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REVIEW

ORGANIC SOLVENTS IN THE PHARMACEUTICAL INDUSTRY

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Abstract: Organic solvents are commonly used in the pharmaceutical industry as reaction media, in separation and purification of synthesis products and also for cleaning of equipment. This paper presents some aspects of organic solvents utilization in an active pharmaceutical ingredient and a drug product manufacturing process. As residual solvents are not desirable substances in a final product, different methods for their removal may be used, provided they fulfill safety criteria. After the drying process, analyses need to be performed to check if amounts of solvents used at any step of the production do not exceed acceptable limits (taken from ICH Guideline or from pharmacopoeias). Also new solvents like supercritical fluids or ionic liquids are developed to replace "traditional" organic solvents in the pharmaceutical production processes.

Keywords: organic solvents, residual solvents, acceptable limits

Organic solvents are constantly present in the pharmaceutical production processes. The pharmaceutical industry is one of the largest users of organic solvents per amount of the final product (1). They are usually used at any step of the synthesis pathway of an active substance or excipients, and sometimes during the drug product formulation process. Because of some physical and chemical barriers, organic solvents cannot be completely eliminated from the product by manufacturing practices, such as drying in an elevated temperature under decreased pressure or by lyophilization (freeze-drying). Usually some small amounts of solvents may remain in the final product. They are called residual solvents (RS), also commonly known as organic volatile impurities (OVI). Additionally, a drug product may also become contaminated by organic solvents from packaging, warehouse storage, or from shipping and transportation.

For toxicological reasons manufacturers aspire to minimize the number and amount of solvents applied in a drug production. Apart from the fact that they have no therapeutical value and may be toxic, they may additionally accelerate decomposition of the product. Special directions published in pharmacopeias and ICH guidelines determine maximum allowable amounts of RS in pharmaceutical products (2-4). If amounts of RS are below the limits the analyzed product is cleared for sale.

In this article, many aspects of organic solvents use in drug product development and manufacturing are presented (acceptable limits and regulations, synthesis, formulation, production, packaging, solvents removal, analytical methods) and new ideas of their replacement with the technologies used in other industries will be mentioned.

Regulations/legislations

Generally, for objective reasons, the pharmaceutical industry is a tightly regulated branch of manufacturing. That is the reason why, based on the toxicity of individual solvents, RS limits for pharmaceutical products and excipients have been set by different associations.

In the past, the pharmaceutical industry needed to unify regulations and limits for residual solvents. For many years the United States Pharmacopoeia was the only pharmacopoeia setting limits for residual solvents in pharmaceutical products (chapter <467> Organic Volatile Impurities). In 1990, limits for RS were proposed in Pharmeuropa (5) and, more recently, in the second International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline draft. In December 1997 the ICH published its Guidance for Industry Q3C which became effective in March 1998. ICH guideline compromised regulatory authorities from Europe,

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Japan and the United States, as well as representatives of the research based pharmaceutical industry.

According to Q3C guideline solvents are divided into four groups (2). The first group (Class 1) contains known human carcinogens, compounds strongly suspected of being human carcinogens, and environmental hazards – Table 1. These solvents should be avoided, unless strongly justified. The limits for Class 1 solvents are listed as absolute parts per million in a material under testing (drug or excipient). Class 2 solvents presented in Table 2 ought to be limited because they are non-genotoxic animal carcinogens or possible causative agents of irreversible toxicity, such as neurotoxicity or teratogenicity. They are also suspected of other significant, reversible toxicities. Class 2 solvents' limits are listed in two ways (2). Option 1 uses the absolute parts per million of solvents contained in the material being tested and is used in cases where the daily dose is known or fixed and is expressed by the formula:

$$\text{Concentration (ppm)} = (1000 \times \text{PDE})/\text{dose (in grams per day)} \quad (2)$$

where: PDE – permissible daily exposure limit in milligrams.

In Option 2, the sum of amounts of residual solvents present in each component of the drug product per day, should be less than given by PDE. The ICH Q3C guideline has illustrative tables showing a passing and failing Option 2 scenario. If a sample fails Option 1, but passes Option 2 criteria, then it passes the residual solvents requirement. If a sample fails both Option 1 and Option 2 criteria then it fails the residual solvents requirement.

