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Review

Stability and compatibility of morphine

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Abstract

Morphine is a widely used analgesic for the treatment of severe cancer pain. For a large number of terminally ill patients oral administration is no longer possible and morphine is administered parenterally using portable pumps allowing comfortable treatment of the patient at home. In this situation the storage of pre-filled reservoirs and/or the administration over a longer period of time are daily practices and require data on the stability of morphine solutions. As most of these patients suffer from several other symptoms, the administration of admixtures with other drugs is common and requires information on the compatibility of morphine. Morphine degrades in aqueous solutions with the formation of mainly pseudomorphine, to a lesser extent morphine-*N*-oxide and probably apomorphine. From the study of the kinetics of morphine degradation it was concluded that the degradation of morphine is accelerated in the presence of oxygen and at higher pH of the solution, whereas temperature and light have only a minor influence on the degradation rate. The data reported on the stability of morphine infusion solutions kept under ambient conditions indicated that oxygen, light, the type of reservoir, the type of diluent, the salt form and the concentration of morphine do not affect the stability of morphine solutions stored for up to 3 months. Morphine solutions should preferably be stored at room temperature in order to avoid precipitation at low temperatures and water evaporation at higher temperatures causing increase in morphine concentration when stored in polymer reservoirs. Analyzing the data available on the compatibility of morphine infusion solutions revealed that differences in the formulation of the drug solutions (drug concentration, salt form, type and concentration of additives) and diluent, as well as temperature and order and ratio of mixing might affect the compatibility. Only few reports provide all necessary information, limiting the information useful for daily practice. Moreover, the majority of the compatibility studies are performed in intensive care units, where other drugs and other concentrations of morphine are required than in palliative care settings, limiting its merit for this sector.

Keywords: Compatibility; Morphine; Stability

1. Introduction

Morphine is the most important alkaloid from opium and is the first plant base to be isolated

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and identified by Sertürner in 1806. Since its isolation and characterisation morphine has been frequently used as an analgesic. Due to the limited solubility of morphine base, the acid salts, mainly the sulfate and the hydrochloride and to a lesser extent the tartrate, have been extensively used in various pharmaceutical preparations (Muhtadi, 1988). The World Health Organisation considers morphine the drug of choice for cancer pain when mild analgesics are no longer strong enough, with the oral use the preferred route of administration because of its simplicity and convenience (Walsh and Saunders, 1981).

The oral administration of morphine is not possible for a large number of patients at a later stage of the disease because of pertinent nausea, swallowing problems or gastro-intestinal obstruction. In these patients parenteral (subcutaneous, intravenous or spinal) administration of morphine using portable pump systems has been found extremely effective and allows the patient to stay at home (Bruera, 1990; Storey et al., 1990). With the delivery of several pre-filled reservoirs for patients at home in order to reduce their hospital visits and with newer pump systems capable of infusion of a reservoir over a longer period without refilling, questions about the stability of morphine solutions arise.

The majority of cancer patients suffer not only from pain but also from different other symptoms such as weakness, anorexia, nausea, vomiting, restlessness and anxiety and often several drugs need to be administered to obtain optimal symptom control (Lichter and Hunt, 1990). The administration of admixtures of morphine solutions with other drug solutions allows reducing the number of injections. Mixing drugs can cause incompatibility with precipitation and/or inactivation of the drugs. Therefore the administration of admixtures requires concrete data on the compatibility of these admixtures.

In this review the degradation process of morphine is described and an overview of the literature on stability and compatibility of morphine is presented and discussed.

2. Degradation of morphine

2.1. Factors affecting the degradation of morphine

The stability of morphine in aqueous solutions had been extensively investigated and it was generally accepted that oxygen of air, sunlight, UV-irradiation, iron and organic impurities catalyse the degradation of morphine. Quantitative studies on the influence of these different factors on the degradation rate however, had never been conducted until Yeh and Lach (1961) studied the influence of oxygen, temperature, molarity of the buffer, ionic strength and morphine concentration on the degradation kinetics of morphine. From their experiments it can be concluded that in the presence of excess of oxygen, the degradation rate and extent increased with increasing pH of the solutions. In closed ampoules the reaction stopped after a certain time, depending on the degradation rate. This was probably due to a lack of oxygen in the system. There was an increase in the degradation rate of morphine with increasing temperature, but this effect was less important than that of the pH or the presence of oxygen in the system. The degradation rate of morphine was found to be independent of the molarity and the ionic strength of the buffer. From the postulated mechanism (see further) and the kinetic data Yeh and Lach (1961) concluded that the degradation rate of morphine in a system containing excess oxygen, can be described by a pseudo first-order rate equation. There was a close agreement between the experimental data and the values obtained using the postulated rate equation (Yeh and Lach, 1961).

2.2. Mechanism of degradation of morphine

The degradation of morphine in aqueous solutions was extensively studied as discoloration occurs during storage of morphine solutions. Kollo (1919) suggested that the degradation of morphine is due to an oxidation reaction resulting in the formation of pseudomorphine and morphine-*N*-oxide in the ratio of 9:1. Orr et al. (1982) also identified apomorphine as a degradation product of morphine. For the identification of apomor-

phine only TLC was used and the R_f-value of the unknown product was only compared to that of other opioids. Interference with further degradation products of morphine or components from the syringe can therefore not be excluded. These findings are contradictory to the fact that the formation of apomorphine from morphine requires heating up to 60–65°C in concentrated HCl for 2–3 h (Osol and Hoover, 1975). Besides, apomorphine degrades rapidly with the formation of blue green coloured degradation products (Ogawa, 1984). Similar discoloration of morphine solutions has never been reported. One could therefore conclude that morphine degrades in aqueous solutions with the formation of mainly pseudomorphine, to a minor extent morphine-*N*-oxide and maybe, though unlikely, apomorphine (Fig. 1).

Concerning the mechanism of degradation, Ionescu-Matiu et al. (1948) suggested already that morphine degrades by oxidation and subsequent dimerisation. They only identified pseudomorphine, but it was clear from their experiments that this could not be the only degradation product formed. Ionescu-Matiu et al. (1948) suggested that the condensation to the dimer pseudomorphine involved the phenolic group. This was in agreement with the fact that morphine derivatives not possessing the free phenolic group, as in the case of codeine and diacetyl morphine, do not undergo this type of reaction. A complete mechanism of degradation, however, was not given before Yeh and Lach (1961). Based on their experiments on the kinetics of morphine degradation Yeh and Lach postulated a complete degradation mechanism of morphine which is in agreement with the mechanism earlier proposed by Ionescu-Matiu et al. (1948) and which is still generally accepted (Fig. 2). As the degradation rate of morphine in aqueous solution is dependent on the presence of oxygen and since no degradation occurs in the absence of oxygen Yeh and Lach (1961) suggested that a free radical reaction was involved in this process. Morphine is oxidized by oxygen to give a semiquinone and a free radical peroxide. This semiquinone is further

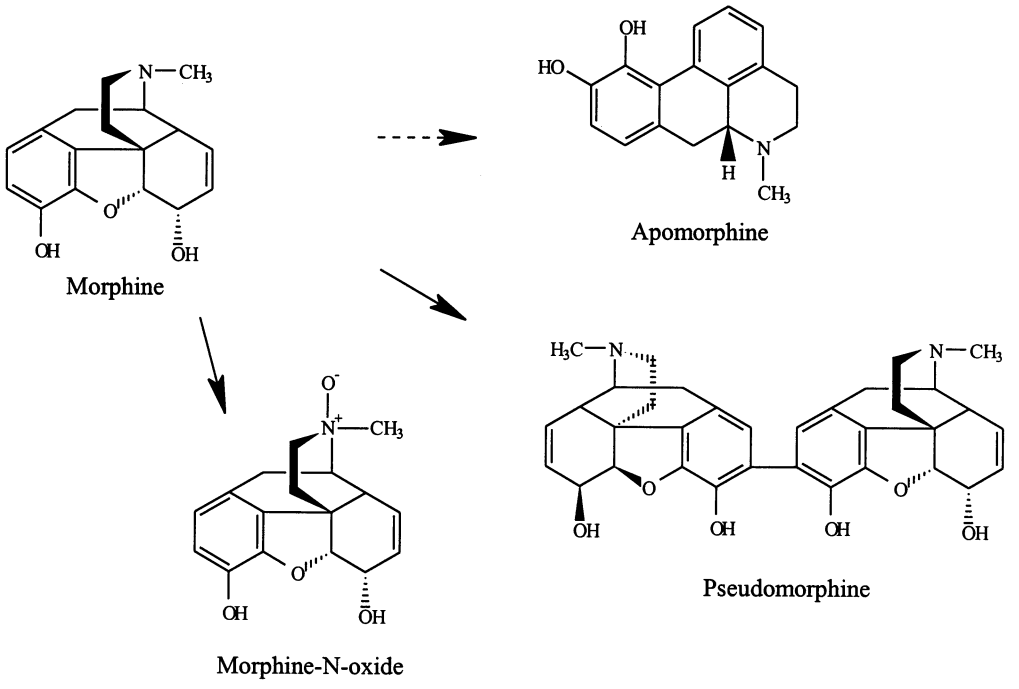

Fig. 1. Overall degradation of morphine. (→) Degradation under ambient conditions; (-- >) questionable degradation under ambient conditions.

