces of solvents such as benzene or dichloromethane, used in the synthesis of acrylic acid polymer, disqualify the material. It is not unusual for this polymer to contain up to 1000 ppm of dichloromethane or up to 100 ppm of benzene. The use of mixed ester solvents helps to reduce residual solvent to below 5 ppm.[8] Polycarbonate pellets from normal production may contain up to 500 ppm solvent. This makes processing polycarbonate to optical products very difficult because of bubble formation. Elimination of volatiles renders the product suitable for optical grade articles.[9] These inventions not only demonstrate how to eliminate solvents but also confirm that the mechanism discussed in Figure 16.1.2 operates in industrial processes. The examples also show that large quantities of residual solvents are retained by products in their normal synthesis.

Many standard methods are used to devolatilize materials. Flash devolatilizer or falling strand devolatilizer are synonyms of equipment in which the falling melt is kept below the saturation pressure of volatiles. Styrene-acrylonitrile copolymers devolatilized in flash devolatilizer had a final concentration of ethylbenzene of 0.04-0.06.[1] Devolatilization of LLDPE in a single-screw extruder leaves 100 ppm of hydrocarbon solvent. 500 ppm chlorobenzene remains in similarly extruded polycarbonate.[1] It is estimated that if the polymer contains initially 1-2% solvent, 50-70% of that solvent will be removed through the vacuum port of an extruder.[1] These data seem to corroborate the information included in the above

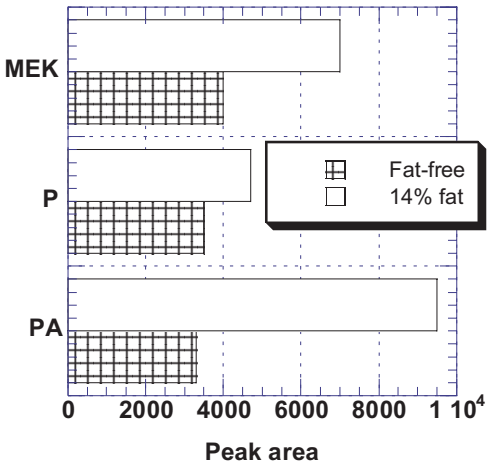

Figure 16.1.3. Volatility of three printing solvents (PA - propyl acetate, P - n-propanol, MEK - methyl ethyl ketone) from fat-free and fat-containing cookies. 20 µg solvent added to 2.5 g cookies. [Data from T Clark, *Paper Film Foil Converter*, **70**, 11, 48 (1996).]

discussed patents. The data show that considerable amounts of residual solvents can be found in polymers and plastic materials.

In the food industry, residual solvents associated with packaging odors enter food products from two sources: packing materials and printing inks.[10] It is estimated that concentrations of residual solvents have recently decreased (from 2000 mg/ream in past to 1000 mg/ream).[10] However, a new problem has become apparent in introduction of low fat or no fat food.[11] It was discovered[11] that more customer complaints about odor were received for these low fat baked goods products. Analysis shows that fat was a good solvent for volatiles (solvents) and consequently solvent odor was not detected because flavor perception is developed relative to the concentration of gaseous flavor compounds. Figure 16.1.3 shows the concentrations of three solvents as detected by gas chromatography. Substantially higher concentrations are detected in solvent-spiked fat-free cookies than in fat-containing cookies.[11] In this experiment solvents were added to the cookies. In another experiment, packaged cookies were exposed to a solvent vapor atmosphere and different trends were recorded for cookies packaged in two different films. If the film had good barrier properties, no difference was noticeable between both types of cookies and the adsorbed quantities of solvents were minimal. If the cookies were packaged in a coextruded film having lower barrier properties, no-fat cookies absorbed 42% more solvent than full fat cookies.

In the construction industry, residual solvent evaporation becomes an increasingly more critical issue, especially in the case of products used for indoor applications. Sealants, adhesives, and paints are now a major focus of this concern since they contribute to indoor pollution. Similar trends are observed in the automotive industry where both solvents and plasticizers are suspected of contributing to a “plastics” odor in car interiors.

In contrast, changes in the solvent evaporation rate may also contribute to product improvement in paints. Small quantities of properly selected solvents can improve physical properties and the appearance of paints. Other applications of residual solvents include time-controlled release of fertilizers and production of materials with controlled morphology.

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16.2 RESIDUAL SOLVENTS IN PHARMACEUTICAL SUBSTANCES

Michel Bauer
International Analytical Department, Sanofi-Synthélabo, Toulouse, France
Christine Barthélémy
Laboratoire de Pharmacie Galénique et Biopharmacie, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille 2, Lille, France

16.2.1 INTRODUCTION

The need to test for residual solvents (RS) in pharmaceutical substances was recognized in the late 70's when some pharmacopoeias like those of USA (USP XX) or Great-Britain (BP 80 + add 82) introduced specific tests for RS in some monographs. But we had to wait until the early 80's to see a rational approach for establishing specifications from toxicological data. This strategy was developed by a working group of the Italian Pharmacopoeia[1] starting from the threshold limit values for Chemical Substances and Physical Agents in the Work Environment published by the American Congress of Governmental Experts for Industrial hygiene.[2] In the late 80's, RS were definitively classified as impurities *per se*. Methods and specifications appeared in different issues of Pharmacopeial Forum and were submitted for discussion and finally integrated in the USP. At the same time only few such monographs could be found in the European Pharmacopoeia (Eur. Ph.) or British Pharmacopoeia (BP). Interestingly, the notion of a content limit for residual solvents in relation to the daily intake of the drug was introduced (see Eur. Ph. 2nd edition), a concept which was taken up later in the ICH Guideline. Numerous publications have been devoted to this subject.[3-9]

Although the number of papers on RS is immense, they are very often limited to specialized areas such as regulatory aspects or methodology aspects. In this chapter, different topics will be considered, starting with the fundamental question: why look for RS in pharmaceutical products? It is worth noting that Witschi and Doelker[10] published in 1997 a very detailed and up-to-date review stressing the importance of this subject in the pharmaceutical field.

16.2.2 WHY SHOULD WE LOOK FOR RS?

As we already have seen in Chapter 14.21.1, RS could have various effects on the drug substances, excipients and drug products.