Class 3 solvents have permissions of daily exposures of 50 mg (0.5%) or less (corresponding to 5000 ppm or 0.5% under Option 1 described for Class 2) per day. Higher amounts may also be acceptable when the manufacturer proves that the amounts of Class 3 solvent is realistic with relation to manufacturing capability and good manufacturing practice. There is no solvent recognized as a human health hazard at levels normally accepted in pharmaceuticals in this group. They are less toxic in acute or short-term studies, and negative in genotoxicity studies.

There is also another group – Class 4 solvents. For this group there is no adequate toxicological data enabling formulation of acceptable limits. If manufacturers want to use Class 4 solvents, they should supply justification for residual levels of this class solvents in a pharmaceutical product (2).

As with other guidelines, Q3C only addresses marketed products and not materials used in clinical trials.

Organic solvents which are most commonly used in the chemical industry are presented in Table 3.

Other reasons for control of residual solvents

Toxicity is the main and unquestionable reason for control of residual solvent amounts, but sometimes the presence of RS at levels well within acceptable limits, could entail the risk of inducing phase transformations and jeopardizing the physicochemical stability of an active substance, and finally the quality of the dosage form. A few reports on residual solvents' effects have appeared in literature, e.g. the effect of methylene chloride on the crystallinity of ampicillin trihydrate $C_{16}H_{19}N_3O_4S{\cdot}3H_2O$) (8) and of residual ethanol on the phase transformation of orthorhombic paracetamol ($C_8H_9NO_2$) (9). Additional arguments for removing organic solvents from the drug product are the odor or the taste they can cause, which are obviously not good drug attributes, both for manufacturers and for patients.

Sources of residual solvents in a drug product

In a task of effectively removing or decreasing the amount of organic solvents present in a drug product it is necessary to investigate ways the drug is contaminated by the solvents. Therefore, a short description of the main technological processes where organic solvents are involved is presented below.

Before a pharmaceutical company obtains the final product – tablets, capsules or other pharmaceu-

Table 1. Class 1 solvents (2)

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

Table 2. Class 2 solvents (2)

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	20.0	2000
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-Trichloroethylene	0.8	80
Xylene	21.7	2170

tical form, some elemental stages have to be performed: (a) synthesis of an Active Pharmaceutical Ingredient (API), (b) production of a Drug Product (DP), (c) packaging.

At each of these stages the product can be potentially contaminated with organic solvents. In Figure 1, different stages of the drug product manufacturing process are presented. Stages marked with thicker frames are processes where organic solvents may be in use or where a pharmaceutical substance or product may become contaminated with organic solvents (packaging). Sometimes the source and means of contamination determine the way of removing them or reducing their quantity. For example, if the solvent is occluded in crystals of an API, recrystallization should be performed and if the solvent is adsorbed on a surface of particles, a drying procedure is recommended.

Synthesis of an Active Pharmaceutical Ingredient (API)

Effective synthesis of an API is, in most cases, a multilevel and complicated process. Generally, chemical synthesis consists of four steps: reaction, separation, purification and drying. During a synthesis process, a kind of solvent and its quality may be a critical parameter. Care must be taken for appropriate solvent selection that may improve the reaction yield and influence product quality. Typical

Table 3. Solvents commonly used in chemical industry (6, 7)

Alcohols	Ketones	Halogenated solvents
Ethanol Butanol 2-Ethylhexanol Isobutanol Isopropanol Methanol Propanol Propylene glycol	Acetone Methyl ethyl ketone Methyl isobutyl ketone Methyl isopropyl ketone Mesityl oxide Trichloroethylene	Ethylene bromide Chloroform Ethylene chloride Dichloromethane Tetrachloroethylene Carbon tetrachloride
Amide	Ethers	Sulfur containing
Dimethylformamide	1,4-Dioxane Butyl ether Ethyl ether Diisopropyl ether Tetrahydrofuran *tert*-Butyl methyl ether	Dimethyl sulfoxide
Amine	Nitriles	Esters
Pyridyne	Acetonitrile	Ethyl acetate
Aliphatic hydrocarbons	Water	Aromatic hydrocarbons
Cyclohexane Hexane		Toluene Xylene

uses of solvents in the synthesis are solubilization (reaction medium), extraction and crystallization (purification). They may also take part in reactions, as reactants or catalysts and also take part in azeotropic or extractive distillations as entrainers.

