Review of Pharmaceutical Applications of N-Methyl-2-Pyrrolidone

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ABSTRACT - N-Methyl-2-pyrrolidone (NMP) is a very strong solubilizing agent that has important applications in different fields of industry. This review presents NMP's physicochemical characteristics, its applications - especially in the pharmaceutical sciences, pharmacokinetics and toxicity. The characteristics of NMP, such as physicochemical properties, solubilization efficacy, toxicity, and adverse effects, are compared with those of other common solvents used in pharmaceutical industries. This review shows that NMP is an acceptable pharmaceutical solvent and that its efficacy, toxicity, and side effects are comparable with those of other common solvents.

INTRODUCTION

1-Methyl-2-pyrrolidone is a liquid, also called by several other names, such as 1-methyl-2-pyrrolidinone, 1-methyl-5-pyrrolidinone, 1-methylazacyclopentan-2-one, 1-methylpyrrolidinone, 1-methylpyrrolidone, methyl-pyrrolidone, N-methyl-2-pyrrolidinone and N-methyl-2-pyrrolidone (NMP). It is a solvent with high power for solubilizing chemicals and pharmaceutical agents. It is a product of the petroleum industry and can be recycled by distillation and extraction with water (1, 2). NMP is a biodegradable solvent therefore, environmental contamination considerations are fewer in its applications (3). It is used in different fields and is considered a safe solvent (4). In a recent study, it has been isolated from a marine sponge, which shows that it may be biosynthesized (5).

PHYSICOCHEMICAL PROPERTIES

In the pharmaceutical sciences, water is the most common solvent; however, organic solvents are also used. Table 1 shows a summary of physicochemical properties of the common organic solvents that have been reported as cosolvents in the literature related to pharmaceutical sciences (6), along with the properties of NMP. NMP belongs to the group of aprotic solvents, is a slightly yellow clear liquid, and is miscible with water; low molecular–weight alcohols; ketones; polyethylene glycols; and other solvents such as ethyl acetate, chloroform, and benzene. It has low volatility and low flammability, with the necessary solubilization power to make it a suitable solvent in different fields of applications. It does not form an azeotropic mixture with water (7).

The mechanism of solubilization of drugs by NMP is ambiguous, and there are various theories for the same, including its action as a cosolvent (8), complexing agent (9), and surfactant (10). Recently, Sanghvi *et al*. investigated the solubilization mechanism of NMP and concluded that it acts as a cosolvent and complexing agent simultaneously (11). The NMP molecule (Figure 1) has nonpolar carbons, which can weaken the hydrogen-bonded structure of water, thus enabling it to act as a cosolvent. In addition, the presence of a large planar nonpolar region can lead to hydrophobic interactions between NMP and drugs (11).

Apart from the useful properties of NMP, some deleterious effects have also been found. Steel parts of apparatuses used in the presence of this solvent have been reported to undergo a corrosive reaction at temperatures above 300° C, which restricts its applications at higher temperatures in a metal-containing setup (12, 13).

INDUSTRIAL APPLICATIONS

NMP has been used in different fields of industrial applications, including electronics, petroleum, paint, textiles, rubber, chemical, polymer, and pharmaceutical industries; various syntheses; and different analytical methods (15). However, the main emphasis of this review is on its pharmaceutical aspects and applications.

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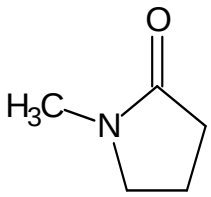

Figure 1. Chemical structure of N-methyl-2-pyrrolidone (NMP)

