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Review

Ficts and facts of epinephrine and norepinephrine stability in injectable solutions

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ABSTRACT

Epinephrine (EPI) and norepinephrine (NE) play an important role in emergency medicine and acute treatment of hypotension and shocks in the intensive care unit. Injectable solutions can either be provided as proprietary medicinal products or as individually prepared dilutions. Due to the chemical structure of EPI and NE, the stability of the corresponding solutions is limited. Thus, most manufacturers of EPI and NE injectable solutions use sulfites and nitrogen for stabilization, Nevertheless, storage conditions such as temperature and light have to be considered, but are often neglected in the daily hospital routine. In addition, hospital pharmacies prepare EPI and NE solutions and dilute commercially available solutions for individual therapy, especially on ICUs. Since the influence of dilution and the presence of excipients and other preservatives are not systematically explored, we collected published data and investigations on stability on the potency of EPI and NE injectable solutions in order to deduce storage recommendations for diluted EPI and NE solutions of different concentration.

Contents

1. Introduction

Epinephrine ((1*R*)-1-(3,4-dihydroxyphenyl)-2-(methylamino) ethanol, EPI) and norepinephrine (NE; N-desmethylepinephrine) are potent α-sympathomimetic drugs and physiological neurotransmitters with the typical core structure of the phenylalkylamines (2-phenyl-1-aminoethane). Their hydrogen tartrate or hydrochloride salts are widely used in injectable solutions for acute treatment of hypotension, anaphylactic shocks, and as vasoconstrictive additives in local anesthetic formulations to prolongate the analgesic effect. Due to their common usage in emergency medicine and intensive care units (ICUs), the typical dosage forms are ampoules for single use and sterile injectable solutions in glass bottles. In the United States Pharmacopoeia (USP), e.g. "Epinephrine" injections are specified explicitly: "Epinephrine injection is a sterile solution of epinephrine in water for injection prepared with the aid of hydrochloric acid or other suitable buffers." (US Pharmacopoeia, 2011). Apart from proprietary medicinal products (Arterenol®, Suprarenin®; cf. Table 1), it is wide practice in hospital pharmacies

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Table 1
Examples of commercially available EPI and NE preparations containing 1 mg mL^{-1} API.

Commercial name	API	Volume, primary packing	Excipients
Arterenol® Sanofi Aventis	Norepinephrine hydrochloride	5 mL, ampoules	Sodium metabisulfite 0.5 mg mL^{-1} Sodium chloride Hydrochloric acid 10% for pH-adjustment Water for injection purposes
		25 mL, glass bottle	Chlorobutanol 4 mg mL^{-1} Sodium metabisulfite 0.5 mg mL^{-1} Sodium chloride Hydrochloric acid 36% for pH-adjustment Water for injection purposes
Suprarenin® Sanofi Aventis	Epinephrine hydrochloride	1 mL, ampoules	Sodium metabisulfite 0.5 mg mL^{-1} Sodium chloride Hydrochloric acid 10% for pH-adjustment Water for injection purposes
		25 mL, glass bottle	Chlorobutanol 4 mg mL^{-1} Sodium metabisulfite 0.5 mg mL^{-1} Sodium chloride Hydrochloric acid 36% for pH-adjustment Water for injection purposes
Fastjekt® MEDA Pharma	Epinephrine hydrochloride	2.05 mL in autoinjector	Sodium chloride 6 mg mL^{-1} Sodium metabisulfite 1.84 mg mL^{-1} Water for injection purposes

to prepare EPI and NE-injectable dilutions in advance (syringes, Perfusors®) under aseptic conditions, especially solutions which are not commercially available from professional manufacturers. Like this, especially in acute emergency situations or when pharmaceutical personnel is missing (weekend, holidays), a quick and constant supply of proper medication can be guaranteed. Moreover, this approach is cost-effective, very practicable and provides medication in suitable concentrations for special fields of application (infants, children, elderly people). Common concentrations of catecholamines in commercial products are 1–2% for adults, whereas for child use, solutions containing 0.5 or 0.15% are appropriate. In dentistry, injections for local anesthetics consist of either EPI or NE within a range of 2.5×10^{-4} to 5×10^{-4}% (Ultracain®, Xylocain®).

However, some issues and problems have to be considered when preparing or diluting NE and EPI solutions:

(1) Can the stability of the active ingredient be assured over a certain storage time, especially when proprietary formulations are diluted and what are the overall degradation rates?
(2) Does the dilution affect the stability of the parent product especially against the background that the solutions are contaminated with oxygen after dilution?
(3) Does the type of solvent and the type of preservatives and excipients affect the stability of the active pharmaceutical ingredient (API)?

Various publications are available on these topics. Here, we review stability data on EPI and NE injectable solutions in order to compare their different stability behavior under different storage conditions and try to find general recommendations for EPI and NE preparations not manufactured by industries.

2. Degradation of catecholamines

2.1. Oxidation and reduction processes

Due to the catechol substructure, EPI and NE can easily undergo oxidation processes. The degradation products and mechanisms are well understood and have already been described in detail by Dolder (1952). Schwedt and Baran were able to identify the intermediates via HPLC and coupled detection techniques (UV, fluorescence, electrochemical) (Baran and Schwedt, 1993). Eventually, slight magenta-colored adrenochromes are formed and ongoing dehydration and polymerization leads to typical black-colored insoluble particles which can be easily observed even shortly after preparing fresh solutions of NE. The process is catalyzed by light, air, elevated temperature, heavy metals, basic conditions or other excipients (Grunert and Wollmann, 1982). The variability of degradation pathways and the catalytic influence of the aforementioned parameters point to the need for protection of EPI and NE solutions, like employed by many commercial manufacturers: brown glass vials, airtight sealing, blanketing with nitrogen, addition of anti-oxidative preservatives such as ethylenediamine tetraacetic acid (EDTA) or addition of sulfites and storage at low temperatures in order to prevent degradation and coloration of the pharmaceutical product. Fig. 1 shows the proposed degradation mechanisms for phenylalkylamines with catechol moiety (1). Loss of hydrogen forms the o-chinon (2). After cyclization (2), either a reductive (to 3, 3a) or an oxidative (to 4, 4a) way is possible, resulting in formation of colorless adrenolutines (3a), and adrenochromes (4a) and oxadrenochromes (5, 5a), the latter representing the colored species (Grunert and Wollmann, 1982). A comprehensive overview on the influence of different storage scenarios can be found at Florey (1978).

