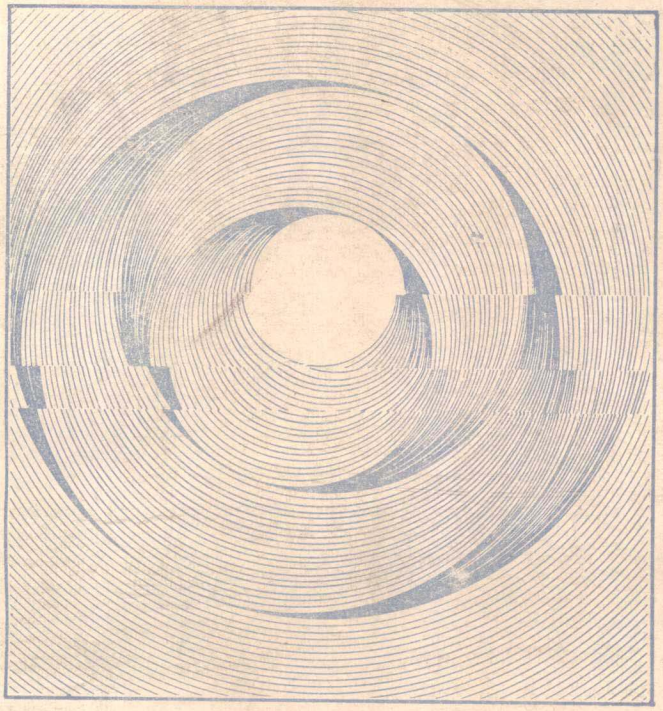
THIRD EDITION

1983



Handbook on Injectable Drugs

LAWRENCE A. TRISSEL

AMERICAN SOCIETY OF HOSPITAL PHARMACISTS

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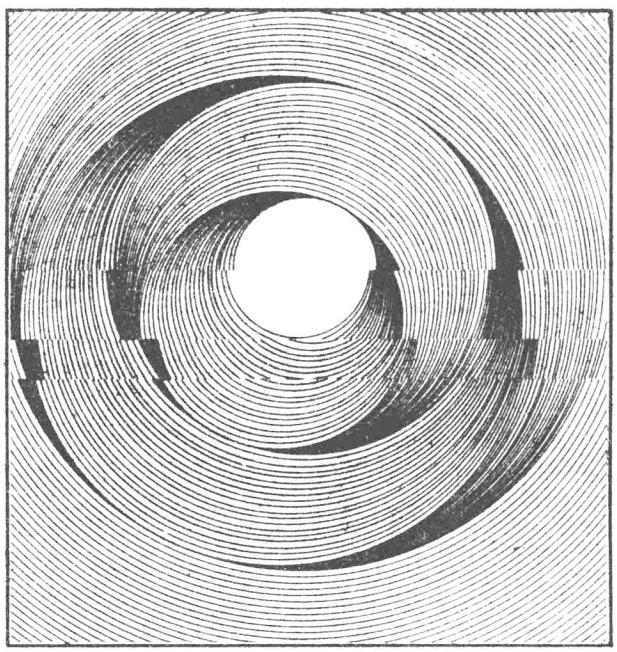

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LAWRENCE A. TRISSEL is a Senior Pharmacist, Clinical Products Section, Pharmaceutical Resources Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute. This book was written by the author in his private capacity. No official support or endorsement by the National Cancer Institute is intended or should be inferred.

Correspondence to the author should be sent in care of the publisher, American Society of Hospital Pharmacists, 4630 Montgomery Avenue, Bethesda, MD 20814.

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PREFACE

The third edition of the *Handbook on Injectable Drugs* is a continuation of my effort to organize and summarize in a concise, standardized format the bulk of the results of the primary research on the stability and compatibility of drugs given by injection. In addition to a complete updating of the existing information on commercial and investigational drugs from the previous edition, 35 new monographs on commercial drugs are presented. Information new to this edition includes that of over 200 additional references. The reader should not overlook the section on the composition and characteristics of the commercially available intravenous infusion solutions. And, once again, David W. Newton has provided this book with a superb introduction. His article, "Physicochemical Determinants of Incompatibility and Instability of Drugs for Injection and Infusion," updated for this edition, remains an excellent general introduction to the subject of compatibility and stability.

But the third edition also contains substantial improvements beyond the updated information. The *Handbook* has been reorganized to enhance its usefulness.

The previously used separate compatibility and incompatibility tables have been discarded in favor of consolidated tables with the information integrated to facilitate retrieval. One simply has to look in fewer places to find all of the information available. Comparisons among studies with differing results will be made more easily. Moreover, the new page size allows the use of larger type and fewer abbreviations, making the text and tables easier to read and use. The narrative information on stability and compatibility has been improved by the inclusion of subheadings to highlight specific topics or drugs so the reader will find the text much easier to scan.

While this edition of the *Handbook* contains much new material and many improvements, I maintain a continuing interest in identifying and implementing further improvements. The comments, criticisms, and suggestions of the users of the *Handbook* are always welcome.

Note of Appreciation

It would not be possible to prepare the *Handbook on Injectable Drugs* without the help of a number of individuals. I am indebted to David W. Newton, Associate Professor, Pharmaceutics, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE, for providing an excellent introduction to the *Handbook*. I would also like to express my gratitude to Robert W. McNair, Chief, Pharmacy Department, Suburban Hospital, Bethesda, MD, and Bona Benjamin, Pharmacy Department, Holy Cross Hospital, Silver Spring, MD, for their valuable assistance. Special thanks are due to Maarten Calon, VA Hospital, Baltimore, MD; Doug Rose, Fairfax Hospital, Fairfax, VA; Judy Roseman, Washington Hospital Center, Washington, DC; Andrea Walsh, Childrens Hospital, Washington, DC; and Pearl Walsh, University of Maryland Hospital, Baltimore, MD. These pharmacists provided advice and criticism to help plan the improvements for this edition of the *Handbook*. James Caro and Shelly Elliott of the American Society of Hospital Pharmacists also receive my appreciation for the contribution of their editorial and publishing skills.

Of course, my deepest thanks go to my wife Pam. Her preparation of an exceedingly difficult manuscript was superb. Her tolerance of my devotion to "the book" is astonishing. Both are truly appreciated.

LAT
March 1983

HOW TO USE THE HANDBOOK

Organization of the Handbook

The *Handbook on Injectable Drugs* has been organized as a collection of monographs on each of 217 commercially available drugs. In addition, information on 57 investigational drugs has been included. A section on the composition and characteristics of the commercially available intravenous infusion solutions is presented at the end of the book. The monographs on the commercial drugs are arranged alphabetically by nonproprietary name. The names of the drugs follow the style of *USAN and the USP Dictionary of Drug Names,* 1982 edition. Also included are some of the trade names and manufacturers of the drug products; this listing is not necessarily comprehensive and should not be considered an endorsement of any product or manufacturer.

All of the information included in the *Handbook* is referenced so that those who wish to study the original sources may find them. In addition, the *American Hospital Formulary Service* Classification System numbers have been included to facilitate the location of therapeutic information on the drugs.

The monographs have been divided into the following subheadings:

Concentration—lists many of the sizes, strengths, and volumes in which the drug is supplied, along with other components of the formulation. Any instructions for reconstitution are included in this section.

Stability—describes the stability of the drug and storage requirements if any. In addition, sorption characteristics of the drug are presented, if available.

pH—presents the pH of the drug.

Dosage—gives the recommended dosages and routes of administration of the drug, primarily from the official labeling and the *American Hospital Formulary Service.*

Compatibility Information—tabulates the results of published reports of compatibility testing of the subject drug with infusion solutions and other drugs.

Additional Compatibility Information—provides additional information and discussions of compatibility presented in narrative form.

Other Information—contains useful auxiliary information concerning the drug.

Organization of the Tables

The Compatibility Information tables present the various citations alphabetically by solution or drug name; the information is completely cross-referenced among the monographs. The data in these tables have been restricted to primary reference sources. General information of interest from sources such as the *American Hospital Formulary Service* and *Martindale: The Extra Pharmacopoeia* has been included in a narrative following the tables under the heading Additional Compatibility Information.

