

8 | Formulation and stability of solutions

OPTIMIZING OXIDATIVE STABILITY

full explanation and justification
for including antioxidants in the drug formulation

Specific evidence must be provided :

1. demonstrates **their use cannot be avoided**
2. and its **concentration** must be justified in terms of **efficacy and safety**

CPMP, Note for Guidance on Inclusion of Antioxidants and
Antimicrobial Preservatives in Medicinal Products. CPMP:
January 1998.

EMEA, Guideline on Excipients in the Dossier for Application
for Marketing Authorization of a Medical Product. EMEA/
CHMP/QWP/396951/2006: 19 June 2007.

داروهای مستعد تخریب اکسیداتیو و/یا فوتولیتیک :

پروتئینهای حاوی اسیدآمینه:

- methionine
- Cysteine
- Cystine
- Histidine
- Tryptophan
- Tyrosine

بسته به کنفورماسیون پروتئین و مواجهه آمینو اسید حساس با حلال و محیط

free-thiol group may oxidize:

- incorrect disulfide bridge,
- alkylation
- addition to double bonds
- complexation with heavy metals.

- Human GH
- Chymotrypsin
- Lysozyme
- Parathyroid hormone
- Human FCSF
- Insulin like GF1
- Fibroblast growth factors
- MAB OKT3
- interleukin 1
- Glucagon

داروهای کوچک مولکول دارای گروههای عاملی:

- phenols
- Catechols
- thioethers

Epinephrine, phenylephrine, dobutamine, dopamine, morphine, Terramycin, ascorbic acid, Menadione , and ...

Easily oxidized in solution

several approaches to protect
the product from oxidative
instability

- dissolved oxygen in solution
- light exposure
- high temperature
- solution pH
- free radicals
- Hydroxyl ions
- metal ions (ppm, even ppb)
- impurities in excipients :
 - such as peroxide

minimizing drug oxidative degradation
requires a combination of several approaches:

- **not only formulation**
- **but also hermetic packaging**
- **oxygen-free processing and table 8-2**

Table 8-2 Various Approaches Used To Minimize Oxidative Drug Degradation

-
- Preparation and storage at low temperatures
 - Use of chelating agents to eliminate metal catalysis
 - Increasing ionic strength
 - Elimination of peroxide and metallic contaminants in formulation additives
 - Protection from light
 - Awareness of possible interaction of light exposure and phosphate buffer in forming free radicals
 - Replacing oxygen with nitrogen or argon during manufacturing
 - Removing oxygen from the headspace of the final container
 - Formulation established at the lowest pH possible while still maintaining adequate solubility and overall stability
 - Use of a container/closure system that allows no oxygen transmission through the package during distribution and storage
 - Assuring that phenolic or other oxidizing cleaning agent residues are minimal in the production environment
-

Excipients:

- Source of trace metals & peroxides

مثال تداخل اکسپیانتها

حضور توئین 80 در فرمولاسیون پروتئین ها :
کاهش مشکلات surface aggregation

- بخاطر تولید پراکسید: اثر تخریبی اکسیداتیو cysteine و methionine در پروتئینها
 - Neupogen®
 - recombinant human ciliary neurotrophic factor

Table 3 Levels of HPO in Some Commonly Used Excipients

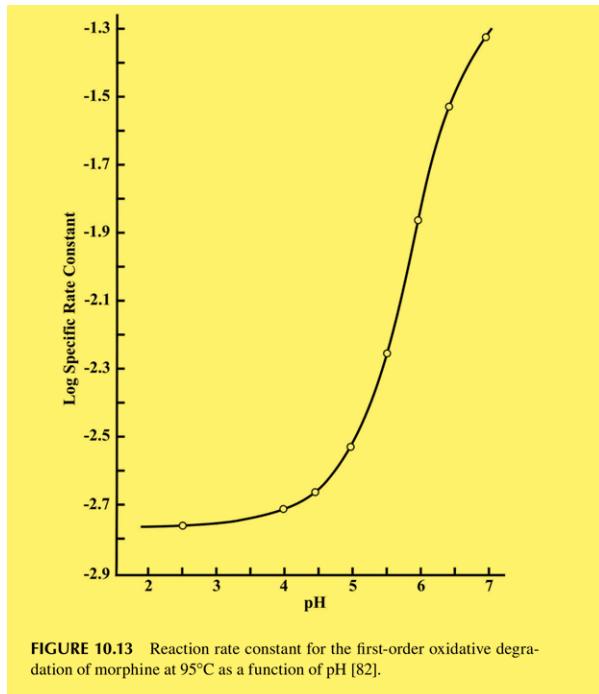
Excipient	Number of batches tested	Average HPO (nmol/gm)	Range of HPO (nmol/gm)
Polyvinylpyrrolidone	5	7,300	3,600–11,000
Polyethylene glycol 400	4	2,200	1,000–3,300
Polysorbate 80	8	1,500	180–4,600
Poloxamer ^a	7	30	10–50
Mannitol	5	<10	<10
Sucrose	5	<10	<10–20

^aDifferent grades (188, 338, and 407) and batches tested.

Abbreviation: HPO, hydroperoxides.

Oxidation potential

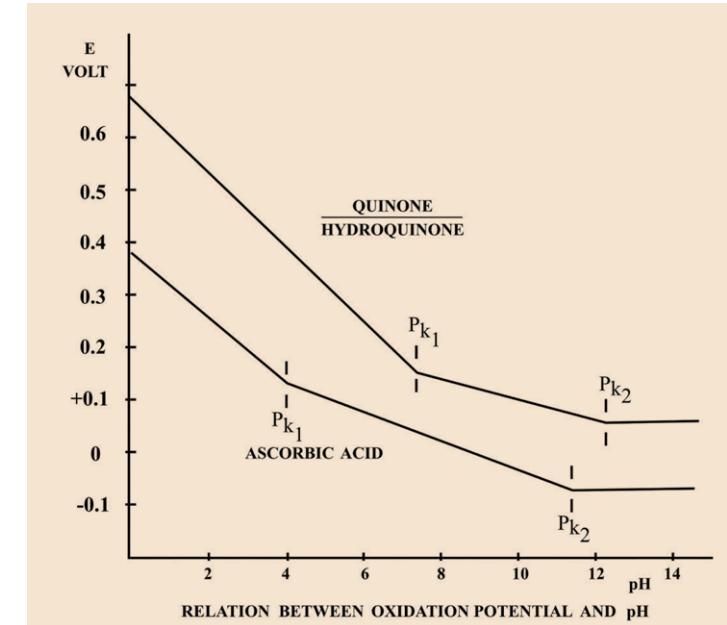
morphine



morphine can be stabilized by

- lowering the pH
- adding an antioxidant (such as ascorbic acid, which will be preferentially and reversibly oxidized between pH 5 and 7)

به حداقل رساندن اکسیداسیون با:
افزایش پتانسیل اکسیداسیون دارو
کاهش pH باعث افزایش پتانسیل اکسیداسیون E میشود



pH-dependent oxidative degradation

معادله ساده شده نرنست

$$E = E^0 + \frac{RT}{2} \log \frac{[H^+] \cdot [Ox]}{[Rd]}$$

انتخاب آنتی اکسیدان موثر

3 groups antioxidants

Antioxidant in combination
bi-functional

1- True antioxidants:

با رادیکالهای آزاد واکنش میدهند
با مکانیسم chain termination

- Alpha-tocopherol acetate
- BHA (oily products),i
- BHT (oily products)
- Alkyl gallates: (fat & oils)
 - Dodecyl gallate
 - Propyl gallate,i
 - Octyl gallate

i, antioxidants possess antimicrobial

- Formulation (aq. , Non-aq.)
- Packaging
- Time of addition of the antioxidant
- Concentration of antioxidant

2. Reducing agents:

دارای پتانسیل redox پائینتر از دارو (آماده
تر از دارو برای اکسیده شدن)

- Ascorbic acid
- Sodium metabisulfite (acidic preparations)
- Sodium bisulfite
- Sodium sulfite (alkaline preparations)
- thiols (oxidize too readily):
 - thioglycerol
 - thioglycolic acid
- Glutathione (blocking the light-catalyzed oxidative chain reaction in menadion)

پس حين عمر قفسه اي دارو، مصرف ميشوند

3. Antioxidant synergists (Chelating agents)

افزايش اثر آنتی اکسیدانها

- Citric acid
- Disodium edetate
- Sodium citrate
- Tartaric acid

Table 8.4 summarizes the antioxidants
, their frequency of use, concentration range, examples of product containing them.

TABLE 8.4

Antioxidants and Reducing Agents

Excipient	Frequency	Range	Example
Acetone sodium bisulfite	4	0.2%–0.4% w/v	Novocaine®
Argon	-	100%	Used to fill headspace of lyophilized or liquid products. TechneScan MAG3®
Ascorbyl palmitate	1		Visudyne®
Ascorbate (sodium/acid)	10	0.1%–4.8% w/v	Vibramycin®
Bisulfite sodium	31	0.02%–0.66% w/v	Amikin®
Butylated hydroxy anisole (BHA)	3	0.00028%–0.03% w/v	Aquasol A®
Butylated hydroxy toluene (BHT)	4	0.00116%–0.03% w/v	Aquasol A®
Cysteine/cysteinate HCl	4	0.07%–1.3% w/v	Acthrel®
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	1	0.10%	Numorphan®
Gentisic acid	1	0.02% w/v	OctreoScan®
Gentisic acid ethanolamine	1	2%	M.V.I. 12®
Glutamate monosodium	1	0.1% w/v	Varivax®
Glutathione	1	0.01% w/v	Advate®
Formaldehyde sulfoxylate sodium	10	0.075%–0.5% w/v	Terramycin solution
Metabisulfite potassium	1	0.10%	Vasoxyl®
Metabisulfite sodium	33	0.02%–1% w/v	Intropin®
Methionine	5	0.01%–0.15%	Depo-subQ provera
Monothioglycerol (thioglycerol)	8	0.1%–1%	Terramycin solution
Nitrogen	-	100%	Used to fill headspace of lyophilized or liquid products
Propyl gallate	3	0.02%	Navane®
Sulfite sodium	8	0.05%–0.2% w/v	Enlon®
Tocopherol alpha	2	0.005%–0.075%	Torisel
α-Tocopherol hydrogen succinate	1	0.02% w/v	Fluarix®
Thioglycolate sodium	1	0.66% w/v	Sus-Phrine®

Antioxidants

Antioxidants

Acetone sodium bisulfite	0.2
Ascorbic acid	0.01
Ascorbic acid esters	0.015
Butylhydroxyanisole	0.02
Butylhydroxytoluene (BHT)	0.02
Cysteine	0.5
Nordihydroguaiaretic acid	0.01
Monothioglycerol	0.5
Sodium bisulfite	0.15
Sodium metabisulfite	0.2
Tocopherols	0.5
Glutathione	0.1
<i>Chelating Agent</i>	
EDTA sodium and calcium salts	0.01–0.075
Pentetic acid	0.01–0.075

Table 10.10 lists some standard oxidation potentials.