2.2. Enantiomeric purity

As only the R enantiomer of EPI and NE is active, the isomerically pure compound is in therapeutic use (Patil et al., 1967). The racemization is possible and, according to cited literature in Eger et al. (2006), depending on pH; it shows a minimum at pH 4.3 (NE) and thus has to be controlled (Riegelman and Fischer, 1962; Schroeter and Higuchi, 1960; Schroeter et al., 1958). This can be checked either by determination of optical rotation, like prescribed in the European Pharmacopoeia (PhEur; values for EPI: −50 to −53.5; NE: −44 to −48, respectively, Council of Europe, 2011), by liquid chromatography on chiral stationary phases (Stepensky et al. reported an overall racemization rate of 5.6% over a period of 2 years) (Stepensky and Chorny, 2003) or, as by Allgire et al. (1985), after chemical reaction with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (derivatization reagent) and liquid chromatography with UV detection. Additionally, capillary electrophoresis (CE)

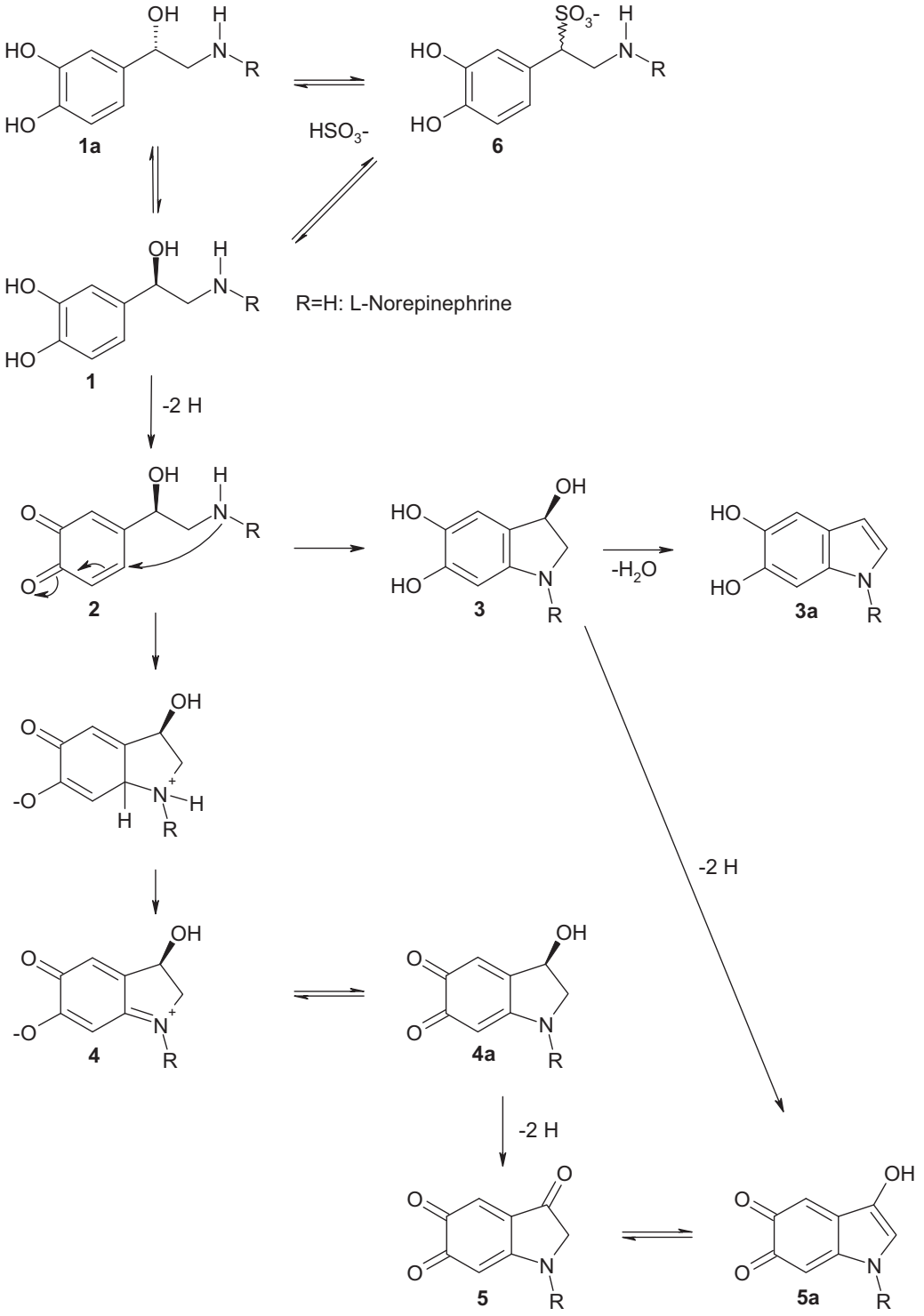

Fig. 1. Degradation pathways of epinephrine and its derivatives.

with cyclodextrines as chiral selectors represents an elegant and effective method for a baseline enantioseparation (e.g. Borst and Holzgrabe, 2010 and literature cited herein).

2.3. *Influence of excipients and antioxidative stabilizing agents*

As EPI and NE are delivered intravenously, the number of possible excipients and preservatives is limited. Isotonic sodium chloride (0.9%) and glucose (5%) solutions are the most common solvents, and interactions with these substances are not very likely from a chemical point of view. However, compatibility information or problems on various combinations with active pharmaceutical substances or other excipients is available (Trissel, 2007).

Sulfite ions (e.g. sodium metabisulfite, $Na_2S_2O_5$) are widely used to delay oxidation and coloration to purple by lowering the pH of the respective solution (Wollmann and Raether, 1983). However, the benzylic alcohol function can be attacked by nucleophilic sulfite ions via S_N2 mechanism at pH values higher than 5, forming the

Table 2
Summary of EPI and NE stability experiment data.