16.2.2.1 Modifying the acceptability of the drug product

The presence of RS could seriously impair customer compliance because of the odor or the taste they can cause in the final pharmaceutical preparation. Rabiant[2] quotes the case of a drug substance having undergone, for technical reasons, a washing with isopropanol not planned in the manufacturing protocol. The oral solution prepared from this batch contained 100 ppm of this solvent and consequently had an odor that the majority of the patients accepted only with reluctance; the batch concerned was finally removed from the market.

16.2.2.2 Modifying the physico-chemical properties of drug substances (DS) and drug products (DP)

The role of the quality of the solvents on the stability e.g. of the raw materials, DS and DP (see Section 14.21.1) has already been discussed. It must be remembered that RS (including water) can show different kinds of interactions with solid substances:[11]

- Solvents adsorbed on the crystal surfaces, which generally are easily removed because of the existence of weak physical interactions.
- Occluded solvents and clathrates which are more difficult to extract without impairing the quality of the drug by, for example, excessive drying.
- Solvents bound to drug molecules in the crystal lattice. These solvents present as solvates (hydrates) are lost at a characteristic temperature and may be stable only over a limited range of relative humidity. The solvates and desolvated solvates, whilst being two different chemical entities, can retain the same crystalline structure (similarity of x-ray diffraction pattern) but show different physico-chemical properties.[12-14]

One of the most important effects of organic solvents absorbed on crystal surfaces is the ability to reduce the wettability of the crystals, especially if the solvent concerned is hydrophobic.[15]

Another interesting aspect, particularly in the case of residual water, is its role as an agent of recrystallization of poorly crystalline substances. It is well known that amorphous or partially amorphous products can undergo a recrystallization[16,17] process over time in presence of water. If amorphous phases are an interesting way to promote the dissolution rate of poorly soluble drugs, their main drawback is their physical instability triggering the possible crystallization of the drug and leading to a decrease in dissolution rate and possibly of bioavailability, over a period of time.

Furthermore the residual adsorbed water may have an impact on the flowability of a powder, which is linked to the solubility of the substance and the hydrophilicity of the crystal faces.[15] Other physico-chemical parameters are influenced by RS, like particle size and dissolution properties. For more information we refer to the publications of Doelker[10] and Guyot-Hermann[15] and references quoted therein. Nevertheless, one example deserves to be mentioned here.[10,16] Residual isopropyl alcohol enhanced the water permeability of Eudragit® L films used as tablet coating for protecting water-sensitive drugs as demonstrated by List and Laun.[16] This implies particular conditions for the storage of coated tablets during the film-drying process. The atmosphere should be as dry as possible.

The need to keep the RS level as low as possible can lead to some problems. It has been reported[15,17] that a drug substance displaying a strong odor of residual solvent was submitted to reprocessing, consisting of the displacement of the residual solvent by a stream of water vapor. During this process which slightly modified the surface crystallinity of the particles, a small amount of an impurity was produced. The consequence was an increase of the surface solubility of this drug substance. During the preparation of the DP using an aqueous wet granulation, a liquification of the granulate was observed making the manufacture impossible. After having removed the impurity by purifying the DS a successful manufacture of the DP was achieved.

There are other aspects linked to the manufacturing process and drying conditions which impact on the final RS content. They are discussed in Chapter 15.2.3 of this book (and references cited therein).

Nevertheless before closing this paragraph, another example of the relationship between the manufacturing process and RS is worth mentioning here. It relates to the formation of volatile compounds produced by radiolysis and which could induce odor. Barbarin et

al.[18] have investigated this subject in different antibiotics belonging to the cephalosporin group (Cefotaxime, Cefuroxime and Ceftazidine). Using GC-MS and GC-IR they were able to identify carbon monoxide, nitric oxide, carbon disulfide, methanol, acetaldehyde, ethyl formate, methyl acetate and acetaldehyde O-methyloxime. In a subsequent publication[19] on cefotaxime, they demonstrated that some of the radio-induced compounds (such as carbon monoxide sulfide (COS) and carbon disulfide) came from the degradation of the drug itself whereas the formation of others required the RS, present before the irradiation. For instance, acetaldehyde arises from the irradiation of methanol. Incidentally, this is a good way to differentiate between radio-sterilized and non-radio-sterilized products.

It is worth remarking that residual humidity can favor[15] microbiological growth especially in some natural products used as excipients (starch, gelatine, etc.). From a physico-chemical point of view, residual humidity may have an impact on the hardness of the tablets as shown by Chowhan,[20] Down and McMullen.[21]

16.2.2.3 Implications of possible drug/container interactions

It is possible that the RS contained in a powder may migrate up to the interface between the contents and the container facilitating the extraction and migration into the drug of additives used during the container manufacture. On the contrary, solvents may be used during the packaging of a drug. An example of this situation is described by Letavernier et al.[22] Cyclohexanone was used for sealing PVC blisters containing suppositories. After 42 months of storage at ambient temperature up to 0.2 mg to 0.3 mg of cyclohexanone was found per gram of suppository.

16.2.2.4 As a tool for forensic applications

Forensic laboratories are interested in identifying and assessing trace impurities in bulk pharmaceutical products with the idea of using the impurity profile as a "fingerprint" of the manufacturer. Of course, RS can be an important aid in this process.[23,24] It has been demonstrated,[25] for instance, that static headspace GS coupled with mass spectrometry (MS) was able to detect and identify volatile impurities, making possible the characterization of illicit heroin or cocaine samples.