The main function of solvents in a reaction step is solubilization. As reaction media, solvents make solutes more reactive by breaking cohesive forces that hold crystalline and liquid solutes together. By alerting solvents, manipulation of reaction rate and, in consequence, product selectivity can be performed. That is why much research has been made to understand and forecast the properties of solvents, which are important in all aspects of chemical behavior. Additionally, they can also be a part of a synthesis reaction, as reagents or catalysts.

An extraction process is the subsequent stage of API production, where a pharmaceutical substance has a contact with organic solvents. In this process synthesis products are separated from post reaction residues. Usually liquid-liquid separations are carried between organic and inorganic fractions. A variety of solvents are used in extraction process, e.g. chlorinated solvents such as dichloromethane or chloroform as well as ketones, ethers, esters and alcohols. In extractions after a fermentation process, organic solvents, such as alcohols, toluene, acetone, acetates, or methylene chloride are utilized.

For the purification of an API, crystallization process is used. In many crystallizations the control of crystal properties, such as size and shape, is a very important factor, especially when the crystal morphology determines the product quality like dissolution rate or stability. Certain solutes, when crystallized from different classes of solvents, exhibit different crystal size and morphology, carboxylic acids and ibuprofen are good examples (10).

When the crystallization is finished, solvents have to be removed. In the situation when they are absorbed only on the surface of crystals, the drying process can be applied. This stage is also a very important process for the integrity of lattice. Defects present in crystals may favor subsequent polymorphic or pseudopolymorphic form of crystalline which may be unstable (11). If the crystallization is led rapidly, solvents can remain inside the crystals. There are some more or less complicated methods of removing them effectively. One of them is recrystallization.

Regardless of the organic solvent function during API production, synthesis, purification and crystallization, the stages where organic solvents are used, are in general current.

Formulation

Formulation is a process by which an API compound is prepared in a form suitable for administration. Drug product formulation is mostly dependent on the route of administration. From this point of view, drug products can be systemized as follows (7):

– oral route: solid dosage forms (tablets, capsules), syrups,
– oto-rhino-laryngology (ORL) route (nasal solution, spray),
– local route (suppositories, transdermal systems, eye-drop formulation, spray),
– intravenous and intramuscular route (injectable solutions, lyophilizate).

Some organic solvents can be used as a component of a final product and do not have to be removed. Usually, they fulfill the function of diluents or solubilizers, mainly in liquid and semisolid drug forms when water cannot be used.

Into the group of liquid pharmaceuticals, creams/ointments, as well as medicines for swallowing and injecting, can be classified. Liquid production consists of dissolving the active pharmaceutical ingredient in an appropriate solvent, often with various preservatives and other additives, and mixing the ingredients completely (with the exception of suspensions, in which solid particles are sedimented). The most popular and the most desirable solvent for all of these medicines is water. The newest technologies successfully avoid organic solvents in favor of water. However, sometimes the use of non-aqueous solvents is necessary. In such cases, they can be used individually or in mixtures of two or more solvents (co-solvents). Usually, organic co-solvents improve solubility (solubilizers) or fulfill the function of preservatives. Substances like ethanol, glycerol and glycols are applied as solubilizers (12). The presence of non-aqueous solvents in a drug form may positively influence API absorption into the system.

Sprays, microemulsions and especially liquids for injections have to be prepared, stored and used in sterile conditions. To prevent infection from microorganisms, some quantities of germicides, fungicides and preservatives are added into solutions. The most popular organic preservatives are ethanol in 15-20% concentration, benzyl alcohol in 1% concentration and phenol in 0.5% concentration.

During the formulation of tablets or capsules, which are classified in solid dosage forms, there are also some stages where the product may have contact with organic solvents. One of these stages is the wet granulation technology.

In the wet granulation process, solvent (granulation fluid) causes massing of a dry mix powder. Solvents for granulation may be used alone or with addition of other substances (binders or binding agents) that improve the adhesive properties of particles. In most cases water is used for the granulation process. However, sometimes water as a solvent can strongly affect drugs stability because of long drying time (long exposure to heat) or when the product is moisture sensitive (12). If water use has to be excluded, solvents like ethanol, isopropanol, acetone or others can replace it.