Drug facts			Storage conditions						Stability data		Ref.
Concentr. (mg mL^{-1})	Diluent	Origin	Reservoir	Temp. (°C)	Light	pH	Time	Add. subst.	Loss on conc.	Col. [a]	
Epinephrine											
1		Ampoules	Glass	23–70–23 °C	Prot.		12 wks		No change		Grant et al. (1994)
0.1		Prefilled syr.	Syringe	23–70–23 °C	Prot.		12 wks		−64%		
1		Ampoules	Glass	23–2.5–23 °C	Prot.		12 wks		No change		
0.1		Prefilled syr.	Syringe	23–2.5–23 °C	Prot.		12 wks		No change		
0.1		Inj. solution	Cartridge; glass vial	Const. 65 °C			7 d	NaCl $NaHSO_3$ Citrate buffer	Complete	+	Church et al. (1994)
0.1		Inj. solution	Cartridge; glass vial	Cyclic 65 °C			7 d		−57%	–	
0.1		Inj. solution	Cartridge; glass vial	Cyclic 65 °C			12 wks		−76%	–	
1		Ampoules	Syringe	26 °C	Prot.	3.17–3.23	12 wks		$99.3 < x < 102.7\%$	+	Kerddonfak et al. (2010)
0.001		Autoclaved cartridge		34–37 °C			3 mos	Xylocaine	−19%	–	Fry and Ciarlone (1980b)
							3 mos	Octocaine	−26%	–	
							3 mos	LIDO	−21%	–	
							3 mos	LIDO	−29%	–	
API				90 °C	Prot.		4 d		−1%	–	Muller et al. (1988)
				80 °C			18 d		−1%	–	
				70 °C			47 d		−1%	–	
				60 °C			120 d		−1%	–	
				50 °C			338 d		−1%	–	
				40 °C			716 d		−1%	–	
				30 °C			1382 d		−1%	–	
0.000565	KRH[b] + 1 M $HClO_4$ (25:1)	API		22 °C		1.96	90 min	$HClO_4$, KRH	−26%	–	Palazzolo and Quadri (1990)
	KRH + 1 M $HClO_4$ (50:1)	API				5.81	90 min		−10%	–	
	KRH	API				7.81	90 min		−46%	–	
	KRH + 1 M $HClO_4$ (25:1)	API		4 °C		1.96	28 d		−80%	–	
	KRH + 1 M $HClO_4$ (50:1)	API				5.81	2 d		−100%	–	
	KRH	API				7.81	2 d		−100%	–	
	KRH + 1 M $HClO_4$ (25:1)	API		−60 °C		1.96	28 d		Stable	–	
	KRH + 1 M $HClO_4$ (50:1)	API				5.81	28 d		Stable	–	
	KRH	API				7.81	28 d		Stable	–	
0.001		Autoclaved cartridge		34–37 °C		–	6 mos	LIDO 2%	−49.5%	–	Fry and Ciarlone (1980a)
0.001	Boric acid 0.45%, sodium tetraborate 0.80%		Open system	Ambient	Not prot.	5.5	21 d	DTPA[c] 1 mM	−10%	+	Wollmann and Raether (1983)
						5.5	3 d	EDTA[d] 1 mM	−10%	+	
						5.5	4 d	Na_2-EDTA[e] 1 mM	−10%	+	
						5.5	3 d	MgNaEDTA[f] 1 mM	−10%	+	
						5.5	7 d	EBTA[g] 1 mM	−10%	+	
0.001	Boric acid 0.45%, $Na_2[B_4O_5(OH)_4]$ 0.80%		Open system	Ambient	Not prot.	5.5	7 d	DCTA[h] 1 mM	−10%	+	
						5.5	6 d	NAA[i] 1 mM	−10%	+	
						5.5	4 d	HETA[j] 1 mM	−10%	+	
						5.5	9 d	EDDA[k] 1 mM	−10%	+	
						5.5	8 d	IAA[l] 1 mM	−10%	+	

Table 2 (*Continued*)

Drug facts			Storage conditions						Stability data		Ref.
Concentr. (mg mL^{-1})	Diluent	Origin	Reservoir	Temp. (°C)	Light	pH	Time	Add. subst.	Loss on conc.	Col. [a]	
						5.5	7 d	NaDHEG[m] 1 mM	−10%	+	
						5.5	14 d	8-HQS[n] 1 mM	−10%	+	
						5.5	4 d	CA 0.5%	−10%	+	
						5.5	8 d	OA[o] 0.5%	−10%	+	
						5.5	9 d	TA[p] 0.5%	−10%	+	
						5.5	7 d	EDA[q] 0.5%	−10%	+	
						5.5	11 d	AA[r] 0.5%	−10%	+	
						5.5	18 d	PG[s] 0.5%	−10%	+	
						5.5	19 d	Thiourea 0.5%	−10%	+	
						5.5	42 d	ACC[t] 0.5%	−10%	+	
						5.5	5 d	$Na_2S_2O_5$ 0.3%	−10%	+	
						5.5	5 d	Na_2SO_3 0.3%	−10%	+	
						5.5	5 d	$NaHSO_3$ 0.3%	−10%	+	
						5.5	4 d	$SnSO_4$ 0.3%	−10%	+	
						5.5	4 d	NaF 0.3%	−10%	+	
										+	
0.001	Boric acid 0.45%, $Na_2[B_4O_5(OH)_4]$ 0.80%		Brown glass vial	Ambient	Prot.	5.5	25 d	DTPAA[u]	−10%	+	
0.001	Boric acid 0.45%, $Na_2[B_4O_5(OH)_4]$		Brown glass vial	Ambient	Prot.	5.5	9 d	EDTA	−10%	+	
						5.5	9 d	MgNaETDA	−10%	+	
						5.5	9 d	EBTA	−10%	+	
						5.5	10 d	HDPTAA[v]	−10%	+	
						5.5	11 d	DCTA	−10%	+	
						5.5	11 d	NAA	−10%	+	
						5.5	10 d	HETA	−10%	+	
						5.5	10 d	EDTA	−10%	+	
						5.5	10 d	IAA	−10%	+	
						5.5	9 d	NaDHEG	−10%	+	
						5.5	17 d	8-HQS	−10%	+	
						5.5	6 d	CA[w] acid 0.5%	−10%	+	
						5.5	12 d	OA 0.5%	−10%	+	
						5.5	11 d	TA 0.5%	−10%	+	
						5.5	11 d	EDA 0.5%	−10%	+	
						5.5	16 d	AA 0.5%	−10%	+	
						5.5	21 d	PG 0.5%	−10%	+	
						5.5	24 d	Thiourea 0.5%	−10%	+	
						5.5	60 d	ACC 0.5%	−10%	+	
						5.5	8 d	$Na_2S_2O_5$ 0.3%	−10%	+	
						5.5	8 d	Na_2SO_3 0.3%	−10%	+	
						5.5	7 d	$NaHSO_3$ 0.3%	−10%	+	
0.001	Boric acid 0.45%, $Na_2[B_4O_5(OH)_4]$		Brown glass vial	Ambient	Prot.	5.5	8 d	$SnSO_4$ 0.3%	−10%	+	
						5.5	8 d	NaF 0.3%	−10%	+	
0.001	Boric acid 0.45%, $Na_2[B_4O_5(OH)_4]$ 0.8%		PE-ND EB[x]	Ambient	Prot.	5.5	30 d	DTPA	−10%	+	
						5.5	10 d	EDTA	−10%	+	
						5.5	10 d	Na_2-EDTA	−10%	+	
						5.5	10 d	MgNaEDTA	−10%	+	
						5.5	11 d	EBTA	−10%	+	
						5.5	12 d	HDPTAA	−10%	+	
						5.5	12 d	DCTA	−10%	+	