PHARMACEUTICAL APPLICATIONS

Solvent or Cosolvent

NMP is one of the main pharmaceutical cosolvents (16), and it acts as a very strong solubilizing agent; it is a solubilizing excipient used in parenteral and oral medications (4). It is an important solvent used in the extraction, purification, and crystallization of drugs (17, 18). A few commercial pharmaceutical products containing NMP, which are all nonaqueous formulations, are currently available in the market. Leuprolide acetate (Sanofi-aventis, Quebec, Canada) is used for the suppression of gonadal sex-hormone production in the treatment of malignant neoplasms of the prostate and is formulated as a solution composed of 55–66% NMP and 34–45% poly(DL-lactide-co-glycolide) for use as a controlled-release gel for subcutaneous injection. After injection, NMP diffuses away from the injection site, providing a depot of drug that is released over a period of 1 to 6 months. Doxycycline hyclate (Atrix Laboratories, Colorado, USA) gel is composed of 100 mg/mL doxycycline hyclate in NMP with 37% poly(DL-lactide) and is used for subgingival administration in the form of a seven-day controlled-release system (4). Florfenicol (Intervet/Schering-Plough Animal Health, Boxmeer, The Netherlands) IV solution and doxycycline gel (Pfizer Animal Health, Quebec, Canada) for the treatment and control of periodontal diseases contain NMP and are used in veterinary medicine (11). NMP can be used in parenteral formulations of drugs, because in addition to its excellent solubilizing power, it has low viscosity, which is a critical parameter in using fine-gauge needles or microcatheters (4). Wei *et al.* have patented a novel form of carvedilol that is solvated with NMP and have named it "carvedilol pharmasolve solvate". The conventional form of the drug is prescribed twice a day, whereas the novel form can be orally prescribed as a unit dose/day or may be administered in other dosage forms (19). In addition to carvedilol, hydrochlorothiazide can also form a solvate with NMP. This solvate is composed of one hydrochlorothiazide and two molecules of NMP (20). Finally, NMP is used as a solubilizing agent for increasing the uptake of poorly soluble drugs such as itraconazole (9). Systematic investigations have been conducted on the solubility of clonazepam, diazepam, lamotrigine, phenobarbital, pioglitazone hydrochloride, estrogen, and griseofulvin in water + NMP mixtures (11, 21, 22). Table 2 shows the solubilization efficacy of NMP for some drugs, in comparison with ethanol and propylene glycol. To investigate the solubilization efficacy of the cosolvents, two definitions are proposed in literature; the solubilization power, defined by Yalkowsky (σ) (23); and a definition derived from the Jouyban-Acree model (ω) (24), represented as following:

$$\sigma = \log\left(\frac{X_c}{X_w}\right)$$

$$\omega = \frac{\log\left(\frac{X_{m,\max}}{X_w}\right)}{f_{2,\max}}$$

Here, X_c and X_w are the solubilities of a drug in the cosolvent and water; $X_{m,\max}$ is the maximum solubility of the drug in water + cosolvent mixture; and $f_{2,\max}$ is the volume fraction of the cosolvent providing the maximum solubility. Usually, in pharmaceutical applications, cosolvents are used up to a fraction of 0.5; hence, another solubilization power has been defined by Yalkowsky's group (23) as follows:

$$\sigma_{0.5} = \log\left(\frac{X_{0.5}}{X_w}\right)$$

where $X_{0.5}$ is the solubility of a drug in a cosolvent fraction equaling 0.5.

Table 1. Properties of seven pharmaceutically applicable solvents: Melting Point (MP), Boiling Point (BP), Flash Point (FP), Refractive Index (RI), Surface Tension (ST), Viscosity (η), Density (ρ), Solubility Parameter (SP), Vapor Pressure (VP), and Molecular Weight (MW).