It is very important that when organic solvents are used as granulation liquids to work with drying equipment (tray or fluid bed dryers), which is explosion proof, all potential sources of sparks should be eliminated. The concentrations of organic vapors and oxygen must be below explosion limits. In case of the granulation with organic solvents it is generally safer to use nitrogen as a process gas.

Besides granulate, also excipients can be a potential source of residual solvents. The raw materials are generally manufactured to a much lower purity requirement than a drug substance (13). Hence, it is easy to understand why they can contain a number of impurities including residual solvents. In this case, solvents' toxicity and concentration levels should be monitored. Also interaction between excipients and an API is possible and new impurities may be created. Formic acid, its esters and formaldehyde are most commonly present in excipients as trace impurities. Even if formic acid (or its esters) is present at low levels, it can interact with amino or hydroxyl groups from pharmaceutical compounds and form amides or esters. Formaldehyde in reaction with some amino groups can form N-methyl derivative (14).

In tablets production, also during the film-coating process organic solvents may be applied. It is a complicated process and its scheme is presented in Figure 2. Typical coating ingredients are: polymers, plasticizers, pigments and wetting agents. In the early 1970s the most popular wetting agents were organic solvents. Now, because of the environmental and toxicological regulations, their usage is reduced and in most cases they are replaced with water. However, certain types of film coatings and coating processes require usage of organic solvents like methanol, ethanol, isopropanol, ethyl acetate, ethyl lactate, acetone, methylene chloride or 1,1,1-trichloroethane (15). In order to obtain a high-quality tablet coating it should be dried immediately. From this point of view, organic solvents are unquestionably better than water because they evaporate quicker. However, after drying some amounts can remain in a drug product.

Packaging

Packaging, transportation, and storage can also impact the level of residual solvents in the drug product. The quality of packing of pharmaceuticals