Table 2 (*Continued*)

Drug facts			Storage conditions						Stability data		Ref.
Concentr. (mg mL^{-1})	Diluent	Origin	Reservoir	Temp. (°C)	Light	pH	Time	Add. subst.	Loss on conc.	Col. [a]	
						5.5	12 d	NAA	−10%	+	
						5.5	11 d	HETA	−10%	+	
						5.5	12 d	EDDA	−10%	+	
						5.5	11 d	IAA	−10%	+	
						5.5	10 d	NaDHEG	−10%	+	
						5.5	20 d	8-HQS	−10%	+	
						5.5	7 d	CA 0.5%	−10%	+	
						5.5	12 d	OA 0.5%	−10%	+	
0.001	Boric acid 0.45%, $Na_2[B_4O_5(OH)_4]$ 0.8%		PE-ND EB	Ambient	Prot.	5.5	12 d	TA 0.5%	−10%	+	
0.001				Ambient	Prot.	5.5	12 d	EDA[y] 0.5%	−10%	+	
0.001				Ambient	Prot.	5.5	16 d	AA 0.5%	−10%	+	
0.001				Ambient	Prot.	5.5	24 d	PG 0.5%	−10%	+	
0.001				Ambient	Prot.	5.5	24 d	Thiourea 0.5%	−10%	+	
0.001				Ambient	Prot.	5.5	66 d	ACC 0.5%	−10%	+	
0.001				Ambient	Prot.	5.5	10 d	$Na_2S_2O_5$ 0.3%	−10%	+	
0.001				Ambient	Prot.	5.5	11 d	Na_2SO_3 0.3%	−10%	+	
0.001				Ambient	Prot.	5.5	10 d	$NaHSO_3$ 0.3%	−10%	+	
0.001				Ambient	Prot.	5.5	10 d	$SnSO_4$ 0.3%	−10%	+	
0.001				Ambient	Prot.	5.5	10 d	NaF 0.3%	−10%	+	
0.05	0.9% NaCl	Suprarenin®	Syringe	20–25 °C			24 hrs		+4.42%	–	Adams et al. (1985)
0.05	0.9% NaCl	Suprarenin®	Syringe	20–25 °C			48 hrs		−23.56%	–	
0.05	0.9% NaCl	Suprarenin®	Syringe	20–25 °C			72 hrs		+5.20%	–	
0.05	0.9% NaCl	Suprarenin®	Syringe	20–25 °C			96 hrs		+7.85%	–	
0.05	5% glucose	Suprarenin®	Syringe	20–25 °C			24 hrs		−3.76%	–	
0.05	5% glucose	Suprarenin®	Syringe	20–25 °C			48 hrs		+0.11%	–	
0.05	5% glucose	Suprarenin®	Syringe	20–25 °C			72 hrs		+1.66%	–	
0.05	5% glucose	Suprarenin®	Syringe	20–25 °C			96 hrs		+2.99%	–	
0.05	0.9% NaCl	Suprarenin®	Syringe	4 °C			24 hrs		+0.74%	–	
0.05	0.9% NaCl	Suprarenin®	Syringe	4 °C			48 hrs		+0.47%	–	
0.05	0.9% NaCl	Suprarenin®	Syringe	4 °C			72 hrs		+0.93%	–	
0.05	0.9% NaCl	Suprarenin®	Syringe	4 °C			96 hrs		+2.51%	–	
0.05	5% glucose	Suprarenin®	Syringe	4 °C			24 hrs		−0.73%	–	
0.05	5% glucose	Suprarenin®	Syringe	4 °C			48 hrs		−0.55%	–	
0.05	5% glucose	Suprarenin®	Syringe	4 °C			72 hrs		+1.83%	–	
0.05	5% glucose	Suprarenin®	Syringe	4 °C			96 hrs		+2.29%	–	
0.05	5% glucose	Suprarenin®	Syringe	4 °C							
0.00001	0.025% $Na_2S_2O_5$		Glass	60 °C		3.8–4	7 d	5% LIDO[z] 0.1% MP[aa] 0.6% NaCl	−6.3%	–	Grubstein and Milano (1992)
0.00001			Glass	60 °C		3.8–4	14 d		−7.4%	–	
0.00001			Glass	60 °C		3.8–4	21 d		−10.5%	–	
0.00001			Glass	60 °C		3.8–4	35 d		−22.1%	–	
0.00001	0.010% $Na_2S_2O_5$		Glass	60 °C		3.8–4	7 d	5% LIDO 0.1% MP 0.6% NaCl	−17.9%	–	
0.00001			Glass	60 °C		3.8–4	14 d		−38%	–	
0.00001			Glass	60 °C		3.8–4	21 d		−41.2%	–	
0.00001			Glass	60 °C		3.8–4	35 d		–	–	
0.00001	0.005% $Na_2S_2O_5$		Glass	60 °C		3.8–4	7 d	5% LIDO 0.1% MP 0.6% NaCl	−51.5%	+	
0.00001			Glass	60 °C		3.8–4	14 d		–	–	
0.00001			Glass	60 °C		3.8–4	21 d		–	–	
0.00001			Glass	60 °C		3.8–4	35 d		–	–	

Table 2 (*Continued*)