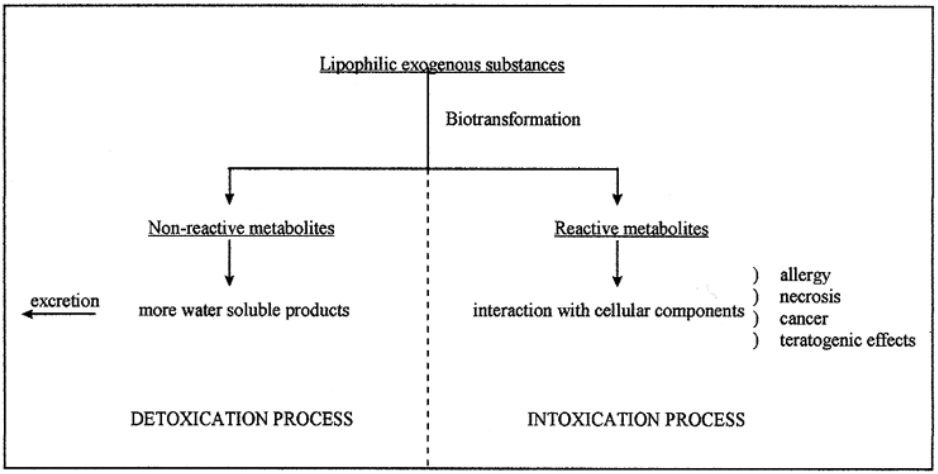
16.2.2.5 As a source of toxicity

16.2.2.5.1 General points

Toxicity is obviously the main reasons for testing for RS. Besides the toxicity of the drug itself, the related impurities,[26] degradants and the RS obviously can each bring their own contribution. A drug could be prescribed to a patient either for a short period of time or a long one. To minimize either acute toxicity or chronic toxicity resulting from some accumulation process, RS have to be kept at the lowest achievable level. When developing new chemical entities, the presence of RS could bias toxicity studies including mutagenicity and carcinogenicity and cause a risk of wrongly ascribing to the drug substance or the formulation, side effects which are actually due to volatile impurities. Knowing the cost of such studies, it is preferable to have the RS under control.

The long-term exposure to solvents has been recognized for a long time as a possible cause of serious adverse effects in human. Tables of maximal tolerated solvent concentrations in air for defined exposures have been published and used to set limits for residual organic solvents in pharmaceuticals.[1-10] In the late 90's, a set of articles appeared in the Pharmacopeial Forum proposing RS limits from toxicological data,[27] including carcinogenicity, mutagenicity, teratogenicity and neurotoxicity.

Table 16.2.1. (After from reference 28)



In the early 80's, the "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use" (ICH) was created. Among the different topics deserving to be harmonized, the need to have an agreement amongst Europe, Japan and the USA on the ways to limit the RS in pharmaceuticals was clearly identified and the topic adopted in June 1994. The final guide was finally adopted in 1998 by the Health Authorities of the three zones and is now in force. This Guideline will be examined in detail in the last paragraph of this part.

16.2.2.5.2 Brief overview of the toxicology of solvents[28,29]

16.2.2.5.2.1 Aspects concerning metabolism

There are four main routes by which solvents can interact with the human body:

- O.R.L. (Otorhinolaryngology)
- transdermal (including the ocular area)
- oral
- injection

Once in the organism, solvents will undergo biotransformation which essentially takes place in the liver. This metabolism very often leads to more water-soluble products than the parent compound[30,31] and, as such, more easily excreted by the kidneys. This detoxication process is beneficial for the individual but varies greatly from one subject to another. Unfortunately, this metabolic detoxication can be complicated by the appearance of reactive intermediates which, if not rapidly inactivated, will destroy the essential constituents of the cells (proteins, nucleic acids, unsaturated lipids) and cause INTOXICATION. The latter ranges from a simple allergic reaction to tissue necrosis or, at worst, to cancer. Table 16.2.1 summarizes the different events which can occur in the organism.

16.2.2.5.2.2 Solvent-related pathology

16.2.2.5.2.2.1 Acute toxicity

It is especially the affinity of the solvents for lipid-rich organs which triggers problems of acute toxicity and these concern primarily the nervous system, the heart, the liver and kidneys. In this acute toxicological process, the molecules act per se without any previous biotransformation. The acute toxicity encompasses:

- nervous toxicity (headache, somnolence, coma, more or less deep, which can extend to death)
- cardiac toxicity[32]
- action on skin and mucous membranes generating irritation (including ocular area)[33]

16.2.2.5.2.2.2 Long-term toxicity

A prolonged exposure, even at low doses, to several liposoluble solvents leads sooner or later to irreversible effects on different organs:

- central nervous system (e.g., toluene could lead to degeneration of the brain)
- peripheral nervous system (e.g., methanol shows a peculiar affinity for the optic nerve leading possibly to blindness)
- liver and kidneys; as solvents are metabolized in the liver and excreted by kidneys, these two organs are, of course, particular targets for these products
- skin and mucous membranes (e.g., dermatitis)
- blood (cyanosis, anaemia, chromosomal abnormality)

With regard to carcinogenicity, benzene has long been recognized as carcinogen in man. It is the reason why its use is strictly limited and not recommended (ICH class I/specifications 2 ppm). Carbon tetrachloride and 1,2-dichloroethane have been demonstrated to be carcinogenic in animals and potentially carcinogenic in man.

The embryotoxicity of solvents must be taken into account. As solvents can cross the placenta, pregnant women should be especially protected.

16.2.2.5.2.2.3 Metabolism of benzene

By way of illustration, Figure 16.2.1 summarizes the metabolic pathway of benzene.[34] Numerous publications dealing with the metabolism of benzene are given in reference 27.2.

16.2.3 HOW TO IDENTIFY AND CONTROL RS IN PHARMACEUTICAL SUBSTANCES?

16.2.3.1 Loss of weight

Historically this is the first method which appeared in the pharmacopoeias, performed either at normal pressure or under vacuum. This is, of course, an easy method, particularly for routine control but there are several drawbacks:

- lack of specificity
- it is product demanding (1-2 g)
- the limit of detection (LOD) is currently about 0.1 %

This determination can now be done by thermogravimetric analysis (TGA) which makes the method more sensitive (possible LOD 100 ppm) and less product demanding (5 - 20 mg). It can also be used as a hyphenated method linking TGA to a mass spectrometer, allowing the identification of the desorbed solvents (specificity). However, whilst this kind of equipment exists, there are no signs of it replacing gas chromatography (GC) in the near future.

16.2.3.2 Miscellaneous methods

Infrared spectroscopy[35] and ^{1}H-NMR[36] have been used occasionally to identify and to quantify residual solvents, but their sensitivity is rather limited if compared with GC. On the other hand specificity is not always assured. The solvent should display signals well separated from those arising from the product, which is not always the case.