Three types of compatibility tables have been used, depending on the kind of test being reported. The first type is for information on the compatibility or incompatibility of a drug in various intravenous infusion solutions and is depicted in Table 1. The second type of table presents information on two or more drugs in intravenous solutions and is shown in Table 2. The third type of table is used for tests of two or more drugs in syringes and is shown in Table 3. A listing of the abbreviations used in these tables appears at the end of this introduction.

Many published articles, especially older ones, do not include all of the information necessary to complete the tables. However, the tables have been completed as fully as possible from the original articles.

The Listing of Concentration

The concentrations of all admixtures in intravenous solutions in the tables have been indicated in terms of concentration per liter to facilitate comparison of the various studies. In some cases, this may result in amounts of the drug that are greater or lesser than those normally administered (as when the recommended dose is tested in 100 ml of vehicle), but the listings do accurately reflect the actual concentrations tested, expressed in standardized terms.

For studies involving syringes, the amounts actually used are indicated. The volumes are also listed if indicated in the original article.

Designating Compatibility or Incompatibility

Each citation in the Compatibility Information tables has been designated as being a determination of compatibility (C) or incompatibility (I) according to specific guidelines. The citation is designated compatible when the results of the original article indicated one or more of the following criteria:

1. Physical compatibility (no visible sign of incompatibility).
2. Stability of the components for at least 24 hours in an admixture under the specified conditions (decomposition of 10% or less).
3. Stability of the components for the entire test period, although in some cases it was less than 24 hours (time periods less than 24 hours have been noted).

The citation is designated as incompatible when the results of the original article indicated one or more of the following criteria:

1. Physical incompatibility (haze, precipitate, color change, etc.).
2. Greater than 10% decomposition of one or more components in an admixture in 24 hours or less under the specified conditions (time periods less than 24 hours have been noted).

Although these criteria have become the conventional definitions of compatibility and incompatibility, the reader should recognize that the criteria may need to be tempered with professional judgment. Inflexible adherence to the compatibility designations should be avoided. Instead, they should be used as aids in the exercising of professional judgment.

Therapeutic incompatibilities or other drug interactions are not within the scope of the *Handbook* and have not been included.

Limitations of the Literature

The literature on drug–drug and drug–vehicle compatibility has many contradictions. With the exception of a study indicating physical compatibility and another indicating chemical decomposition of the same admixture, such conflicting information has been included. The conflicting information will be readily apparent to the

Table 1.

Solution Compatibility

Monograph drug name

Solution	*Mfr*	*Mfr*	*Conc/L*	*Remarks*	*Ref*	*C/I*
(1)	(2)	(3)	(4)	(5)	(6)	(7)

1. Solution in which the test was conducted.
2. Manufacturer of the solution.
3. Manufacturer of the drug about which the monograph is written.
4. Concentration of the drug about which the monograph is written.
5. Description of the results of the test.
6. Reference to the original source of the information.
7. Designation of the compatibility (C) or incompatibility (I) of the test result according to conventional guidelines.

Table 2.

Additive Compatibility

Monograph drug name

Drug	*Mfr*	*Conc/L*	*Mfr*	*Conc/L*	*Test Soln*	*Remarks*	*Ref*	*C/I*
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)

1. Test drug.
2. Manufacturer of the test drug.
3. Concentration of the test drug.
4. Manufacturer of the drug about which the monograph is written.
5. Concentration of the drug about which the monograph is written.
6. Infusion solution in which the test was conducted.
7. Description of the results of the test.
8. Reference to the original source of the information.
9. Designation of the compatibility (C) or incompatibility (I) of the test result according to conventional guidelines.

Table 3.

Drugs in Syringe Compatibility

Monograph drug name

Drug (in syringe)	*Mfr*	*Amt*	*Mfr*	*Amt*	*Remarks*	*Ref*	*C/I*
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)

1. Test drug.
2. Manufacturer of the test drug.
3. Actual amount of the test drug.
4. Manufacturer of the drug about which the monograph is written.
5. Actual amount of the drug about which the monograph is written.
6. Description of the results of the test.
7. Reference to the original source of the information.
8. Designation of the compatibility (C) or incompatibility (I) of the test result according to conventional guidelines.

reader because of the content of the Remarks as well as the C and I designations following each citation. Many factors influence the compatibility and stability of drugs, and absolute statements are often difficult or impossible to make. Differences in buffering systems, preservatives, vehicles, temperatures, concentrations, and order of mixing may all play a role. By reviewing a variety of reports, the practitioner is better able to exercise professional judgment with regard to the compatibility of the admixture. If only one reference is used, valuable alternatives may be overlooked or marginal compatibility conditions may not be recognized.

Further, it should be noted that many of the citations designated incompatible are not absolute. While a particular admixture may incur more than 10% decomposition within 24 hours, the combination may be useful for a lesser time period. The concept of "utility time" or the time to 10% decomposition may be useful in these cases. Unfortunately, such information is often not available. Included in the Remarks columns of the tables is the amount of decomposition, the time period involved, and the temperature at which the study was conducted when this information is available.

Another limitation is that much of the work done has evaluated only "physical" compatibility, perhaps better described as visual compatibility. While a finding of precipitation, haze, or other visually observable effect may be a definite incompatibility, the lack of such changes does not indicate nonvisual deterioration. In many cases,

drugs originally listed as compatible because of their lack of a visual change were later shown to undergo chemical decomposition. (As previously noted, such physical compatibility citations have not been included in the *Handbook*.) The reader must always bear this possibility in mind when physical compatibility is the only information available.

Solution Abbreviations

AA	Amino acids (percentage specified)
D	Dextrose solution (percentage unspecified)
D5LR	Dextrose 5% in Ringer's injection, lactated
D5R	Dextrose 5% in Ringer's injection
D-S	Dextrose–saline combinations
D2.5½S	Dextrose 2.5% in sodium chloride 0.45%
D2.5S	Dextrose 2.5% in sodium chloride 0.9%
D5¼S	Dextrose 5% in sodium chloride 0.225%
D5½S	Dextrose 5% in sodium chloride 0.45%
D5S	Dextrose 5% in sodium chloride 0.9%
D10S	Dextrose 10% in sodium chloride 0.9%
D5W	Dextrose 5% in water
D10W	Dextrose 10% in water
DXN-S	Dextran 6% in sodium chloride 0.9%
IDCM	Ionosol DCM
IG	Ionosol G
IM	Isolyte M
IP	Isolyte P
IS	Invert sugar
LR	Ringer's injection, lactated
NM	Normosol M
NR	Normosol R
NS	Sodium chloride 0.9%
PH	Protein hydrolysate
R	Ringer's injection
S	Saline solution (percentage unspecified)
SL	Sodium lactate 1/6 M
TPN	Total parenteral nutrition solution
W	Sterile water for injection

Manufacturer and Compendium Abbreviations

AB	Abbott
ACC	American Critical Care
AD	Adria
AH	Allen & Hanburys
AQ	American Quinine
AR	Armour
AS	Arnar-Stone
AST	Astra
AY	Ayerst
BA	Baxter
BE	Beecham
BN	Breon
BP	British Pharmacopoeia[a]
BPC	British Pharmaceutical Codex[a]
BR	Bristol
BV	Ben Venue
BW	Burroughs Wellcome
BY	Bayer
CI	Ciba
CN	Connaught
CO	Cole
CU	Cutter
DI	Dista
DM	Dome
EA	Eaton
EN	Endo
ES	Elkins-Sinn
FA	Farmitalia
FI	Fisons
GL	Glaxo
HO	Hoescht-Roussel
HR	Horner
IMS	IMS Ltd.
IN	Intra
IV	Ives
IX	Invenex
KA	Kabi
KN	Knoll
LE	Lederle
LI	Lilly
MA	Mallinckrodt
MB	May and Baker
MG	American McGaw
MJ	Mead Johnson
MN	McNeil
MRN	Merrill-National
MSD	Merck Sharp & Dohme
MY	Maney
NA	National
NCI	National Cancer Institute
NF	National Formulary[a]
NO	Nordic
OR	Organon
PD	Parke-Davis
PF	Pfizer
PH	Pharmacia
PO	Poulenc
PR	Pasadena Research
PX	Pharmax
RB	Robins
RC	Roche
RI	Riker
RP	Rhone-Poulenc
RR	Roerig
RS	Roussel
SC	Schering
SE	Searle
SKF	Smith Kline & French
SQ	Squibb
ST	Sterilab
SZ	Sandoz
TE	Teva
TR	Travenol
UP	Upjohn
USP	United States Pharmacopeia[a]
USV	USV Pharmaceuticals
VI	Vitarine
VT	Vitrum
WC	Warner-Chilcott
WI	Winthrop
WY	Wyeth