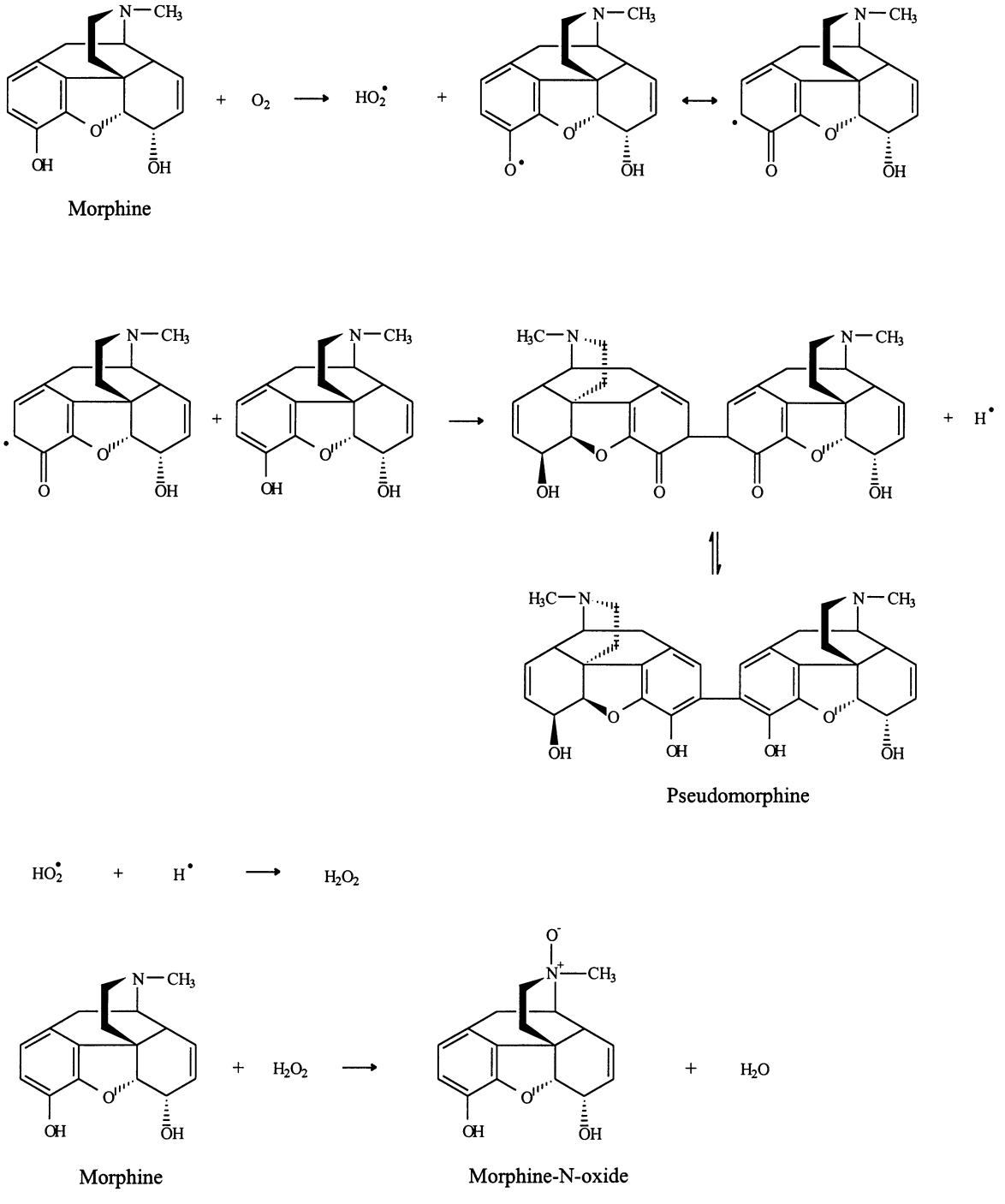

Fig. 2. Degradation mechanism of morphine.

transformed to a free radical quinone which can undergo coupling with: (a) itself, (b) the undissociated morphine, and (c) the protonated morphine. Since the amount of activated or free radical morphine species present in the system is small compared to the protonated or free base forms, interaction or union of two such activated species is unlikely. Interaction of this activated species with the protonated or free base form of morphine is more probable resulting in the formation of the dimer pseudomorphine with the simultaneous elimination of a hydrogen-free radical. This hydrogen-free radical can then react with the peroxide-free radical to form hydrogen peroxide. The hydrogen peroxide that is formed in such a process can react with morphine to form morphine-*N*-oxide or may decompose to give water and a free radical oxygen which can also react with morphine base to give morphine-*N*-oxide.

Although the mechanism of degradation is well-known, the yellowish to brown discoloration of morphine solutions during storage remains unexplained. Roksvaag et al. (1980) suggested that this discoloration is due to the formation of pseudomorphine as they found a good correlation between the absorbance measured at 450 nm and the concentration of pseudomorphine. These data are in agreement with the data reported by Vermeire and Remon (1997), who found also an increase in pseudomorphine concentration with increasing discoloration. A solution of pseudomorphine however is colourless, as is a solution of morphine-*N*-oxide. As the development of a yellow to brown colour usually goes together with the formation of pseudomorphine and morphine-*N*-oxide, it was suggested that this discoloration is due to further degradation (probably polymerisation) of the original degradation products (Connors et al., 1986). Vermeire and Remon (1997) reported that even in dark brown morphine solutions the degradation remained below 5% and there was no discrepancy between the decrease in morphine concentration and the increase in pseudomorphine concentration. This suggests that if the discoloration is due to further degradation of pseudomorphine this only occurs to a very small extent and strongly coloured products are formed.

2.3. Activity and toxicity of the degradation products

2.3.1. Pseudomorphine

Travell (1932), Schmidt and Livingston (1933) and Misra and Mule (1972) studied the pharmacology of pseudomorphine in different animals (cats, dogs, rabbits, rats and guinea pigs). They reported that pseudomorphine caused no effect after oral or subcutaneous administration although it did after intravenous or intramuscular administration. After intravenous or intramuscular administration (< 0.1 mg kg^{-1}) in dogs, pseudomorphine caused peripheral vasodilatation, as after intravenous or intramuscular administration of morphine, though stronger for similar doses (Travell, 1932; Schmidt and Livingston, 1933).

Conflicting data were reported on the activity of pseudomorphine at the central nervous system. Travell (1932) reported nausea, respiratory depression, vomiting, defecation and convulsions after intravenous and intramuscular administration (> 2 mg kg^{-1}) but only in some species; rabbit, dog and cat. Intravenous administration of higher doses in rabbits (> 25 mg kg^{-1}) and in dogs (> 60 mg kg^{-1}) resulted in death. These data conflict with those reported by Schmidt and Livingston (1933) who reported that intravenous administration of similar and much higher doses (up to 200 mg kg^{-1}) to the dog had no effect on the central nervous system. The same investigators, however, reported that vomiting occurred frequently after intravenous administration of pseudomorphine to the dog. Despite these findings the authors suggested that the circulatory effects occurring after intramuscular or intravenous administration of pseudomorphine were mainly or completely due to peripheral vasodilatation. This is in agreement with the later experiments of Misra and Mule (1972) showing that pseudomorphine, unlike morphine, did not penetrate through the blood–brain barrier. Pseudomorphine, that is often present at low concentrations in morphine solutions, does not interfere with the phenomena of tolerance and abstinence caused by morphine (Schmidt and Livingston, 1933). There are no data reported on the activity or toxicity of pseudomorphine in man.

2.3.2. Morphine-N-oxide

Morphine-*N*-oxide has weak analgesic effects in mice, with an acute subcutaneous and intravenous toxicity, respectively three to eight times smaller than that of morphine (Fennessy and Fearn, 1969). Chronic administration of morphine-*N*-oxide has no teratogenic effects in mice (Fennessy and Fearn, 1969). No data are available on the activity or toxicity of morphine-*N*-oxide in man.

3. Stability of morphine infusion solutions

The kinetic study of the forced degradation of morphine in aqueous solutions (Yeh and Lach, 1961) allowed to postulate a mechanism of degradation of morphine, but in daily practice there is a need for data on the stability of morphine infusion solutions stored under normal conditions.

In Tables 1–3 the available data on the stability of aqueous infusion solutions of, respectively, morphine sulfate, morphine hydrochloride and morphine tartrate, stored under normal conditions are presented. Based on these data the influence of factors such as oxygen, light, temperature, reservoir, diluent, concentration and salt form on the stability of morphine solutions under normal conditions was evaluated.

Since in forced degradation studies oxygen accelerated the degradation of morphine in aqueous solutions, the influence of the headspace volume and of gassing ampoules with nitrogen on the stability of morphine solutions was the subject of several studies. Roksvaag et al. (1980) reported a faster degradation of morphine in glass ampoules than in glass syringes, but the degradation in the glass ampoules remained limited, as confirmed by Deeks et al. (1983). Deeks et al. (1983) studied the influence of gassing ampoules with nitrogen on the stability of morphine and measured a higher concentration of pseudomorphine in ampoules not gassed with nitrogen versus that in ampoules gassed with nitrogen. This difference was most obvious during storage at elevated temperatures, whereas under normal conditions, the concentration of pseudomorphine remained below 5% even in the ampoules not gassed with nitrogen, which were stored for 48 weeks protected from light (Deeks et al., 1983).

Different investigators examined the influence of light on the stability of morphine solutions (Macias et al., 1985; Hung et al., 1988; Vecchio et al., 1988; Strong et al., 1994; Oustric-Mendes et al., 1997), as it is known that light catalyzes oxidation reactions and oxidation is responsible for the degradation of morphine. In most of these studies the light source was not or only partly specified. Moreover, the different studies were conducted in different diluents, at different morphine concentrations, in different reservoirs and/or under different storage conditions, which makes it difficult to compare these results. From the experiments of Hung et al. (1988) and Oustric-Mendes et al. (1997), who evaluated the stability of morphine in solutions protected and unprotected from light, light appeared to accelerate only slightly the degradation of morphine. Strong et al. (1994) on the contrary, reported a 2- to 6-fold acceleration of the degradation of morphine solutions stored in syringes unprotected from light in comparison with the solutions stored under protection from light, and found less than 50% of the initial concentration of morphine after 12 weeks. These different results could be due to the different light sources used. It should however be noticed that Strong et al. (1994) found also very low concentrations of morphine in the solutions stored protected from light and that no pseudomorphine or morphine-*N*-oxide was detected, even in the solutions where more than 10% degradation occurred. The fact that from none of the other studies it was concluded that storage of morphine solutions at room temperature unprotected from light caused stability problems, the accelerated degradation of morphine solutions stored at room temperature for no longer than 3 months in the presence of light is very unlikely.