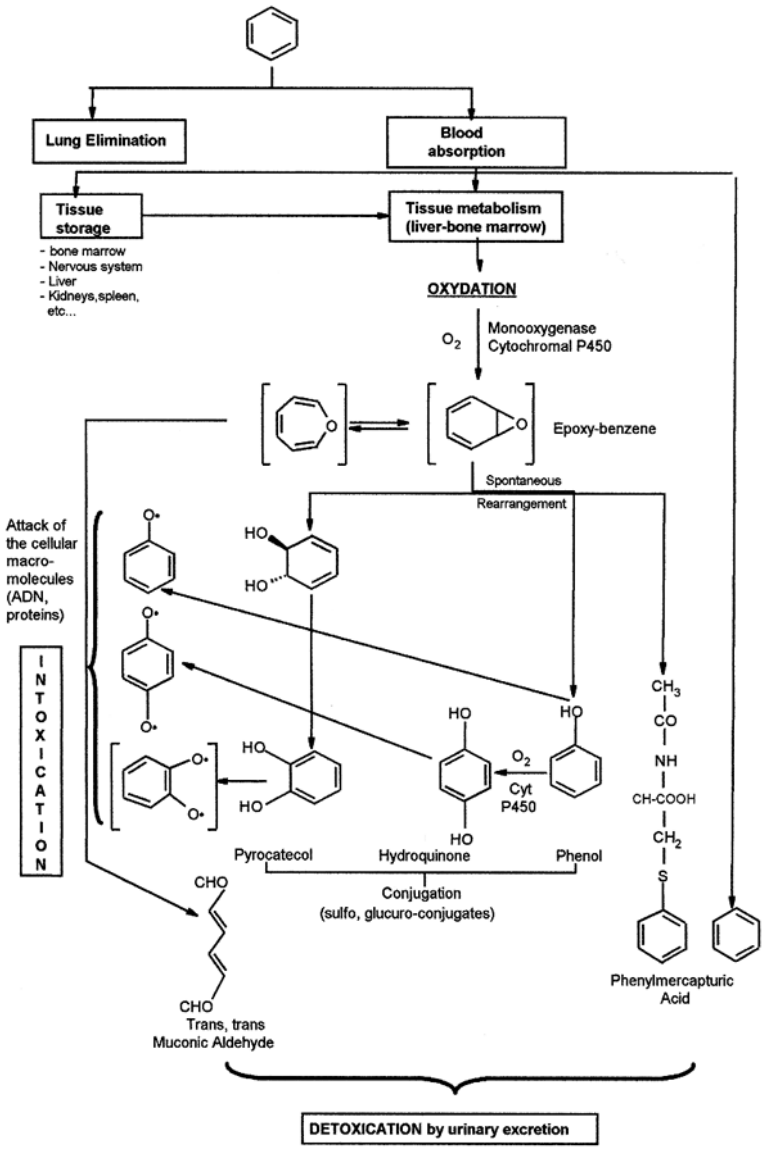


Figure 16.2.1. Overview of benzene metabolism (after reference 34).

16.2.3.3 Gas chromatography (GC)

16.2.3.3.1 General points

This is, of course, the method of choice which has long been used to determine RS whatever the area of application (pharmaceuticals, polymers, water analysis, etc.).[37-40] From the late 70's to the beginning of the 80's, there was a large number (or flood) of publications dealing with different possible GC techniques which could be applied for detecting or analyzing residual solvents especially in pharmaceuticals (intermediates of synthesis, drug sub-

stances, excipients and drug products). So much has been written that it is difficult to be original. Methodological aspects will be briefly covered in the next paragraph. The paper of Witschi and Doelker[10] is particularly recommended. With 171 references, it represents a worthwhile, up-to-date review of the different GC techniques available. The last part of this chapter concerns pharmacopoeial methods.

16.2.3.3.2 Review of methods

Regarding GC methodology, four aspects must be examined:

- injection systems
- columns
- detectors
- method validation

16.2.3.3.2.1 Injection systems

16.2.3.3.2.1.1 Direct injection

After having dissolved the substance containing the RS to be looked for in an appropriate solvent, it is possible to directly inject into the system 100% of an aliquot of the solution (if packed columns are used) or partially through a split system (if capillary, narrow-bore and wide-bore columns are used). It is simple, accurate and repeatable (with an internal standard). The main drawback is that samples very often contain non-volatile substances which are retained by the column, leading rapidly to a loss of efficiency and a dramatic decrease in sensitivity.[41] In the current literature dealing with the RS, the direct injection process is less frequently used. Nevertheless, publications have appeared until recently using split/splitless injection.[42,43]

16.2.3.3.2.1.2 Static headspace injector

The solubilized or suspended sample in an appropriate vehicle is heated at a defined temperature in a tightly closed vial until thermodynamic equilibrium is reached between the liquid phase and the gas phase. A known aliquot is then transferred either with the aid of a syringe or by an automatic transfer system onto the column. The main advantage is that only volatile products including solvents are injected into the column greatly improving its lifetime. The sensitivity is good and the system is easily automated.

The main drawback is the existence of matrix effects and the possible non- ideality of the solvents mixture. These imply that ideally one should determine the calibration curve by adding standard solutions of the solvents of interest to the sample matrix, free of solvents. Because it is very difficult to obtain such a sample matrix, the classical standard addition method is recommended. It consists of adding to the sample matrix to be analyzed a known amount of the solvents to be determined. This method requires two analyses for the final calculation but the main advantage is that the matrix effect is overcome. The linearity of the response has, of course, to be demonstrated before the use of the simplified version mentioned above. Nevertheless, if based on a sound validation, external calibration can be used.[41,44]

The nature of the solvent used to prepare the solution (e.g., water, dimethylformamide, dimethylacetamide, 1,3-dimethyl-2-imidazolidinone (DMI)), equilibration temperature, the ratio between the gas phase and the liquid phase and the possible need to promote a salting out effect by adding mineral salts are the parameters, amongst others, which should be investigated and optimized to improve the sensitivity (LOD, LOQ) of the method.[45-47]

Another version of this static headspace chromatography is what has been called by Kolb[48] multiple headspace extraction (MHE) chromatography. This is a multi-step injection

technique which was alluded to in the Suzuki publication[39] and more openly developed by MacAuliffe.[49] The principle of this method is the following.[50,51] After the first extraction has been made and the aliquot injected, the gas phase is removed by ventilating the vial and re-establishing the thermodynamic equilibrium. The equilibrium between the analyte in the solid or liquid phase and the gas phase will be displaced each time. After n extractions, the analyte content in the liquid or solid phase becomes negligible. It is then sufficient to sum the peak areas obtained for each extraction (which decrease exponentially) and, from an external calibration curve determine the amount of RS in the substance.