TABLE 10.10

Some Commonly Used Antioxidants and Their Oxidation Potentials

Substance	E° (V) ^a	pH	Temperature (°C)
Riboflavin	+0.208	7.0	30
Dithiothreitol	+0.053	7.0	30
Sodium thiosulfate	+0.050	7.0	30
Thiourea	+0.029	7.0	30
Ascorbic acid ^a	+0.003 −0.115 −0.136	7.0 5.2 4.58	25 30 30
Methylene blue	−0.011	7.0	30
Sodium metabisulfite ^a	−0.114	7.0	25
Sodium bisulfite ^a	−0.117	7.0	25
Propyl gallate ^a	−0.199	7.0	25
Acetylcysteine ^a	−0.293	7.0	25
Vitamin K	−0.363	-	20
Epinephrine	−0.380	7.0	30
Hydroquinone	−0.673	-	-
Resorcinol	−1.043	-	-
Phenol ^a	−1.098	-	-

^a Common in parenteral products.

TABLE 17.7 Standard Oxidation Potentials for Various Antioxidants^a

Compound	E^0 V	pH	Temperature (°C)
Dithiothreitol ^b	+0.208	7.0	30
Sodium thiosulfate ^b	+0.050	7.0	30
Thiourea ^b	+0.029	7.0	30
Ascorbic acid	+0.003 ^b -0.390 ^c	7.0	25
Sodium metabisulfite ^b	-0.114	7.0	25
Sodium bisulfite ^b	-0.117	7.0	25
Propyl gallate ^b	-0.199	7.0	25
Acetyl cysteine ^b	-0.293	7.0	25
Cysteine ^b	-0.34		
Vitamin K ^b	-0.363		
Glutathione ^b	-0.430		
Hydroxyquinone ^c	-0.601		
Pyrogallol ^c	-0.661		
Hydroquinone ^c	-0.673		
α -Tocopherol ^c	-0.684		
<i>p</i> -Cresol ^c	-1.038		
<i>m</i> -Cresol ^c	-1.080		
Phenol ^c	-1.089		

^aSulfites may cause allergic-type reactions, and a warning to that effect must be on the label of any prescription drug, regardless of the quantity (21 CFR 201.22).

^bAkers (1979).

^cNash (1958).

تداخلات و ناسازگاری ها و سمیت نمکهای سولفور دی اکسید

با وقوع اکسیداسیون:

- سولفیتها به سولفات تبدیل میشوند
- مقادیر کم باریم یا کلسیم استخراج شده حتی از شیشه نوع I تولید سولفات نامحلول میکند
- لزوم پایش حضور ذرات ریزدر ظروف شیشه ای حاوی فرآورده داروهای سولفاته یا دارای آنتی اکسیدانهای سولفیتی

غیر فعال شدن برخی داروها توسط بی سولفیتها :

- اپینفرین : تولید اپینفرین سولفونات (غیر فعال)
- اورتو و پارا-هیدروکسی بنزیل الکلها (پارابنها) غیر فعال میشوند

عوارض سولفیتها در فرآورده های تجویز تزریقی:
flushing, pruritus, urticaria, dyspnea, bronchospasm

- برخی آنتی اکسیدانها
- برای برخی فرمولاسیونهای دارویی

اسکوربات: در حضور اکسیژن و Fe^{3+} القای اکسیداسیون متیونین در پپتیهای کوچک

اسکوربات یک دهنده الکترون قوی:

براحتی اکسیده میشود به دهیدرواسکوربات (تولید گونه های اکسیژن بسیار واکنشگر نظیر هیدروژن پراکسید و رادیکالهای پراکسیل میکند)

اثر پرو-اکسیدانت، اکسیداسیون متیونین اسکوربات:

- وابسته به غلظت است
- در pH 6 to 7 محیا میشود

در حضور اسکوربیک اسید :

بافر فسفات ، تخریب متیونین را تسريع میکند

اسکوربیک اسید:

- ناسازگار با alkalis & oxidizing materials (نظیر فنیل افرین)

The addition of EDTA did not enhance stability even though ferric ion and other transition metals were components in the formulation, either purposely added or as trace components of the buffer and peptide.

Compatibility of antioxidants

For example,:

- **tocopherols** (absorb onto plastics)
- **propyl gallate** forms complexes with metal ions (such as sodium, potassium and iron)

Compatibility of antioxidants with:

- the drug
 - packaging system
 - and the body
- should be studied carefully

چندین فرمولاسیون تجاری :

- که تمام نیاز با شلات کننده مرتفع شده
- هیچ آنتی اکسیدانی در فرمولاسیون ندارند
- محافظت ماده موثره علیه

metal-catalyzed oxidation

- Nebcin®
- Decadron-LA®
- Versed®,
- Cleocin®

کمک به:

- مهار تشکیل رادیکال آزاد
- مهار اکسیداسیون ماده موثره
- complex trace heavy metal ions
- copper
- Iron
- Calcium
- Manganese
- zinc.

Excipient	Frequency	Range	Example
Calcium disodium EDTA ^a	11	0.01%–0.1%	Wydase®
Disodium EDTA	48	0.01%–0.11%	Calcijex®
Sodium EDTA	1	0.20%	Folvite®
Calcium versetamide Na	1	2.84% w/v	OptiMARK®
Calteridol	1	0.023% w/v	Prohance®
DTPA ^b	3	0.04%–1.2%	Omniscan™

^a EDTA, Ethylenediaminetetraacetic acid.

^b DTPA, Diethylenetriaminepentaacetic acid; Pentetic acid.

2-Citrate buffer :

شلات کننده
کمتر از DSEDTA موثر است

عوامل شلات کننده کاربرد و احتیاطها

disodium ethylenediaminetetraacetic acid
(DSEDTA)

- very low concentrations ($\leq 0.04\%$)
 - احلال بسیار آهسته:
 - جزء اولین اجزای فرمولاسیون حین آماده سازی محصول
 - قبل از سایر اجزا حتی ماده موثره

DSEDTA باعث تسریع تخریب اکسیداتیو

متیونین در محلول

human insulin-like growth factor I:

- اکسیداسیون متیونین با وجود نور، یونهای فریک در حضور EDTA

- EDTA فعال میکند یونهای فریک را با انتقال الکترونها از یونهای فریک به یونهای فروس متیونین موجود در پروتئین، توسط نور، رادیکالیزه میشود و سپس به متیونین سولفوکسید اکسیده میشود
- نور همینین باعث تولید رادیکاهای هیدروکسیل با تخریب آب میشود که اکسیده کننده متیونین خواهد شد

منع استفاده DSEDTA در فرمولاتیونهای متابولیپروتئینها:

- **Insulin**
- **hemoglobin**
- **fibrolase**

metal پروتئینهاست ، بخشی از کنفورماتیون پایدار این

فرمولاتور بدون پشتوانه علمی EDTA را در فرمولاتیون پروتئین ها وارد کند بدون تعیین دقیق کمک واقعی آن در پایدارسازی اکسیداتیو پروتئین

Inert Gases

Inert gases are frequently used in production of sterile dosage forms:
must be :

- **high quality grade**
- **be sterilized, usually with a 0.22-m hydrophobic membrane filter**
- **The integrity of the gas filter is tested before and after use**
- **by diffusion flow methods**

Nitrogen
Argon (expensive)
Helium (expensive)

Argon, more efficient in displacing oxygen
because it is heavier than air
and will more readily stay in the vial compared to nitrogen

Inert Gases

Inert gases are frequently used in production of sterile dosage forms:

- **solution saturation**
- **headspace**

Addition to water and compounding solutions prior to aseptic filtration saturates the solution and minimizes the level of dissolved oxygen.

However, oxygen is never completely displaced with an inert gas when the solution is sparged.

dual needle

that permits simultaneous filling of a liquid and purging of gas at the same time.

Inert gas introduced into the headspace of a filled vial right before the vial is stoppered with a rubber closure theoretically displaces oxygen in the headspace.

Again, a **dual needle** can be used to fill solution and purge gas into the final container at the same time.

if the packaging system is inadequate from an integrity standpoint
the product will readily degrade



Figure 4-2 Glass vials with rubber closures and aluminum seal.



Figure 4-1 Glass sealed ampoules.