Drug facts			Storage conditions						Stability data		Ref.
Concentr. ($mg\,mL^{-1}$)	Diluent	Origin	Reservoir	Temp. (°C)	Light	pH	Time	Add. subst.	Loss on conc.	Col. [a]	
0.00001	0.010% $Na_2S_2O_5$ 0.1% citric acid		Glass	60 °C		3.8–4	7 d	5% LIDO 0.1% MP 0.6% NaCl	−8.4%	–	
0.00001			Glass	60 °C		3.8–4	14 d		−17.9%	–	
0.00001			Glass	60 °C		3.8–4	21 d		−37.9%	–	
0.00001			Glass	60 °C		3.8–4	35 d		–	–	
0.00001	0.010% $Na_2S_2O_5$ 0.01% Na_2-EDTA		Glass	60 °C		3.8–4	7 d	5% LIDO 0.1% MP 0.6% NaCl	−10.5%	–	
0.00001			Glass	60 °C		3.8–4	14 d		−9.5%	–	
0.00001			Glass	60 °C		3.8–4	21 d		−13.7%	–	
0.00001			Glass	60 °C		3.8–4	35 d		−15.3%	–	
0.00001	0.0075% $Na_2S_2O_5$ 0.01% Na_2-EDTA		Glass	60 °C		3.8–4	7 d	5% LIDO 0.1% MP 0.6% NaCl	−10.5%	–	
0.00001			Glass	60 °C		3.8–4	14 d		−9.5%	–	
0.00001			Glass	60 °C		3.8–4	21 d		−13.7%	–	
0.00001			Glass	60 °C		3.8–4	35 d		−15.3%	–	
0.00001	0.005% $Na_2S_2O_5$ 0.01% Na_2-EDTA		Glass	60 °C		3.8–4	7 d	5% LIDO 0.1% MP 0.6% NaCl	−8.5%	–	
0.00001			Glass	60 °C		3.8–4	14 d		−6.3%	–	
0.00001			Glass	60 °C		3.8–4	21 d		−8.5%	–	
0.00001			Glass	60 °C		3.8–4	35 d		−10.6%	–	
0.00001	0.01% Na_2-EDTA		Glass	60 °C		3.8–4	7 d	5% LIDO 0.1% MP 0.6% NaCl	−7.3%	–	
0.00001			Glass	60 °C		3.8–4	14 d		−11.4%	–	
0.00001			Glass	60 °C		3.8–4	21 d		−13.3%	–	
0.00001			Glass	60 °C		3.8–4	35 d		−16.6%	–	
0.00001	0.05% $Na_2S_2O_5$		Glass	RT[bb]		3.8–4	3 mos	5% LIDO 0.1% MP 0.6% NaCl	−0.0%	–	
0.00001			Glass	RT		3.8–4	6 mos		−3.2%	–	
0.00001			Glass	RT		3.8–4	11 mos		−5.5%	–	
0.00001			Glass	RT		3.8–4	29 mos		−8.5%	–	
0.00001			Glass	RT		3.8–4	41 mos		−15.0%	–	
0.00001	0.005% $Na_2S_2O_5$ 0.01% EDTA		Glass	RT		3.8–4	3 mos	5% LIDO 0.1% MP 0.6% NaCl	+0.3%	–	
0.00001			Glass	RT		3.8–4	6 mos		−2.9%	–	
0.00001			Glass	RT		3.8–4	11 mos		−3.8%	–	
0.00001			Glass	RT		3.8–4	29 mos		−6.3%	–	
0.00001			Glass	RT		3.8–4	41 mos		−8.9%	–	
0.00001	0.05% $Na_2S_2O_5$		Cartridge	RT		3.8–4	1 mo	5% LIDO 0.1% MP 0.6% NaCl	−1.8%	–	
0.00001			Cartridge	RT		3.8–4	11 mos		−5.9%	–	
0.00001			Cartridge	RT		3.8–4	24 mos		−13.2%	–	
0.00001			Cartridge	RT		3.8–4	34 mos		−15.7%	–	
0.00001	0.005% $Na_2S_2O_5$ 0.01% EDTA		Cartridge	RT		3.8–4	1 mo	5% LIDO 0.1% MP 0.6% NaCl	+0.8%	–	
0.00001			Cartridge	RT		3.8–4	11 mos		−4.0%	–	
0.00001			Cartridge	RT		3.8–4	24 mos		−6.8%	–	

Table 2 (*Continued*)

Drug facts			Storage conditions						Stability data		Ref.
Concentr. ($mg\,mL^{-1}$)	Diluent	Origin	Reservoir	Temp. (°C)	Light	pH	Time	Add. subst.	Loss on conc.	Col. [a]	
0.00001			Cartridge	RT		3.8–4	34 mos		−10.0%	–	
Norepinephrine											
0.1	NaCl 0.9%	Arterenol®	Syringe	5–8 °C			26/36 d	$NaHSO_3$	–	–	Palazzolo and Quadri (1990)
0.01			Syringe	5–8 °C			26/36 d		–		
0.1			Syringe	−31 °C			7 d		$90 < x < 115\%$		
0.01			Syringe	−31 °C			7 d		$90 < x < 115\%$		
0.004	5% glucose	Ampoule	PVC bag	20 °C	Not prot.		168 hrs	$NaHSO_3$ NaCl ACA[cc] SCD[dd]	−4.3%	No	Tremblay et al. (2008)
0.004	Normal saline						168 hrs		−3.6%		
0.016	Glucose 5%	Ampoule	PVC bag	20 °C			168 hrs		+4.5%		
0.016	Normal saline	Ampoule	PVC bag	20 °C			168 hrs		−3.6%		
0.004	0.9% NaCl	Ampoules	Glass	22 °C		6.5	4 hrs	NaCl $NaHSO_3$ Metazin TA	−4%		Haggendal and Johnsson (1967)
0.004	5.5% glucose	Ampoules	Glass	22 °C		5.0	4 hrs		−1%		
0.0044	1.4% $NaHCO_3$	Ampoules	Glass	22 °C		7.9	4 hrs		−4%		
0.000565	KRH + 1 M $HClO_4$ (25:1)	API		22 °C		1.96	28 d		Stable	–	
	KRH + 1 M $HClO_4$ (50:1)	API				5.81	28 d		Stable	–	
	KRH	API				7.81	28 d		−34%	–	
	KRH + 1 M $HClO_4$ (25:1)	API		4 °C		1.96	28 d	$HClO_4$, KRH	−50%	–	
	KRH + 1 M $HClO_4$ (50:1)	API				5.81	2 d		−100%	–	
	KRH	API				7.81	2 d		−100%	–	
	KRH + 1 M $HClO_4$ (25:1)	API		−60 °C		1.96	28 d		Stable	–	
	KRH + 1 M $HClO_4$ (50:1)	API				5.81	28 d		Stable	–	
	KRH	API				7.81	28 d		Stable	–	
0.00015	NaCl KCl $CaCl_2$ $MgSO_4$ $NaHCO_3$ KH_2PO_4 glucose CO_2 5% aerated			27°, 32°, 37°		–	–	NaCl KCl $CaCl_2$ $MgSO_4$ $NaHCO_3$ KH_2PO_4 Glucose CO_2 5% aerated	Temperature-dependent degradation (not specified)		Hughes and Smith (1978)
0.05	0.9% NaCl	Arterenol®	Syringe	20–25 °C		–	24 hrs	–	+3.35%	–	Asmus and Freed (1979)
0.05	0.9% NaCl	Arterenol®	Syringe	20–25 °C		–	48 hrs	–	+5.94%	–	
0.05	0.9% NaCl	Arterenol®	Syringe	20–25 °C		–	72 hrs	–	+4.10%	–	
0.05	0.9% NaCl	Arterenol®	Syringe	20–25 °C		–	96 hrs	–	+10.04%	–	
0.05	5% glucose	Arterenol®	Syringe	20–25 °C		–	24 hrs	–	−3.44%	–	
0.05	5% glucose	Arterenol®	Syringe	20–25 °C		–	48 hrs	–	+3.44%	–	
0.05	5% glucose	Arterenol®	Syringe	20–25 °C		–	72 hrs	–	−0.97%	–	
0.05	5% glucose	Arterenol®	Syringe	20–25 °C		–	96 hrs	–	+6.35%	–	
0.05	0.9% NaCl	Arterenol®	Syringe	4 °C		–	24 hrs	–	+0.37%	–	
0.05	0.9% NaCl	Arterenol®	Syringe	4 °C		–	48 hrs	–	+2.72%	–	
0.05	0.9% NaCl	Arterenol®	Syringe	4 °C		–	72 hrs	–	+5.62%	–	
0.05	0.9% NaCl	Arterenol®	Syringe	4 °C		–	96 hrs	–	−1.5%	–	