Property (Reference)	Ethanol	Dimethylacetamide	Dimethylsulfoxide	Glycerol	Isopropanol	NMP	Propylene glycol
Chemical Abstracts Service no. (7)	64-17-5	127-19-5	67-68-5	56-81-5	67-63-0	872-50-4	57-55-6
Simplified molecular input line entry specification or SMILES (7)	C(C)O	C(N(C)C)(C)=O	S(C)(C)=O	C(CO)(CO)O	C(C)(C)O	C1(N(CCC1)C)=O	C((C@@H)(C)O)O
International Chemical Identifier (InChI; 7)	InChI=1/ C2H6O/ c1-2-3/ h3H,2H2,1H3	InChI=1/ C4H9NO/ c1-4(6)5(2)3/ h1-3H3	InChI=1/ C2H6OS/ c1-4(2)3/ h1-2H3	InChI=1/ C3H8O3/ c4-1-3(6)2-5/ h3-6H,1-2H2	InChI=1/ C3H8O/ c1-3(2)4/ h3-4H,1-2H3	InChI=1/ C5H9NO/ c1-6-4-2-3-5(6)7/ h2-4H2,1H3	InChI=1/ C3H8O2/ c1-3(5)2-4/ h3-5H,2H2,1H3
MP (K) (14)	159	253	291.5	291	183.5	249	213
BP (K) (14)	351	438	462	563	356	475	460
FP (K) (14)	286	343	368	433	285	368	372
RI (14)	1.359	1.436	1.476	1.4746	1.375	1.468	1.431
ST (dyn/cm) (14)	22.3	34.0	43.7	64.0	21.7	40.7	72.0
η (cP) (14)	1.08	0.92	2.00	1200.00	2.00	1.80	54.00
ρ (g/cm-3) (14)	0.789	0.945	1.101	1.261	0.786	1.03	1.0362
SP (MPa1/2) (14)	13.4	11.0	13.0	21.1	11.5	11.0	14.8
logP (7)	–0.31	–0.77	–1.35	–1.76	0.05	–0.38	–0.92
VP (mm Hg) (7)	59.3	2	0.61	0.000168	45.4	0.345	0.129
Formula (7)	C2-H6-O	C4-H9-N-O	C2-H6-O-S	C3-H8-O3	C3-H8-O	C5-H9-N-O	C3-H8-O2
MW (7)	46.07	87.12	78.13	92.09	60.10	99.13	76.09

The data in Table 2 show that NMP has better σ and ω values than ethanol and propylene glycol, which indicate that it is a good candidate for use in pharmaceutical formulations.

Penetration Enhancer

NMP is a chemical penetration enhancer (27, 28) and is used for enhancement of transdermal delivery of hydrophilic and hydrophobic drugs from an aqueous phase (29). It is used as a good enhancer in topical formulations of griseofulvin, delivering effective concentrations of the drug (30); it is also used in combination with other enhancers, such as 1-dodecylazacycloheptan-2-one (Azone), for improvement in skin permeation of fluoxetine hydrochloride (31). The effects of chemical enhancers in the transdermal delivery of lidocaine have been investigated, and NMP is a good enhancer of hydrophobic molecules, such as lidocaine, for transdermal delivery. Combination of NMP and isopropyl myristate may have utility in the delivery of other hydrophobic molecules (32).

Table 2. Comparison of the solubilization powers of NMP, ethanol, and propylene glycol

Drug	ω			σ			$\sigma_{0.5}$		
	Ethanol	Propylene glycol	NMP	Ethanol	Propylene glycol	NMP	Ethanol	Propylene glycol	NMP
Diazepam	3.28	2.45	3.93	2.78	2.45	3.93	2.05	1.28	2.35
Clonazepam	2.43	2.29	3.85	2.10	2.29	3.85	1.66	1.01	2.13
Phenobarbital	2.22	2.08	3.18	2.04	2.08	2.64	1.25	1.03	2.25
Lamotrigine	2.22	2.45	1.90	1.28	2.45	1.90	1.40	1.24	1.61
Pioglitazone–HCl	3.14	2.24	3.39	1.51	2.21	2.86	1.56	1.86	1.59
Estrone	ND	ND	ND	ND	ND	ND	2.82	1.99	3.00
Griseofulvin	ND	ND	ND	ND	ND	ND	2.54	1.66	2.62

Solubility data of diazepam, clonazepam, and lamotrigine in ethanol + water mixtures taken from reference 25; phenobarbital in ethanol + water taken from references 82 diazepam, clonazepam, phenobarbital, and lamotrigine in propylene glycol + water and NMP + water mixtures taken from references 26 and 22, respectively; pioglitazone hydrochloride in ethanol + water, propylene glycol + water, NMP + water taken from reference 21; and estrone and griseofulvin in ethanol + water, propylene glycol + water, NMP + water taken from reference 11. Solubility data of estrone and grisolfulvin in cosolvent + water mixtures were reported up to volume fractions of 50%, so ώ and σ are not calculated.