From the various studies on the stability of morphine solutions stored at different temperatures, temperature seemed not to affect morphine stability, even storage of morphine solutions at 37°C for 3 months involved no stability problems ($< 5\%$ degradation) (Vermeire and Remon, 1997). From the findings of Deeks et al. (1983) it can be concluded that, morphine ampoules can be auto-

Table 1
Stability of morphine sulfate infusion solutions[a]

Morphine sulfate		Storage				Stability					References
Conc. (mg ml^{-1})	Diluent	Reservoir	Temp. (°C)	Light	Time	Visual	Concentration after storage (%)			pH	
							Morphine	Pseudomorphine	Morphine-*N*-oxide		
0.2	0.9% NaCl	Glass	14–22	Protec.	48 weeks	–	–	2.5	–	5.59–5.67	Deeks et al. (1983)
		+Gassed with nitrogen	115+14–22	Protec.	30's+48 weeks	–	–	4	–	5.62–6.06	
			115+14–22	Protec.	2×30' s+48 weeks	–	–	5.5	–	5.4–5.41	
			115+14–22	Protec.	3×30' s+48 weeks						
		Glass	14–22	Protec.	48 weeks	–	–	4.5	–	5.97–5.44	
		Not gassed with nitrogen	115+14–22	Protec.	1×30' s+48 weeks	–	–	6	–	5.77–5.78	
			115+14–22	Protec.	2×30' s+48 weeks	–	–	5	–	5.89–5.70	
			115+14–22	Protec.	3×30' s+48 weeks	–	–	4.5	–	6.33–5.59	
		Glass	32	Protec.	32 weeks	–	–	11.5	–	5.59–5.57	
		+Gassed with nitrogen	115+32	Protec.	1×30' s+32 weeks	–	–	10	–	5.41–5.52	
			115+32	Protec.	2×30' s+32 weeks	–	–	11	–	5.50–5.41	
			115+32	Protec.	3×30' s+32 weeks	–	–	11	–	5.59–5.40	
		Glass	32	Protec.	32 weeks	–	–	17	–	6.24–5.56	
		Not gassed with nitrogen	115+32	Protec.	1×30' s+32 weeks	–	–	16.5	–	5.72–5.39	
			115+32	Protec.	2×30' s+32 weeks	–	–	11	–	6.26–5.41	
			115+32	Protec.	3×30' s+32 weeks	–	–	9.5	–	5.40–5.49	

Table 1 (Continued)

0.04 and 0.4	5% dextrose	Glass	4	Protec.	7 days	No precipitate or discoloration	>90	–	–	–	Vecchio et al. (1988)
	and 0.9% NaCl			Light*	7 days	No precipitate or discoloration	>90	–	–	–	
		Glass	23	Protec.	7 days	No precipitate or discoloration	>90	–	–	–	
				Light*	7 days	No precipitate or discoloration	>90	–	–	–	
10	–	Glass	23	–	30 days	–	96.4	–	–	–	Walker et al. (1988)
2 and 15	–	Glass (syringe)	4	–	12 days	No precipitate or discoloration	101–106	–	–	Constant	Duafala et al. (1990)
			23	–	12 days	No precipitate or discoloration	97–100	–	–	Constant	
1	0.9% NaCl+ benzylalc.	Glass	4	Protec.	91 days	No precipitate or discoloration	>99	–	–	4.49–4.34	Nahata et al. (1992)
			22	Protec.	91 days	No precipitate or discoloration	>96	–	–	4.51–3.92	
2	H_2O	PP-syringe A	3	–	12 weeks	No precipitate or discoloration	>98	<0.05	–	–	Hung et al. (1988)
			22	Protec.	12 weeks	No precipitate or discoloration	>98	<0.05	–	–	
			22	Light	12 weeks	No precipitate or discoloration	>97	<2.5	–	–	
		PP-syringe B	3	–	12 weeks	No precipitate or discoloration	>98	<0.05	–	–	
			22	Protec.	12 weeks	No precipitate or discoloration	>98	<0.15	–	–	

Table 1 (Continued)

			22	Light	12 weeks	No precipitate or discoloration	>97	<0.5	–	–	
5	H_2O + preservative + anti-oxidant	PP-syringe A	3	–	12 weeks	No precipitate or discoloration	>99	<0.02	–	–	
			22	Protec.	12 weeks	No precipitate or discoloration	>99	<0.02	–	–	
			22	Light	12 weeks	No precipitate or discoloration	>98	<2	–	–	
		PP-syringe B	3	–	12 weeks	No precipitate or discoloration	>99	<0.02	–	–	
			22	Protec.	12 weeks	No precipitate or discoloration	>99	<0.02	–	–	
			22	Light	12 weeks	No precipitate or discoloration	>98	<0.02	–	–	
1	5% dextrose	PP-syringe	−20	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	Strong et al. (1994)
			4	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Light	12 weeks	Yellowish to brown after 1 week	40.6	Detected	Detected	3–5	
5	5% dextrose	PP-syringe	−20	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			4	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Light	12 weeks	Yellowish to brown after 1 week	43.3	Detected	Detected	3–5	

Table 1 (Continued)

1	0.9% NaCl	PP-syringe	−20	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			4	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Light	12 weeks	Yellowish to brown after 3 weeks	65	Detected	Detected	3–5	
5	0.9% NaCl	PP-syringe	−20	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			4	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Protec.	12 weeks	No discoloration	80–85	Not found	Not found	3–5	
			23	Protec.	12 weeks	Yellowish to brown after 3 weeks	47	Detected	Detected	3–5	
10	H_2O+HCl	PVC-cassette	4	–	13 days	–	97	–	–	–	Landersjö and Nyhammar (1987)
	ad pH 3	PVC-cassette	35	–	10 days	–	106	–	–	–	
5	5% dextrose	PVC-cassette	23	–	30 days	–	99.6	–	–	–	Walker et al. (1988)
	0.9% NaCl	PVC-cassette	23	–	30 days	–	101	–	–	–	
10	–	PVC-cassette	23	–	30 days	–	98.6	–	–	–	
10	5% dextrose ± preservative	PVC-cassette	4	–	31 days	No precipitate or discoloration	92–95	–	–	2.9–3.4	Walker et al. (1989)
			23	–	31 days	No precipitate or discoloration	96–99	–	–	2.9–3.4	
	0.9% NaCl ± preservative	PVC-cassette	4	–	31 days	No precipitate or discoloration	94–96	–	–	2.9–3.4	
			23	–	31 days	No precipitate or discoloration	100–104	–	–	2.9–3.4	

Table 1 (Continued)

			23–25	Protec.	15 days	No precipitate or discoloration	101	–	–	Constant	
0.5	0.9% NaCl	Kalex-bag	5	Protec.	14 days	No precipitate or discoloration	106	–	–	4.7	Altman et al. (1990)
			37	Protec.	14 days	No precipitate; pale brown	110	–	–	4.7	
15	0.9% NaCl	Kalex-bag	5	Protec.	14 days	No precipitate or discoloration	100	–	–	4.7	
			37	Protec.	14 days	No precipitate; pale brown	103	–	–	4.7	
30	0.9% NaCl	Kalex-bag	5	Protec.	14 days	No precipitate or discoloration	100	–	–	4.7	
			37	Protec.	14 days	No precipitate; pale brown	102	–	–	4.7	
60	0.9% NaCl	Kalex-bag	5	Protec.	14 days	White precipitate	51	–	–	4.7	
			37	Protec.	14 days	No precipitate; pale brown	102	–	–	4.7	
2 and 15	–	Infuse®[1]	4	Protec.	12 days	No precipitate or discoloration	95–96	–	–	Constant	Duafala et al. (1990)
			23–25	Protec.	12 days	No precipitate or discoloration	93–99	–	–	Constant	
			31	Protec.	12 days	No precipitate or discoloration	100–101	–	–	Constant	
2 and 15	–	Intermit®[2]	4	Protec.	15 days	No precipitate or discoloration	98	–	–	Constant	Duafala et al. (1990)
			23–25	Protec.	15 days	No precipitate or discoloration	98	–	–	Constant	
			31	Protec.	12 days	No precipitate or discoloration	99–100	–	–	Constant	

[a] –, no data reported; Protec., protected from light; light, not protected from light, but no light source specified; light*, standard fluorescent light; [s], sterilisation by autoclaving; [1], Baxter, Deerfield, IL; [2], Infusion Systems Corporation, Huntington Beach, CA.

Table 2
Stability of morphine hydrochloride solutions[a]

Morphine HCl Conc.		Storage				Stability					References
(mg ml^{-1})	Diluent	Reservoir	Temp. (°C)	Light	Time	Visual	Concentration after storage (%) Morphine	Pseudomorphine	Morphine-*N*-oxide	pH	
20	–	Glass (ampoule)	–	–	43 years	–	49	6	–	2–6	Roksvaag et al. (1980)
		Glass (syringe)	–	–	37 years	–	105	<0.5	–		
20	–	Glass	–	–	>10 years	–	100	1.17	–	–	Ebel and Rost (1980)
					10 years	–	101	0.33	–	–	
					6 years	–	101	0.31	–	–	
					6 years	–	101	0.24–0.27	–	–	
					7 years	–	101	0.25–0.30	–	–	
					11 years	–	101	0.23–0.30	–	–	
0.2	0.9% NaCl	Glass	–	–	9 months	No precipitate or discoloration	–	–	–	–	Orr et al. (1982)
5	7% dextrose	Glass	4	–	2 months	No precipitate or discoloration	–	Not found	–	5.5	Caute et al. (1988)
	7% dextrose	Glass	37	–	2 months	No precipitate or discoloration	–	Not found	–	5.5	
10	0.9% NaCl	Glass	4	–	2 months	No precipitate or discoloration	–	Not found	–	5.3	
	0.9% NaCl	Glass	37	–	2 months	No precipitate or discoloration	–	Not found	–	5.3	
2	H_2O + OH-benzoate	Glass	24	Light* 1–2 h/day	12 months	Pale yellow colour after 6 months	95	–	–	–	Kingsley and Yinfoo (1988)
10, 20, 30, 40 and 50	H_2O, NaCl[I], Dex.[I]	Glass	4	Protec.	3 months	White precipitate at conc. ≥20 mg ml^{-1} in NaCl[I] and at conc. ≥ 30 mg ml^{-1} in H_2O and Dex.[I]	Constant	<0.10	≤0.20	3–5	Vermeire and Remon (1997)

Table 2 (Continued)