Table 2 (*Continued*)

Drug facts			Storage conditions						Stability data		Ref.
Concentr. ($mg\,mL^{-1}$)	Diluent	Origin	Reservoir	Temp. (°C)	Light	pH	Time	Add. subst.	Loss on conc.	Col. [a]	
0.05	5% glucose	Arterenol®	Syringe	4 °C		–	24 hrs	–	+2.39%	–	
0.05	5% glucose	Arterenol®	Syringe	4 °C		–	48 hrs	–	+13.92%	–	
0.05	5% glucose	Arterenol®	Syringe	4 °C		–	72 hrs	–	+9.74%	–	
0.05	5% glucose	Arterenol®	Syringe	4 °C		–	96 hrs	–	+11.83%	–	

[a] +, coloration, –, no coloration of the solution.
[b] Krebs–Ringer–Hensleit buffer: 117 mM NaCl, 4.7 mM KCl; 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 2.5 mM $CaCl_2$, 24.8 mM $NaHCO_3$, 11.1 mM glucose.
[c] Diethylene triamine pentaacetic acid.
[d] Ethylenediamine tetraacetic acid.
[e] Disodium ethylene-diaminetetraacetate.
[f] Magnesium sodium ethylenediamine tetraacetate.
[g] Ethyleneglycolbisamino tetraacetic acid.
[h] Diaminocyclohexanetetraacetic acid.
[i] Nitriloacetic acid.
[j] Hydroxyethylethylendiaminotriacetic acid.
[k] Ethylenediaminediacetic acid.
[l] Iminodiacetic acid.
[m] Sodium dihydroxyethylglycine.
[n] 8-Hydroxyquinolinesulfate.
[o] Oxalic acid.
[p] Tartric acid.
[q] Ethylenediamine.
[r] Ascorbic acid.
[s] Propyl gallate.
[t] N-acetylcysteine.
[u] Diethylene triamine pentaacetic acid.
[v] Hydroxydiaminopropanetetraacetic acid.
[w] Citric acid.
[x] Polyethylene (normal density) eyedrop-bottle.
[y] Ethylenediamine.
[z] Lidocaine HCl.
[aa] Methylparaben.
[bb] Room temperature.
[cc] Anhydrous citric acid.
[dd] Sodium citrate dihydrate.

sulfonic acid analog having no physiological effect but is harmless. Below pH 5, S_N1 reactions take place, which is accompanied with the racemization (cf. Fig. 1); mono- and bimolecular reactions are very likely to happen at the same time at lower pH values (Schroeter and Higuchi, 1960).

Nevertheless, the use of sulfites is state-of-the-art and applied in the majority of commercial products (cf. Table 1). General information on the allergic potential coming from these derivatives is given in several package leaflets.

Heavy metal ions diffusing from water or glass containers are triggering the degradation of catecholamines even in trace concentrations in a catalytic manner. A common strategy is the complexation by chelating agents, such as EDTA or its derivatives. Nevertheless, many preparations of NE and EPI show a good long-term stability even without adding chelators (cf. Table 2).

Of note, the primary packaging material must prevent the penetration of oxygen as might happen with polyethylene containers and leachables, which we have observed by measurements conducted in our laboratory (unpublished results).

3. Stability of epinephrine and norepinephrine solutions

3.1. Stability-indicating analytical approaches for EPI and NE quantification

Whereas in early studies, EPI was determined fluorometrically (Bonevski et al., 1978; Haggendal and Johnsson, 1967), nowadays high-performance liquid chromatography (HPLC) with UV detection is employed (Bonevski et al., 1978; Haggendal and Johnsson, 1967; Waraszkiewicz et al., 1981; Zarghi et al., 2001). The USP and the PhEur prescribe reverse-phase HPLC-UV (RP-HPLC) with acidic mobile phases containing an ion-pairing additive such as either sodium octane-1-sulfonate (SOS) or sodium heptasulfonate (SHS) for quantification (Council of Europe, 2011; US Pharmacopoeia, 2011). Here, the hydrophilic character of the analytes is masked and a sufficient retention is achieved on RP-18 silica columns. Enantiomeric purity is checked via determination of optical rotation; notably the paragraph "Related Substances" of the PhEur monograph describes impurities related to synthesis whereas the USP prescribes the determination of adrenalone and NE in EPI.

Early investigations by Schroeter and Higuchi as well as Sokoloski and Higuchi aimed to identify different EPI degradation products (Schroeter et al., 1958; Sokoloski and Higuchi, 1962). Additionally, in 1993 a comprehensive study was conducted by Baran and Schwedt, whose objective was to conceive the different degradation products at the same time coupling several detection techniques, such as UV/vis, fluorescence, electrochemical, hydrogen peroxide oxidation and the trihydroxyindole derivatization method according to Schwedt et al. (Schwedt and Hildebrandt, 1975). They were able to identify eight different degradation products, including different adrenochromes and adrenochinones (Baran and Schwedt, 1993).

Asmus et al. replaced the ion-pair reagent alkyl sulfates with simple inorganic and organic acids (such as nitric acid, sulfuric acid or trichloroacetic acid) in combination with a commercially available C18-phase (Asmus and Freed, 1979). These methods were able to separate different catecholamines. Nevertheless, nothing has been reported on identification and quantification of EPI and NE degradation products, so that the use of this methodology is questionable when it comes to reliable impurity profiling.

One major problem in determination of degradation products is the choice of detection in general. While simple methods solely employ UV detection (what is suitable for analytes with extended chromophores), better results can be achieved via combination of different, orthogonal detection regimes, such as fluorescence or electrochemistry. The latter was fielded by Ochs et al. (2005) resulting in separation and quantification of different aminochromes, i.e. dopaminochrome, noradrenochrome or adrenochrome, with high sensitivity in nanomolar concentration ranges. Waraszkiewicz et al. (1981) connected three different detectors in series and obtained separation between lidocaine, EPI, EPI sulfonic acid and the respective adrenochrome. However, electrochemical detection is laborious and often not robust and not advisable for routine use, as it requires experienced analysts and is not available everywhere, not even in laboratories dealing with drug quality assurance.