NMP can be used as a permeability enhancer for both hydrophilic and lipophilic drugs in ophthalmic drug-delivery systems. It is a nonirritant compound at concentrations of 0–10% (v/v) (33, 34). Recently, NMP has been used in a nanoemulsion system for the transdermal delivery of granisetron hydrochloride (35). Examples of drugs that their topical formulations may contain NMP as an absorption enhancer include, griseofulvin (30), fluoxetine HCl (31), lidocaine (32), granisetron HCl (35), insulin (36), estradiol (37, 38), levonorgestrel (37), bupranolol (39), spantide II (40), luteinizing-hormone-releasing hormone (41), ibuprofen (42), flurbiprofen (42) and morphine–HCl (43).

Other Applications of NMP in the Pharmaceutical Area

NMP is used in pharmaceutical analysis. For example, an additional syringe wash with NMP can improve the consistency of injections using gas chromatogaraphy syringes by improving peak symmetry and reproducibility (44). This solvent can

improve bone morphogenetic protein (BMP) activity by enhancing the kinase activity of the BMP–receptor complex and has been proposed as a potent drug for bone-tissue regeneration (45). NMP is also used to enhance delivery of hypericin, which is an antitumor, photodynamic, and photodiagnostic agent with very low water solubility, into solid tumors and enhances the photodynamic therapeutic effects of hypericin on human bladder carcinoma (46)**.** Finally, NMP can play important roles in chemical reactions, such as hydrolysis, oxidation, condensation, conversion with chlorinating agents, polymerization, o-alkylation, and related reactions (15). Recently, NMP has been used as a reducing agent to synthesize metal nanoparticles (47). It can also be used in preparing nanotubes (48).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION PROPERTIES

Absorption

NMP is easily absorbed from the human skin gastrointestinal and respiratory tracts (49). The permeability of commercial solvents through human skin has been investigated in a study, and the permeability rate of NMP was found to be higher than that of other solvents (50).

Distribution

NMP is quickly distributed in most organs, with a relatively high concentration in the sexual organs. Repeated exposures may be one of the reasons for infertility (49). The volume of distribution (Vd) of NMP is 0.7 L/kg, and the half-life of unchanged NMP in the plasma after oral or dermal administration and inhalation exposure are 9–12 h and 4 h, respectively (51).

Metabolism

NMP is hyroxylated to 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) by the isoform 1E of

cytochrome P450 (CYP1E) and oxidized to *N*-methylsuccinimide (MSI); MSI is then hyroxylated to 2-hydroxy-*N*-methylsuccinimide (2-HMSI). 2-Pyrrolidone is reported as another metabolite of NMP (52, 53). Figure 2 shows the metabolic pathway of NMP (53).

Elimination

The main route of excretion of NMP and its metabolites, such as 5-HNMP, is by the kidneys through urine (49). Elimination of NMP is a saturable process, and unchanged NMP is intensively reabsorbed by the glomeruli (51).

TOXICITY

Knowledge about the toxicity and side effects of NMP in humans and animals is useful, and this information is required by regulatory authorities to approve any drug formulation containing NMP. Numerous studies have been carried out on living organisms, including bacteria (7), human cell lines (7), mice (54, 55), rats (54–62), dogs (63), and humans (64–71). This solvent is classified as a teratogenic compound in PubChem, and twelve bioassays reported its effects on living organisms. Studies on mice, rats, dogs, and human subjects yielded conflicting results and are described in more detail in this review. Furthermore, NMP has significant cardiovascular toxicity, and the arterial pressure change induced after interarterial infusion is more than that caused by other solvents (72).

Bioassays

According to the data available at PubChem, three NMP-activity bioassay reports are found regarding its carcinogenic potency on MultiCellCall, SingleCellCall, and mouse subjects. However, no carcinogenic potency is reported for rat and salmonella; moreover, it is reported to have anticancer activity toward seven types of cancerous subjects (73).

Animal Toxicity Studies

A study conducted in 1982 on the teratogenicity of NMP on rats when administered through the skin has concluded that doses of 75 and 235 mg/kg per day are not teratogenic; however, a dose of 750 mg/kg has been found to cause maternal abnormalities in rats (56). Becci and coworkers have studied the chronic toxicity of orally administered NMP at doses of 25, 79, and 250 mg/kg per day for 13 weeks on dogs.