			22	Protec.	3 months	Yellowish to brown discoloration	Constant	≤0.30	<0.30	3–5	
			40	Protec.	3 months	Yellowish to brown discoloration	Constant	<1.30	<0.40	3–5	
2	0.9% NaCl	Glass	25	Protec.	6 days	Discolouration to pale yellow	>99.4	≤0.33	Not found	5.4–5.7	Le Hoang et al. (1998)
			40	Protec.	6 days	Discolouration to pale yellow	>97.5	≤0.30	Not found	5.4–5.9	
0.2	0.9% NaCl	Plastic syringe	–	–	20 min	Apomorphine detected with TLC	–	–	–	–	Orr et al. (1982)
0.1, 0.3, 0.5 and 1	0.9% NaCl	PP-syringe	T_R	–	36 h	–	>98	–	–	–	Bray et al. (1986)
1, 5 and 10	5% dextrose	PP-syringe	37	Protec.	2 days	No precipitate or discoloration	Constant	<2	–	–	Truelle-Hugon et al. (1997)
	0.9% NaCl	PP-syringe	37	Protec.	2 days	No precipitate or discoloration	Constant	<2	–	–	
10, 20, 30, 40 and 50	H_2O, NaCl[I], Dex.[I]	PP-syringe	4	Protec.	3 months	White precipitate at conc. ≥20 mg ml^{-1} in NaCl[I] and at conc. ≥ 30 mg ml^{-1} in H_2O and Dex.[I]	Constant	≤0.15	<0.25	3–5	Vermeire and Remon (1997)
			22	Protec.	3 months	Yellowish to brown discoloration	Constant	<0.35	<0.20	3–5	
			40	Protec.	3 months	Yellowish to brown discoloration	Constant	≤1.60	<0.40	3–5	
2	0.9% NaCl	PCA-syringe[1]	25	Protec.	6 days	Discolouration to pale yellow	>99	≤0.46	Not found	5.3–5.5	Le Hoang et al. (1998)
			40	Protec.	6 days	Discolouration to pale yellow	>97.5	≤0.26	Not found	5.4–5.5	

Table 2 (Continued)

10	H_2O+HCl and pH 3	PVC-cassette	4	–	13 days	–	98.7	–	–	–	Landersjö and Nyhammar (1987)
			35	–	7 days	–	103	–	–	–	
0.5	0.9% NaCl	PVC-cassette	32	–	60 days	No precipitate or discoloration	113	–	–	4.5–5.0	Roos et al. (1992)
1.5	0.9% NaCl	PVC-cassette	32	–	60 days	No precipitate or discoloration	108	–	–	4.0–4.2	
2.5	0.9% NaCl	PVC-cassette	32	–	60 days	No precipitate or discoloration	108	–	–	3.8–4.0	
20	0.9% NaCl	PVC-cassette	T_R	Protec.	90 days	No precipitate or discoloration	113	–	–	–	Wulf et al. (1994)
1	0.9% NaCl	PVC-cassette	37	Protec.	14 days	Discolouration to pale yellow	110	<2	–		Truelle-Hugon et al. (1997)
	5% dextrose	PVC-cassette	37	Protec.	14 days	Discolouration to pale yellow	105	<2	–		
120	0.9% NaCl	PVC-cassette	37	Protec.	14 days	Discolouration to pale yellow	106	<2	–		
10, 20, 30, 40 and 50	H_2O, NaCl[I], Dex.[I]	PVC-cassette	4	Protec.	3 months	White precipitate at conc. ≥20 mg ml^{-1} in NaCl[I] and at conc. ≥ 30 mg ml^{-1} in H_2O and Dex.[I]	Constant	<0.25	<0.30	3–5	Vermeire and Remon (1997)
			22	Protec.	3 months	Yellowish to brown discoloration	↑ to 110	< 0.35	<0.25	3–5	
			40	Protec.	3 months	Yellowish to brown discoloration	↑ to 200	< 1.90	<0.60	3–5	
0.14 and 0.19	0.9% NaCl	PVC-bag	4	–	30 days	No precipitate or discoloration	Constant	–	–	Constant	Gila-Azanedo et al. (1994)
			T_R	–	30 days	No precipitate or discoloration	Constant	–	–	Constant	

Table 2 (Continued)

2.5	NaCl[I]	Infusor®[2]	T_R	Light	30 days	–	Constant	0.2	Not found	3.6–5.9	Oustric-Mendes et al. (1997)
			T_R	Protec.	30 days	–	Constant	0.5	Not found	3.6–5.9	
	NaCl[I]+0.1% SMBS	Infusor®[2]	T_R	light	30 days	–	Constant	<0.01	Not found	3.7–4.7	
			T_R	Protec.	30 days	–	Constant	<0.01	Not found	3.7–4.7	
5	NaCl[I]	Infusor®[2]	T_R	Light	30 days	–	Constant	0.8	Not found	3.8–5.5	
			T_R	Protec.	30 days	–	Constant	1	Not found	3.8–5.5	
	NaCl[I]+0.1% SMBS	Infusor®[2]	T_R	Light	30 days	–	Constant	<0.01	Not found	3.5–4.4	
			T_R	Protec.	30 days	–	Constant	<0.01	Not found	3.5–4.4	
1	5% dextrose	Celinject®[3]	37	Protec.	14 days		109	< 2	–		Truelle-Hugon et al. (1997)
	0.9% NaCl	Celinject®[3]	37	Protec.	14 days		110	< 2	–		
20	H_2O	Celinject®[3]	37	Protec.	14 days		112	< 2	–		
5	7% dextrose	Secor[4]	4	–	2 months	No precipitate or discoloration	–	Present from day 3 < 0.1% after 1 month	–	5.5	Caute et al. (1988)
	7% dextrose	Secor[4]	37	–	2 months	No precipitate or discoloration	–	Present from day 3 < 0.1% after 1 month	–	5.5	
10	0.9% NaCl	Secor[4]	4	–	2 months	Discolouration to yellow	–	Present from day 3 < 1% after 1 month	–	5.3	
	0.9% NaCl	Secor[4]	37	–	2 months	Discolouration to yellow	–	Present from day 3 < 1% after 1 month	–	5.3	
2	H_2O + parabens	PE-bottle[5]	24	Light* 1–2 h/day	12 months	No discoloration	98	–	–	–	Kingsley and Yinfoo (1988)
0.1	–	VIP 30[6]	37	–	8 weeks	–	>98	–	–	–	Sadjak and Wintersteiger (1995)

[a] –, no data reported; protec., protected from light; light, no protection from light, but no light source given; light*, standard fluorescent light; [I]solutions isotonized with dextrose (Dex. [I]) or sodium chloride (NaCl [I]); SMBS, sodium metabisulfite; [1], composition not given; [2], Baxter, Deerfield, IL; [3], B-Braun, composition not given; [4], silicone-polysulfone pumpreservoir, Cordis Europa; [5], high-density polyethylene bottle with polypropylene closure and celloseal closing liner, Containers Pty., N.S.W.; [6], polysulfone UDEL, PET, polysulfone hollow fiber filter F60, silicate glass and silicone; Fresenius AG.

Table 3
Stability of morphine tartrate infusion solutions[a]

Morphine tartrate Conc.		Storage				Stability					References
(mg ml^{-1})	Diluent	Reservoir	Temp. (°C)	Light	Time	Visual	Concentration after storage (%)			pH	
							Morphine	Pseudomorphine	Morphine-*N*-oxide		
1	–	PP-syringe	4.5	Protec.	52 weeks	–	Constant	Constant	–	–	Chai et al. (1994)
			23	Protec.	52 weeks	–	Constant	↑ After 6 months	–	–	
			23	Light*	52 weeks	–	Constant	↑ After 6 months	–	–	
4	–	PP-syringe	4–8	–	21 days	No precipitate or discoloration	99.8	–	–	Constant	Targett et al. (1997)
		–	21–23	–	21 days	No precipitate; pale yellow	97.5	–	–	Constant	
80	–	PP-syringe	4–8	–	21 days	No precipitate or discoloration	93.5	–	–	Constant	
			21–23	–	21 days	No precipitate, pale yellow	97.8	–	–	Constant	

[a] –, no data reported; protec., protected from light; light*, standard fluorescent light.

claved without causing any major degradation, since repeated ($n = 3$) autoclaving caused no or only a slight increase in pseudomorphine concentration. Although one expects, as concluded from the kinetic study on the degradation of morphine (Yeh and Lach, 1961), that the degradation rate is accelerated at higher temperatures, these studies show that it is, in contradiction to what is often recommended, not necessary to store morphine solutions in the refrigerator. On the contrary, concentrated morphine solutions should not be stored at low temperatures in order to avoid precipitation as reported by Altman et al. (1990) and Vermeire and Remon (1997). Vermeire and Remon (1997) reported a difference in solubility of about 30% when comparing the solubility of morphine hydrochloride in water at room temperature (49 mg ml^{-1} at 22°C and 55 mg ml^{-1} at 25°C) with that at 4°C (35 mg ml^{-1}).

From none of the studies reported there seems to be a marked influence of the reservoir on the stability of morphine solutions. Some investigators, who determined the concentration of morphine and pseudomorphine, reported slightly higher concentrations of pseudomorphine in syringes versus in pump reservoirs (Caute et al., 1988; Le Hoang et al., 1998). In some reservoirs, i.e. PVC cassettes and Kalex® bags, however, a marked increase in morphine concentration was measured (Landersjö and Nyhammar, 1987; Stiles et al., 1989; Altman et al., 1990; Roos et al., 1992; Wulf et al., 1994; Truelle-Hugon et al., 1997; Vermeire and Remon, 1997). An increase in morphine concentration of more than 10% was reported after 14 days of storage in these reservoirs at temperatures above 30°C or after longer periods when stored at room temperature. Such an increase in morphine concentration during storage can lead to overdosing of the patient and in the case of concentrated morphine solutions can cause precipitation and by this blockage of the catheter and/or local irritation at the infusion site. Specific studies on the sorption of morphine to pump reservoirs were not reported. Caute et al. (1988), Hung et al. (1988), Roos et al. (1992) and Le Hoang et al. (1998) studied the leaching of compounds from the polymer reservoirs into the morphine solution. In all these studies the concentration of the possibly toxic additives in the morphine solutions was below 1 ppm, which indicated that morphine solutions stored in these reservoirs are safe to be administered.

From comparison of the stability of morphine in different diluents it appeared that there is no difference in stability of morphine solutions prepared in water for injection, in a 0.9% sodium chloride solution and in a 5% dextrose solution (Tables 1–3). Only Caute et al. (1988) reported a slightly faster degradation and discoloration of morphine hydrochloride solutions prepared in a 7% dextrose solution versus morphine hydrochloride solutions prepared in a 0.9% sodium chloride or a 5% dextrose solution. A possible explanation for this could be that the pH of the morphine hydrochloride solutions prepared in 0.9% sodium chloride and in 5% dextrose was almost the same, while the pH of the solutions prepared in 7% dextrose was lower.