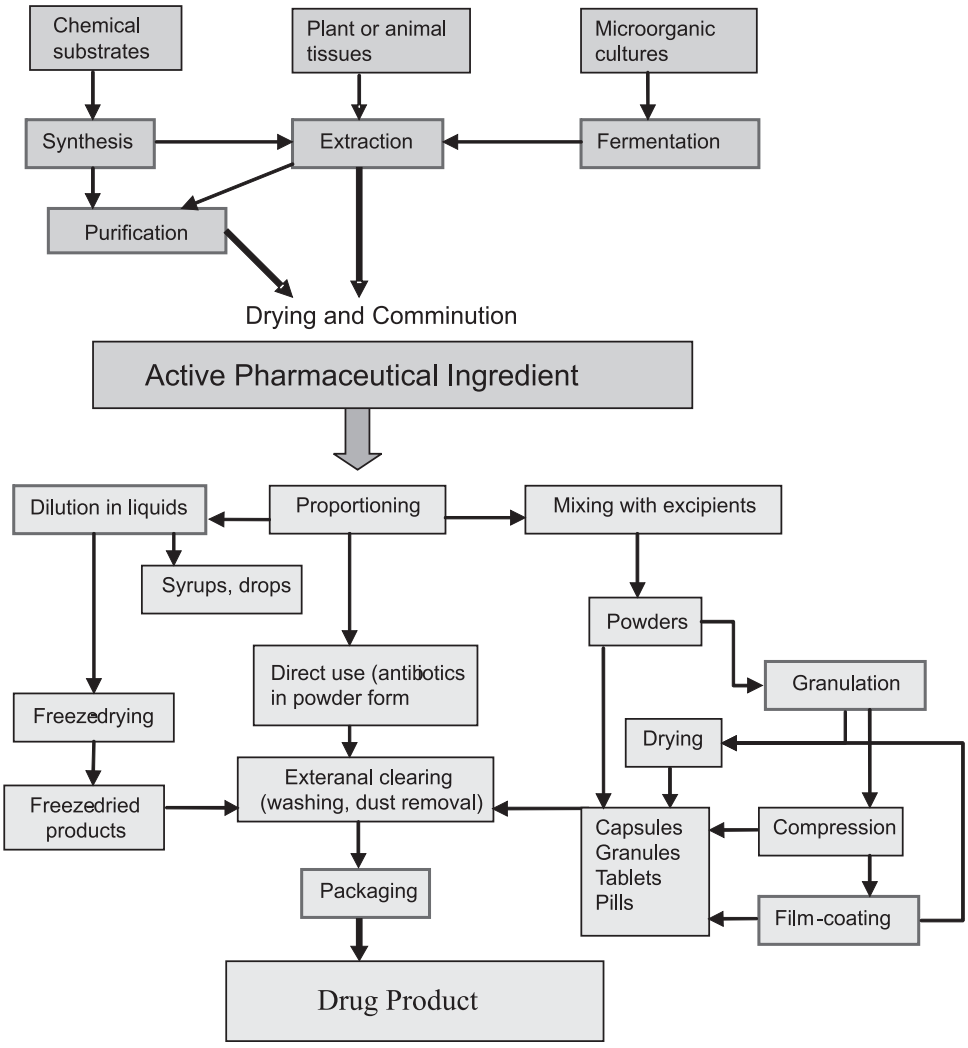

Figure 1. Diagram of a selected manufacturing process in pharmaceutical industry

is a very important factor for the quality of the product. Final pharmaceutical drug products are packaged in many different types of containers such as plastic or glass bottles, foil blister packs, pouches or sachets, tubes and sterile vials. Mechanical equipment fills, caps, labels, cartons and packs the final products in shipping containers. Drug packaging typically contains a complex mixture of chemicals which could compromise the biological safety and efficacy of the drug.

In the case of liquid drug products, possible interactions between medium and packaging material (especially polymeric materials like PCV-PVDC) should be checked. Also at this stage, drug products may have contact with organic solvents that can remain in the packaging as residues from material production. Accidental contamination during packaging, handling, or shipping should be managed through good handling and shipping practices as well as appropriate monitoring of final product quality.

Removal of organic solvents

In the removal of undesirable organic solvents, the drying process is involved. Different drying techniques are commonly used in the pharmaceutical industry, such as: static bed drying (tray or truck ovens), fluidized bed drying, moving bed drying (turbo bed dryers) or spray drying. Other, less popular methods include dielectric (microwave) drying, tunnel drying and rotary current drying. Systems

with vacuum, microwave or infrared drying have become more popular and sometimes their usage may be necessary. It should be pointed out that the drying process of substances containing organic solvents is dangerous and it is conducted under vacuum conditions (16). Usually a granulate, tablets or an active substance are placed in one of several types of dryers, then the dryer is sealed and a vacuum is applied, the temperature is elevated and nitrogen flows through the dryer.

Some physical and chemical barriers that control solvent removal are sometimes so strong that additional actions have to be performed to remove or reduce the amount of residual solvents. For this task extraction with supercritical CO_2 can be used. This technique is adapted to be used with polymeric microparticles (17) and, unfortunately, is basically limited to slightly polar solvents.

Also, there are some special cases where residual solvents are removed from therapeutic substances in different ways. A good example of this kind of procedure is radioactive holmium-166 loaded poly(L-lactic) microspheres, prepared with the use of chloroform by neutron irradiation in a nuclear reactor. High energy radiation (neutron irradiation or a gamma irradiation at a dose of 200 kGy) removes chloroform, which might have remained in the microspheres. As a result of radiolysis, chloroform is turned into chloride (18).

Control of residual solvents – analytical methodologies

To assure the quality of drugs, residual solvents must be monitored carefully. Selective analytical methods need to be developed. For this task, meaningful and reliable analytical data should be generated at various steps of the new drug development (19). A variety of methods and analytical techniques are available for monitoring this kind of impurities. The primary criterion is the ability to differentiate between the compounds of interest. Other important factors are sensitivity, simplicity of sample preparation and time consumed by the analysis. These requirements reduce the availability of methods primarily to some separation methods. Also, in some cases thermal and spectroscopic techniques may be used. Only a brief review of analytical methods for RS testing is presented here and more information on this topic will be described precisely in the next paper.

Gas chromatography (GC) is a very useful technique for analysis of residual solvents. It can provide the desired resolution, selectivity and quantification. Moreover, it is dedicated to volatile components and organic solvents in vast majority belong to this group of substances. Pharmacopoeias in their general chapters recommend GC coupled with headspace (HS) sampling system for qualitative and quantitative determinations of organic volatile impurities (3, 4). Apart of HS-GC, other techniques like solid-phase microextraction (SPME) (20) or single drop microextraction (SDME) (21) can also be employed for residual solvents determinations. Flame ionization detector (FID) is usually used for the detection of resolved compounds, but when the identity of analytes need to be confirmed, mass spectrometry (MS) can be coupled with GC. Also other specific or non-specific detectors e.g. electron capture detector (ECD), photoionization detector (PID) or thermal conductivity detector (TCD) are used. In summary, gas chromatography in different configurations (HS-GC, GC-MS, HS-GC-MS, SPME-GC, SDME-GC) is an excellent tool for the determination of volatile organic impurities.