Table 3
Loss of EPI content at different pH values and temperatures (%) (taken from Bonevski et al., 1978).

pH	Temp.		
	−60 °C	4 °C	22 °C
1.96	Stable	−80% (28 d)	−26% (2 d)
5.81	Stable	−100% (2 d)	−10% (2 d)
7.81	Stable	−100% (2 d)	−46% (2 d)

3.2. Stability of EPI and NE under different storage conditions and additives

In general, seven different parameters influence the stability of EPI and NE solutions: temperature, exposure to light, pH of the solution, presence of additives, concentration of API, presence of oxygen, and duration of storage. The screening of various studies reported in the literature (cf. Table 2) revealed elevated temperatures and pH values to have the highest impact on the stability.

In general, pH dependency of EPI and NE stability necessitates either buffering of solutions or adjustment of pH to acidic conditions, as both oxidation and racemization occur retarded. For optimum stability, a pH range of 3–4 (EPI) and 3.6–6 (NE) is recommended (Trissel, 2007). Unfortunately, extended investigation on the influence of acidity and basicity on the stability is scarcely considered in any publication, and often the APIs were quantified only. However, Higuchi and Schroeter reported a clear pH-dependency for the sulfonation of EPI (Schroeter and Higuchi, 1960).

Light exposure may play a certain role, but as shown by Tremblay et al., even at ambient temperature, NE solutions remain stable for 14 days when stored unprotected (Tremblay et al., 2008). Häggendal et al. observed NE degradation rates of approximately 4% after 4 h in solutions stored unprotected from light and pH values above 6.0, indicating that less acidic conditions influence the stability in a non-neglectable way (Haggendal and Johnsson, 1967).

Gruenert and Wollmann compared the influence of light exposure from different sources, i.e. ultraviolet (UV) light, sunlight, daylight, and artifical light (Grunert and Wollmann, 1982). The highest degradation rates were observed in UV light, which could be avoided best by storing the solutions in colored polypropylene containers. Effective protection can be achieved through the use of these materials instead of glassware that is enabling heavy metal ions to leach into the solution and catalyze further degradation. However, it has to be mentioned that both publications investigated sulfite-preserved solutions.

Palazzolo et al. measured EPI and NE solutions without any preserving additives, but the solutions were adjusted to three different pH values (1.96, 5.81, and 7.81) by mixing different percentages of 1 M perchloric acid with a physiological Krebs–Ringer–Heinsleit buffer (cf. Tables 1 and 3) and stored at three different temperatures (−60, 4 and 22 °C) (Palazzolo and Quadri, 1990). EPI and NE were found to be stable for at least 28 days under both acidic and basic conditions when stored in a freezer, while at higher temperatures (4 °C and above), concentration loss of 100% after two days (4 °C) or 90 min (22 °C) occurred. These findings were confirmed by Mueller

Table 4
Different combinations of preservatives showing synergistic effects on shelf-life of 1% NE solutions at different temperatures, pH = 5.5 (modified after Table 2).

Comp. 1	Comp. 2	Comp. 3	Brown glass vial, room temperature: shelf-life (days)	Brown glass vial, 40 °C: shelf-life (days)	Coloration
Ascorbic acid	DTPA	–	40	3	+
Ascorbic acid	8-HQS	–	35	3	+
Ascorbic acid	N-acetylcysteine	–	74	5.5	+
N-acetylcysteine	DTPA	–	85	4.5	+
N-acetylcysteine	8-HQS	–	76	4	+
DTPA	8-HQS	–	32	2	+
DTPA	L-Cysteine	–	35	2	+
$Na_2S_2O_5$	DTPA	–	>100	8	–
$Na_2S_2O_5$	8-HQS	–	90	7.5	–
$Na_2S_2O_5$	Ascorbic acid	–	90	7	+
$Na_2S_2O_5$	N-acetylcysteine	–	>100	10	+
$Na_2S_2O_5$	L-Cysteine	–	19	1	+
Ascorbic acid	DTPA	$Na_2S_2O_5$	–	12	+
N-acetylcysteine	DTPA	$Na_2S_2O_5$	–	20	–

et al. who observed rapidly decreasing $t_{0.99}$ values after storage at 30 °C and higher (Muller et al., 1988).

3.2.1. EPI and NE in combination with local anesthetics

Fry et al. stored pre-autoclaved injection cartridges containing local anesthetics and catecholamines at temperatures of 34–37 °C (cf. Table 2) and found concentration losses of overall 30% over 3 months (Fry and Ciarlone, 1980a,b). Temperature-dependent degradation behavior was also confirmed by Hughes et al., who determined NE in very low concentration (0.00015 mg mL^{-1}) stored at 27, 32, and 37 °C in solutions containing physiological saline alone (Hughes and Smith, 1978). However, the stability would be increased by adding ascorbic acid and EDTA in different concentrations (56.8–284.1 μM and 27.0–135.1 μM, respectively).

In cooperation with the American Food and Drug Administration (FDA), Kirchhoefer et al. collected numerous samples (>450 from different manufacturers) of either aqueous fixe-dose lidocaine hydrochloride, and EPI and EPI alone, respectively throughout US hospitals (Kirchhoefer et al., 1986a,b). Analysis for EPI content, related substances and isomers was conducted in order to learn more about a possible decline in quality during shelf-life. The overall findings confirm: when stored according to the product specification (unfortunately, no detailed information on storage conditions prescribed in the package leaflets from the original products is given in both references), no loss in content or formation of degradation products was observed within shelf-life. As a matter of fact, after having passed the expiration date, preparations containing EPI should not be used for patient treatment, as all samples analyzed after the declared expiration date failed the tests.

3.2.2. Dilution of commercial products

The question remains whether NE and EPI are stable when confected from commercial products by transferring and/or diluting them into syringes (Adams et al., 1985; Kerddonfak et al., 2010; Wolf and Scherbel, 2011). Notably, through dilution the concentration of previously added preservatives such as sulfites is reduced, as in general, common diluents do not contain such substances. Wolf et al. diluted commercial Arterenol® and Suprarenin® preparations with 0.9% NaCl (without sodium metabisulfite) to obtain concentrations of 0.1 and 0.01 mg mL^{-1}. Only EPI showed significant degradation after storage at room temperature for 10 days (Wolf and Scherbel, 2011); EPI and NE were within specification throughout storage at a maximum of 8 °C in the confected form. This is confirmed by the work of Kerddonfak et al., whose intention was to determine stability behavior of 1.0 mg mL^{-1} EPI when transferred into disposable syringes and who were not able to detect any noteworthy loss of concentration of EPI preparations within 12 weeks of storage at 26 °C (Kerddonfak et al., 2010). Coloration of the solutions was not observed, but they recommended changing the injection needle after filling the syringe.