[a] *While reference to a compendium does not indicate the specific manufacturer of a product, it does help to indicate the formulation that was used in the test.*

INTRODUCTION

Physicochemical Determinants of Incompatibility and Instability of Drugs for Injection and Infusion

David W. Newton

In the spring of 1982, a hospital pharmacy resident asked me for literature on hyperalimentation therapy teams. I offered a notebook full of metabolic and clinical considerations of total parenteral nutrition (TPN). Having his own similar sources, he declined mine, resignedly specifying that he sought information on *implementing* the interprofessional management team *per se* but had been unsuccessful. Voila! The paucity of published resolutions to our diverse, locally unique, and politically disposed administrative challenges is commensurate with their difficulty, in contrast to an abundance of papers attesting to the inherently qualifiable or solvable nature of scientific and therapeutic problems. Likewise, dispensing medication orders and providing stability information from functional intravenous admixture services are less formidable tasks than implementing them.[1-3]

Pharmacists are acknowledged as being exclusively qualified to dispense and assure the quality of injectable drugs and intravenous admixtures.[4-6] The continually increasing quantity of possible injectable drug, infusion, and TPN solution combinations and the proliferation of intravenous admixture services[7,8] dictate that pharmacy courses on these subjects emphasize broadly applicable stability and compatibility precepts.[9] Fortunately, other accessible sources[10-26] in the pharmacy literature explain or exemplify physicochemical factors and phenomena whose consideration is antecedent to compounding and administering safe, efficacious injectable drugs and intravenous admixtures.

Incompatibility generally connotes preventable or reversible physicochemical phenomena that most commonly manifest as dilution-dependent precipitation and acid–base reactions, the products representing usually a change in physical state or protonation–deprotonation equilibria. Incompatibility problems often result in *visual* or *physical* evidence including precipitates, effervescence, color change, turbidity or haziness, viscosity change, and distinct immiscible liquid layers.

Instability refers primarily to retardable, but irreversible, incessant chemical reactions such as hydrolysis and oxidation. The distinctly different degradation products of unstable drugs can be both therapeutically inactive and otherwise toxic, and the reactions may or may not show visible evidence.

For practical purposes, the terms *instability* and *incompatibility* are synonymous.

I. Some Precautionary Guidelines

A. The prevention of incompatibility, the control of instability, and the assurance of sterility in injectable drugs and intravenous admixtures must not be undertaken at the expense of the health and safety of persons preparing them.[27,28]

B. The clinical effects of administering injectable (or other) drugs containing 100 ± 10% of labeled or nominal potency are rarely significant or even perceptible. The ±10% range represents the content requirement of many USP and NF monographs as well as the consensus shelflife or t_{90}, the time it takes for a drug concentration to decline to 90% of its original potency, i.e., its expiration date. Ironically, the variability in labeled concentrations caused by volume errors with syringes and needles and overfill of 10% or more in parenteral solutions may exceed that resulting from instability and incompatibility problems. Serendipitously, as much as 20% deviation from labeled concentrations will produce clinically insignificant effects in most cases.

C. When compounding an intravenous admixture, add one drug at a time to the infusion solution. Then mix it thoroughly and examine it visually for any evidence of incompatibility or instability before adding other drugs or dispensing it. This practice conserves time, materials, and money and provides rudimentary quality assurance.

D. Some incompatibility problems are concentration and time dependent. It is usually best to add the most concentrated injectable drug (on a moles per liter basis!) to an infusion solution first, mix it thoroughly to avoid concentration or pH layering,[8] and then add and mix the more dilute additives. Interionic and intermolecular collisions are less frequent and proximities are more distant in dilute solutions. For example, compare the results of mixing *(a)* 40 mg of tobramycin sulfate (per 1.0 ml) and 1000 units of heparin sodium (per 1.0 ml) and diluting to 100 ml with normal saline with *(b)* diluting the 1000 units of heparin in 100 ml of saline, mixing, and then adding the tobramycin.

E. Chemical analogs or congeners in families of drugs react similarly because common bonds and functional groups determine the mechanism but not necessarily the rate or kinetics of the reaction. Thus, when explicit compatibility information is unavailable for one drug, such information for its analog may be used to make a conservative estimate of stability.[29] Cephalosporins, penicillins, and tetracyclines are examples.

F. The intense yellow color of riboflavin in vitamin B complex injections can camouflage chemical degradation in similarly colored solutions (e.g., tetracyclines and amino acids) and fine, sparse precipitates (diazepam). When multiple drug additives including riboflavin injection are unavoidable, riboflavin should be mixed last in the intravenous admixture.

G. When compounding parenteral admixtures for which compatibility and stability data are unavailable, make two identical specimens. One is for the patient; the other is for observation and evaluation. As soon as any evidence of incompatibility or instability is detected after dispensing, the patient care unit should be instructed immediately to discontinue the intravenous admixture. Furthermore, the observations should be recorded for future reference. This practice is obviously limited to rare and new "stat" orders that cannot be studied comprehensively at the time of dispensing.

David W. Newton, Ph.D., R.Ph., is an Associate Professor, Department of Pharmaceutics, College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska 68105.

Dr. Newton is grateful to Mrs. Marilyn Kircher for her technical assistance.

II. Physicochemical Determinants

A. Chemical and Related Phenomena

1. Concentration Dependence. Increasing the initial concentration of most drugs causes an exponential increase in their decomposition rates, i.e., apparent or pseudo-first-order kinetics. Autocatalysis, pH-buffer effects, or both, as with ampicillin,[29] elicit the rate increases. Equations 1 and 2, respectively, are used to find the drug concentration, C, at time, t, and the elapsed time, t_{90}, when 90% of the labeled concentration remains in solutions of drugs subject to pseudo-first-order kinetics, where k and C_0 are the first-order rate constant and the initial concentration, respectively:

$$\log C = \log C_0 - kt/2.303 \quad (1)$$

$$t_{90} = 0.105/k \quad (2)$$

Drugs in the solid state, e.g., powders and suspensions, tend to decompose at a constant or concentration-independent zero-order rate that is comparatively slower than first-order kinetics.[13, 23, 25, 30] The zero-order equations analogous to Equations 1 and 2 are:

$$C = C_0 - kt \quad (3)$$

$$t_{90} = 0.1C_0/k \quad (4)$$

Elevated temperatures increase the dissolved fraction of drug that usually degrades according to first-order kinetics, thereby increasing the overall decomposition rate of suspended drugs. A few drugs in solution appear to undergo slower first-order degradation at higher concentration or zero-order instead of expected first-order stability kinetics. Examples include autoxidation of catecholamines and tetracaine[31] and the slower hydrolysis of 3% (w/v) versus 0.2% (w/v) nafcillin in admixtures with aminophylline.[32] Apparently, the greater buffer concentration in 3% than in 0.2% nafcillin solutions slows its hydrolysis.

Table 1. Selected Sources of Compatibility and Stability Information on Injectable Drugs

Books

Caplik JF and Walters JK, Jr: Guidelines for the preparation of intravenous solutions, Cutter Medical, Berkeley, California, 1980.