When only Class 3 impurities are involved in the active substance or raw materials and the drug product, then loss of weight method can be applied (3, 4). Other more sophisticated techniques like thermogravimetric analysis (TGA), differential thermal analysis (DTA) or differential scanning calorimetry (DSC) are used as well. With the use of the above-mentioned methods only the sum of residual organic solvents and water can be determined.

Various other techniques like infrared spectroscopy (IR) (22) and nuclear magnetic resonance (NMR) (23, 24) have been applied to determine RS.

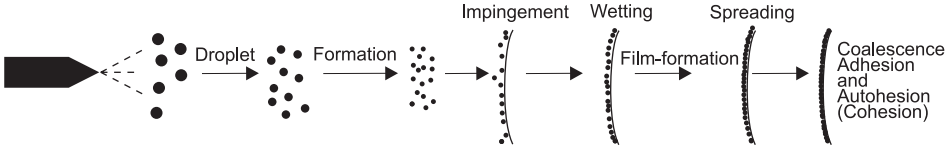

Figure. 2. Schematic presentation of film-coating process (15).

However, they can be effectively used only for selected solvents and usually detection limits obtained are not satisfactory.

Ways of avoiding organic solvents

Much effort has been put to decrease the amount of organic solvents involved in API synthesis and a drug product manufacturing. Pharmaceutical companies constantly attempt to eliminate the usage of organic solvents by following other industries, those that are more environmentally friendly. The manufacturers try to exchange more toxic solvents to more friendly ones with similar properties (like replacing benzene with toluene) or look for some new innovations. Substances such as water, supercritical fluids, fluorous phases, surfaces or interiors of clays, zeolites, silica gels, alumina and ionic liquids are taken into consideration as a potential reaction media.

Supercritical fluids (SCFs)

An example of those alternatives are supercritical fluids (SCF). The term supercritical fluid means a substance above its critical point, at which the phase boundaries diminish. To exceed critical point, special temperature and pressure conditions need to be obtained. Supercritical fluids have the mobility similar to gases and dissolving properties, resembling liquid solvents which results in a high mass transfer, efficient penetration into porous matrices and high solvency. Their solubilizing power is sensitive to small changes in operating conditions, so it is possible to fine-tune the pressure and the temperature to adapt the solvent capacity of supercritical fluids to a particular process (25).

Despite the fact that over the last two decades significant and effective progress has been made in the utilization of supercritical fluids, they are still not widely used in the pharmaceutical industry. They can be an ecological alternative to organic solvents, because they are neither restricted as residual solvents nor in the food or pharmaceutical industry. Nowadays, the most popular area of their use in this industry is for the extraction of natural products like aromatic oils or caffeine. Supercritical fluids can be useful as solvents in the production of some particular drugs, as well as in the extraction and separation of active pharmaceutical ingredients or particle size reduction. They offer novel solventless techniques, for the preparation of drug-loaded microspheres, compared to traditional microencapsulation which use large amounts of organic solvents. Moreover, SCF technology offers innovative and economical methods to achieve solvent-free particulate delivery systems.

Although many SCF are suitable for pharmaceutical applications, carbon dioxide is the most widely used because of its non-flammability, non-toxicity and low critical temperature (31˚C), which is a very important feature in case of temperature sensitive ingredients. Supercritical fluids have very high solvation power or solute capacity at their critical points, and additionally their solubility can be modified by incorporating co-solvent or co-solute. Co-solvents are added to SCF in small quantities (1-5%) to receive required polarity and solvent strength. Methanol, ethanol, acetone or dimethyl sulfoxide are typically used as co-solvents (26).

There are some supercritical fluid technologies exploited in the pharmaceutical industry, like Rapid Expansion of Supercritical Solutions (RESS), Gas Antisolvent Recrystallization (GAS) or Solution-enhanced Dispersion by Supercritical Fluids, which are being used to obtain increased quality of API or other substance particles size. As the result of these technologies the smaller and the narrow sized particles can be obtained. Also, in other stages of drug product formulation supercritical fluids may replace organic solvents. If so, why are they not commonly used in the pharmaceutical industry?