Yeh and Lach (1960, 1971) and Oustric-Mendes et al. (1997) investigated the effect of anti-oxidants on the stability of morphine solutions. From these studies it was concluded that the addition of sodium metabisulfite to morphine solutions inhibited the transformation of morphine to pseudomorphine and that an interaction product of morphine and sodium metabisulfite was formed. No data are available on the toxicity of this interaction product and since storage of morphine solutions without sodium metabisulfite involved no stability problems, the addition of sodium metabisulfite to morphine solutions should be avoided.

Yeh and Lach (1961) concluded from their study on the kinetics of morphine degradation that the degradation rate of morphine is concentration dependent. As high concentrations are frequently used in palliative care settings, the influence of concentration on the stability of morphine solutions stored under normal conditions might be important. In most of the studies under ambient conditions the stability of morphine solutions up to concentrations of 20 mg ml^{-1} was investigated. From the few studies on the stability of morphine solutions at higher concentrations it can be concluded that the morphine concentration did not affect its stability when stored under

normal conditions (Stiles et al., 1989; Walker et al., 1989; Altman et al., 1990; Targett et al., 1997; Vermeire and Remon, 1997).

Comparison of the data presented in Tables 1–3 revealed that the type of morphine salt did not influence the stability of morphine when stored under normal conditions.

4. Compatibility of morphine infusion solutions

Tables 4–6 give an overview of the compatibility data of, respectively, morphine sulfate, morphine hydrochloride and morphine tartrate. It should be noticed that most of the studies were conducted on intensive care units, where other drugs are combined with morphine and other concentrations are used than in palliative care settings.

Based on the data available some important factors that can affect the compatibility, such as the drug concentration in the solutions mixed, the formulation of the drug solutions mixed (salt, additives, diluent), the ratio and order of mixing and the temperature of preparation and/or storage as well as the stability of the admixtures are discussed.

In most studies the compatibility was only evaluated at one concentration. The few compatibility studies performed at multiple concentrations of both morphine and the admixed drug, revealed that compatibility can be concentration dependent (Baker et al., 1985; Pugh et al., 1991; Vermeire and Remon, 1998). Most of the studies were carried out on intensive care units where the concentration of both morphine and the admixed drug is usually low, whereas in palliative care often admixtures with high drug concentrations are required. Since compatibility has been shown to be possibly concentration dependent, these tests performed at a single low drug concentration are of limited use in palliative care settings.

In most cases no influence of the diluent on the compatibility was noticed (Cutie, 1983; Karnatz et al., 1988; Baltz et al., 1990; LeBelle et al., 1995; Nixon et al., 1995; Chandler et al., 1996; Xu et al., 1996; Vermeire and Remon, 1998), except a study of Baker et al. (1985) on the compatibility of morphine sulfate with heparin (Na) which indicated that the choice of diluent can affect the compatibility. The influence of diluents is probably due to a different solubility of one or both drugs in the different diluents.

A comparison of the study of LeBelle et al. (1995) and that of Vermeire and Remon (1998) on the compatibility of haloperidol lactate with, respectively, morphine sulfate and morphine hydrochloride, clearly showed that the salt form can affect the compatibility.

A study of Vermeire and Remon (1998) on the compatibility of morphine hydrochloride with two dexamethasone formulations (Decadron® and Decadron® Pack), differing only in concentration and additives, revealed that the additives played a major role in the compatibility and the stability.

When compatibility is studied one should therefore state not only the drug name and the salt form, but also the composition of the formulation used. It is not sufficient to specify the trade name of the drug solution as the composition of a commercially available solution might change in time or from continent to continent. For the same reason no trade names are specified in the table.

Only a few reports mention the way of preparation (e.g. concentration of drug solution used to prepare the admixture, the order and ratio of mixing) of the admixtures (if not stated in the table it was not given by the author). Udeani et al. (1994) showed that the concentration of the drug solution can affect the pH of the admixture and so the compatibility. Vermeire and Remon (1998) have shown that if drugs can be mixed in a ratio 1/1 (v/v) there is no influence of the order of mixing on the compatibility. When the ratio at which the drugs can be mixed is different from 1/1 (v/v), e.g. drug/morphine: 1/10 (v/v) the smallest volume (here drug solution) should be added to the largest volume (here morphine solution) in order to avoid compatibility problems. If the largest volume is added to the smallest volume, the ratio drug/morphine is varying from 1/0 over 1/1 to 1/10 (v/v). The high morphine concentration occurring when preparing the admixture by adding the morphine solution to the drug solution is incompatible, so a precipitate is formed which does not redissolve when more of the largest

Table 4
Compatibility of morphine sulfate infusion solutions[a]

Drug (D)			Morphine sulfate (M)		Ratio $v_D/v_m/v$ (Dil.)	Compatibility visual (C/I)	Storage			Stability			References
Name	Conc. (mg ml^{-1})	Dil.	Conc. (mg ml^{-1})	Dil.			Reservoir	Temp. (°C)	Light	Time	Visual	Conc. afterpH storage	
1. Anti-emetics:													
Haloperidol (lactate)	5	–	5	H_2O	1/1/0	I (precipitate)	Glass	20–25	Protec.	14 days	I (precipitate)	[morphine] >94%–[haloper.] <60%	LeBelle et al. (1995)
				Dex.	1/1/0	I (precipitate)	Glass	20–25	Protec.	14 days	I (precipitate)	[morphine] >95%–[haloper.] <60%	
				NaCl	1/1/0	I (precipitate)	Glass	20–25	Protec.	14 days	I (precipitate)	– –	
			10	H_2O	1/1/0	I (precipitate)	Glass	20–25	Protec.	14 days	I (precipitate)	[morphine] – >100% [haloper.] <50%	
				Dex.	1/1/0	I (precipitate)	Glass	20–25	Protec.	14 days	I (precipitate)	[morphine] >95%–[haloper.] <40%	
				NaCl	1/1/0	I (precipitate)	Glass	20–25	Protec.	14 days	I (precipitate)	– –	
	0.2	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	– –	Chandler et al. (1996)
Methotrimeprazine	0.2	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light				
Metoclopramide (HCl)	0.2	Dex.	1	–	1/1/0	C	Glass	25	Light*	4 h	–	– –	Pugh et al. (1991)
	5	–	30	–	$6^b/2^b/52^a$(NaCl)	–	Glass	4+32	Protec.	182+7 days	–	[morphine] 97.6%cte [metocl.] 98.9%	Nixon et al. (1995)
								22+32	Protec.	35+7 days	–	[morphine] 92.3%cte [metocl.] 96.4%	
							PP-syringe	4+32	Protec.	182+7 days	–	[morphine] 96.4%cte [metocl.] 98.7%	
								22+32	Protec.	35+7 days	–	[morphine] 95.1%cte [metocl.] 96.0%	
					$10^b/3^b/77^a$(NaCl)	–	Viaflex®-bag	4+32	Protec.	182+7 days	–	[morphine] 97.9%cte [metocl.] 101.6%	
								22+32	Protec.	35+7 days	–	[morphine] 97.6%cte [metocl.] 98.4%	
					$6^b/2^b/52^a$(Dex.)	–	Glass	4+32	Protec.	182+7 days	–	[morphine] 98.6%cte [metocl.] 81.7%	
								22+32	Protec.	35+7 days	–	[morphine] 93.1%cte [metocl.] 79.3%	
							Infusor®	4+32	Protec.	182+7 days	–	[morphine] cte 106.5% [metocl.] 88.3%	
								22+32	Protec.	35+7 days	–	[morphine] 98.3%cte [metocl.] 84.5%	
	5		1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	– –	Chandler et al. (1996)
Ondansetron (HCl)	0.1[a]	NaCl	1 [a]	NaCl	–	C	PVC-bag	32	–	7 days	C	[morphine] >97%–[ondans.] >100%	Trissel et al. (1994)
							PVC-bag	4+22	–	31 days	C	[morphine] >92%–[ondans.] >100%	

Table 4 (Continued)

	1 [a]	NaCl	1 [a]	NaCl	–	C	PVC-bag	32	–	7 days	C	[morphine] >100% [ondans.] >100%	–	
						.	PVC-bag	4+22	–	31 days	C	[morphine] >94% [ondans.] >99%	–	
Prochlorperazine (edysilate)	5	–	8–10–15	–	–	C	PP-syringe	25	–	24 h	C	–		Zuber (1987)
2. Hypnotics, sedatives and anxiolytics:														
Diazepam	0.5	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
Fenobarbital (Na)	2	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
Hydroxyzine (HCl)	4	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
Lorazepam	0.1	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
Midazolam (HCl)	5	–	10	–	$1^{a}/1^{b}/0$	C	Glass	25	Light*	4 h	C	–	–	Forman and Souney (1987),
	5	–	10	–	$2^{c}/2.5^{b}/95.5^{a}$(Dex)	C	Glass	24	Light*	3 h	C	[morphine] >98% [midazol.] >98%	cte	Johnson et al. (1994)
					$10^{c}/2.5^{c}/87.5^{a}$(Dex.)	C	Glass	24	Light*	3 h	C	[morphine] >100% [midazol.] >99%		
					$2^{c}/10^{b}/88^{a}$(Dex.)	C	Glass	24	Light*	3 h	C	[morphine] >97% [midazol.] >98%		
					$10^{c}/10^{b}/80^{a}$(Dex.)	C	Glass	24	Light*	3 h	C	[morphine] >99% [midazol.] >98%		
	5	–	5	H_2O, Dex., NaCl	1/1/0	C	Glass	20–25	Protec.	14 days	C	[morphine] >90% [midazol.] >90%		LeBelle et al. (1995)
			10	H_2O, Dex., NaCl	1/1/0	C	Glass	20–25	Protec.	14 days	C	[morphine] >90% [midazol.] >90%		
	0.2	–	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
3. Analgesic, antipyretic and anti-inflammatory drugs:														
Anakinra (recombinant human IL-1 receptor antagonist)	4	NaCl	0.5	–	1/1/10	C	PP-vial	22	Light*	4 h	C	[morphine] >99% [anakinra] >98%	cte	Nahata and Morosco (1995)
	36	NaCl	0.5	–	1/1/0	C	PP-vial	22	Light*	4 h	C	[morphine] >95% [anakinra] >98%	cte	
Ketorolac (tromethamine)	1	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
4. Corticosteroids:														
Dexamethasone (sodium phosphate)	0.2	Dex.	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
	1	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)