Similarily, Adams et al. prepared NE and EPI dilutions of commercially available products with 0.9% sodium chloride and 5% glucose (again without sodium metabisulfite), respectively, in sterile water and stored them at 4 and 20–25 °C for eight days. None of the samples showed a considerable degradation of the API. However, the authors referred to a broad measuring error within their method of analysis resulting in an apparent rise of content and did not have an explanation for this finding (Adams et al., 1985).

3.2.3. Influence of preservatives and additives

Lundgren and Strom (1966), Morch and Morch (1965) and Hamnett (1975) already published studies on the influence of additives in the 1960s, but the group of Wollmann and Raether (1983) were the first who studied the influence of preservatives and additives such as stabilizing agents systematically, divided in three subgroups i.e. (i) chelators, such as EDTA; (ii) direct anti-oxidative agents, such as ascorbic acid; (iii) inhibitors of coloration, such as bisulfites (Wollmann and Raether, 1983), in addition to combination of those. EPI content in stabilized model solutions was compared to EPI content in equivalent unstabilized solutions, revealing the following results:

(1) From the division of EDTA derivatives, diethylenetriaminepentaacetic acid (DTPA) and 8-hydroxyquinoline sulfate (8-HQS) showed best results by extending the overall half-life period by 9.3 and 17.7 days (no data available on the previous half-life period), compared to unstabilized solutions, respectively. EDTA itself showed no relevant stabilization effects and even promoted coloring of the samples at pH value of 5.5; as a matter of fact, EDTA efficacy is pH-dependent. This was also anticipated by Cox and Boer who reported that EDTA shows protective character below pH 3.0, whereas at pH 7.4, no such effect can be observed (Cox and Boer, 1975).
(2) From the anti-oxidative agents group, organic compounds such as N-acetylcysteine and ascorbic acid showed good efficacy whereas among the inorganic representatives, only sodium pyrosulfite yielded acceptable stability values what can best be explained by a slightly lowered pH value from the formation of the sulfuric analog under which EPI has a greater stability. Consequently, pyrosulfites can inhibit coloration and are an essential tool in preservation and pH-stabilization. Table 4 shows different shelf-lives of EPI solutions with mixtures of

either two or three of the aforementioned stabilizers. When two compounds from different groups (coloration protectors and antioxidative agents, e.g. ascorbic acid/acetylcysteine, N-acetylcysteine/DTPA, sodium pyrosulfite/DTPA) were combined, expected synergistic preservation effects at room temperature could be observed. Triple combinations (e.g. N-acetylcysteine/DTPA/sodium pyrosulfite) showed optimal stabilizing effects even at 40 °C. By applying this concept, shelf-life of commercial preparations could be extended by a factor of thirty. This investigation clearly indicated that only sulfites, alone or in combination, provide adequate protection of solutions as already shown by Schroeter and Higuchi (1960).

As can be seen from Table 2, concentration of EPI and NE did not affect the stability in a significant way, even though from the thermodynamic point of view, higher concentrated solutions are supposed to degrade faster, as molecular collisions and interactions are statistically more likely to happen. Both low (0.00001 mg mL^{-1}) and high (1 mg mL^{-1}) concentrated preparations did not show an overall decline of content.

3.3. Fix-dose combinations of local anesthetics and catecholamines

Grubstein and Milano prepared numerous combinations of local anesthetic (lidocaine hydrochloride) and catecholamine (EPI) solutions, as widely used in dentistry, with different concentrations of sodium pyrosulfite (0.005–0.025%) and EDTA (0.01%). The samples were either stored short-term at 60 °C or long-term at room temperature (Grubstein and Milano, 1992). All samples contained 0.6% sodium chloride and 0.1% methylparaben (methyl 4-hydroxybenzoate).

(1) When pyrosulfite was used alone, the highest loss of concentration was about 0.025%. Above (triggering of degradation pathway) and underneath (preserving effect not significant), higher degradation rates and coloration of the samples could be observed.
(2) When combined with citric acid, decomposition could be attenuated, but replacing citric acid by EDTA significantly improved stability by trapping heavy metal ions and inhibited coloration to purple, even at very low bisulfite levels.

Whether the two different APIs or, in general, local anesthetics and catecholamines, interacted with each other, was not reported; however, Trissel recommends to use freshly prepared mixtures of EPI with local anesthetics immediately as changes in pH may influence the stability of EPI. On the other hand, commercially available combination injectable solutions are buffered so that no loss of API is expected (Trissel, 2007).

4. Conclusion

Even though no overall strategies for stabilization of catecholamines in solutions exist two established stabilization regimes have to be emphasized: (i) conservation of injectable preparations with sulfites and blanketing with nitrogen and (ii) storage at low temperatures and protected from light, e.g. refrigerated; however, low temperatures are not implicitly required to obtain an acceptable shelf-life. The concentration of the API does not seem to affect stability, thus dilution of required medication is possible without any major problems when adhered to the aforementioned storage conditions.

From the microbiological point of view (what was not part of any investigation), the quality of aseptic preparations should be guaranteed through sterile handling and production units following common manufacturing practices (GMP). Sterile filtration, if necessary, cannot be considered to be preferable to autoclaving if temperature during the process does not exceed 98 °C (Sixsmith et al., 1982). Hamnett (1975) was able to show that after steaming of EPI eyedrop solutions, there is only a minor loss on concentration.

Commercial products show that by combination of strategies (i) and (ii), satisfying stability can be achieved. The package leaflet from Arterenol® prescribes: "Arterenol (...) can be preserved for 30 months. If ampoules (...) are withdrawn from the refrigerator during shelf-life and stored at ambient temperature (25 °C), shelf-life shortens to a maximum of six months. (...) Date of withdrawal from the refrigerator shall be noted on the bottle. (...) Once opened, bottles shall be used within five days (...), solutions prepared from Arterenol shall be used within 24 h." Consequently, the PhEur prescribes the storage of EPI and NE in an "airtight container, or preferably in a sealed tube under vacuum or under an inert gas, protected from light" (Council of Europe, 2011).Concerning hospital pharmacies and emergency medication, proprietary medication or dilutions of any concentration can be prepared even with solutions not containing sulfites. They are stable for at least seven days when stored at 5 °C. If the diluted solutions occurred to be kept on a simple shelf of an intensive care unit or other hospital units even for a short time period it should not be used any longer.

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