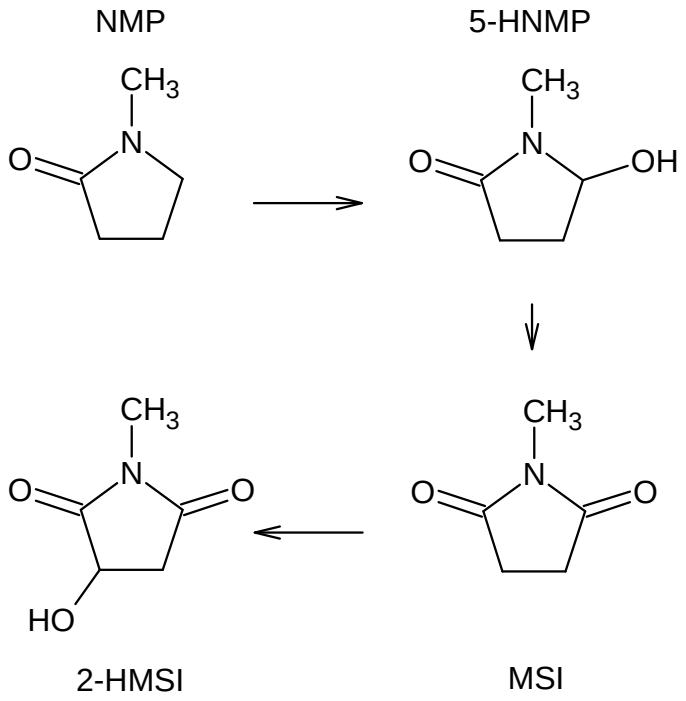

Figure 2. The metabolites of NMP

They reported no significant changes in physiological signs, except a dose-dependent decrease in body weight and increase in platelet count in both male and female dogs, in addition to a decrease in blood cholesterol in male dogs (63). In another study on rats by Lee and coworkers, it has been shown that NMP has no teratogenicity when inhaled at doses of 0.1 and 0.36 mg/L for 6 h/day; and no toxicity at doses of 0.1 and 0.5 mg/L for 6 h/day, 5 days/week for 4 weeks; however, in rats that had an intake of 1 mg/L, lethargy, respiratory difficulty, and excessive mortality has been found, in association with focal pneumonia, bone-marrow hypoplasia, and atrophy of the lymphoid tissue in the spleen and thymus, which are all reversible after 2 weeks of survival. Doses of 0.04 or 0.4 mg/L for 6 h/day, 5 days/week for 2 years on male rats show no significant life-shortening effects (57). After exposure of pregnant rats to 150 parts per million (ppm) of NMP for 6 h/day, as reported by Hass and coworkers in 1994, newborn rats had lower weights, with delayed physical growth, and could perform simple tasks similar to other rats; nevertheless, they could not perform tasks that were more complex (58). In a study by Malek and coworkers on male and female rats and mice, oral administration of NMP has been reported to have "no observable adverse effect level" (NOAEL) up to 6000 and 18000 ppm for male and female rats, respectively, with 2500 ppm being the limit for mice. In higher doses, NMP causes a decrease in body weight (54). In another study on rats and mice by Malley and coworkers, rats fed 15000 ppm NMP for 2 years showed loss of body weight, nephropathy, and possible oncogenicity; and mice fed 7200 ppm of NMP showed liver-related pathologies. Their findings suggest that the NOAEL for rats is 5000 ppm; and for male and female mice, 600 and 1200 ppm, respectively (55). In two studies by Saillenfait and coworkers on rats, it has been shown that a dose of 500 mg/kg/day of orally administered NMP and 120 ppm of NMP administered by the inhalation route can damage the fetus (59, 60). In a recent study by Saillenfait and coworkers, it has been shown that two metabolites of NMP (5-hydroxy-N-methyl-2-pyrrolidone and 2-hydroxy-N-methylsuccinimide) have no significant effects on embryos, whereas another metabolite (N-methylsuccinimide) has lower toxicity in comparison with NMP (61). In a more recent work by Sitarek and Stetkiewicz, it has been shown that daily exposure to 1000 mg/kg of NMP causes infertility in male rats (62).