SVP injectable products are packaged in:

- Ampule
- **glass vials with rubber closures**
- **syringes with rubber plungers.**

- **The rubber-glass interface**
- and the **oxygen transmission coefficient of the rubber closure** will dictate the quality of the container/closure system

30 | Sterile product-package integrity testing

Dana Morton Guazzo*

Oxygen transmission coefficients

Rubber formulations having the lowest oxygen transmission coefficients are:

- the synthetic butyl type
- the synthetic halobutyl type

curing agents

leach out of the rubber formulation with time

The formulator should determine from the rubber manufacturer
how the halobutyl rubber is cured (shaped, molded):

- common curing agents are :

- zinc oxide
- aluminum,
- and peroxide

which potentially can leach out of the rubber formulation with time and catalyze oxidative degradation

Many drugs are sensitive to light:

- Catecholamines
- Cephalosporins
- Aminoglycosides
- some steroids
- Iron containing molecules
- and many others)

داروهای حساس به نور

There is no practical formulation approach to stabilize light-sensitive drugs; good packaging is the key to protect against light degradation

Effective packaging is the primary (in most cases only) way to protect drugs from light degradation:

1. Good light protective secondary packaging
2. use of amber-colored primary packaging :
 - more expensive
 - difficult to inspect for particulate matter
3. maintaining product storage in the dark

مواد محافظ ضد میکروبی Preservatives

Contamination source:

مواد خام، موادبسته بندی ، لوازم
تولید ، کارگاهان ،
محیط ساخت ، فرد مصرف کننده

Ideal preservatives:

- Broad spectrum of M.O.
- Stable
- Non-toxic, non-allergic
- Soluble

منطق استفاده Rational

Pharmacopoeia: It is imperative that
“preservatives should never be used as a
substitute for inadequate cGMP”

Not for:

- LVPs
- single-dose SVPs (according to USP)
- Drug itself bacteriostatic
- Injected via intracisternal,
- Injected retro-ocular which access cerebrospinal fluids
- Prohibited by compendial monograph:
 - Methohexital sodium for injection
 - Most of cytotoxic anticancer products

Antimicrobial preservative

- **Multiple-dose containers:**
 - to prevent growth of microorganisms which may accidentally enter the container during withdrawal of the dose
- **SVPs (according to BP and Ph.Eur)**
 - Ph. Eur. and BP allow aqueous preparations less than 15 ml
 - manufactured using aseptic techniques (not terminally sterilized)
 - to contain suitable preservatives

مواد محافظ در محصولات لیوفیلیزه in lyophilization

Several **preservatives** can volatilize easily:

- (e.g., benzyl alcohol, phenol)

and therefore should not be used in a lyophilized dosage form

Preservative in diluent
Rarely in freeze dry formulation

USP:
some restrictions on the maximum concentration of preservatives allowed in a formulation to address:

- toxicity (contraindicated in Neonates)
- allergic reactions (allergic to mercury)

TABLE 8.6
Maximum Permissible Amount of Preservatives and Antioxidants

Excipient	Maximum Limit in USP (%)
Mercurial compounds	0.01
Cationic surfactants	0.01
Chlorobutanol	0.50
Cresol	0.50
Phenol	0.50
Sulfur dioxide or an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium	0.20

Minimizing preservatives

WHO:
an estimated total acceptable daily intake for sorbate (as acid, calcium, potassium and sodium salts):
as not more than 25 mg/kg body weight

TABLE 10.11

List of Commonly Used Antibacterial Preservatives and Their MIC

Agent	MIC ^a Range	Amount Most Often Used (%)
Benzalkonium chloride	0.005–0.03	0.01
Benzethonium chloride	0.005–0.03	0.01
Benzyl alcohol	1.0–10.0	1.0
Chlorobutanol	0.2–0.8	0.5
Chlorocresol	0.1–0.3	0.1–0.25
Cresol	0.1–0.6	0.3
Parabens (methyl, ethyl, propyl, butyl esters)	0.05–0.25 methyl 0.005–0.03 others	0.18 0.02
Phenol	0.1–0.8	0.5
Phenylmercuric nitrate	0.001–0.05	0.002
Thimerosal	0.005–0.03	0.01

^a Affected by product pH, ionic strength, storage temperature, packaging materials, etc.

Table 6-7 Examples of Commercial Sterile Dosage Forms Containing Antimicrobial Preservative Agents and Their Concentrations

AP agent	Concentration	Examples (all®)
Benzyl alcohol	0.9%–3.0%	VePesid and Vumon
Phenol	0.002%–0.5%	Hydeltrasol and Sus-Phrine
Meta-Cresol	0.25%–0.3%	Humatropé and Genotropin
Phenoxyethanol	0.5%–1.0%	Poliovax and Ipol™
Thimerosal	0.0002%–0.012%	Recombivax and Hyperab
Chlorobutanol	0.25%–0.5%	Aquasol and Oxytocin
Methylparaben	0.02%–0.2%	Intron A and Gentamicin
Propylparaben	0.002%–0.02%	Bicillin L-A and Tobramycin
Phenylmercuric acetate, borate, nitrate	0.001%–0.002%	Several topical ophthalmic medications
Benzalkonium/Benzethonium chloride	0.01%–0.02%	Benadryl and many topical ophthalmic medications

TABLE 8.5

Antimicrobial Preservatives

Excipient	Frequency	Range	Example
Benzalkonium chloride	1	0.02% w/v	Celestone Soluspan®
Benzethonium chloride	4	0.01%	Benadryl®
Benzyl alcohol	90	0.75%–5%	Dimenhydrinate Inj.
Chlorbutanol	19	0.25%–0.5%	Codeine phosphate
m-Cresol	13	0.1%–0.315%	Humalog®
Myristyl gamma-picolinium chloride	2	0.0195%–0.169% w/v	Depo-Provera®
Paraben methyl	55	0.05%–0.18%	Inapsine®
Paraben propyl	45	0.005%–0.1%	Xylocaine w/ Epinephrine
Phenol	55	0.15%–0.5%	Calcimar®
2-Phenoxyethanol	4	0.50%	Havrix®
Phenyl mercuric nitrate	3	0.001%	Antivenin®
Thimerosal	50	0.003%–0.012%	Atgam®

Antimicrobial preservative effectiveness test (PET) USP chapter 51

The test typically consists of inoculating 10^5 – 10^6 CFU/mL microorganisms (e.g., bacteria and fungi) per container at time zero and evaluating the log reduction over time.

The criterion used for passing this test is as follows:

Table 8-5 Comparison of USP and EP Preservative Efficacy Tests

Test	USP <51>	EP <Chapter 5.1.3>
Bacterial Challenge	1-log reduction within 7 days	2-log reduction within 6 hours
Fungal challenge	3-log reduction with 14 days No increase after 28 days	3-log reduction within 24 hours 2-log reduction with 7 days
Overall requirement	Bacteriostatic	Bacteriocidal

- Bacteria: Not less than 1.0 log reduction from the initial calculated count at 7 days, not less than 3.0 log reduction from the initial calculated count at 14 days, and no increase from the 14 days' count at 28 days.
- Yeasts and molds: No increase from the initial calculated count at 7, 14, and 28 days.

Satisfactory PET results on finished aqueous preserved parenteral product in the commercial package can be used up to a maximum of 28 days after the container has been opened.

Un-preserved product should preferably be used immediately following opening, reconstitution or dilution

Preservatives:

1. Acids

- Phenol, cresol
- Parabens

2. Quaternary ammonium

- Benzethonium chloride
- benzalkonium cl

3. Mercurial

- Phenylmercuric ,
- Methyl mercuric

4. Neutral:

- Benzyl alcohol
- Chlorobutanol
- Myristyl gamma picolinium Chloride

TABLE 15-2. Some Pharmaceutically Useful Preservatives

Class	Usual Concentration (%)
<i>Acidic</i>	
Phenol	0.2–0.5
Chlorocresol	0.05–0.1
O-phenyl phenol	0.005–0.01
Alkyl esters of parahydroxybenzoic acid	0.001–0.2
Benzoic acid and its salts	0.1–0.3
Boric acid and its salts	0.5–1.0
Sorbic acid and its salts	0.05–0.2
<i>Neutral</i>	
Chlorbutanol	0.5
Benzyl alcohol	1.0
β-phenylethyl alcohol	0.2–1.0
<i>Mercurial</i>	
Thimerosal	0.001–0.1
Phenylmercuric acetate and nitrate	0.002–0.005
Nitromersol	0.001–0.1
<i>Quaternary Ammonium Compounds</i>	
Benzalkonium chloride	0.004–0.02
Cetylpyridinium chloride	0.01–0.02

Benzyl alcohol

most common

Benzyl alcohol is an aromatic primary alcohol and is effective against most Gram-positive bacteria, yeast, and mold. But is less effective against Gram-negative bacteria.

Its solubility in water is 1 in 25 (w/w) at 25°C.

The optimum antimicrobial activity occurs at pH less than 5 and is less active above pH 8.3.

It may be stored in glass or metal containers or in polypropylene containers coated with Teflon or other inert fluorinated polymers

Parabens are benzoic acid esters

2nd most common

have a broad spectrum of antimicrobial activity at a pH range of 4–8 but are more effective against yeasts and molds when compared to bacteria.

Antimicrobial activity is normally enhanced when combinations of parabens are used with excipients such as PG, phenylethyl alcohol, and edetic acid

Aqueous solutions of parabens are stable at a pH range of 3–6 but degrade by hydrolysis at pH greater than 8.

The solubility of methylparaben and propylparaben in water is 1 in 400 (w/w) at 25°C, and 1 in 2,500 at 20°C, respectively

Due to inherent low solubilities, sodium salts are frequently utilized in the final dosage forms.

Phenol is:

- a bacteriostatic when present in 1% w/v solution and
- has activity against mycobacteria, fungi, and viruses

The solubility of phenol in water is 1 in 15 (w/w) at 20°C.

Aqueous solutions of phenol are stable, can be sterilized by dry heat or autoclaving, and should be maintained in containers that are protected from light.

Phenol is incompatible with albumin and gelatin, which will result in precipitates possibly due to phenolinduced denaturation of these molecules.

There is a low likelihood of adverse reactions from phenol in parenteral products due to the low concentrations used in these products.

thimerosal

also common

especially in vaccines

even though some individuals are sensitive to mercurics

Chlorocresol

Chlorocresol

is purported to be a good preservative for parenterals
but no currently marketed parenteral products containing
chlorocresol were found

British Pharmaceutical Codex and Martindale
list chlorocresol for preservative use in multi-dose aqueous injections
At concentration of 0.1%,
but no examples of injectable products have been provided.