Durant WJ, Kenna FR, Hegarty J, et al.: Admixture study for fluids in Viaflex plastic containers, Travenol Laboratories, Deerfield, Illinois, 1974.

Florey K (ed): Analytical profiles of drug substances, Vols 1–10, Academic Press, New York, New York, 1972–1981.

King JC: Guide to parenteral admixtures, Cutter Laboratories, St. Louis, Missouri, 1978 (supplemented quarterly).

Michalski D and Cohon MS: Intravenous incompatibilities, Drug Information Center, Department of Pharmacy, University of Wisconsin Hospitals, Center for Health Sciences, Madison, Wisconsin, 1974.

Trissel LA: Handbook on injectable drugs, 3rd ed, American Society of Hospital Pharmacists, Bethesda, Maryland, 1983.

Physicians' desk reference, current ed, Medical Economics Company, Oradell, New Jersey.[a]

Serial Publications[b]

American Journal of Hospital Pharmacy
Journal of the Parenteral Drug Association
Drug Intelligence and Clinical Pharmacy
Hospital Formulary
Hospital Pharmacy (Lippincott's)
International Journal of Pharmaceutics
International Pharmaceutical Abstracts
Journal of Clinical Pharmacy
Journal of Pharmaceutical Sciences
Journal of Pharmacy and Pharmacology

[a] *Drug product monographs contain the FDA-approved official labeling.*
[b] *"To the editor" and correspondence sections in journals are useful sources.*

Table 2. Examples of Buffer Systems in Small Volume Injectable Drug Products

Injectable Drug Brand Name[a]	Buffer System	Milligrams of Buffer per Milligram of Drug Ingredient
Achromycin	Ascorbic acid	2.50
Aldomet	Citric acid	0.10
Flagyl	Citric acid	0.046
	Sodium phosphate[b]	0.095
Isuprel	Lactic acid	0.60
	Sodium lactate	9.00
Keflin	Sodium bicarbonate	0.034
Phenergan	Acetic acid	–[c]
	Sodium acetate	–[c]
Solu-Medrol[d]	Sodium biphosphate[e]	0.013
	Sodium phosphate[b]	0.139
Terramycin	Ascorbic acid	4.00
Valium	Benzoic acid	0.24
	Sodium benzoate	9.76
Vibramycin	Ascorbic acid	4.30
Yutopar	Acetic acid	0.078[f]
	Sodium acetate	0.49[f]

[a] *Baker CE, Jr (pub): Physicians' desk reference, 36th ed, Medical Economics Company, Oradell, New Jersey, 1982.*
[b] *Na_2HPO_4.*
[c] *Amount not listed.*
[d] *Mix-O-Vials, 125, 500, and 1000 mg.*
[e] *NaH_2PO_4.*
[f] *Values based on a stoichiometric reaction between acetic acid and sodium hydroxide in Yutopar injection.*

2. Solution pH. The degradation of many drugs is catalyzed by extremes of pH, i.e., hydronium and hydroxyl ion concentrations. Stability data for many drugs reveal that the pH range of 4 to 8 generally yields a minimum t_{90} of four to 24 hours for drugs in intravenous admixtures and reconstituted injectable drug solutions. Optimum pH conditions for specific drugs should be sought from a source in Table 1. Typical buffer systems used to stabilize selected injectable drugs are listed in Table 2.[33] Large volume parenteral (LVP) solutions are not buffered, and small volume injectable drugs have low buffer capacities to preclude perturbation of the life-sustaining homeostatic pH 7.4 of the blood–buffer system.

3. Acid–Base Reactivity.[13, 15, 33-41] The compatibility (solubility) of weakly dissociated or ionized (usually organic) electrolytes depends on their pK_a values and concentrations, the solution pH, ionic strength, dielectric constant or polarity, temperature, age, agitation, and mixing order. Weakly acidic and basic drugs and adjuvants are most soluble in aqueous solvents when they are essentially ionized, i.e., >99%. For example, the water solubilities of phenytoin and its sodium salt at 25 °C are approximately 20 μg/ml and 70 mg/ml, respectively, a difference of 3500-fold.[a]

The pK_a value of a drug is needed for use in the Henderson-Hasselbalch equations, 5–12. The pK_a values of many drugs can be obtained from a tabulation,[36] the ASHP "American Hospital Formulary Service" monographs, and "Analytical Profiles of Drug Substances" [Florey K (ed), Academic Press, through Vol. 10 in 1981]. The Henderson-Hasselbalch equations[b] for calculating the ratio and percentage of anionic (A^-) and neutral (HA) species of weak acids, predicting the pH at or below which precipitation of HA could occur,

[a] *Unpublished data from experiments by the author.*
[b] *Square brackets, [ ], denote concentration terms.*

pHp, and calculating the pH needed for a certain percentage of A^- are:

$$pH = pK_a + \log([A^-]/[HA]) \quad (5)$$

$$\% \text{ ionized} = 100/\{1 + 10^{(pK_a - pH)}\} \quad (6)$$

$$pHp = pK_a + \log(S - S_0/S_0) \quad (7)$$

where S is the concentration of acidic drug desired for injection and S_0 is the saturated water solubility of the acid (HA), and:

$$pH = pK_a - \log\{(100/\%A^-) - 1\} \quad (8)$$

Equations 5 to 8 are used for both undissociated acids and their salts. Analogous formulas for neutral or "free" bases (B) and their salts (HB^+) are:

$$pH = pK_a + \log([B]/[HB^+]) \quad (9)$$

$$\% \text{ ionized} = 100/\{1 + 10^{(pH - pK_a)}\} \quad (10)$$

$$pHp = pK_a + \log(S_0/S - S_0) \quad (11)$$

where pHp is the pH at or above which insolubility occurs, and:

$$pH = pK_a + \log\{(100/\%HB^+) - 1\} \quad (12)$$

Equations 5 to 12 apply only to solutions containing either a single acid and its salt or a base and its salt.

Both neutral bases, B, and anionic conjugate bases, A^-, from $A^-{}^+M$ salts (where M^+ is usually Na^+ or K^+) react as proton acceptors. Likewise, neutral acids, HA, and salts of bases or cationic conjugate acids, $HB^+{}^-X$ (where X^- is the anion of a mineral or an organic acid), react as proton donors. Neutral acids can precipitate when $A^-{}^+M$ salts are mixed in solutions with $pH < (pK_a + 2)$; neutral bases can precipitate, usually forming emulsions, when $HB^+{}^-X$ salts are mixed in solutions with $pH > (pK_a - 2)$. Precipitates (↓) as complex organic salts can result from the following combination of drug and adjuvant species:

$$HB^+{}^-X + A^-{}^+M \rightarrow (HB^+{}^-A)\downarrow + M^+ + X^- \quad (13)$$

The predominant influence of pH over the precipitation of phenytoin, HP, from intravenous admixtures of its sodium salt, $P^-{}^+Na$:[42-46]

$$P^-{}^+Na + H_3O^+ \text{ (from excess HA or } HB^+) \rightarrow HP\downarrow \quad (14)$$

and the precipitates composed of (aminoglycosides$^+{}^-$heparin) such as can occur in unflushed heparin locks per Equation 13 illustrate common acid–base reactions. Finally, carbonates and bicarbonates generate carbon dioxide gas in acidic solutions, e.g., $pH < 3$, such as tetracycline hydrochloride buffered with ascorbic acid ($pH \cong 2$):

$$HCO_3^- + H_3O^+ \rightarrow CO_2\uparrow + 2H_2O \quad (15)$$

4. Insoluble Salts. The precipitation of silver chloride from chloride-containing water used to prepare silver nitrate solutions for topical burn treatment is a well-known dispensing problem. Similar, but obviously more dangerous, precipitates of calcium phosphate and carbonate can occur in intravenous admixtures and nutrient solutions. The pK_a for proton dissociation from $H_2PO_4^-$ is 7.2; therefore, at pH 4.2 to 9.2, the fraction of HPO_4^{-2} varies from 0.1 to 99%[47] (Equation 6). It is in solutions of pH 4 and above that precipitates of $CaHPO_4$ can occur.[47] Calcium carbonate, chalk, can precipitate from mixtures of Ca^{+2} and bicarbonate (HCO_3^-) because a small fraction of HCO_3^- exists in equilibrium with H_3O^+ and CO_3^{-2}. Formation of such insoluble salts are largely dependent on mixing order, concentration, and pH.