This method is particularly useful for insoluble products or in cases where the partition coefficient of the RS is too favorable relative to the liquid phase. It has been recently successfully applied to the determination of RS in transdermal drug delivery systems.[51]

16.2.3.3.2.1.3 Dynamic headspace injection

In the dynamic headspace method, the sample is put in a thermal desorption unit in order to desorb the RS; a continuous flow of a carrier gas pushes the RS into a trapping system which is refrigerated and where they are accumulated prior to analysis. Then the RS are rapidly desorbed by rapid heating and carried onto the column via the carrier gas. There are different ways to apply this technique.[10,52] The arrangement when purge gas passes through the sample is often called the purge and trap technique (some other equipment uses the acronym DCI (desorption, concentration, injection)). This method is particularly useful for very low concentrations of RS as the total amount of a substance is extracted and can be applied directly to powders without need to dissolve them. The main drawback is that the dynamic headspace methods are not readily automated.[41]

16.2.3.3.2.1.4 Other techniques

Several others techniques dealing with the injection problems have been developed. Among them the solid-phase microextraction method[52-55] (SPME) and the full evaporation technique[56] must be mentioned. According to Camarasu,[53] the SPME technique seems to be very promising for RS determination in pharmaceuticals, with much better sensitivity than the static headspace technique.

16.2.3.3.2.2 Columns

The wealth of publications dealing with RS determination by GC is so impressive that it is difficult to provide an exhaustive review. The interested reader will find plenty of information in the references quoted so far and in others recently published, mentioned below. Packed columns,[57] wide or narrow bore columns, capillary columns, etc. have been used for RS determination. It is true to say that capillary columns and narrow bore columns are the most often mentioned techniques. Today it is almost certain that any user can find in the literature[10] the stationary phase and the relevant conditions to resolve his RS problem, at least in terms of selectivity. By way of example, it has been shown by Brinkmann and Ebel[58,59] how it was possible to screen 65 of the 69 solvents mentioned in the ICH Guideline (discussed in paragraph 16.2.4) using capillary columns filled with two stationary phases (DB 624 and Stabilwax) which basically constitute the strategy proposed by the European Pharmacopoeia.

16.2.3.3.2.3 Detectors

The almost universally used detector is the flame ionization detector (FID) which works with all organic solvents but which is not selective. The mass spectrometer detector (MSD) is now more and more utilized.[24,53,55,60,61] It can be either universal in its electron ionization (EI) mode or selective in its selective ion monitoring mode (SIM). Other detectors, selective

and/or universal, can be used.[10,62] Among them the electron capture detector has to be mentioned when looking for chlorinated solvents, even if its use is not straightforward.

16.2.3.3.2.4 Method validation

Whatever the technique used for determining the RS content in pharmaceuticals, a thorough validation of the complete analytical process has to be conducted according to the ICH Guidelines [Text on "validation of analytical procedures" and "validation of analytical procedures: methodology"[63]]. For testing impurities in a quantitative manner the following items have to be completed:

- specificity (or more appropriately selectivity)
- accuracy
- precision
  - repeatability
  - intermediate precision (first part of reproducibility)
- limit of detection (LOD), limit of quantification (LOQ)
- linearity of the response
- the range which is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

In the publications mentioned above,[24,41-43,51-54,58,59,64] it is possible for reader to find experimental procedures to conduct validation efficiently. Attention is drawn to the fact that, when using the static headspace technique in particular some other parameters have to be investigated, such as:[24,51]

- ratio gas phase/solid or liquid phase
- temperature of equilibrium between the two phases and time to reach it
- temperature of the transfer line
- pressurization time and sampling time when using a fully automated headspace injector

Finally, some additional comments are worth making:

- As regards reproducibility, it is true that the best way to assess it is to set up an inter-laboratory study. It is of course burdensome but this is probably the only way to infer reasonable suitability parameters for the routine quality control monograph (resolution, plate number, tailing factor, repeatability, LOD, LOQ) and specifications. It is worth noting that the latter should take the performance of the analytical method into account. But for those who cannot follow this approach, sound ruggedness testing has to be performed. Maris et al. have designed a method[65] for evaluating the ruggedness of a gas chromatographic method for residual solvents in pharmaceutical substances.
- When using the static headspace injector the possible matrix effect should be studied and can be evaluated by a statistical method.[66,67]
- One of the most important suitability parameters in case of RS determination is, of course, the LOQ (and LOD). In order to avoid an unrealistic value in the QC monograph, it is highly recommended to use a working limit of quantification WLOQ (and WLOD) which consists of determining a reasonable upper limit for LOQ (and LOD). In fact, the LOQ derived from the validation package is obtained in what we can call an ideal or optimized environment.

A way for determining α (> 1) in the relationship:

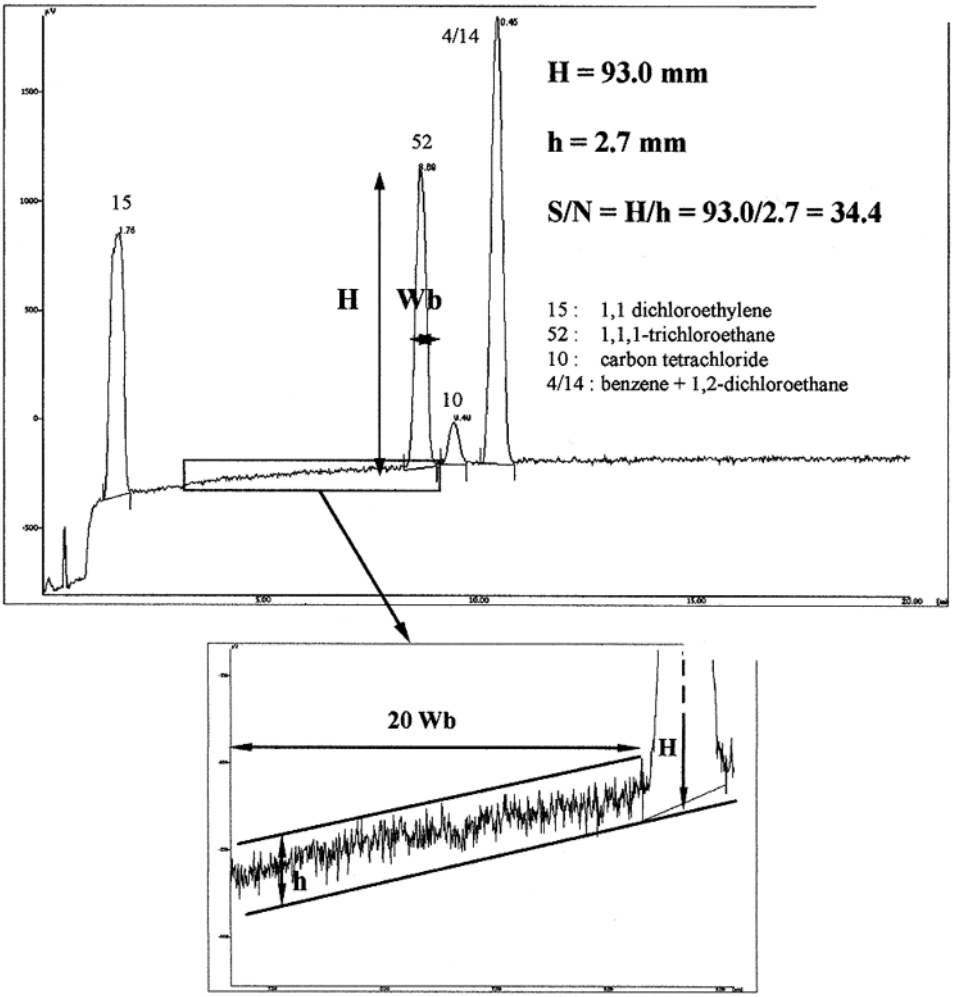


Figure 16.2.2. Head-space injection of the gaseous sample into the chromatographic system. Typical chromatogram of class 1 solvents using the conditions described for System A (European Pharmacopoeia method). Flame-ionization detector: calculation of H/h for 1,1,1-trichloroethane.

$$WLOQ = \alpha\, LOQ$$

is to calculate the LOQ according to the signal to noise ratio S/N method[63,68] (see Figure 16.2.2) and to repeat this determination independently several times (e.g., n = 6) during the intermediate precision determination. If LOQ_m is the mean value and σ the standard deviation, a possible definition of WLOQ could be the upper limit of the one side confidence limit at a specified risk α (e.g., 0.05).

$$WLOQ = LOQ_m + t_{n-1,\alpha}\sigma$$

where t is Student's coefficient.

16.2.3.3.3 Official GC methods for RS determination

Current official GC methods are described in USP XXIII under chapter 467 "Organic volatile impurities". Four methods (I, IV, V, VI) are mentioned. Methods I, V and VI are based on direct injection. They are suitable for water-soluble drugs and V for water insoluble drugs. Method IV describes the static headspace technique and is used for water soluble drugs. Method VI is very general and refers to the individual monograph which describes the chromatographic conditions (injection, column, conditions) which should be used. The main characteristics of these four methods are summarized in Table 16.2.2.

The European Pharmacopoeia[69] used a two-tiered process based on two different columns:

System A. Fused silica capillary or semi capillary column (30 m x 0.32 mm (ID) or 30 m x 0.53 mm (ID)) DB 264 (1.8 µm or 3 µm film thickness of the phase (6 per cent cyanopropylphenyl-94 percent dimethylpolysiloxane)) which is identical to the USP method V.

System B. Fused silica capillary or semi-capillary column (30 m x 0.32 mm (ID) or 30 m x 0.53 mm (ID) DB-wax (0.25 µm film thickness of Macrogol 20000R)).

Table 16.2.2. Gas chromatographic methods described in USP 23 (from ref. 10)

Method	Sample	Standardization	Column	Detector
USP <467> Method I: Direct GC injection	Dissolved in water or another appropriate solvent	External	30 m x 0.53 mm ID, fused silica, with 5µm crosslinked G27[a] stationary phase and A 5 m x 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 x 0.53 mm ID, fused silica with 3 µm G43[b] stationary phase and a 5 m x 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

Method	Sample	Standardization	Column	Detector
USP <467> Method for dichlormethane 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

*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, polyethyleneglycol compound (polyethyleneglycol compound 20M or carbowax 20 %; G27, see a; G39, polyethyleneglycol (M_w 1500).

The static headspace injector has been selected and the method developed for water soluble products using water as dissolution medium or using N,N-dimethylformamide for water-insoluble products. If N,N dimethylacetamide and/or N,N-dimethylformamide are suspected in the drug under investigation 1,3-dimethyl 2-imidazolinone (DMI) is used as dissolving medium.

The method has been designed:

- in order to identify most class 1 and class 2 RS potentially present in drug substances, excipients or drug products.
- as a limit test for class 1 and class 2 RS present in drug substances, excipients and drug products.
- to quantify class 2 RS where the content is higher than 1000 ppm or class 3 RS if the need arises.

Figures 16.2.3, 16.2.4, 16.2.5, and 16.2.6 illustrate the separations obtained in the two systems for solvents belonging to class 1 and class 2 solvents. This general method is the outcome of European working party which has been published in Pharmeuropa.[70]

It should be stressed that the use of a general pharmacopeial method is not a reason not to validate the latter when analyzing a particular substance. The matrix effect, in particular, has to be investigated when using the static headspace mode of injection.

16.2.4 HOW TO SET SPECIFICATIONS? EXAMINATION OF THE ICH GUIDELINES FOR RESIDUAL SOLVENTS

The introduction briefly summarizes the strategies dealing with the setting of specifications in pharmaceuticals which appeared during the 80's.

From the early 90's onwards, the International Conference on Harmonization was initiated in three important pharmaceutical regions (Europe, Japan, USA) in order to define a common way of preparing a registration file acceptable in the three zones. The topics included in this harmonization process are:

- Quality
- Safety
- Efficacy

Regarding Quality a set of Guidelines have been already adopted. Three of them are particularly relevant with regard to this article:

- Guideline Q3A: Impurities in new active substances
- Guideline Q3B: Impurities in new medicinal products
- Guideline Q3C: Note for guidance on impurities: residual solvents