آیا پرزرواتیو میتواند اثر بر پایداری فرآورده داشته باشد؟
علاوه بر محافظت در برابر الودگی

For example:

Phenolic preservatives have a profound effect on the conformation of insulin in solution
and the assembly of the specific type of LysPro insulin hexamer

Furthermore, phenol and/or *m*-cresol in insulin solutions will have a tendency to be adsorbed by and permeate rubber closures

Therefore, rubber formulations must be designed to minimize these potential problems.

آیا پرزرواتیو میتواند باعث افزایش ناپایداری فرآورده شود؟

APs are known to interact with proteins and can cause stability problems such as aggregation.

For example, phenolic compounds will cause aggregation of hGH.

Benzyl alcohol, above certain concentrations and depending on other formulation factors, will interact with recombinant human interferon- causing aggregation of the protein

Antimicrobial selection

main consideration:

- **Compatibility:**
 - Binding with surfactant, pharmaceuticals, rubber closers
 - parabens binding to polysorbate
- **Effectiveness**
- **Irritation**

Antimicrobial preservative effectiveness test USP chapter 51

Osmoticity

is of great importance in parenteral injections

its effects depending on such factors as:

- the degree of deviation from tonicity
- the concentration
- the location of the injection,
- the volume injected
- the speed of the injection
- the rapidity of dilution and diffusion

When formulating hypotonic parenterals,
they usually have tonicity adjusted by the addition of

glucose

or sodium chloride

Or...

Hypotonic and hypertonic solutions usually are administered :

- slowly
- in small volumes
- or into a large vein such as the subclavian

where dilution and distribution occur rapidly.

Excessive infusion of ***hypotonic*** fluids may cause:

- swelling of red blood cells
- hemolysis
- and water invasion of the body's cells in general

Excessive infusion of ***hypertonic*** fluids leads to a wide variety of complications For example:

the sequence of events when the body is presented with a **large IV load of hypertonic fluid, rich in glucose**, is as follows:

hyperglycemia, glycosuria and intracellular dehydration, osmotic diuresis, loss of water and electrolytes, dehydration, and coma

Formulation principles: Tonicity

Isotonic:

- less irritating
- less toxicity
- less hemolysis

1. Not essential that all injections be isotonic:
 - Hypertonic SC, IM:
 - Facilitate absorption,
 - Local effusion of tissue fluids
 - IV: Isotonicity becomes less important:
 - If “Slow infusion”: good dilution
2. Intrap spinal: must be isotonic, slow circulation of cerebrospinal fluid

Tonicity adjusting agents:

- Same osmotic pressure as blood plasma
- Membrane of RBC
 - ✓ lose of fluid
 - ✓ Shrinkage
 - ✓ swelling

Isotonic: LVPs, Aqueous SC, id, im , intrathecal

colligative properties

there are four properties of solutions that depend only on the number of *particles* in the solution. They are:

- 1. osmotic-pressure elevation***
- 2. boiling-point elevation***
- 3. vapor-pressure depression***
- 4. freezing-point depression.***

freezing point of normal, healthy human blood is -0.52°C .

it is assumed that *any aqueous solution freezing at -0.52°C is isotonic with blood*

Isotonicity/iso-osmotic

The usual practice is to add either sodium chloride or glucose to adjust hypotonic parenteral solutions to isotonicity.

Certain solutes, including:

ammonium chloride, boric acid, urea, glycerin, and propylene glycol cause hemolysis even when they are present in a concentration that is **iso-osmotic**, and such solutions obviously are not isotonic and do not act as a solvent, semi-permeable membrane

Hypertonic/ hypotonic

normal serum osmolality to be 285 mOsmol/kg

fluids with an osmolality of 50 mOsmol or more above normal are hypertonic;

and if they are 50 mOsmol or more below normal, they are hypotonic

<785> Osmolality and osmolarity

Osmometer For freezing point depression measurement



methods to calculate tonicity:

1-Sodium chloride equivalent method

the most convenient

The sodium chloride equivalent of a substance :
can be determined from
its ability to lower the freezing point of water

A 1% sodium chloride solution has a freezing point of -0.58°C
and is assigned a sodium chloride equivalent, E, of 1.00

The freezing point of blood (serum) is -0.52°C
the same as a 0.9% w/v solution of sodium chloride

Sodium Chloride Equivalent Method

A sodium chloride equivalent, *E value*, is defined as the weight of sodium chloride that will produce the same osmotic effect as 1 g of the drug

For example, in Appendix A,

Dexamethasone sodium phosphate has an **E value** of:

0.18 g NaCl/g drug at 0.5% drug concentration

0.17 g NaCl/g drug at 1% drug concentration

and a value of 0.16 g NaCl/g drug at 2% drug

This slight variation in the sodium chloride equivalent with concentration is due to **changes in interionic attraction at different concentration of drug**

**the E value is not directly proportional to concentration,
as was the freezing-point-depression.**

APPENDIX A: Sodium Chloride Equivalents, Freezing-Point Depressions, and Hemolytic Effects of Certain Medicinals in Aqueous Solution

	Iso-Osmotic Concentration ^a														
	0.5 %		1 %		2 %		3 %		5 %		%	E	D	H	pH
	E	D	E	D	E	D	E	D	E	D					
Acetrizoate methylglucamine	0.09		0.08		0.08		0.08		0.08	12.12	0.07		0	7.1	
Acetrizoate sodium	0.10	0.027	0.10	0.055	0.10	0.109	0.10	0.163	0.10	0.273	9.64	0.09	0.52	0	6.9†
Acetylcysteine	0.20	0.055	0.20	0.113	0.20	0.227	0.20	0.341			4.58	0.20	0.52	100*	2.0
Adrenaline HCl											4.24			68	4.5
Alphaprodine HCl	0.19	0.053	0.19	0.105	0.18	0.212	0.18	0.315			4.98	0.18	0.52	100	5.3
Alum (potassium)			0.18				0.15		0.15		6.35		0.14	24*	3.4
Amantadine HCl	0.31	0.090	0.310	0.180	0.31	0.354					2.95	0.31	0.52	91	5.7
Aminoacetic acid	0.42	0.119	0.41	0.235	0.41	0.47					2.20	0.41	0.52	0*	6.2
Aminohippuric acid	0.13	0.035	0.13	0.075											
Aminophylline				0.098 ^c											
Ammonium carbonate	0.70	0.202	0.70	0.405							1.29	0.70	0.52	97	7.7
Ammonium chloride				1.12							0.8	1.12	0.52	93	5.0
Ammonium lactate	0.33	0.093	0.33	0.185	0.33	0.37					2.76	0.33	0.52	98	5.9
Ammonium nitrate	0.69	0.200	0.69	0.400							1.30	0.69	0.52	91	5.3
Ammonium phosphate, dibasic	0.58	0.165	0.55	0.315							1.76	0.51	0.52	0	7.9
Ammonium sulfate	0.55	0.158	0.55	0.315							1.68	0.54	0.52	0	5.3
Amobarbital sodium			0.25	0.143 ^c			0.25				3.6	0.25	0.52	0	9.3
d-Amphetamine HCl											2.64			98	5.7
Amphetamine phosphate			0.34	0.20			0.27	0.47			3.47	0.26	0.52	0	4.5
Amphetamine sulfate			0.22	0.129 ^c			0.21	0.36			4.23	0.21	0.52	0	5.9
Amprotoprine phosphate											5.90			0	4.2
Amyleaine HCl			0.22				0.19				4.98	0.18		100	5.6
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	5.13	0.18	0.52	12	2.6
Antazoline phosphate											6.05			90	4.0
Antimony potassium tartrate			0.18				0.13		0.10						
Antipyrine			0.17	0.10			0.14	0.24	0.14	0.40	6.81	0.13	0.52	100	6.1
Apomorphine HCl			0.14	0.080 ^c											
Arginine glutamate	0.17	0.048	0.17	0.097	0.17	0.195	0.17	0.292	0.17	0.487	5.37	0.17	0.52	0	6.9
Ascorbic acid				0.105 ^c							5.05	0.52b	100*	2.2	
Atropine methylbromide			0.14				0.13		0.13		7.03	0.13			
Atropine methylnitrate											6.52			0	5.2
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	8.85	0.10	0.52	0	5.0
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12					

	0.5 %		1 %		2 %		3 %		5 %		Iso-Osmotic Concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Barbital sodium			0.30	0.171 ^c			0.29	0.50			3.12	0.29	0.52	0	9.8
Benzalkonium chloride			0.16				0.14		0.13						
Benztropine mesylate	0.26	0.073	0.21	0.115	0.15	0.170	0.12	0.203	0.09	0.242					
Benzyl alcohol			0.17	0.09 ^c			0.15								
Bethanechol chloride	0.50	0.140	0.39	0.225	0.32	0.368	0.30	0.512			3.05	0.30		0	6.0
Bismuth potassium tartrate			0.09				0.06		0.05						
Bismuth sodium tartrate			0.13				0.12		0.11		8.91	0.10		0	6.1
Boric acid	0.50	0.288 ^c									1.9	0.47	0.52	100	4.6
Brompheniramine maleate	0.10	0.026	0.09	0.05	0.08	0.084									
Bupivacaine HCl	0.17	0.048	0.17	0.096	0.17	0.193	0.17	0.29	0.17	0.484	5.38	0.17	0.52	83	6.8
Butabarbital sodium	0.27	0.078	0.27	0.155	0.27	0.313	0.27	0.47			3.33	0.27	0.52	0	6.8
Butacaine sulfate			0.20	0.12			0.13	0.23	0.10	0.29					
Caffeine and sodium benzoate			0.26	0.15			0.23	0.40			3.92	0.23	0.52	0	7.0
Caffeine and sodium salicylate			0.12	0.12			0.17	0.295	0.16	0.46	5.77	0.16	0.52	0	6.8
Calcium aminosalicylate											4.80			0	6.0
Calcium chloride			0.51	0.298 ^c							1.70	0.53	0.52	0	5.6
Calcium chloride (6 H ₂ O)			0.35	0.20							2.5	0.36	0.52	0	5.7
Calcium chloride, anhydrous			0.68	0.39							1.3	0.69	0.52	0	5.6
Calcium disodium edetate	0.21	0.061	0.21	0.120	0.21	0.240	0.20	0.357			4.50	0.20	0.52	0	6.1
Calcium gluconate			0.16	0.091 ^c			0.14	0.24							
Calcium lactate			0.23	0.13			0.12	0.36			4.5	0.20	0.52	0	6.7
Calcium lactobionate	0.08	0.022	0.08	0.043	0.08	0.085	0.07	0.126	0.07	0.197					
Calcium levulinate			0.27	0.16			0.25	0.43			3.58			0	7.2
Calcium pantothenate			0.129								5.50			0	7.4
Camphor			0.12 ^d												
Capreomycin sulfate	0.04	0.011	0.04	0.02	0.04	0.042	0.04	0.063	0.04	0.106					
Carbachol				0.205 ^c							2.82			0	5.9
Carbenicillin sodium	0.20	0.059	0.20	0.118	0.20	0.236	0.20	0.355			4.40	0.20	0.52	0	6.6
Carboxymethylcellulose sodium	0.03	0.007	0.03	0.017	0.145										
Cephaloridine	0.09	0.023	0.07	0.041	0.06	0.074	0.06	0.106	0.05						
Chloramine-T					0.06 ^d						4.10			100*	9.1
Chloramphenicol															
Chloramphenicol sodium succinate	0.14	0.038	0.14	0.078	0.14	0.154	0.13	0.230	0.13	0.382	6.83	0.13	0.52	partial	6.1