Table 4 (Continued)

Methylprednisolone (sodium succinate)	2.5	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
5. Antibacterial drugs:														
Amikacin (sulfate)	5	Dex.	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Ampicillin (Na)	20	NaCl	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Ampicillin (Na)–Sulbactam (Na)	30	NaCl	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Aztreonam	20	Dex.	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Carbenicillin (Na_2)	50	Dex.	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Cefalothin (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Cefamandole (nafate)	20	Dex.	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
	40	Dex.	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Cefapirin (Na)	20	Dex.	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Cefazolin (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Cefoperazone (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Ceforanide (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Cefotaxime (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Cefotetan (Na_2)	20–40	Dex.	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Cefoxitin (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
	40	Dex.	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Ceftazidime ($5H_2O$)	20–40	Dex.	1	–	1/1/0	C	Glass	25	Light	4 h	C	–	–	Pugh et al. (1991)
Ceftizoxime (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Ceftriaxone (Na)	20–40	Dex.	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Cefuroxime (Na)	30	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Chloramfenicol (sodium succinate)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Clindamycin (phosphate)	12	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Doxyxycline (hyclate)	1	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Erythromycin (lactobionate)	5	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Gentamicin (sulfate)	0.8	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)

Table 4 (Continued)

	1.2–2	NaCl	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Kanamycin (sulfate)	2.5	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Mezlocillin (Na)	80	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Minocycline (HCl)	0.2	–	1	Dex.	1/1/0	I (disolour. Yel-low → green)	Glass	25	Light*	4 h	I (disolour. yel-low → green)	–	–	Nieves-Cordero et al. (1985)
Moxalactam (Na_2)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Nafcillin (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
	30	Dex.	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Oxacillin (Na)	20	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Penicillin G (potassium)	0.1 milj. IU/ml	–	1	Dex.	1/1/0	I (disolour. Yel-low → green)	Glass	25	Light*	4 h	I (disolour. yel-low → green)	–	–	Nieves-Cordero et al. (1985)
Piperacillin (Na)	60	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	–	–	–	Nieves-Cordero et al. (1985)
Tacrolimus	0.01–0.04	NaCl	1–3	NaCl	1/1/0	C	Glass	23–25	Light*	4 h	C	[morphine] > 98%5 [tacrolimus] > 98%		Johnson et al. (1999)
	0.01–0.04	Dex.	1–3	NaCl	1/1/0	C	Glass	23–25	Light*	4 h	C	[morphine] > 98%5 [tacrolimus] > 98%		
Tetracycline (HCl)	2.5	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Ticarcillin (Na_2)	60	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Ticarcillin (potass. Clavulanate)	31	NaCl	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	–	Smythe et al. (1990)
Tobramycin (sulfate)	0.8	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
	1.6–2–2.4	Dex.	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Trimethoprim-sulfamethoxazole	0.8													
	4	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
Vancomycin (HCl)	5	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
6. Antiviral drugs:														
Aciclovir (Na)	5	Dex.	0.08	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Forman et al. (1987)
	5	Dex.	1	–	1/1/0	C	Glass	25	Light*	4 h	I (white cryst.-prec. after 2 h)	–	cte	Pugh et al. (1991)
Foscarnet (Na)	24	–	1	Dex.	1/1/0	C	Glass	25	Light	24 h	C	–	–	Baltz et al. (1990)
			1	NaCl	1/1/0	C	Glass	25	Light	24 h	C	–	–	

Table 4 (Continued)

	24	–	1	–	1/1/0	C	Glass	T_R	Light*	24 h	C	–	–	Lor and Takagi (1990)
	24	–	15	–	$1^b/1^a/0$	C	Glass	25	Light*	24 h	C	–	cte	DiStefano and Outman (1992)
			5	NaCl	$1^b/1^a/0$	C	Glass	25	Light*	24 h	C	–	cte	
Zidovudine	4	Dex.	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Bashaw et al. (1988)
7. Antifungal drugs:														
Fluconazole	1	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	cte	Pugh et al. (1991)
	2	Dex.	25	–	1/1/0	C	Glass	T_R	Light*	24 h	C	–	–	Lor et al. (1991)
	2	–	0.5	Dex.	1/1/0	–	Glass	25	Light*	72 h	–	[fluconaz.] >85%	2	Hunt-Fugate et al. (1993)
8. Antiprotozoal drugs:														
Metronidazole (HCl)	5	–	1	Dex.	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Nieves-Cordero et al. (1985)
9. Drugs used for stomach and duodenum pathology:														
Cimetidine (HCl)	150	–	10	–	$2^a/1^b/0$	C	Glass	25	Light*	4 h	C	–	–	Souney et al. (1984)
Famotidine	0.2	Dex.	0.2	Dex.	$1^a/1^b/0$	C	Glass	25	Light*	4 h	C	–	–	Jay et al. (1988)
	0.2		1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Ranitidine (HCl)	25	–	10	–	$2^a/1^b/0$	C	Glass	25	Light*	1 h	C	–	–	Parker (1985)
	0.5	–	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
10. Antineoplastic drugs:														
Amsacrine (lactate)	1	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	T_R	Light*	4 h	C	–	–	Trissel et al. (1990)
Fludarabine (phosphate)	1	Dex.	1	Dex.	$1^{a,b}/1^{a,b}/0$	C	Glass	T_R	Light*	4 h	C	–	–	Trissel et al. (1991)
Fluorouracil (Na)	1	–	1	Dex.	–	I (precipitate)	–	32	–	7 days	I (precipitate)	[morphine] <30% [fluorour.] >98%		Xu et al. (1996)
							–	−20, 4 and 23	–	35 days	I (precipitate)	[morphine] <45% [fluorour.] >99%		
				NaCl	–	I (precipitate)	–	32	–	7 days	I (precipitate)	[morphine] <35% [fluorour..] >97%		
							–	−20, 4 and 23	–	35 days	I (precipitate)	[morphine] <75% [fluorour.] >96%		
11. Drugs used in anesthesia:														
Atracurium (besylate)	0.5	Dex.	1	Dex.	1/1/0	C	Glass	28	Light*	24 h	C	–	–	Savitsky (1990)
Ketamine (HCl)	100	–	10	–	$4^b/2^b/14^a$(NaCl)	–	PP-syringe	T_R	Light*	4 h	–	[morphine] >95% [ketamine] >95%	[ke--	Edwards and Reilly (1994)
	100	–	30	–	2.4/4/0	C	–	21	Light*	24 h	C	[morphine] cte [ketamine] cte	[ke-3.4	Lau et al. (1998)
Nembutal (Na)	50	–	16.2	–	10/1/0	C	–	–	–	–	–	–	–	Jones et al. (1961)
Pancuronium (HBr)	0.05	Dex.	1	Dex.	1/1/0	C	Glass	28	Light*	24 h	C	–	–	Savitsky (1990)

Table 4 (Continued)

12. Cardiovascular drugs:														
Recombinant human t-PA	1	H_2O	2	Dex.	1/1/0	C	Glass	25	–	24 h	C	[morphine] 78% [t-PA] 96%	7.3	Lam et al. (1995)
				NaCl	1/1/0	C	Glass	25	–	24 h	C	[morphine] 90% [t-PA] 92%	7.2	
Atenolol	0.5	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Bumetanide	0.25	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Bupivicaine (HCl)	7.5[f]	–	129[f]	–	morphine powder added to drug solution	C	PP-syringe	25	Day–Light	30 days	C	–	–	Neels (1992)
	50	–	25	–	1.25/0.4/98.35(NaCl)	C	PVC-bag	23–25	Light*	72 h	C	[morphine] >100% [bupivic.] >98%	5.5–5.7	Johnson et al. (1997)
					1.25/2/96.75(NaCl)	C	PVC-bag	23–25	Light*	72 h	C	[morphine] >99% [bupivic.] >99%	4.8–5.2	
					2.5/0.4/97.1(NaCl)	C	PVC-bag	23–25	Light*	72 h	C	[morphine] >99% [bupivic.] >100%	5.3–5.4	
					2.5/2/95.5(NaCl)	C	PVC-bag	23–25	Light*	72 h	C	[morphine] >99% [bupivic.] >100%	4.8–4.6	
Digoxin	0.25	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Dobutamine (HCl)	2	Dex.	10	–	1/1/0	C	Glass	21	Light*	24 h	C	–	–	Hasegawa and Eder (1984)
		NaCl	10	–	1/1/0	C	Glass	21	Light*	24 h	C	–	–	
Dopamine (HCl)	1.6	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Esmolol (HCl)	250	–	15	–	4[c]/100[a]/96[b](Dex.)	C	Glass	T_R	Light	8 h	C	–	–	Karnatz et al. (1988)
					4[c]/100[a]/96[b](NaCl)	C	Glass	T_R	Light	8 h	C	–	–	
Furosemide (Na)	0.8	–	1	–	1/1/0	C	Glass	25	Light*	4 h	I (white prec.) after 1 h	–	–	Pugh et al. (1991)
	2.4	–	1	–	1/1/0	I (prec. on adding, disapp. fast)	Glass	25	Light*	4 h	I (white prec.) after 1 h	–	–	
	10.0	–	1	–	1/1/0	I (white precipitate)	Glass	25	Light*	4 h	I	–	–	
Heparin (Na)	100–200 IU/ml[f]	–	1–2	H_2O	$D^{a,b}/M^{a,b}/0$	C	Glass	22.5	–	24 h	C	[morphine] >90%	cte	Baker et al. (1985)
			–5[f]											
			10[f]	H_2O	$D^{a,b}/M^{a,b}/0$	I (white precipitate)	Glass	22.5	–	24 h	I (white prec.)	[morphine] >90%	cte	
			1–2	NaCl	$D^{a,b}/M^{a,b}/0$	C	Glass	22.5	–	24 h	C	[morphine] >100%	cte	
			–5											
			10[f]											
	60 I IU/ml	–	2	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	cte	Smythe et al. (1990)
Labetalol (HCl)	1	Dex.	1	Dex.	1/1/0	C	Glass	18	Light*	24 h	C	–	–	Colucci et al. (1988)
	5	–	1	–	1/1//0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
	1	Dex.	0.5	Dex.	1/1/0	C	Glass	20–25	Light*	4 h	C	[morphine] >97% [labetalol] >98%	cte	Hassan et al. (1994)
Lidocaine (HCl)	1	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Methyldopa (HCl)	2.5	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Metoprolol (tartrate)	1	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Milrinone	1	–	8	–	5.25/5/0	–	Glass	T_R	Light*	20 min	–	[morphine] 101% [milrinone] 98%	–	Wilson and Forde (1990)