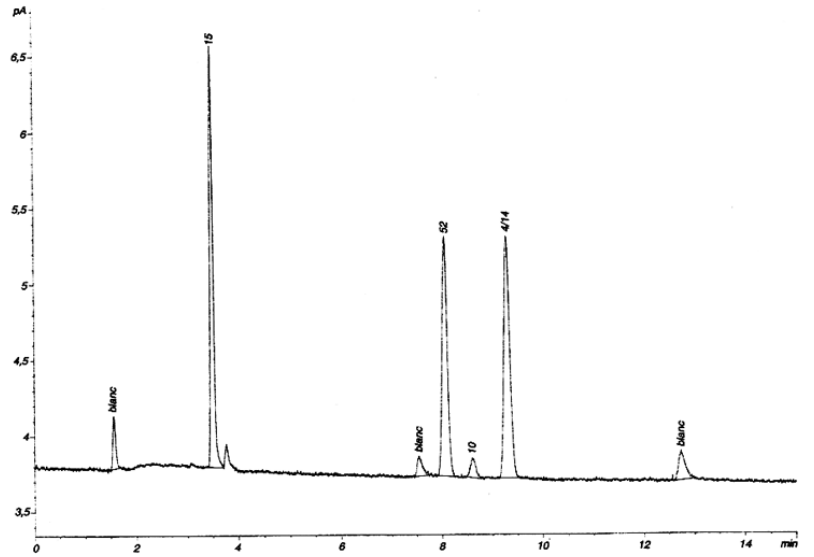


Figure 16.2.3. Typical chromatogram of class 1 solvents using the conditions described for system A and procedure 1. Flame-ionization detector. 4: benzene; 10: carbon tetrachloride; 14: 1,2-dichloroethane; 15: 1,1-dichloroethylene; 52: 1,1,1-trichloroethane. [Adapted, by permission, from **European Pharmacopoeia**, **Addendum 2000**, pp31-36.] [Please note that information concerning residual solvents are susceptible to be modified in the successive editions of the European Pharmacopeia.]

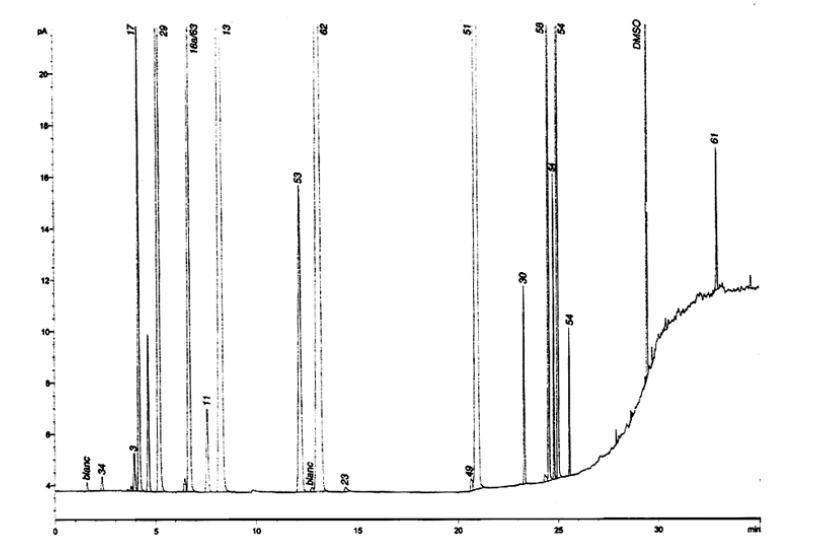


Figure 16.2.4. Chromatogram of class 2 solvents using the conditions described for system A and procedure 1. Flame-ionization detector. 3: acetonitrile; 11: chloroform; 13: cyclohexane; 16a: cis-1,2dichloroethylene; 17: dichloromethane; 29: hexane; 30: 2-hexanone; 34: methanol; 49: pyridine; 51: toluene; 53: 1,1,2-trichloroethylene; 54: xylene ortho, meta, para; 58: chlorobenzene; 61: tetraline; 62: methylcyclohexane: 63; nitromethane; 64: 1,2-dimethoxyethane. [Adapted, by permission, from **European Pharmacopoeia**, **Addendum 2000**, pp31-36.] [Please note that information concerning residual solvents are susceptible to be modified in the successive editions of the European Pharmacopeia.]

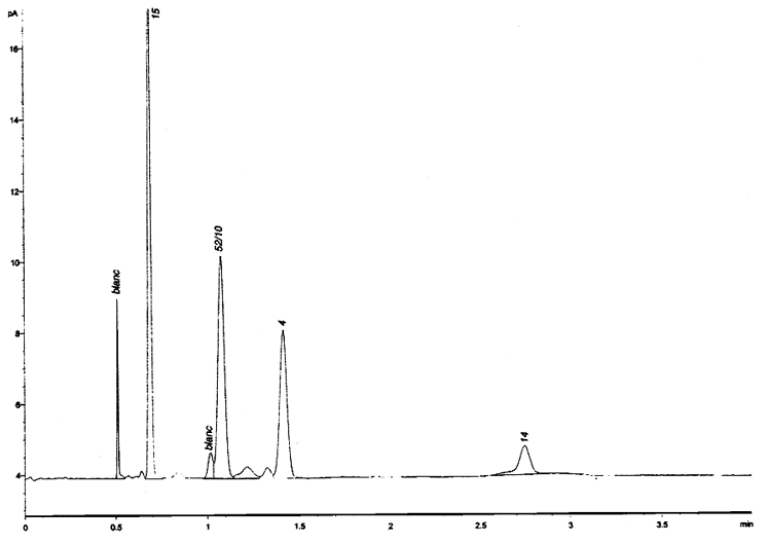


Figure 16.2.5. Chromatogram of class 1 residual solvents using the conditions described for system B and procedure 1. Flame-ionization detector. 4: benzene; 10: carbon tetrachloride; 14: 1,2-dichloroethane; 15: 1,1-dichloroethylene; 52: 1,1,1-trichloroethane. [Adapted, by permission, from **European Pharmacopoeia**, **Addendum 2000**, pp31-36.] [Please note that information concerning residual solvents are susceptible to be modified in the successive editions of the European Pharmacopeia.]