	Iso-Osmotic Concentration ^a														
	0.5 %		1 %		2 %		3 %		5 %		%	E	D	H	pH
	E	D	E	D	E	D	E	D	E	D		E	D	H	pH
Chlordiazepoxide HCl	0.24	0.068	0.22	0.125	0.19	0.220	0.18	0.315	0.17	0.487	5.50	0.16	0.52	66	2.7
Chlorobutanol (hydrated)			0.24	0.14											
Chloroprocaine HCl	0.20	0.054	0.20	0.108	0.18	0.21									
Chloroquine phosphate	0.14	0.039	0.14	0.082	0.14	0.162	0.14	0.242	0.13	0.379	7.15	0.13	0.52	0	4.3
Chloroquine sulfate	0.10	0.028	0.09	0.050	0.08	0.090	0.07	0.127	0.07	0.195					
Chlorpheniramine maleate	0.17	0.048	0.15	0.085	0.14	0.165	0.13	0.22	0.09	0.265					
Chlortetracycline HCl	0.10	0.030	0.10	0.061	0.10	0.121									
Chlortetracycline sulfate			0.13	0.08			0.10	0.17							
Citric acid			0.18	0.10			0.17	0.295	0.16	0.46	5.52	0.16	0.52	100*	1.8
Clindamycin phosphate	0.08	0.022	0.08	0.046	0.08	0.095	0.08	0.144	0.08	0.242	10.73	0.08	0.52	58*	6.8
Cocaine HCl			0.16	0.090 ^e			0.15	0.26	0.14	0.40	6.33	0.14	0.52	47	4.4
Codeine phosphate			0.14	0.080 ^e			0.13	0.23	0.13	0.38	7.29	0.12	0.52	0	4.4
Colistimethate sodium	0.15	0.045	0.15	0.085	0.15	0.170	0.15	0.253	0.14	0.411	6.73	0.13	0.52	0	7.6
Cupric sulfate			0.18	0.100 ^e			0.15		0.14		6.85	0.13		trace*	3.9
Cyclizine HCl	0.20	0.060													
Cyclophosphamide	0.10	0.031	0.10	0.061	0.10	0.125									
Cytarabine	0.11	0.034	0.11	0.066	0.11	0.134	0.11	0.198	0.11	0.317	8.92	0.10	0.52	0	8.0
Deferoxamine mesylate	0.09	0.023	0.09	0.047	0.09	-0.093	0.09	0.142	0.09	0.241					
Demecarium bromide	0.14	0.038	0.12	0.069	0.10	0.108	0.08	0.139	0.07	0.192					
Dexamethasone sodium phosphate	0.18	0.050	0.17	0.095	0.16	0.18	0.15	0.260	0.14	0.410	6.75	0.13	0.52	0	8.9
Dextroamphetamine HCl	0.34	0.097	0.34	0.196	0.34	0.392					2.64	0.34	0.52		
Dextroamphetamine phosphate			0.25	0.14			0.25	0.44			3.62	0.25	0.52	0	4.7
Dextroamphetamine sulfate	0.24	0.069	0.23	0.134	0.22	0.259	0.22	0.380			4.16	0.22	0.52	0	5.9
Dextrose			0.16	0.091 ^e			0.16	0.28	0.16	0.46	5.51	0.16	0.52	0	5.9
Dextrose (anhydrous)			0.18	0.101 ^e			0.18	0.31			5.05	0.18	0.52	0	6.0
Diatrizoate sodium	0.10	0.025	0.09	0.049	0.09	0.098	0.09	0.149	0.09	0.248	10.55	0.09	0.52	0	7.9
Dibucaine HCl				0.074 ^e											
Dicloxacillin sodium (1 H ₂ O)	0.10	0.030	0.10	0.061	0.10	0.122	0.10	0.182							
Diethanolamine	0.31	0.089	0.31	0.177	0.31	0.358					2.90	0.31	0.52	100	11.3
Dihydrostreptomycin sulfate			0.06	0.03			0.05	0.09	0.05	0.14	19.4	0.05	0.52	0	6.1
Dimethylpyrindene maleate	0.13	0.039	0.12	0.07	0.11	0.12					2.16	0.42	0.52	100	7.6
Dimethyl sulfoxide	0.42	0.122	0.42	0.245	0.42	0.480									
Diperodon HCl	0.15	0.045	0.14	0.079	0.13	0.141									

	0.5 %		1 %		2 %		3 %		5 %		Iso-Osmotic Concentration ^a					
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH	
Diphenhydramine HCl					0.161 ^c						5.70			88*	5.5	
Diphenidol HCl	0.16	0.045	0.16	0.09	0.16	0.180										
Doxapram HCl	0.12	0.035	0.12	0.070	0.12	0.140	0.12	0.210								
Doxycycline hyclate	0.12	0.035	0.12	0.072	0.12	0.134	0.11	0.186	0.09	0.264						
Dyphylline	0.10	0.025	0.10	0.052	0.09	0.104	0.09	0.155	0.08	0.245						
Echothiophate iodide	0.16	0.045	0.16	0.090	0.16	0.179										
Edetate disodium	0.24	0.070	0.23	0.132	0.22	0.248	0.21	0.360			4.44	0.20	0.52	0	4.7	
Edetate trisodium monohydrate	0.29	0.079	0.29	0.158	0.28	0.316	0.27	0.472			3.31	0.27	0.52	0	8.0	
Emetine HCl				0.058 ^c					0.17		0.29					
Ephedrine HCl		0.30		0.165 ^c				0.28			3.2	0.28		96	5.9	
Ephedrine sulfate		0.23		0.13			0.20	0.35			4.54	0.20	0.52	0	5.7	
Epinephrine bitartrate		0.18		0.104			0.16	0.28	0.16	0.462	5.7	0.16	0.52	100*	3.4	
Epinephrine hydrochloride		0.29		0.16 ^b			0.26				3.47	0.26				
Ergonovine maleate				0.089 ^c												
Erythromycin lactobionate	0.08	0.020	0.07	0.040	0.07	0.078	0.07	0.115	0.06	0.187						
Ethyl alcohol											1.39			100	6.0	
Ethylenediamine				0.253 ^c							2.08			100*	11.4	
Ethylmorphine HCl		0.16		0.088 ^c				0.15	0.26	0.15	0.43	6.18	0.15	0.52	38	4.7
Eucatropine HCl				0.11 ^d												
Ferric ammonium citrate (green)											6.83			0	5.2	
Floxuridine	0.14	0.040	0.13	0.076	0.13	0.147	0.12	0.213	0.12	0.335	8.47	0.12	0.52	3*	4.5	
Fluorescein sodium			0.31	0.181 ^c			0.27	0.47			3.34	0.27	0.52	0	8.7	
Fluphenazine 2-HCl	0.14	0.041	0.14	0.082	0.12	0.145	0.09	0.155								
d-Fructose											5.05			0*	5.9	
Furtrethonium iodide	0.24	0.070	0.24	0.133	0.22	0.250	0.21	0.360			4.44	0.20	0.52	0	5.4	
Galactose											4.92			0	5.9	
Gentamicin sulfate	0.05	0.015	0.05	0.030	0.05	0.060	0.05	0.093	0.05	0.153						
D-Glucuronic acid											5.02			48*	1.6	
Glycerin			0.203 ^c								2.6			100	5.9	
Glycopyrrolate	0.15	0.042	0.15	0.084	0.15	0.166	0.14	0.242	0.13	0.381	7.22	0.12	0.52	92*	4.0	
Gold sodium thiomalate	0.10	0.032	0.10	0.061	0.10	0.111	0.09	0.159	0.09	0.250						
Hetacillin potassium	0.17	0.048	0.17	0.095	0.17	0.190	0.17	0.284	0.17	0.474	5.50	0.17	0.52	0	6.3	
Hexafluorenium bromide	0.12	0.033	0.11	0.065												
Hexamethonium tartrate	0.16	0.045	0.16	0.089	0.16	0.181	0.16	0.271	0.16	0.456	5.68	0.16	0.52			
Hexamethylene sodium acetaminosalicylate	0.18	0.049	0.18	0.099	0.17	0.199	0.17	0.297	0.16	0.485	5.48	0.16	0.52	0*	4.0	