A list of the LD_{50} values in different animals for NMP and other common pharmaceutical cosolvents is presented in Table 3.

Human Studies

In a study by Ochiai in 1981, an increase has been reported in the hemoglobin amount and leukocyte count of the peripheral blood of workers exposed to vapors of a mixture of N-dimethylacetamide and NMP (64). In addition, there has been an elevation in the levels of glutamate pyruvate transaminase and glutamate oxaloacetate transaminase during the ensuing two years of surveillance (64).

In a case report in 1996 by Gina *et al.*, a 23-year-old woman was reported to deliver a stillborn fetus after chronic and acute laboratory exposure to NMP during pregnancy (65). NMP was considered responsible for the outcome, because no other possible risk factor was present that could have caused the stillbirth. In addition, studies on animals had shown that NMP is a fetotoxic solvent (65), thus Gina and coworkers concluded that NMP might be fetotoxic in humans also (65). However, in a reply to this case report in 1997, these conclusions have been questioned and rejected by Bower (66).

In a study on six healthy male volunteers carried out in 1997 to evaluate the irritation-producing effect of NMP, it has been reported that exposure of eight hours per day to NMP, in the range of 10–50 mg/m^3, does not cause nose, eye, and airway irritations (67).

However, the authors also discussed that their findings were not in agreement with a previous report in which considered an exposure to 3–6 mg/m^3 of NMP at a rate of 8 h/day was considered unacceptable due to the emergence of eye irritation (68, 69).

Further studies were conducted to measure the amount of evaporated NMP that is absorbed through the cutaneous and inhalation routes as a consequence of experimental or workplace exposures (52, 67, 70, 78). Akesson and Paulsson have concluded that exposure to 10, 25, and 50 mg/m^3 NMP does not cause eye, nose, and airway irritation (66). Bader and coworkers have concluded that workplace exposure to NMP does not cause any health complaints, except in the case of persons not using personal health–protecting equipments (69).

Table 3. LD_{50} values (mg/kg) of seven pharmaceutically applicable solvents in different animals, extracted from reference 7.

	Ethanol	Dimethylacetamide	Dimethylsulfoxide	Glycerol	Isopropanol	NMP	Propylene glycol
			Oral				
Mouse	3450	4620	7920	4090	3600	5130	22000
Rat	7060	4300	14500	12600	5045	3914	20000
			IV				
Mouse	1973	3020	3100	4250	1509	55	6630
Rat	1440	2640	5360	5566	1088	81	6423
			Skin				
Rabbit	-	2240	-	> 10000	12800	8000	20800

In another study, Bader and coworkers have concluded that a significant amount of NMP can be taken up from the vapor phase after dermal exposure to the vapors (70). After evaluating the possible effects of NMP exposure in the workplace on human health, Nishimura *et al.* concluded that there is no significant changes in human physiology (71).

The common side effects and acute toxicity signs of the pharmaceutically applicable solvents, including NMP, in addition to their mutagenicity, carcinogenicity, and teratogenicity data are listed in Table 4. Careful review of the data shows that NMP is an acceptable pharmaceutical solvent and its side effects/possible toxicity is comparable to those of other common cosolvents.

REGULATORY STATUS

NMP is listed in a number of pharmacopeias. A monograph in the European Pharmacopeia is dedicated to NMP (74), and it is cited in the reagents list of the United States Pharmacopeia/National Formulary (75) and the British Pharmacopeia (76). The United States Food and Drug Administration (FDA) has approved a daily exposure of 5.30 mg/day for NMP and has classified it as a class-2 solvent. NMP is also approved by the FDA as a constituent in medical devices and is included in the list of indirect additives in food-contact materials (45, 77).

CONCLUSIONS AND FUTURE PERSPECTIVES

NMP is a strong solubilizing agent and is used in controlled-released delivery systems comprising parenteral formulations of veterinary drugs. The available veterinary formulations that use NMP as an excipient are florfenicol IV solution (an antibiotic) and doxycycline gel for the treatment and control of periodontal diseases.