Table 4 (Continued)

Propranolol (HCl)	1	–	1	–	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)
Verapamil (HCl)	2.5	–	15	–	16[b]/1[c]/500[a](Dex.)	C	–	–	–	48 h	C	–	–	Cutie (1983)
		–	15	–	16[b]/1[c]/500[a](NaCl)	C	–	–	–	48 h	C			
13. Antiepileptic drugs:														
Fenytoin (Na)	2	Dex.	1	Dex.	1[a,b]/1[a,b]/0	I (precipitate)	Glass	22	Light*	48 h	I (precipitate)	–	–	Chandler et al. (1996)
		NaCl	1	Dex.	1[a,b]/1[a,b]/0	I (precipitate)	Glass	22	Light*	48 h	I (precipitate)	–	–	
14. Drugs for the treatment of spasticity:														
Atropine (sulfate)	0.4	–	1	Dex.	1[a,b]/1[a,b]/0	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
Baclofen	0.2[f]	NaCl	1 – 1.5[f]	NaCl	–	C	–	37	–	30 days	C	[morphine] > 99% [baclofen] > 95%	cte	Sitaram et al. (1995)
	0.8[f]	NaCl	1 – 1.5[f]	NaCl	–	C	–	37	–	30 days	C	[morphine] > 98% [baclofen] > 93%	cte	
	1.5[f]	–	7.5[f]	–	–	C	Glass	37	–	30 days	C	[morph.] 96–102% [baclof.] 96–102%	5.25–5.0	Sitaram et al. (1997)
	1[f]	–	15[f]	–	–	C	Glass	37	–	30 days	C	[morph.] 98–100% [baclof.] 98–101%	5.0–4.7	
							Infusaid®	37	–	30 days	C	[morphine] > 94% [baclofen] > 94%		
	0.2[f]	–	21[f]	–	–	C	Glass	37	–	30 days	C	[morph.] 97–101% [baclof.] 97–102%	3.8–3.6	
Diphenhydramine (HCl)	2	Dex.	1	Dex.	1[a,b]/1[a,b]/0	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
Scopolamine (HBr)	0.05	Dex.	1	Dex.	1[a,b]/1[a,b]/0	C	Glass	22	Light*	48 h	C	–	–	Chandler et al. (1996)
15. Drugs for treatment of bronchospasms:														
Salbutamol (sulfate)	1	–	10	NaCl	–	C	Glass	23	Light	1 h	–	–	cte	Donnelly and Farncombe (1994)
16. Immunomodulators:														
Sargramostim (recombinant human granulocyte –macrophage colony stimulating fact.)	0.01	NaCl	1	NaCl	1[a,b]/1[a,b]/0	C	Glass	22	Light*	4 h	I (hazy after 1h)	–	–	Trissel et al. (1992)
Interleukin-2	10^6 U/ml	NaCl	1	–	1/1/0	C	–	4	–	28 days	C	cte. activity interleukin-2	–	Anderson et al. (1992)
17. Insulin:														
Insulin	0.2 IU/ml	–	1	NaCl	1/1/0	C	Glass	25	Light*	1 h	C	–	–	Smythe and Malouf (1991)
	0.2 IU/ml	NaCl	5	Dex.	1[a]/1[b]/0	C	Glass	25	Light*	2 h	C	–	cte	Smythe and Malouf (1991)

Table 4 (Continued)

18. Enteral and parenteral feeding:														
Isocal®	–	–	0.5 – –1[f]	D[a]/M[b]/0	I (phase separ., disappears with shaking)	Glass	4+24	–	24+24 h	–	[morphine] >95%	6.2–6.6	Michelini et al. (1988)	
						Feeding-bag	25	–	24 h	C	[morphine] >97%	6.2–6.4		
Jevity®	–	–	2 –	1/1/0	I (protein prec.+phase separ.)	–	22, 37, 50	–	48 h	–	[morphine] >98%	cte	Udeani et al. (1994)	
			20 –	1.8/0.2/0	C	–	22, 37, 50	–	48 h	C	[morphine] >98%	cte		
Osmolite®	–	–	2 –	1/1/0	I (protein prec. + phase separ.)	–	22, 37	–	48 h	–	[morphine] >98%	cte	Udeani et al. (1994)	
			20 –	1.8/0.2/0	C	–	22, 37	–	48 h	C	[morphine] >99%	cte		
Pulmocare®	–	–	2 –	1/1/0	I (protein prec. + phase sep.)	–	22, 37	–	48 h	–	[morphine] >98%	cte	Udeani et al. (1994)	
			20 –	1.8/0.2/0	C	–	22, 37	–	48 h	C	[morphine] >98%	cte		
TPN	–	–	0.1 –	–	–	PVC-bag	21.5	Light	36 h	No precipitate	[morphine] cte	5.4	Macias et al. (1985)	
	–	–	1 –	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)	
TPN+vit+spore el.	–	–	1 –	1/1/0	C	Glass	25	Light*	4 h	C	–	–	Pugh et al. (1991)	
Vivonex® standard	–	–	0.5 – –1[f]	–	C	Glass	4+25	–	24+24 h	–	[morphine] >94%	5.1–5.4	Michelini et al. (1988)	

[a] –, no data reported; [f], final concentration in admixture; [I], isotonized with dextrose (Dex. [I]) or sodium chloride (NaCl [I]); Dil., diluent; Ratio $v_D/v_M/v$(Dil.), volume ratio: drug solution (D)/morphine solution (M)/diluent (H_2O (= water for injection) Dex.(= 5% dextrose) or NaCl (= 0.9% NaCl); [a], first solution added to recipient; [b], solution added to solution a; [c], solution added to admixture of a and b; [a,b], both orders of mixing have been tested; D[a]/M[b]/0, morphine solution added to drug solution, but no ratio given; C, compatible; I, incompatible; protec., protected from light; light, not protected from light, but no light source given; light*, standard fluorescent light.

Table 5
Compatibility of morphine hydrochloride[a]

Drug (D)			Morphine HCl (M)		Ratio, v/v/v (Dil.)	Compatibility visual (C/I)	Storage				Stability			References
Name	Conc. (mg ml^{-1})	Dil.	Conc. (mg ml^{-1})	Dil.			Reservoir	Temp (°C)	Light	Time	Visual (C/I)	Concentration after storage	pH	
1. Anti-emetics:														
Haloperidol (lactate)	1.25[f]	–	20[f]	–	–	C	–	4	–	3 days	I (crystals after 1–day)	–	–	Ottesen and Monrad (1992)
	2[f]	–	8[f]	–	–	C	–	4	–	3 days	I (crystals after some hours)	–	–	
							–	25	–	3 days	C	–	–	
							–	36	–	3 days	C	–	–	
	1	H_2O	10 and 50	D^I	$1^{a}/10^{b}/0$	C^o	Glass	22	Protec.	28 days	C	[morphine] > 99% [haloper.] > 95%	4–5	Vermeire and Remon (1998)
	2.5	H_2O	10 and 50	D^I	$1^{a}/10^{b}/0$	C^o	Glass	22	Protec.	28 days	C	[morphine] > 99% [haloper.] > 98%	3–4	
	5	–	10	H_2O, $NaCl^I$ and $Dex.^I$	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	C^o (7) up to 10/10/0	Glass	22	Protec.	28 days	C^o up to 10/10/0	–	–	
			20	H_2O, $NaCl^I$ and $Dex.^I$	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	C^o (7) up to 10/10/0	Glass	22	Protec.	7 days	C^o up to 10/10/0	–	–	
			30	H_2O, $NaCl^I$ and $Dex.^I$	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	C^o (7) up to 8/10/0	Glass	22	Protec.	7 days	C^o up to 8/10/0; I–at 9/10/0 to 10/10/0		–	
			40	H_2O, $NaCl^I$ and $Dex.^I$	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	C^o (7) up to 6/10/0	Glass	22	Protec.	7 days	C^o up to 6/10/0; I–at 7/10/10 to 10/10/0		–	
			50	H_2O, $NaCl^I$ and $Dex.^I$	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	C^o (7) up to 5/10/0	Glass	22	Protec.	7 days	C^o up to 5/10/0; I at 6/10/0 to 10/10/0			
				$Dex.^I$	$1^{b}/10^{a}/0$	C^o	Glass	22	Protec.	28 days	C	[morphine] > 99% [haloper.] > 97%	3–4	
	5	–	5, 10, 20 and 30	–	$1^{a}/1^{b}/0$	C	Glass	23	Light	7 days	C	[morphine] > 90% [haloper.] > 90%	–	Schrijvers et al. (1998)
								31	Light	7 days	C	[morphine] > 90% [haloper.] > 90%	–	
Metoclopramide (HCl)	9[f]	–	18[f]	–	–	–	PVC-cassette	25	–	10 days	–	[morphine] > 95% [metocl.] 100%	–	Ottesen and Monrad (1992)
	9.8[f]	–	36.4[f]	–	–	–	PVC-cassette	25	–	10 days	–	[morphine] > 95% [metocl.] > 95%	–	
	10[f]	–	10[f]	–	–	–	PVC-cassette	25	–	10 days	–	[morphine] > 90% [metocl.] > 100%	–	
	16.7[f]	–	16.7[f]	–	–	–	PVC-cassette	25	–	10 days	–	[morphine] > 90% [metocl.] > 90%	–	
	20[f]	–	10[f]	–	–	–	PVC-cassette	25	–	10 days	–	[morphine] > 90% [metocl.] > 90%	–	
	5	–	5, 10, 20 and 30	–	$2^{a}/1^{b}/0$	C	Glass	23	Light	7 days	C	[morph.] > 100% [metocl.] > 97%	–	Schrijvers et al. (1998)
								31	Light	7 days	C	[morph.] > 100% [metocl.] > 96%	–	

Table 5 (Continued)