	0.5 %		1 %		2 %		3 %		5 %		Iso-Osmotic Concentration ^a					
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH	
Hexobarbital sodium					0.15 ^c											
Hexylcaine HCl											4.30			100	4.8	
Histamine 2HCl	0.40	0.115	0.40	0.233	0.40	0.466					2.24	0.40	0.52	79*	3.7	
Histamine phosphate					0.149 ^c						4.10	0	4.6			
Histidine HCl											3.45			40	3.9	
Holocaine HCl			0.20	0.12												
Homatropine hydrobromide			0.17	0.097 ^c			0.16	0.28	0.16	0.46	5.67	0.16	0.52	92	5.0	
Homatropine methylbromide			0.19	0.11			0.15	0.26	0.13	0.38						
4-Homosulfanilamide HCl											3.69			0	4.9	
Hyaluronidase	0.01	0.004	0.01	0.007	0.01	0.013	0.01	0.02	0.01	0.033						
Hydromorphone HCl											6.39			64	5.6	
Hydroxyamphetamine HBr					0.15 ^d						3.71			92	5.0	
8-Hydroxyquinoline sulfate											9.75			59*	2.5	
Hydroxystilbamidine isethionate	0.20	0.06	0.16	0.090	0.12	0.137	0.10	0.17	0.07	0.216						
Hyoscyamine hydrobromide											6.53			68	5.9	
Imipramine HCl	0.20	0.058	0.20	0.110	0.13	0.143										
Indigotindisulfonate sodium	0.30	0.085	0.30	0.172												
Intracaine HCl											4.97			85	5.0	
Iodophthalein sodium					0.07 ^c						9.58			100	9.4	
Isomethcptene mucate	0.18	0.048	0.18	0.095	0.18	0.196	0.18	0.302			4.95	0.18	0.52	0	6.2	
Isoproterenol sulfate	0.14	0.039	0.14	0.078	0.14	0.156	0.14	0.234	0.14	0.389	6.65	0.14	0.52	trace	4.5	
Kanamycin sulfate	0.08	0.021	0.07	0.041	0.07	0.083	0.07	0.125	0.07	0.210						
Lactic acid					0.239 ^c						2.30			100*	2.1	
Lactose				0.07	0.040 ^c		0.08		0.09		9.75	0.09		0*	5.8	
Levallorphan tartrate	0.13	0.036	0.13	0.073	0.13	0.143	0.12	0.210	0.12	0.329	9.40	0.10	0.52	59*	6.9	
Levorphanol tartrate	0.12	0.033	0.12	0.067	0.12	0.136	0.12	0.203								
Lidocaine HCl					0.13 ^c						4.42			85	4.3	
Lircamycin HCl	0.16	0.045	0.16	0.090	0.15	0.170	0.14	0.247	0.14	0.40	6.60	0.14	0.52	0	4.5	
Lobeline HCl					0.090*											
Lyapolate sodium	0.10	0.025	0.09	0.051	0.09	0.103	0.09	0.157	0.09	0.263	9.96	0.09	0.52	0	6.5+	
Magnesium chloride					0.45						2.02	0.45		0	6.3	
Magnesium sulfate				0.17	0.094 ^c		0.15	0.26	0.15	0.43	6.3	0.14	0.52	0	6.2	
Magnesium sulfate, anhydrous	0.34	0.093	0.32	0.184	0.30	0.345	0.29	0.495			3.18	0.28	0.52	0	7.0	

	0.5 %		1 %		2 %		3 %		5 %		Iso-Osmotic Concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Mannitol				0.098 ^c					5.07			0*	6.2		
Maphenide HCl	0.27	0.075	0.27	0.153	0.27	0.303	0.26	0.448			3.55	0.25	0.52		
Menadiol sodium diphosphate											4.36		0	8.2	
Menadione sodium bisulfite					0.12 ^d						5.07		0	5.3	
Menthol															
Meperidine HCl					0.125 ^e						4.80			98	5.0
Mepivacaine HCl	0.21	0.060	0.21	0.116	0.20	0.230	0.20	0.342			4.60	0.20	0.52	45	4.5
Merbromin				0.08 ^b											
Mercuric cyanide			0.15	0.06*			0.14		0.13						
Mersalyl															
Mesoridazine besylate	0.10	0.024	0.07	0.04	0.05	0.058	0.04	0.071	0.03	0.087					
Metaraminol bitartrate	0.20	0.06	0.20	0.112	0.19	0.21	0.18	0.308	0.17	0.505	5.17	0.17	0.52	59	3.8
Methacholine chloride					0.184 ^e						3.21		0	4.5	
Methadone HCl					0.101 ^e						8.59			100*	5.0
Methamphetamine HCl					0.213 ^e						2.75			97	5.9
Methdilazine HCl	0.12	0.035	0.10	0.056	0.08	0.08	0.06	0.093	0.04	0.112					
Methenamine			0.23				0.24				3.68	0.25		100	8.4
Methiodal sodium	0.24	0.068	0.24	0.136	0.24	0.274	0.24	0.41			3.81	0.24	0.52	0	5.9
Methitural sodium	0.26	0.074	0.25	0.142	0.24	0.275	0.23	0.407			3.85	0.23	0.52	78	9.8
Methocarbamol	0.10	0.03	0.10	0.06											
Methotrimeprazine HCl	0.12	0.034	0.10	0.060	0.07	0.077	0.06	0.094	0.04	0.125					
Methoxyphenamine HCl	0.26	0.075	0.26	0.150	0.26	0.300	0.26	0.450			3.47	0.26	0.52	96	5.4
p-Methylaminoethanol-phenol tartrate	0.18	0.048	0.17	0.095	0.16	0.19	0.16	0.282	0.16	0.453	5.83	0.16	0.52	0	6.2
Methyldopate HCl	0.21	0.063	0.21	0.122	0.21	0.244	0.21	0.365			4.28	0.21	0.52	partial	3.0
Methylergonovine maleate	0.10	0.028	0.10	0.056											
N-Methylglucamine	0.20	0.057	0.20	0.111	0.18	0.214	0.18	0.315	0.18	0.517	5.02	0.18	0.52	4	11.3
Methylphenidate HCl	0.22	0.065	0.22	0.127	0.22	0.258	0.22	0.388			4.07	0.22	0.52	66	4.3
Methylprednisolone Na succinate	0.10	0.025	0.09	0.051	0.09	0.102	0.08	0.143	0.07	0.20					
Minoxycline HCl	0.10	0.030	0.10	0.058	0.09	0.107	0.08	0.146							
Monoethanolamine	0.53	0.154	0.53	0.306							1.70	0.53	0.52	100	11.4
Morphine HCl			0.15	0.086 ^e			0.14								
Morphine sulfate			0.14	0.079 ^e			0.11	0.19	0.09	0.26					
Nalorphine HCl	0.24	0.07	0.21	0.121	0.18	0.210	0.17	0.288	0.15	0.434	6.36	0.14	0.52	63	4.1
Naloxone HCl	0.14	0.042	0.14	0.083	0.14	0.158	0.13	0.230	0.13	0.367	8.07	0.11	0.52	35	5.2
Naphazoline HCl			0.27	0.14 ^d			0.24				3.99	0.22		100	5.3

	0.5 %		1 %		2 %		3 %		5 %		Iso-Osmotic Concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Neoarsphenamine											2.32		17	7.80	
Neomycin sulfate		0.11	0.063 ^c				0.09	0.16	0.08	0.232					
Neostigmine bromide		0.22	0.127 ^c				0.19				4.98		0	4.6	
Neostigmine methylsulfate		0.20	0.115 ^c				0.18		0.17		5.22	0.17			
Nicotinamide		0.26	0.148 ^c				0.21	0.36			4.49	0.20	0.52	100	7.0
Nicotinic acid		0.25	0.144 ^c												
Nikethamide			0.100 ^c								5.94		100	6.9	
Novobiocin sodium	0.12	0.033	0.10	0.057	0.07	0.073									
Oleandomycin phosphate	0.08	0.017	0.08	0.038	0.08	0.084	0.08	0.129	0.08	0.255	10.82	0.08	0.52	0	5.0
Orphenadrine citrate	0.13	0.037	0.13	0.074	0.13	0.144	0.12	0.204	0.10	0.285					
Oxophenarsine HCl											.67			trace*	2.3
Oxymetazoline HCl	0.22	0.063	0.22	0.124	0.20	0.232	0.19	0.335			4.92	0.18	0.52	86	5.7
Oxyquinoline sulfate	0.24	0.068	0.21	0.113	0.16	0.182	0.14	0.236	0.11	0.315					
d-Pantothenyl alcohol	0.20	0.053	0.18	0.100	0.17	0.193	0.17	0.283	0.16	0.468	5.60	0.16	0.52	92	6.8
Papaverine HCl			0.10	0.061 ^c											
Paraldehyde	0.25	0.071	0.25	0.142	0.25	0.288	0.25	0.430			3.65	0.25	0.52	97	5.3
Pargyline HCl	0.30	0.083	0.29	0.165	0.29	0.327	0.28	0.491			3.18	0.28	0.52	91	3.8
Penicillin G, potassium			0.18	0.102 ^c			0.17	0.29	0.16	0.46	5.48	0.16	0.52	0	6.2
Penicillin G, procaine				0.06 ^d											
Penicillin G, sodium			0.18	0.100 ^c			0.16	0.28	0.16	0.46	5.90			18	5.2
Pentazocine lactate	0.15	0.042	0.15	0.085	0.15	0.169	0.15	0.253	0.15	0.42					
Pentobarbital sodium				0.145 ^c							4.07			0	9.9
Pentolinium tartrate				0.09 ^d							5.95			55*	3.4
Phenacaine HCl				0.09											
Pheniramine maleate				0.09 ^d											
Phenobarbital sodium			0.24	0.135 ^c			0.23	0.40			3.95	0.23	0.52	0	9.2
Phenol	0.35	0.20									2.8	0.32	0.52	0*	5.6
Phentolamine mesylate	0.18	0.052	0.17	0.096	0.16	0.173	0.14	0.244	0.13	0.364	8.23	0.11	0.52	83	3.5
Phenylephrine HCl			0.32	0.184 ^c			0.30				3.0	0.30		0	4.5
Phenylephrine tartrate											5.90			58*	5.4
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283									
Phenylpropanolamine HCl			0.38	0.219 ^c							2.6	0.35		95	5.3
Physostigmine salicylate			0.16	0.090 ^c											
Physostigmine sulfate				0.074 ^c											
Pilocarpine HCl			0.24	0.138 ^c			0.22	0.38			4.08	0.22	0.52	89	4.0
Pilocarpine nitrate			0.23	0.132 ^c			0.20	0.35			4.84	0.20	0.52	88	3.9
Piperocaine HCl				0.12 ^d							5.22			65	5.7
Polyethylene glycol 300	0.12	0.034	0.12	0.069	0.12	0.141	0.12	0.216	0.13	0.378	6.73	0.13	0.52	53	3.8