5. Reduction–Oxidation, RedOx.[13, 17, 19, 20, 23, 25, 26] These reactions involve exchange of electrons and changes in the valence or oxidation state of reacting atoms. Oxidizing agents such as permanganate are reduced, and reducing agents are oxidized in a RedOx reaction. The latter process is exploited with antioxidants, including ascorbic acid, sodium bisulfite, and tocopherol, that are more labile to autoxidation than the drugs they stabilize.

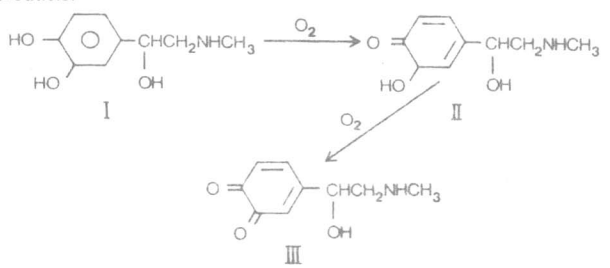
a. Oxidation occurs as electron loss, causing a positive increase in valence, as the addition of oxygen, and as the loss of hydrogen such as from phenolic hydroxy groups. *Autoxidation*, a spontaneous reaction under ambient conditions of substrates with atmospheric oxygen, is a common problem with phenol derivatives, particularly 3,4-dihydroxy phenyl compounds or catechols.[31,48] The oxidation products are usually pink, amber, brown, or black and are therapeutically inactive or otherwise toxic. In clinical dilutions, the virtually complete autoxidation of catecholamines can precede its visual detection.[31] Autoxidation is usually initiated and propagated by free radical formation, and it is catalyzed by ultraviolet light, alkaline pH (OH^- ion), heavy or "coinage" metal ions (Co^{+2}, Cu^{+2}, Fe^{+2}, Mn^{+2}, Ni^{+2}, and Zn^{+2}), and elevated temperature. The catecholamines are most stable at pH values below 5 where they are essentially nonionized, i.e., <0.1% anionic phenoxide species. Oxidation is retarded by using combinations of the following:[17, 19, 20, 23, 49]

(1) 0.01 to 0.1% of disodium EDTA and up to 1% of citrates or tartrates, divalent cation-sequestering agents.
(2) Antioxidants including sodium bisulfite ($NaHSO_3$) and metabisulfite ($Na_2S_2O_5$, where $S_2O_5^{-2} + H_2O \rightarrow 2HSO_3^-$), 0.1 to 1%, and ascorbic acid, 0.02 to 0.1%.
(3) Opaque wrappings (e.g., aluminum foil) and amber glass vials and ampuls. Because amber glass containers are tinted with iron oxide, drugs labile to iron-catalyzed autoxidation, e.g., catecholamines, cannot be autoclaved therein.
(4) Nitrogen or carbon dioxide gas atmospheres, the latter when compatible, in vials and ampuls to displace oxygen (air).

Some autoxidation products of epinephrine, typifying catecholamines, are illustrated in Figures 1 and 2.[19, 20, 50] Therapeutically rational, but chemically unstable, intravenous admixtures containing both catecholamines and aminophylline should be avoided.[31]

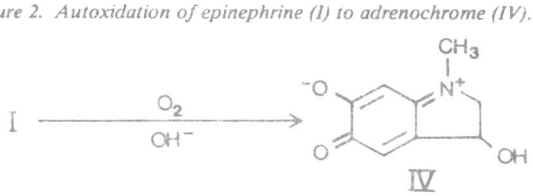
b. Reduction occurs as an electron gain, causing a reduction in valance, and as the addition of halogen and hydrogen atoms to C=C bonds. Reduction reactions of injectable drugs are rare. The β-lactam antibiotics (cephalosporins and penicillins) hydrolyze, producing reducing aldehydes; hexoses such as dextrose are also reducing agents. Another clinically important reduction reaction is the displacement of platinum (II) from cisplatin by aluminum from needles, resulting in the precipitation of platinum (0) black.[22] The problem has not been observed with stainless steel needles in contact with cisplatin solutions for

Figure 1. Autoxidation of epinephrine (I) to semiquinone (II) and quinone (III) products.



I II III

Figure 2. Autoxidation of epinephrine (I) to adrenochrome (IV).



IV

up to 24 hours.[22] This and other metal-metal displacement reactions follow the electromotive series in which elemental metals with high oxidation potentials can reduce the oxidized species (valence > 0) of those with lower oxidation potentials.

6. Photodegradation.[13, 17, 20, 22, 25, 51] The oxidation and hydrolysis of drugs can be catalyzed by light. According to Planck's theory, the energy per photon of light increases as its wavelength decreases.[52, 53] Therefore, ultraviolet light is more deleterious than visible light to photolabile drugs. As with autoxidation, photodegradation is mediated by free radicals, usually forming dark colored products. Low actinic amber glass, cardboard overwraps, and thick aluminum foil wrappings effectively preclude light from degrading injectable drugs. Following is an illustrative list of photolabile injectable drugs: amphotericin B, sodium nitroprusside, nifedipine, nitroglycerin, corticosteroids (dexamethasone), phenol derivatives (morphine and phenylephrine), catecholamines (α,β-adrenergic agents), benzodiazepines (chlordiazepoxide, diazepam, and lorazepam), sulfonamides (sulfisoxazole diolamine), aminoglycosides (kanamycin), tetracyclines (doxycycline), phytonadione, phenothiazines (chlorpromazine, prochlorperazine, and promethazine), and amino acids (tryptophan) in TPN solutions. It is important to realize that photodegradation reactions are dependent on the intensity as well as the wavelength of light.[53] The closer to fluorescent ceiling fixtures that the uncovered intravenous admixtures are suspended, the faster will be the decomposition of photolabile drugs.

A summary of information on wavelength ranges radiated from different sources of illumination follows:[52-54]

Visible Range—Wavelengths from 380 to 780 nm.

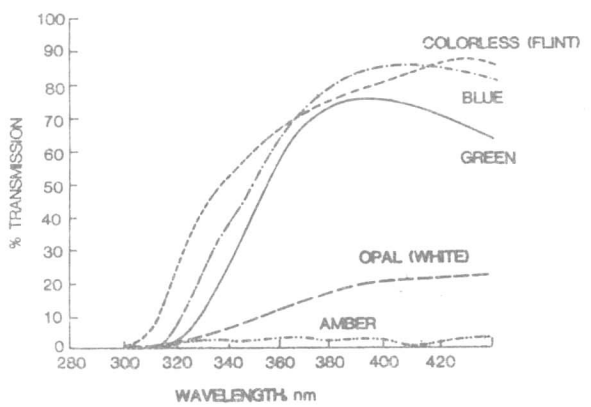
UV Range—Wavelengths from 185 to 380 nm, comprising less than 1% of ambient sunlight reaching the earth.

Sunlight—That reaching earth is composed of the visible range and the 290–380-nm ultraviolet range. The high energy band of 290–320 nm that catalyzes much photodegradation of drugs and causes sunburn comprises approximately 0.2% of sunlight.

Fluorescent Light—These bulbs emit visible and potentially deleterious 320–380-nm ultraviolet radiation.

Incandescent Light—Tungsten filament or common light bulbs radiate visible wavelengths longer than 390 nm. Figure 3[c] illustrates the percentage of light transmitted by various glasses. Clear, colorless (flint) glass prevents transmission of >80% of radiation in the 280-320-nm range, and amber glass transmits <5% of wavelengths 500 nm and shorter. By qualitative comparison, colorless clear and amber plastics transmit about twice as much light as the corresponding glasses at the same wavelengths according to similar spectra.[d]

Figure 3. Percentage of light transmitted through 2.0-mm thicknesses of pharmaceutical glasses over the wavelength range of 300 to 440 nm.