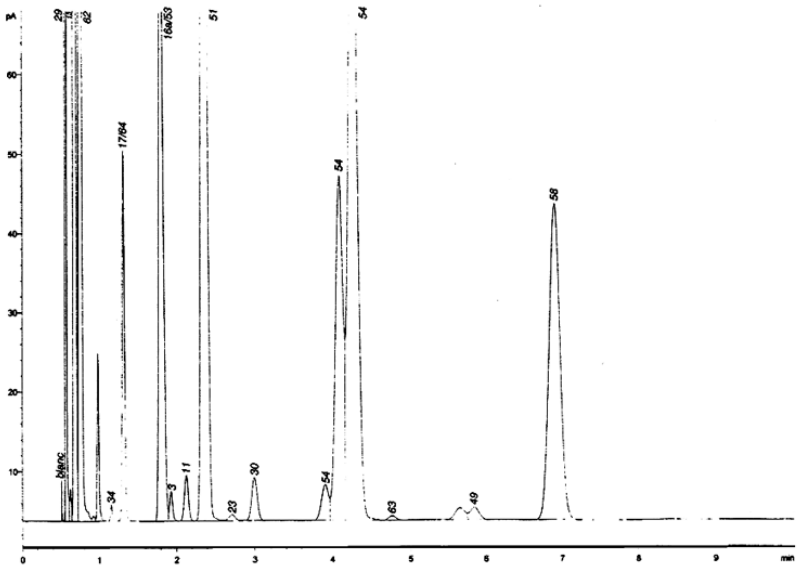


Figure 16.2.6. Typical chromatogram of class 2 residual solvents using the conditions described for system B and procedure 1. Flame ionization detector. 3: acetonitrile; 11: chloroform; 13: cyclohexane; 16a: cis-1,2-dichloroethylene; 17: dichloromethane; 23: 1,4-dioxane; 29: hexane ; 30: 2-hexanone; 34: methanol; 49 : pyridine ; 51 : toluene ; 53 : 1,1,2-trichloroethylene ; 54 : xylene, ortho, meta, para; 58: chlorobenzene; 61: tetralin; 62: methylcyclohexane; 63: nitromethane; 64: 1,2-dimethoxyethane. [Adapted, by permission, from **European Pharmacopoeia**, **Addendum 2000**, pp31-36.] [Please note that information concerning residual solvents are susceptible to be modified in the successive editions of the European Pharmacopeia.]

Comments on the latter are given below. The full text can be found in the US Pharmacopoeia, in the European Pharmacopoeia or in Journals[71] (there is also a website - www.ifpma.org/ich1.htm).

16.2.4.1 Introduction

The Guideline recommends acceptable amounts of RS in pharmaceuticals which are safe for the patient. Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of active substances or excipients, or in the preparation of medicinal products. It is stated that medicinal products should contain no higher levels of residual solvents than can be supported by safety data. Three classes of solvents have been defined based on risk assessment.

16.2.4.2 Classification of residual solvents by risk assessment

Class 1 solvents: solvents to be avoided, known as human carcinogens or strongly suspected carcinogens and environmental hazards.

Class 2 solvents: solvents to be limited. Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicities such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

Class 3 solvents: Solvents with low toxic potential to man: no health-based exposure limit is needed. Class 3 solvents have permitted daily exposures (PDE) of 50 mg or more per day.

16.2.4.3 Definition of PDE. Method for establishing exposure limits

The PDE is defined as a pharmaceutically acceptable intake of RS. The method used to establish PDEs for RS is described in the references cited above.[27,71]

16.2.4.4 Limits for residual solvents

Table 16.2.3. Class 1 solvents in pharmaceutical products (solvents that should be avoided)

Solvent	Concentration limit, ppm	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1.2-Dichloroethane	5	Toxic
1.1-Dichloroethene	8	Toxic
1.1.1-Trichloroethane	1500	Environmental hazard

Solvents of class 1 (see Table 16.2.3) should not be employed. However, if their use is unavoidable in order to produce a significant therapeutic advance, then their levels should be restricted as shown in Table 16.2.3, unless otherwise justified.

Solvents of class 2 (see Table 16.2.4). Two options are available when setting limits for class 2 solvents.

Option 1

The concentration limits in ppm stated in Table 16.2.4 can be used. They were calculated using the equation [16.2.1] by assuming a product mass of 10 g is administered daily.

$$concentration\,(ppm) = \frac{1000 \times PDE}{dose}$$

where PDE is given in mg/day and dose is given in g/day.

Table 16.2.4. Class 2 solvents in pharmaceutical products

Solvent	PDE, mg/day	Concentration limit, ppm
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene	21.7	2170

Option 2

It is not considered necessary for each component of the medicinal product to comply with the limits given in option 1. The PDE in terms of mg/day as indicated in Table 16.2.4 can be used with the known maximum daily dose and equation [16.2.1] to determine the concentration of residual solvent allowed in the medicinal product. Option 2 may be applied by adding the amounts of RS present in each of the components of the pharmaceutical formulation. The sum of the amounts of solvent per day should be less than that given by the PDE.

Table 16.2.5. Class 3 solvents which should be limited by GMP or other quality-based requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methyl ethyl ketone
tert-Butyl methyl ether	Methyl isobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Tetrahydrofuran

Table 16.2.6. Solvents for which no adequate toxicological data was found

1,1-Diethoxypropane
1,1-Dimethoxymethane
2,2-Dimethoxypropane
Isooctane
Isopropyl ether
Methylisopropyl ketone
Methyltetrahydrofuran
Petroleum ether
Trichloroacetic acid
Trifluoroacetic acid

Solvents with low toxic potential solvents of class 3 (see Table 16.2.5) may be regarded as less toxic and of lower risk to human health. It is considered that amounts of these RS of 50 mg per day or less (corresponding to 5000 ppm or 0.5 % under option 1) would be acceptable without justification. Higher amounts may be acceptable provided they do not have a negative impact on the processability and the stability of the pharmaceutical product.

Solvents for which no adequate toxicological data was found (Table 16.2.6). These solvents can be used in the manufacture of drug substances, excipients and drug products, but the manufacturer should supply justification for residual levels of these solvents in pharmaceutical products.

16.2.4.5 Analytical procedures

If only class 3 solvents are present, a non-specific method such as loss of drying may be used. In the other cases a selective method (e.g., GC) is required. Especially if solvents of class 2 and class 3 are present at greater than their option 1 limits or 0.5 %, respectively, they should be identified and quantified.

16.2.4.6 Conclusions regarding the ICH Guideline

The lists are not exhaustive and other solvents can be used and added later to the lists. Recommended limits of class 1 and class 2 solvents or classification of solvents may change as new safety data become available.

Nevertheless this Guideline is of great interest for those involved in the pharmaceutical development in order to prepare successfully a pharmaceutical dossier acceptable everywhere in the world.

16.2.5 CONCLUSIONS

Those who have worked for many years in pharmaceuticals will have observed continuous progress in standards of Quality and Control in manufacturing.

Solvents including water are still used in almost every step of the elaboration of a drug product. Their residues could be detrimental for the processability and stability of the pharmaceutical products and the safety of patients. At the end of this millennium it can be said that the testing and control of RS has been thoroughly assessed and is based on robust and sensitive techniques, for which the limitations are known, resulting in a sound strategy accepted almost everywhere in the world.

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