International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 6 Issue 5, July-August 2022 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Residual Solvents, Their Limits and PDE: A Review

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How to cite this paper: Nitin Thorat | Prof. Santosh Waghmare | Dr. Hemant Kamble "Residual Solvents, Their Limits and PDE: A Review" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-6 | Issue-5, August 2022, pp.311-313, URL: www.ijtsrd.com/papers/ijtsrd50465.pdf

IJTSRD50465

INTRODUCTION

#The objective of this Review Paper is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The Review Paper recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques.

Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This Review Paper does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, Table 1) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, Table 2) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, Table 3) should be used where practical.

GENERAL PRINCIPLES

Classification of Residual Solvents by Risk Assessment The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance

Class 1 solvents: Solvents to be avoided Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

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

Class 3 solvents: Solvents with low toxic potential Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

1. Solvents to Be Avoided

Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. 1,1,1-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of the safety data.

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

solvents	Concentration Limits (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 Hazards

2. Solvents to Be Limited

Solvents in Table 2 should be limited in pharmaceutical products because of their inherent toxicity. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

TABLE 2 Class 2 solvents in pharmaceutical Product

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene	0.7	70
Cyclohexane	38.8	3880
1,2 Dichloroethane	18.7	1870
N, N Dimethyl Acetamide	10.9	1090

3. Solvents with Low Toxic Potential

Solvents in Class 3 (shown in Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents 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 also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice.

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

Acetic Acid	1-butanol	Heptane
Acetone	2-butanol	Isobutyl Acetate
Anisole	Butyl Acetate	Methyl Acetate

PDE FOR TRIETHYLAMINE

TRIETHYLAMINE

Introduction

Triethylamine (TEA) is used as catalytic solvent in chemical synthesis (1,2). It is a colourless liquid that is soluble in water, ethanol, carbon tetrachloride, and ethyl ether, and very soluble in acetone, benzene, and chloroform. TEA has a vapour pressure of 54 mmHg (20°C), and has been reported to be irritating to the lung and nasal passage with strong ammoniac odour (2,3). Data from human studies show that TEA is easily absorbed via the oral or inhalation route and is rapidly excreted, mainly in the urine, as the parent compound and/or its N-oxide (4-6). In studies in human volunteers, exposures of more than 2.5 ppm (10 mg/m3) caused transient visual disturbance (4,7) due to a locally induced cornea swelling; no systemic effects were observed at the exposures which showed the cornea effect. The odour thresholds ranged from 0.0022 to 0.48 mg/m3 (8-10).

Genotoxicity

In an Ames test TEA did not induce mutations in standard Salmonella strains with or without metabolic activation (11). TEA did not induce sister chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation (12). In an in vivo study, TEA induced aneuploidy but was not clastogenic in the bone marrow of rats exposed to 1 mg/m3 (0.25 ppm) and 10 mg/m3 (2.5 ppm) TEA via continuous inhalation for 30 or 90 days (13). The weak aneugenic effect was observed at the low dose and early time point only; due to study deficiencies the relevance of this finding is highly questionable. Overall, the available data do not provide evidence for a relevant genotoxic potential of TEA.

Carcinogenicity

No data available.

Reproductive toxicity

No reliable information about reproductive toxicity is available. A three-generation reproductive study in which rats (10/sex/group) were administered 0, 2, or 200 ppm (c.a. 0, 0.14 or 14 mg/kg/day) TEA in drinking water was cited in the United States Environmental Protection Agency (US EPA) Integrated Risk Information System assessment review (14). The high dose was increased to 500 ppm in the third generation due to a lack of observed

symptoms. No apparent effects occurred at 200 ppm through two generations. However, due to deficiencies in end-points measured the study data were disregarded from determining a Permitted Daily Exposure (PDE).

Repeated dose toxicity

A sub-chronic inhalation study (similar to Organisation for Economic Cooperation and Development [OECD] Test Guideline 413 and OECD Test Guideline 452) in rats is considered to be the most relevant published animal study for deriving a PDE. F344 rats (50 rats/group/sex) were exposed by whole body inhalation at concentrations of 0, 25, or 247 ppm (0, 0.10 or 1.02 mg/L) for 6 hours/day, 5 days/week for 28 weeks (15). No statistically significant treatment-related systemic effects were observed at all dose groups. Body weight gain was not statistically affected, although a slight dose-related decrease of body weight in male rats was observed. The No Observed Effect Level (NOEL) of this study was 247 ppm.

Conclusion

The calculated PDE for TEA based upon the NOEL of the rat sub-chronic inhalation study is 62.5 mg/day. Since the proposed PDE is greater than 50 mg/day it is recommended that TEA be placed into Class 3 ("solvents with low toxic potential") in Table 3 in the ICH Impurities: Residual Solvents Guideline.

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#ICH Q3C-R8 GUIDELINE

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