	0.5 %		1 %		2 %		3 %		5 %		Iso-Osmotic Concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Polyethylene glycol 400	0.08	0.022	0.08	0.047	0.09	0.098	0.09	0.153	0.09	0.272	8.50	0.11	0.52	0	4.4
Polyethylene glycol 1500	0.06	0.015	0.06	0.036	0.07	0.078	0.07	0.120	0.07	0.215	10.00	0.09	0.52	4	4.1
Polyethylene glycol 1540	0.02	0.005	0.02	0.012	0.02	0.028	0.03	0.047	0.03	0.094					
Polyethylene glycol 4000	0.02	0.004	0.02	0.008	0.02	0.02	0.020	0.033	0.02	0.067					
Polymyxin B sulfate			0.09	0.052			0.06	0.10	0.04	0.12					
Polysorbate 80	0.02	0.005	0.02	0.010	0.02	0.02	0.020	0.032	0.02	0.055					
Polyvinyl alcohol (99% hydrol)	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.035	0.03	0.075					
Polyvinylpyrrolidone	0.01	0.003	0.010	0.006	0.01	0.01	0.01	0.017	0.01	0.035					
Potassium acetate	0.59	0.172	0.59	0.342							1.53	0.59	0.52	0	7.6
Potassium chlorate											1.88			0	6.9
Potassium chloride		0.76	0.439 ^c								1.19	0.76	0.52	0	5.9
Potassium iodide		0.34	0.196 ^c								2.59	0.34	0.52	0	7.0
Potassium nitrate		0.56	0.324 ^c								1.62	0.56	0	5.9	
Potassium phosphate		0.46	0.27								2.08	0.43	0.52	0	8.4
Potassium phosphate, monobasic		0.44	0.25								2.18	0.41	0.52	0	4.4
Potassium sulfate		0.44									2.11	0.43		0	6.6
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.87	0.32	0.52	0	4.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			4.18	0.22	0.52	45	4.6
Procainamide HCl		0.22	0.13				0.19	0.33	0.17	0.49					
Procaine HCl		0.21	0.122 ^c				0.19	0.33	0.18		5.05	0.18	0.52	91	5.6
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065					
Promazine HCl	0.18	0.050	0.13	0.077	0.09	0.102	0.07	0.112	0.05	0.137					
Proparacaine HCl	0.16	0.044	0.15	0.086	0.15	0.169	0.14	0.247	0.13	0.380	7.46	0.12	0.52		
Propiomazine HCl	0.18	0.050	0.15	0.084	0.12	0.133	0.10	0.165	0.08	0.215					
Propoxyceaine HCl											6.40			16	5.3
Propylene glycol											2.00			100	5.5
Pyrathiazine HCl	0.22	0.065	0.17	0.095	0.11	0.123	0.08	0.140	0.06	0.17					
Pyridostigmine bromide	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.377			4.13	0.22	0.52	0	7.2
Pyridoxine HCl											3.05			31*	3.2
Quinacrine methanesulfonate				0.06 ^c											
Quinine bisulfate				0.09	0.05		0.09	0.16							
Quinine dihydrochloride				0.23	0.130 ^c		0.19	0.33	0.18		5.07	0.18	0.52	trace*	2.5
Quinine hydrochloride				0.14	0.077 ^c		0.11	0.19							
Quinine and urea HCl				0.23	0.13		0.21	0.36			4.50	0.20	0.52	64	2.9
Resorcinol		0.161 ^c									3.30			96	5.0

	Iso-Osmotic Concentration ^a													
	0.5 %		1 %		2 %		3 %		5 %		%	E	D	H
	E	D	E	D	E	D	E	D	E	D				
Rolitetracycline	0.11	0.032	0.11	0.064	0.10	0.113	0.09	0.158	0.07	0.204				
Rose Bengal	0.08	0.02	0.07	0.04	0.07	0.083	0.07	0.124	0.07	0.198	14.9	0.06	0.52	
Rose Bengal B	0.08	0.022	0.08	0.044	0.08	0.087	0.08	0.131	0.08	0.218				
Scopolamine HBr			0.12	0.07			0.12	0.21	0.12	0.35	7.85	0.11	0.52	8
Scopolamine methylnitrate			0.16				0.14		0.13	6.95	0.13	0	6.0	
Secobarbital sodium			0.24	0.14			0.23	0.40			3.9	0.23	0.52	trace
Silver nitrate			0.33	0.190 ^c							2.74	0.33	0.52	0*
Silver protein, mild			0.17	0.10			0.17	0.29	0.16	0.46	5.51	0.16	0.52	0
Silver protein, strong				0.06 ^d										9.0
Sodium acetate			0.46	0.267							2.0	0.45	0.52	
Sodium acetazolamide	0.24	0.068	0.23	0.135	0.23	0.271	0.23	0.406			3.85	0.23	0.52	
Sodium aminosalicylate				0.170 ^e							3.27			0
Sodium ampicillin	0.16	0.045	0.16	0.090	0.16	0.181	0.16	0.072	0.16	0.451	5.78	0.16	0.52	0
Sodium ascorbate											3.00			6.9
Sodium benzoate			0.40	0.230 ^c							2.25	0.40	0.52	0
Sodium bicarbonate			0.65	0.375							1.39	0.65	0.52	0
Sodium biphosphate (H ₂ O)			0.40	0.23							2.45	0.37	0.52	0
Sodium biphosphate (2 H ₂ O)			0.36								2.77	0.32		4.0
Sodium bismuth thioglycollate	0.20	0.055	0.19	0.107	0.18	0.208	0.18	0.303	0.17	0.493	5.29			8.3
Sodium bisulfite			0.61	0.35							1.5	0.61	0.52	0*
Sodium borate			0.42	0.241 ^c							2.6	0.35	0.52	0
Sodium bromide											1.60			6.1
Sodium carbonate, monohydrated			0.32				0.28				3.3	0.27		8.0
Sodium cephalothin	0.18	0.05	0.17	0.095	0.16	0.179	0.15	0.259	0.14	0.400	6.80	0.13	0.52	partial
Sodium chloride			1.00	0.576 ^e			1.00	1.73	1.00	2.88	0.9	1.00	0.52	0
Sodium citrate			0.31	0.178 ^c			0.30	0.52			3.02	0.30		7.8
Sodium colistimethate	0.16	0.045	0.15	0.087	0.14	0.161	0.14	0.235	0.13	0.383	6.85	0.13	0.52	0
Sodium hypophosphite											1.60			7.3
Sodium iodide			0.39	0.222 ^c							2.37	0.38	0.52	0
Sodium iodohippurate											5.92			7.3
Sodium lactate											1.72			6.5
Sodium lauryl sulfate	0.10	0.029	0.08	0.046	0.07	0.068	0.05	0.086			5.30			8.4
Sodium mercaptomerin												0		
Sodium metabisulfite			0.67	0.386 ^c							1.38	0.65	0.52	5*
														4.5

	0.5 %		1 %		2 %		3 %		5 %		Iso-Osmotic Concentration ^a					
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH	
Sodium methicillin	0.18	0.050	0.18	0.099	0.17	0.192	0.16	0.281	0.15	0.445	6.00	0.15	0.52	0	5.8	
Sodium nafcillin	0.14	0.039	0.14	0.078	0.14	0.158	0.13	0.219	0.10	0.285		1.36	0.66	0	6.0	
Sodium nitrate			0.68									1.08	0.83	0*	8.5	
Sodium nitrite			0.84	0.480 ^c								6.64	0.14	0.52	0	6.0
Sodium oxacillin	0.18	0.050	0.17	0.095	0.16	0.177	0.15	0.257	0.14	0.408		0.27	0.52	0	6.0	
Sodium phenylbutazone	0.19	0.054	0.18	0.104	0.17	0.202	0.17	0.298	0.17	0.488	5.34	0.17	0.52			
Sodium phosphate			0.29	0.168			0.27	0.47			3.33	0.27	0.52	0	9.2	
Sodium phosphate, dibasic (2 H ₂ O)			0.42	0.24							2.23	0.40	0.52	0	9.2	
Sodium phosphate, dibasic (12 H ₂ O)			0.22				0.21				4.45	0.20		0	9.2	
Sodium propionate			0.61	0.35							1.47	0.61	0.52	0	7.8	
Sodium salicylate			0.36	0.210 ^c							2.53	0.36	0.52	0	6.7	
Sodium succinate	0.32	0.092	0.32	0.184	0.31	0.361					2.90	0.31	0.52	0	8.5	
Sodium sulfate, anhydrous			0.58	0.34							1.61	0.56	0.52	0	6.2	
Sodium sulfite, exsiccated			0.65	0.38							1.45			0	9.6	
Sodium sulfobromophthalein	0.07	0.019	0.06	0.034	0.05	0.060	0.05	0.084	0.04	0.123						
Sodium tartrate	0.33	0.098	0.33	0.193	0.33	0.385					2.72	0.33	0.52	0	7.3	
Sodium thiosulfate			0.31	0.181 ^c							2.98	0.30	0.52	0	7.4	
Sodium warfarin	0.18	0.049	0.17	0.095	0.16	0.181	0.15	0.264	0.15	0.430	6.10	0.15	0.52	0	8.1	
Sorbitol (A H ₂ O)											5.48			0	5.9	
Sparteine sulfate	0.10	0.03	0.10	0.056	0.10	0.111	0.10	0.167	0.10	0.277	9.46	0.10	0.52	19*	3.5	
Spectinomycin HCl	0.16	0.045	0.16	0.092	0.16	0.185	0.16	0.280	0.16	0.460	5.66	0.16	0.52	3	4.4	
Streptomycin HCl			0.17	0.10 ^c			0.16	0.16								
Streptomycin sulfate			0.07	0.036 ^c			0.06	0.10	0.06	0.17						
Sucrose			0.08	0.047 ^c			0.09	0.16	0.09	0.26	9.25	0.10	0.52	0	6.4	
Sulfacetamide sodium			0.23	0.132 ^c			0.23	0.40			3.85	0.23	0.52	0	8.7	
Sulfadiazine sodium			0.24	0.14			0.24	0.38			4.24	0.21	0.52	0	9.5	
Sulfamerazine sodium			0.23	0.13			0.21	0.36			4.53	0.20	0.52	0	9.8	
Sulfapyridine sodium			0.23	0.13			0.21	0.36			4.55	0.20	0.52	5	10.4	
Sulfathiazole sodium			0.22	0.13			0.20	0.35			4.82	0.19	0.52	0	9.9	
Tartaric acid				0.143 ^c							3.90			75*	1.7	
Tetracaine HCl			0.18	0.109 ^c			0.15	0.26	0.12	0.35						
Tetracycline HCl			0.14	0.081 ^c		0.10										
Tetrahydrozoline HCl											4.10			60*	6.7	
Theophylline				0.02*												