7. Epimerization or Racemization.[13, 17, 19, 20, 25] These terms identify a phenomenon whereby a substituent chemical group undergoes steric rearrangement, producing an epimer with certain properties distinctly different from the parent drug. The epimerization of the —H and $—N(CH_3)_2$ groups at the 4-position of tetracyclines occurs in solutions of pH 4 to 8 within 24 hours but requires longer (≅48 hours) at pH 2 to 3.[55-57] The epitetracyclines are intensely dark and therapeutically inactive; they stain glass and other materials and cause Fanconi's syndrome. The epimerization from the *l* to the *d*-form of epinephrine, a slow insidious process decreasing pharmacologic potency, is another example of this clinically important, yet subtle, chemical change.[19, 25, 58]

8. Temperature.[13, 17-20, 22-25] Temperature elevation increases reaction rates both in vitro and in vivo. An empirical rule is that each 10 °C increase causes a two- to fivefold rate increase. For most drugs, a plot of the logarithm of the reaction rate constant, $\log k$, versus reciprocal absolute temperature, $1/T$, yields a linear Arrhenius relationship, which can be used to estimate a t_{90} at the storage temperature of the injectable drug.[23] A reduction at 5 °C to 10 to 25% of the hydrolysis rates of β-lactam antibiotics at 25 °C illustrates the important effect of temperature on drug stability. Prolonged thawing at ambient or higher temperatures of some frozen antibiotic and other drug solutions can obviously accelerate their hydrolysis. In such cases, the use of a microwave oven for thawing is a valuable asset.[59]

An apparent exception to hydrolysis catalyzed by temperature is that of ampicillin, and possibly other antibiotics, frozen at −20 °C in normal saline and dextrose.[59] This effect was not evident when ampicillin solutions were frozen at −70 °C.[59] The essentially equal degradation rate at −20 °C as that at 27 °C in 5% dextrose injection could be attributed to *(a)* a progressive increase in ampicillin concentration concurrent with the decreasing volume of liquid solution as freezing occurs, i.e., enhanced first-order kinetics; *(b)* coexistence of a small volume of highly concentrated ampicillin solution centrally located within the frozen mass; and *(c)* specific dextrose catalysis[59] involving *(a)* or *(b)*.

9. Maillard Reaction.[60-62] The Maillard or "browning" reaction is the reason why pharmaceutical manufacturers do not market premixed solutions containing both amino acids or protein hydrolysates and dextrose for TPN therapy. This reaction occurs slowly under ambient conditions but rapidly during autoclaving, eliciting diverse products from the condensation of primary amino groups ($—NH_2$) of amino acids and peptides with the aldehyde carbonyl group (—HC=O) of aldoses such as dextrose. The solutions darken initially, followed by a loss of transparency because of color intensification and polymeric precipitates. A general scheme illustrating the formation of glycosylamines via the Maillard reaction and the subsequent Amadori rearrangement to ketosamines in acidic solutions is shown in Figure 4.[61]

10. Hydrolysis.[13, 17, 20, 23, 25] This reaction involves (usually nucleophilic) attack of labile bonds in dissolved drug molecules by water, whereupon both water and the drug undergo fission. When the attack is by solvents other than water, the reaction is called solvolysis. Hydrolysis is the preponderant cause of instability of drugs in general and injectable drugs in particular. Functional groups labile to hydrolysis in general decreasing order include lactams, esters, amides, and imines. Abundant studies verify that hydrolysis reactions follow apparent first-order kinetics, with few drugs excepted. Catalysts of hydrolytic degradation include OH^- and other anionic bases (citrates and phosphates), H_3O^+ (acids), the heavy metal divalent cations, heat, ultraviolet and visible light, solution dielectric constant and ionic strength, increased initial

[c] *From Electrical Testing Laboratories, New York, New York (date prior to 1963).*

[d] *Personal communications from Frank R. Bacon, Owens-Illinois Glass Container Division, Toledo, Ohio, June 30 and September 30, 1978.*

drug concentrations, and enzymes (e.g., β-lactamases from *Staphylococcus aureus*). Products from hydrolysis are more polar, often more water soluble, and usually visually indistinguishable from the parent drugs. Prodrugs such as clindamycin phosphate hydrolyze, producing the active moiety, whereas intact efficacious drugs such as cephalosporins and penicillins hydrolyze to therapeutically inactive, sensitizing haptens.

Trissel[12] collated abundant data from hydrolysis studies by which pharmacists can estimate and assure the stability of labile drugs to within clinically tolerable accuracy. Figures 5 to 12 illustrate various possible hydrolysis products of esters, amides, lactams, and imines. The —OH group from water always bonds with the carbon or phosphorus atom that is double bonded with oxygen in the labile drug bond of esters, amides, and lactams.

a. Esters have the functional group RCOOR′, where R is aliphatic or aromatic and R′ is usually aliphatic organic (e.g., succinyl) or inorganic. Simple hydrolysis of organic esters yields an alcohol, R′OH, and a carboxylic acid, RCOOH, or its conjugate base, $RCOO^-$, depending on its pK_a and the solution pH. Likewise, hydrolysis of inorganic esters also produces an alcohol but a mineral acid or its anion instead of the carboxylic acid. The ester hydrolyses of clindamycin-2-phosphate (inorganic),[48] methyldopate, and chloramphenicol sodium succinate are depicted in Figures 5 to 7, respectively.

b. Amides are more stable against hydrolytic attack than their corresponding esters. For example, compare the stabilities of lidocaine (amide) and procaine (ester). The amido group is RCONR′R″, where R is that for esters, and R′,R″ are hydrogen atoms or organic substituents. Amide hydrolysis products are carboxylic acids (see *Esters* above) and amines, R′NHR″ or $R'NH_2R''$, as shown for chloramphenicol in Figure 8.[54]

Figure 4. Schematic illustration of the Maillard reaction (M) of primary amino acids (R′-NH_2) and aldehyde carbonyl groups of sugars. The glycosylamine product can undergo Amadori rearrangement (A), forming a ketosamine.

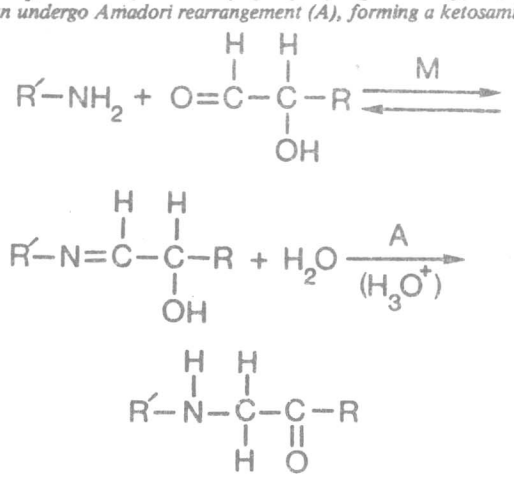
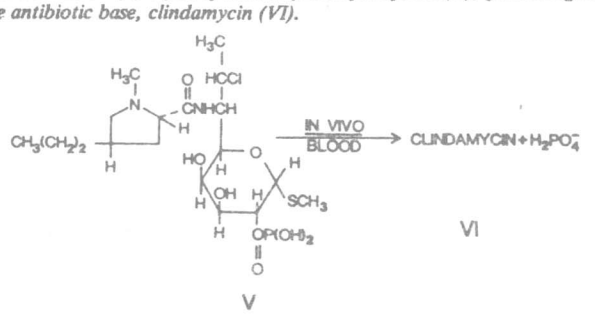


Figure 5. Ester hydrolysis of clindamycin-2-phosphate (V), generating the active antibiotic base, clindamycin (VI).