2. Hypnotics, sedatives and anxiolytics:														
Midazolam (HCl)	1	H_2O	10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [midazol.] >99%	5–6	Vermeire and Remon (1998)
	2.5	H_2O	10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [midazol.] >99%	4–5	
	5	–	10, 20, 30, 40 and 50	H_2O, NaCl[I] and Dex.[I]	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	–**	Glass	22	Protec.	7 days	C up to 10/10/0	–	–	
			10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [midazol.] >100%	3–4	
3. Corticosteroids:														
Dexamethasone (sodium phosphate)	0.83	H_2O	10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C[o]	[morphine] >99% [dexam.] >80%	4–7	Vermeire and Remon (1998)
	1.67	H_2O	10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [dexam.] >85%	5–7	
	3.33	–	10, 20, 30, 40 and 50	H_2O, NaCl[I] and Dex.[I]	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	–**	Glass	22	Protec.	7 days	C[o] up to 1/10/0, I at 2/10/0 up to 10/10/0	–		
		–	10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [dexam.] >97%	6–7	
	4	H_2O	10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [dexam.] >92%	4–7	
	10	H_2O	10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [dexam.] >92%	5–7	
	20	–	10, 20, 30, 40 and 50	H_2O, NaCl[I] and Dex.[I]	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	–**	Glass	22	Protec.	7 days	C[o] up to 1/10/0, I at 2/10/0 to 10/10/0	–		
			10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [dexam.] >96%	6–7	
Methylprednisolone (sodium succinate)	5	H_2O	10, 20, 30, 40 and 50	H_2O, NaCl[I] and Dex.[I]	$1^{b}/10^{a}/0$	–**	Glass	22	Protec.	7 days	C[o]	–	–	Vermeire and Remon (1998)
			10 and 50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [methylpr.] >65%	3–7	
	10	H_2O	10, 20, 30, 40 and 50	H_2O, NaCl[I] and Dex.[I]	$1^{b}/10^{a}/0$	–**	Glass	22	Protec.	7 days	C[o] for MHCl 10, 20 and 30; I for MHCl 40 and 50	–	–	
			50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [methylpr.] >60%	3–6	
	15	H_2O	10, 20, 30, 40 and 50	H_2O, NaCl[I] and Dex.[I]	$1^{b}/10^{a}/0$	–**	Glass	22	Protec.	7 days	C[o] for MHCl 10 and 20; I for MHCl 30, 40 and 50	–	–	
			50	Dex.[I]	$1^{b}/10^{a}/0$	C	Glass	22	Protec.	28 days	C	[morphine] >99% [methylpr.] >45%	3–6	

Table 5 (Continued)

50	H_2O	10, 30, 40 and 50	20,H_2O, $NaCl^I$ and $Dex.^I$	$1^b/10^a/0$	–**	Glass	22	Protec.	7 days	C^o for MHCl 10 and 20; I for MHCl 30, 40 and 50	–		
			10	$Dex.^I$	$1^b/10^a/0$	C^o			28 days	C	[morphine] >99% [methylpr.] >77%	6–7	
	100	H_2O	10, 20, 30, 40 and 50	H_2O, $NaCl^I$ and $Dex.^I$	$1^{a,b}/10^{a,b}/0$ $-10^{a,b}/10^{a,b}/0$	–**	Glass	22	Protec.	7 days	C^o for MHCl 10; I for MHCl 20, 30, 40 and 50	–	–	
			10	$Dex.^I$	$1^b/10^a/0$	C^o	Glass	22	Protec.	28 days	C	[morphine] >99% [methylpr.] >77%	6–7	
4. Drugs for stomach and duodenum pathology:													
Ranitidine (HCl)	25	–	5, 10, 20 and 30	–	$2^a/1^b/0$	C	Glass	23	Light	7 days	Yellow	[morphine]–[ranitid.] >100%	–	Schrijvers et al. (1998)
								31	Light	7 days	Yellow	[morphine]–[ranitid.] >100%	–	
5. Cardiovascular drugs:													
Clonidine (HCl)	0.075^f	NaCl	2^f	NaCl	–	–	PVC-cassette	35	–	14 days	–	[morphine] >99% [clonidine] >98%	–	Landersjö and Nyhammar (1989)
6. Drugs for the treatment of spasticity:													
Atropine (sulfate)	1	–	5, 10, 20 and 30	–	$1^a/1^b/0$	C	Glass	23	Light	7 days	C	[morphine] >96%–[atropine]–		Schrijvers et al. (1998)
								31	Light	7 days	C	[morphine] >99% [atropine]–	–	
Butylhyoscine (bromide)	20	–	5, 10, 20 and 30	–	$1^a/1^b/0$	C	Glass	23	Light	7 days	C	[morph.] >100% [butylhyosc.]–	–	Schrijvers et al. (1998)
								31	Light	7 days	C	[morph.] >100% [butylhyosc.]–	–	

[a] –, no data reported; [f], final concentration in admixture; [I], isotonized with sodium chloride ($NaCl^I$) or dextrose (D^I); Dil., diluent; Ratio $v_D/v_M/v$ (Dil.), volume ratio: drug solution (D)/morphine solution (M)/diluent (H_2O (= water for injection), Dex. (= 5% dextrose), NaCl (= 0.9% NaCl); [a], first solution added to recipient; [b], solution added to solution a; [c], solution added to admixture of a and b; [a,b], both orders of mixing have been tested; $D^a/M^b/0$, morphine solution added to drug solution, but no ratio given; C, compatible; I, incompatible; C^o, compatible only if the other drug is added to the morphine solution and incompatible for the inverse order of mixing; **, no data given since delayed incompatibility was noted after 1 or more days, therefore only the compatibility after 7 days is given; protec., protected from light; light, not protected from light, but no light source specified; light*, standard fluorescent light.

Table 6
Compatibility of morphine tartrate infusion solutions[a]

Drug (D)			Morphine tartrate (M)		Ratio $v_D/v_M/v$ (Dil.)	Compatibility visual (C/I)	Storage				Stability			References
Name	Conc. (mg ml^{-1})	Dil.	Conc. (mg ml^{-1})	Dil.			Reservoir	Temp. (°C)	Light	Time	Visual (C/I)	Concentration after storage	pH	
1. Drugs used in anesthesia:														
Ketamine (HCl)	11[f]	NaCl	26.67[f]	NaCl	–	C	Syringe	4	Protec.	10 days	C	–	–	Ambados (1995)
								T_R	Protec.	10 days	C	–	–	
	100	–	80	–	2.4/6.25/0	C	–	21	Light*	24 h	C	[morphine] cte [ketamine] cte	4.85	Lau et al. (1998)

[a] –, no data reported; [f], final concentration in admixture; Dil., diluent; Ratio $v_D/v_M/v$ (Dil.), volume ratio: drug solution (D)/morphine solution (M)/diluent (H_2O = water for injection), Dex. (= 5% dextrose), NaCl (= 0.9% NaCl); C, compatible; I, incompatible; protec., protected from light; light*, standard fluorescent light.

volume is added. These few reports confirm the experience from daily practice that the way of preparation can affect compatibility and should, therefore, always be stated when reporting compatibility data.

Although not much attention is usually paid on the temperature it was clear from our compatibility study (Vermeire and Remon, 1998) that small differences in temperature (3–5°C) can cause significantly different results concerning the compatibility, which are mainly based on solubility. In our study we mostly noticed a decrease in the maximal concentration at which compatibility was observed with decreasing temperature. Data on the compatibility at elevated temperatures are not reported, but Vermeire and Remon (1998) reported that heating of compatible admixtures could cause precipitation. This can be explained by the fact that reactions are usually faster at elevated temperatures, so a reaction between two components in the admixture could occur within the period that one noticed no incompatibility at ambient temperature.

Compatibility was mostly studied only for a short period of time, as most of the studies are conducted in intensive care units where one is mainly interested in the compatibility during Y-site administration. Some studies on the long-term compatibility reported delayed incompatibilities (Pugh et al., 1991; Trissel et al., 1992; Vermeire and Remon, 1998) indicating that initial compatibility or compatibility for 24 h does not guarantee the compatibility of the admixture over longer periods of time.

An important aspect of compatibility is the chemical stability of drugs in the admixtures. Although it is generally accepted that the chemical stability of both drugs should be precisely known in order to allow the administration of the admixture after storage and/or for infusion over a longer period of time, only in a minority of the studies the concentration of both drugs were determined. Often it is concluded that when no physical problems are noticed probably no chemical stability occurs. It should be emphasized that chemical instability might occur in some visually stable admixtures, e.g. instability of methylprednisolone-21-sodium succinate in physically stable admixtures with morphine hydrochloride (Vermeire and Remon, 1998).

5. Conclusion

It can be concluded that morphine degrades in aqueous solutions with the formation mainly of pseudomorphine and to a lesser extent, morphine-*N*-oxide. The formation of apomorphine from morphine appears unlikely, but data on this are conflicting.

From the study of the kinetics of morphine degradation it was concluded that the degradation of morphine is accelerated in the presence of oxygen and at higher pH of the solution, whereas temperature and light have only a minor influence on the degradation rate.

From the data concerning the stability of morphine solutions stored under normal conditions it can be concluded that the degradation of morphine solutions prepared using different salts of morphine, at different concentrations, in different diluents and stored under different conditions of light and temperature and in different reservoirs is limited and that they can be stored for at least 3 months without stability problems ($< 5\%$ degradation). Morphine solutions should, however, preferably be stored at room temperature to avoid precipitation of concentrated solutions (at low temperatures) or increase of the morphine concentration due to water evaporation when stored in some pump reservoirs (at high temperatures). Although oxygen, high pH, light and elevated temperatures do not affect morphine stability during short periods of time these factors accelerate the degradation of morphine solutions and should be avoided when morphine solutions are stored and/or infused for longer periods of time. Concerning the compatibility of morphine infusion solutions it can be concluded that although the compatibility of morphine has been extensively studied, the information useful for palliative care settings is limited. The data available on the compatibility of morphine clearly show that differences in formulation of the drug solutions used (concentration of drug, salt form, type and concentration of additives), in diluent as well as in order and ratio of

mixing and temperature of preparation might affect the compatibility. The compatibility was in most cases investigated at a single (mostly low) concentration and/or without detailed information on the ratio and order of mixing or composition of the drug solutions used. Besides, the compatibility was in most cases only studied for a very short period of time. When interpreting compatibility data one should be aware that these data do not give any information on the compatibility of an admixture of the same drugs in different concentrations, in different diluents, prepared using different salts or formulations, prepared in a different way, at different temperatures or during longer periods of time.

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