	0.5 %			1 %			2 %			3 %			5 %			Iso-Osmotic Concentration ^a				
	E	D	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH			
Theophylline sodium glycinate													2.94			0	8.9			
Thiamine HCl					0.139 ^c								4.24			87*	3.0			
Thiethylperazine maleate	0.10	0.030	0.09	0.050	0.08	0.089	0.07	0.119	0.05	0.153			3.50			74	10.3			
Thiopental sodium				0.155 ^c																
Thiopropazate diHCl	0.20	0.053	0.16	0.090	0.12	0.137	0.10	0.170	0.08	0.222										
Thioridazine HCl	0.06	0.015	0.05	0.025	0.04	0.042	0.03	0.055	0.03	0.075										
Thiotepa	0.16	0.045	0.16	0.090	0.16	0.182	0.16	0.278	0.16	0.460	5.67	0.16	0.52	10*	8.2					
Tridihexethyl chloride	0.16	0.047	0.16	0.096	0.16	0.191	0.16	0.28	0.16	0.463	5.62	0.16	0.52	97	5.4					
Triethanolamine	0.20	0.058	0.21	0.121	0.22	0.252	0.22	0.383			4.05	0.22	0.52	100	10.7					
Trifluoperazine 2HCl	0.18	0.052	0.18	0.100	0.13	0.144														
Triflupromazine HCl	0.10	0.031	0.09	0.051	0.05	0.061	0.04	0.073	0.03	0.092										
Trimeprazine tartrate	0.10	0.023	0.06	0.035	0.04	0.045	0.03	0.052	0.02	0.061										
Trimethadione	0.23	0.069	0.23	0.133	0.22	0.257	0.22	0.378			4.22	0.21	0.52	100	6.0					
Trimethobenzamide HCl	0.12	0.033	0.10	0.062	0.10	0.108	0.09	0.153	0.08	0.232			5.50			100	6.3			
Tripeleannamine HCl				0.13 ^d																
Tromethamine	0.26	0.074	0.26	0.15	0.26	0.30	0.26	0.45			3.45	0.26	0.52	0	10.2					
Tropicamide	0.10	0.03	0.09	0.050																
Trypan blue	0.26	0.075	0.26	0.150																
Tryparsamide				0.11 ^e																
Tubocurarine chloride				0.076 ^c																
Urea			0.59	0.34							1.63	0.55	0.52	100	6.6					
Urethan				0.18 ^b							2.93			100	6.3					
Uridine	0.12	0.035	0.12	0.069	0.12	0.138	0.12	0.208	0.12	0.333	8.18	0.11	0.52	0*	6.1					
Valethamate bromide	0.16	0.044	0.15	0.085	0.15	0.168	0.14	0.238	0.11	0.324										
Vancomycin sulfate	0.06	0.015	0.05	0.028	0.04	0.049	0.04	0.066	0.04	0.098										
Viomycin sulfate				0.08	0.05		0.07	0.12	0.07	0.20										
Xylometazoline HCl	0.22	0.065	0.21	0.121	0.20	0.232	0.20	0.342			4.68	0.19	0.52	88	5.0					
Zinc phenolsulfonate				0.15	0.086 ^c			0.13	0.23	0.12	0.35	7.65	0.12		0*	5.4				
Zinc sulfate											5.40									

^a The unmarked values were taken from Hammarlund *et al.*²⁶⁻²⁹ and Sapp *et al.*³⁰

^b Adapted from Lund *et al.*²⁵

^c Adapted from *British Pharmaceutical Codex*.³¹

^d Obtained from several sources.

^e, sodium chloride equivalents; d, freezing-point depression, °C; H, hemolysis, %, at the concentration that is iso-osmotic with 0.9% NaCl, based on freezing-point determination or equivalent test; pH, approximate pH of solution studied for hemolytic action; *, change in appearance of erythrocytes and/or solution³⁰⁻³²; † t, pH determined after addition of blood.

Note: See also Budavari S, ed. *Merck Index*, 11th edn, Rahway, NJ: Merck, 1988: MISC 79–103.

methods to calculate tonicity:

2-Liso

TABLE 10.13

L_{iso} Values for Various Types of Additives in Parenteral Formulations

Compound Type	L_{iso}	Example
Nonelectrolyte	1.9	Sucrose
Weak electrolyte	2.0	Phenobarbital
Divalent electrolyte	2.0	Zinc sulfate
Univalent electrolyte	3.4	Sodium chloride
Uni-divalent electrolyte	4.3	Sodium sulfate
Di-univalent electrolyte	4.8	Calcium chloride
Uni-trivalent electrolyte	5.2	Sodium phosphate
Tri-univalent electrolyte	6.0	Aluminum chloride

$$E = 17 \frac{L_{\text{iso}}}{M}$$

TABLE 10.12

Sodium Chloride Equivalents and Freezing Point Depression for 1% Solutions

Agent	Sodium Chloride Equivalent	Freezing Point Depression
Atropine sulfate	0.13	0.075
Barbital sodium	0.30	0.171
Benzyl alcohol	0.17	0.09
Boric acid	0.50	0.288
Calcium chloride	0.51	0.298
Calcium disodium edetate	0.21	0.120
Calcium gluconate	0.16	0.191
Chlorobutanol	0.24	0.14
Citric acid	0.18	0.10
Codeine phosphate	0.14	0.080
Dextrose	0.16	0.091
Dimethyl sulfoxide	0.42	0.245
Eddetate disodium	0.23	0.132
Ephedrine HCL	0.30	0.165
Isoproterenol sulfate	0.14	0.078
Penicillin G potassium	0.18	0.102
Phenol	0.35	0.20
Pilocarpine nitrate	0.23	0.132
PEG 300	0.12	0.069
PEG 400	0.08	0.047
Sodium bisulfite	0.61	0.35
Sodium cephalothin	0.17	0.095
Sodium chloride	1.00	0.576
Sodium citrate	0.31	0.178
Sodium phosphate, dibasic	0.42	0.24
Sodium sulfate, anhyd.	0.58	0.34
Sucrose	0.08	0.047
Urea	0.59	0.34

TABLE 10.14

Comparison of Measured Osmolality Values with Those Calculated from Sodium Chloride Equivalents

Solution (g/100 mL)	Measured Osmolality Mean mOsm ± S.D.	Sodium Chloride Equivalent Method	
		Osmolality	Percent of Measure
<i>Dextrose</i>			
5.0	262 ± 5.9	249	95.0
10.0	547 ± 6.2	499	91.2
20.0	1176 ± 14.9	998	84.9
<i>Alanine Glycine</i>			
1.0	246 ± 0.5	256	104
2.0	480 ± 1.7	512	107
5.0	1245 ± 10.8	1281	103
0.2 NaCl in 5% dextrose	311 ± 5.85	312	100
0.45% NaCl in 5% dextrose	385 ± 5.48	390	98.7
Ringer's solution, USP	294 ± 4.98	281	95.6
Lactated ringer's, USP	264 ± 3.23	248	93.9
Travasol 5.5%	554 ± 11.4	596	107.6
67% Travasol (5.5%) 33% dextrose (50%)	1330 ± 29.6	1323	91.9

Isotonicity/iso-osmotic

normal serum osmolality to be 285 mOsmol/kg

Hyperosmoticity of parenteral medications serves as an indicator for potential risks, including thrombophlebitis, pain at injection site,

as

serum osmolality increases due to water deficit, the following signs and symptoms usually are found to accumulate progressively at approximately these values: 294 to 298—thirst (if the patient is alert and communicative); 299 to 313—dry mucous membranes; 314 to 329—weakness, doughy skin; above 330—disorientation, postural hypotension, severe weakness, fainting, CNS changes, stupor, and coma. As serum osmolality decreases due to water excess, the following may occur: 275 to 261—headache; 262 to 251—drowsiness, weakness; 250 to 233—disorientation, cramps; below 233—seizures, stupor, and coma

Another current practice that can cause confusion is the use of the terms *normal* or *physiological* for isotonic sodium chloride solution (0.9%).

The solution surely is iso-osmotic.

However, as to being physiological, the concentration of ions is each of 154 mEq/L, whereas serum contains about 140 mEq of sodium and about 103 mEq of chloride.