c. Lactams or cyclic amides are often more readily hydrolyzed than their acyclic analogs. This functional group is recognized as the C=O at 7- and 8-positions of penicillins and cephalosporins (β-lactam antibiotics), respectively, and as the 2-position C=O of 1,4-benzodiazepines. Hydrolysis products from lactams in penicillins,[61, 62] cephalothin,[67, 68] and diazepam[69-72] and of the similar cyclic diureides or barbiturates[73, 74] are shown in Figures 9 to 12. The generation of carbon dioxide gas, CO_2, from hydrolyzed penicillins (Figure 9) warrants caution when venting older, but not necessarily expired, vials of powders for injection and degraded solutions. The resulting increased pressure jeopardizes personnel to sensitization via inhalation of, and dermal contact with, droplets and powders.

d. Imines,[72, 75] azomethines, or Schiff bases are compounds with C=N bonds. They have the typical formula RR′—C=N—R″, where R,R′ and R″ are organic substituents or hydrogen atoms. Cyclic imines, such as 1,4-benzodiazepines, result when R—R″ or R′—R″ bonds occur within the molecule. When R″ is aromatic, the imine is a Schiff base, which is more resistant to hydrolysis than when R″ is hydrogen or aliphatic organic. Depending on R,R′, the products of imino group hydrolysis are aldehydes, ketones, and amino derivatives; the latter depend on R″. Equation 16 is a general scheme for imine hydrolysis, and Figure 11 shows the hydrolysis of the 4,5-azomethine bond in diazepam that is common to 1,4-benzodiazepines:[69-72, 75]

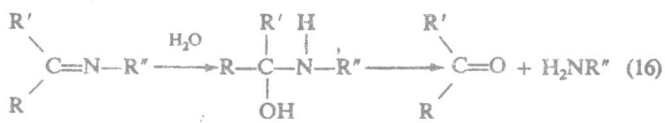


Figure 6. Ester hydrolysis of methyldopate hydrochloride (VII), generating the active antihypertensive agent, methyldopa (VIII), and a molecule of ethanol (IX).

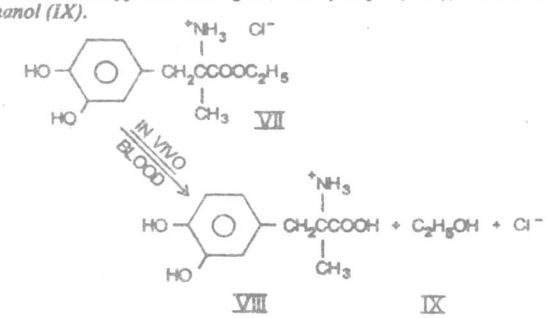


Figure 7. Ester hydrolysis of chloramphenicol sodium succinate (X), generating the active antibiotic, chloramphenicol (XI), and monosodium succinate (XII).

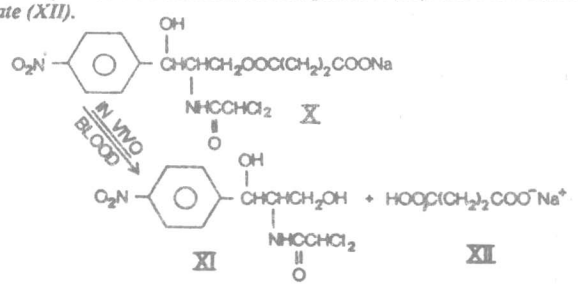


Figure 8. Amide hydrolysis of chloramphenicol (XI), generating 1-(p-nitrophenyl)-2-amino-1,3-propanediol (XIII) and dichloroacetic acid (XIV).

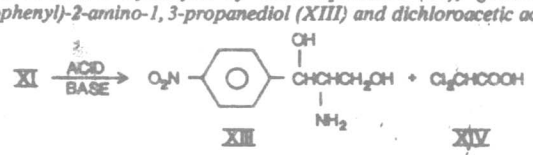


Figure 9. General hydrolysis scheme for penicillins (XVI), generating penicilloic acid (XVII), penilloic acid (XVIII), penicillamine (XIX), penaldic acid (XX), penillaldehyde (XXI), penillic acid (XXII), and carbon dioxide products.

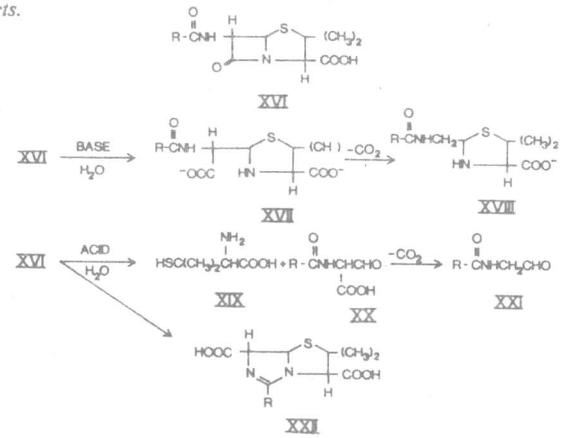
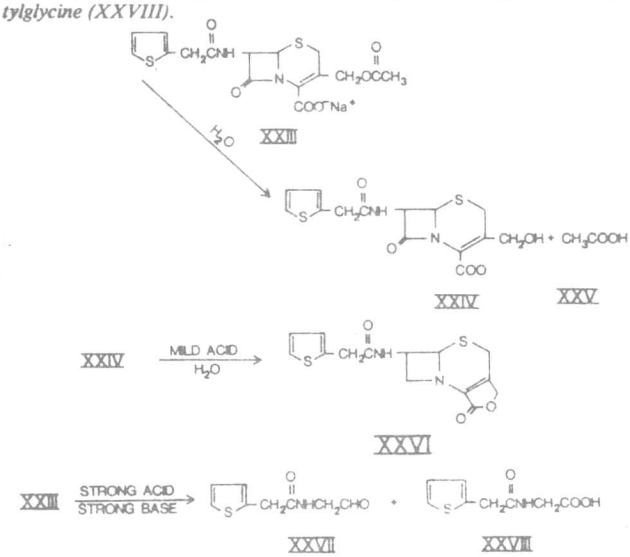


Figure 10. Hydrolysis scheme for cephalothin sodium (XXIII), generating deacetylcephalothin (XXIV) and acetic acid or acetate (XXV), cephalothin lactone (XXVI), thienyl acetamidoacetaldehyde (XXVII), and thienylacetylglycine (XXVIII).



B. Physical Phenomena

The determinants of injectable drug incompatibility outlined under this category primarily involve the physical state and solution–container (or administration set) equilibria of drug molecules instead of chemical changes thereto.

1. Solvent System Polarity. Drugs are prepared in alcoholic and hydroalcoholic solvent systems to increase solubility and retard hydrolysis (Table 3).[e] The dielectric constant, ϵ, is the optimum empirical parameter for assessing the polarity of hydroalcoholic solvents for semipolar[f] injectable drugs.[76] For drugs including the barbiturates and 1,4-benzodiazepines, a plot of log (solubility) versus ϵ or cosolvent concentration describes part or approximates all of the ϵ range as a straight line.[70, 76-79] Unique solvent effects of different cosolvents are evidenced by the fact that different hydroalcoholic mixtures of equal ϵ yield unequal phenobarbital solubility.[76, 79] The ϵ values at 20 to 25 °C of some injectable drug cosolvents and adjuvants are alcohol, USP, 27; benzyl alcohol, 13; ethanol, 24; glycerin, 42; polyethylene glycol 200 to 400, 35;[g] and propylene glycol, 32. The ϵ values of aqueous LVP solutions range from 75 to 79, i.e., essentially the value of water, 79. The foregoing values can be used to approximate dielectric constants from Equation 17,[76, 80] and, therefrom, drug solubility or compatibility in dilutions of hydroalcoholic injections in aqueous fluids can be estimated from the dilution factor:[77]

$$\epsilon_{\text{dilution}} = \Sigma\,(\epsilon \text{ of each solvent})(\text{volume fraction of each solvent}) \quad (17)$$

For example, the ϵ of alcohol, USP = (24)(0.95) + (79)(0.05) = 27.