The formulations for human use include a controlled-release gel for the subcutaneous injection of leuprolide acetate and a subgingival form of doxycycline hyclate, both of which contain NMP. This solvent can be used as a cosolvent in parenteral formulations and as an enhancer in topical dosage forms. In addition, it can be used for crystallization of drugs, in pharmaceutical analysis, and as a drug-delivery agent. It is biodegradable and can be easily recycled. Therefore, environment pollution considerations are fewer and it is more compatible with green-chemistry guidelines.

Table 4. Mutagenicity (Muta.), carcinogenicity (Carc.), teratogenicity (Terat.), adverse effects, and acute toxicity of pharmaceutically applicable solvents; extracted from references 79–81.

Solvent	Muta. (79)	Carc. (79)	Terat. (79)	Adverse effects (80)	Signs of acute toxicity (81)
Ethanol	+	+	+	Neurotoxin (central nervous system (CNS) solvent syndrome), hepatotoxin (secondary)	Inhalation: Cough, headache, fatigue, drowsiness. Ingestion: Burning sensation, headache, confusion, dizziness, unconsciousness. Skin: Dry skin. Eye: Redness, pain, burning sensation.
Dimethyl acetamide	-	-	+	Neurotoxin (CNS solvent syndrome), hepatotoxin (primary)	Inhalation: Headache, nausea. Ingestion: Abdominal cramps, diarrhea. Skin: May be absorbed! Redness. Eye: –
Dimethyl sulfoxide	+	NA	NA	Neurotoxin (CNS solvent syndrome), hepatotoxin (secondary)	Inhalation: Headache, nausea. Ingestion: Nausea, vomiting, drowsiness. Skin: May be absorbed! Dry skin. Eye: Redness, blurred vision.
Glycerol	-	NA	NA	NA	Inhalation: – Ingestion: Diarrhea. Skin: Dry skin. Eye: –
Isopropanol	NA	-	NA	Neurotoxin (CNS solvent syndrome)	Inhalation: Cough, dizziness, drowsiness, headache, sore throat. Ingestion: Abdominal pain, labored breathing, nausea, unconsciousness, vomiting. Skin: Dry skin. Eye: Redness.
NMP	NA	+	+	Neurotoxin (CNS solvent syndrome), hepatotoxin (secondary), skin sensitizer	Inhalation: Headache. Ingestion: – Skin: May be absorbed! Dry skin, redness. Eye: Redness, pain, blurred vision.
Propylene glycol	-	NA	NA	Neurotoxin (CNS solvent syndrome), skin sensitizer	Inhalation: – Eye: Redness, pain.

Every compound has its limitations in terms of application because it may induce toxicity by intake through different routes. These limitations might be ignorable (for water) or life-threatening (for organophosphorus). Most pharmaceutical agents should be administered only when their benefits overcome their side effects, and all medicines should be given to patients in doses that are lower than the toxic levels. This rule also should be considered for the amount of excipients (including cosolvents) used in the formulations. In this review a list of potential and possible adverse effects of pharmaceutically applicable solvents is presented. Almost every cosolvent has its own limitations in applications. Those with lower solubilizing power are less harmful and those with higher power are more harmful.

NMP appears to have more solubilizing power than other solubilizers. It is a potent penetration enhancer. Also it is thermally stable. The safety of NMP under various conditions and with high doses and prolonged exposure needs more detailed studies. According to available studies on animals, lower doses of NMP can cause adverse and toxic effects on males, in comparison with females. In addition, exposure to high concentrations of NMP during pregnancy in rats can cause abnormalities in fetuses. Nevertheless, no significant and robust data about human subjects are available. It must be taken into account that ethanol, which is the most frequently used cosolvent, has teratogenic and carcinogenic potentials (78). However, caution must be applied in administering NMP to human subjects and studies that are more comprehensive are required to arrive at a decision about the teratogenicity, mutagenicity, or toxicity of NMP on human subjects. Another suggestion is that comprehensive studies on the toxic effects of the previously studied solvents should be undertaken on animal models.

Finally, it must be stressed that NMP can easily solubilize medicinal agents at lower quantities compared to other common cosolvents. This may be useful in applications where a small amount of cosolvent is required.

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