The answer is connected with some limitations, which cause that SCF are not widespread in the production processes. Challenges, facing successful implementation of this new technologies in practice, include the lack of complete understanding of the fundamental principles involved, as well as the costs associated with the specialized equipment needed for required operating pressure and temperature. Sometimes it is hard to maintain accurate pressure and temperature conditions to achieve supercritical state for solvents. Another comes from the fact that there is no accurate and precise solubility database for the essential lab-scale model. The technology of supercritical fluids is still in development stage, and also for this reason it is not commonly used in continuous production (27).

Ionic liquids (ILs)

Ionic liquids, often called “green solvents”, are salts in which ions are poorly coordinated, what results that these salts are liquid below 100˚C or even at room temperature (room temperature ionic liquids – RTILs). It is possible to distinguish between them using three criteria: the number of components in the melt, ion type – organic or inorganic and acid–base character of the ion. For one- and multi-component inorganic ionic liquids almost every combination of cation and anion is possible, which results in literally thousands of melts. The situation is different for

organic ionic liquids, where the number of applied organic cations and anions is limited.

Ionic liquids, in general, exhibit low or even imperceptible volatility, high solvency, wide liquidus range, thus their properties may be used in many different ways, which are commonly regarded as the replacement of organic solvents in the chemical and pharmaceutical industry. The pharmaceutical industry has cautiously studied their properties as an alternative for solvents used in the synthesis of an API or in crystallization. There are hopes, that their usage will make the synthesis process more efficient and thus lower the usage of raw materials. However, ionic liquids do not yet appear in a common use due to the questions regarding purity, toxicity and regulatory approval. Actually, it is still not known how to dispose wastes which ionic liquids form and how they affect air and water. The effect of contamination of drug products with ionic liquids is also still unknown. Moreover, manufactures can have problems with getting approval from regulatory agencies (like FDA). This would probably be significant that each process would require its own recycle, storage and recovery units (28). It is expected that the answers to these questions and doubts will be found soon and the pharmaceutical industry will exchange conventional organic solvents to the ones mentioned as alternatives or find an even better solution.

GMP and drug regulations in developing countries

To be able to consistently control residual solvents, the API and the drug product manufacturers must apply GMP. Drug product manufacturers often buy API from developing countries, like China or India, for economical reasons. Some problems with fulfilling GMP criteria may be encountered at API production sites. In most countries API manufacturers are not inspected for compliance with GMP well enough (29). The developing countries do not have resources, or the capacity to regulate the API manufacturers, drug regulations are rather weak and can provoke circulation of non–efficacious or harmful drugs. Creating an effective drug regulatory mechanism in a developing country, is an expensive task which requires professionals, appropriate legislations and institution arrangements. Only then, the developing countries may rely on the approval of the regulatory agencies in developed countries, designed to meet specific regulations (29).

CONCLUSIONS

There are many processes and activities during manufacturing of a drug product where organic solvents are used in many different aspects. Sometimes, their usage improves product quality and is a necessary factor. Good selection of a solvent may also be critical for a given process. However, in most cases their presence in a final product is undesirable and manufacturers have to employ safe and effective methods to remove them. New technologies in polymers production, replaced organic solvents usage in a film-coating process almost entirely. Also, in a wet–granulation process, water is nowadays the most frequently used solvent and only during more complex formulations, when the API is sensitive to moisture or the process requires short time of drying, some organic solvents are involved. However, during an API synthesis, which is a complex process and requires different solvents, organic solvents cannot be easily replaced by water. Even with the use of modern equipment for drying, some amounts of organic solvents can still remain in the final product. The acceptable limits for residual solvents are being published in pharmacopoeias and in ICH Guideline and analytical methods need to be sensitive enough for this task. Thanks to new technologies in many cases the organic solvents can be replaced by water, supercritical fluids, ionic liquids or other innovations. Still it worth underlining that the aim of drug production is to provide the medicine with an effective therapeutic function and minimize the acquirable risk for human health.

It can be concluded from the above presentation that determination of trace organic solvents in pharmaceutical products appears as an important task, for which the relevant analytical methods will be presented in the next paper.

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