When hydroalcoholic drug injections are diluted in aqueous fluids, an exponential *decrease* in solubility should be anticipated.[77, 81] When 1 volume of such injections is diluted with 10 or more volumes of aqueous solution, the resulting dielectric constant is 75 or greater, thereby more closely resembling water in solvent properties.[44, 81] To illustrate, the solubility of diazepam in aqueous LVP solutions and

Figure 11. Acid-catalyzed 1,2-lactam and 4,5-azomethine hydrolysis of diazepam (XXIX), generating 2-methylamino-5-chlorobenzophenone (XXX) and glycine or glycinium ion (XXXI).

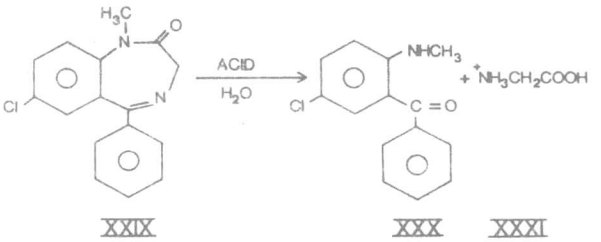
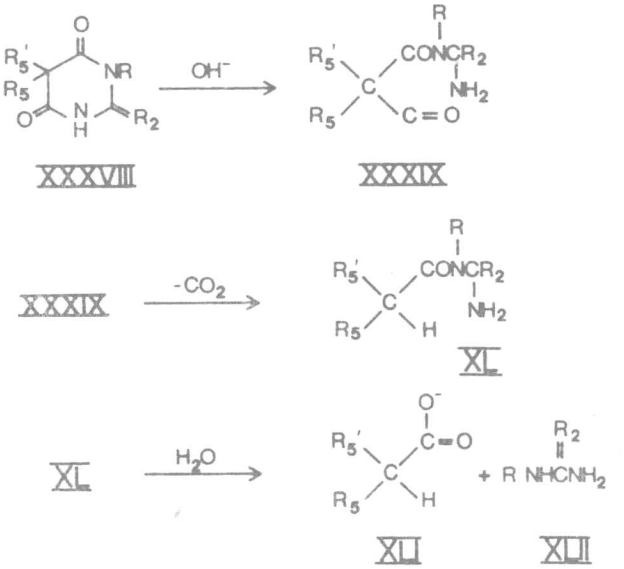


Figure 12. General scheme for hydrolysis of barbiturates (XXXVIII) in alkaline solution, generating carbon dioxide, and malonic acid (XXXIX), acetylurea (XL, $R_2 = O$) or thiourea (XL, $R_2 = S$), and acetic acid (XLI) derivatives, and urea (XLII, $R_2 = O$) or thiourea (XLII, $R_2 = S$) products.



[e] *Besides containing less water than aqueous vehicles, hydroalcoholic solvent systems have a lower effective concentration of "free" water because of alcohol–water intermolecular hydrogen bonding.*

[f] *The neutral (nonsalt) forms of drugs such as 1,4-benzodiazepines and phenytoin have low water solubility because of hydrophobic substituents, e.g., phenyl and chloro. They have higher alcohol solubility because of strong dipolar groups, e.g., keto oxygen atoms, that elicit dipole–dipole intermolecular attraction. The lower dielectric constants of hydroalcoholic solvents also favor the occurrence of dipole-induced dipole and London dispersion solvent–solute intermolecular forces.*

[g] *Estimate based on value of 37 for ethylene glycol.*

Table 3. Examples of Injectable Drugs Prepared in Alcoholic and Hydroalcoholic Solvents

Generic Name	Cosolvent, % v/v[a]			
	Alcohol, USP	Benzyl Alcohol	Polyethylene Glycol	Propylene Glycol
Diazepam	10.5[b]	1.5	–	40
Digoxin	10	–	–[c]	40
Dimenhydrinate	–	5	–	50
Lorazepam	–	2	18[d]	80
Nitroglycerin	30[e], 50[e,f]	–	–	30[e], 50[f]
Pentobarbital sodium	10	–	–	40
Phenytoin sodium	10	–	–	40
Secobarbital sodium	–	–	50[g]	–
Trimethoprim and sulfamethoxazole	10.5[b]	1	–	40

[a] *The remaining volume of the vehicles, if any, is composed primarily of sterile water for injection.*
[b] *Labeled as a 10% content of ethanol in Bactrim, Septra; Valium.*
[c] *As the 400 molecular weight polymer.*
[d] *Tridil brand by American Critical Care.*
[e] *Labeled as 50% dehydrated alcohol.*
[f] *Glyceryl trinitrate injection by Abbott Laboratories.*
[g] *Polymer molecular weight 200 to 400.*

water with $\epsilon > 75$ is 0.04–0.06 mg/ml.[81, 82] Thus, a 1:10 or further dilution of diazepam injection, 5 mg/ml, can result in a 99% decrease in solubility. Dilutions of a few hydroalcoholic injectable drugs even in the 1 to 2 ml of fluid in 10 to 20 cm of tubing distal to injection Y-sites can produce precipitation.[83] However, acid–base reactions, as with phenytoin sodium, rather than dielectric constant effects seem to be the primary reason for this result.

2. Sorption. Sorption describes the loss of drugs from solutions into semipermeable plastic and rubber matrixes. The lipophilicity of the solute, the polarity, ϵ, of the solvent, and the nature of the plastic seem to be the predominant factors controlling sorption. Flexible polyvinyl chloride (PVC) containing up to 40% of dioctyl phthalate,[b, 84] a nonviscous, slightly volatile liquid plasticizer, has unequivocally shown the highest affinity for sorption of all parenteral component polymers.[82, 85–89] These collective data suggest that the plasticizer serves as a solvent for the drugs that diffuse into the flexible PVC matrix. The rate of sorptive loss increases as the ratio of bag surface area to solution volume increases; the latter occurs as the bag is emptied.[82, 89] The lipophilicity of weak electrolyte drugs increases as the ratio of nonionized to ionized species increases. Nonelectrolytes such as nitroglycerin are inherently lipophilic.[89] As Figure 13 illustrates, sorption of neutral dipolar ions, $^{+}I^{-}$, unprotonated bases, B, and undissociated acids, HA, causes a net loss of drug from solution, although the ratio of the species in intravenous admixtures is fixed by the solution pH and drug pK_a, i.e., Equations 5 and 9. As typified by tetracyclines, the dipolar ions of ampholytes are more lipophilic, i.e., have higher partition coefficients, than their predominantly cationic, $^{+}I^{0}$, and anionic, $^{0}I^{-}$, conjugates.[90] Finally, data from studies of sorbic acid,[91] diazepam,[82, 88, 89] and lorazepam[92] imply that as the solution dielectric constant decreases, its polarity tends to become optimum for the drugs and sorption declines. If precipitation or turbidity occurs immediately after compounding an intravenous admixture in a flexible PVC bag and then disappears within an hour or two, sorption is the likely reason.

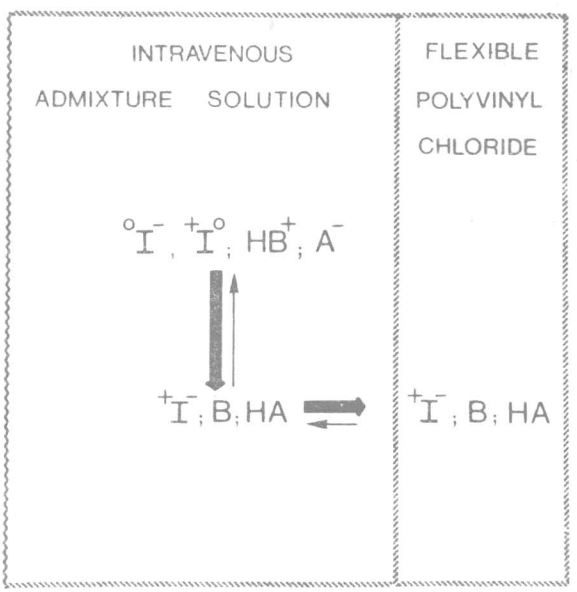
3. Solvent Loss. Evaporation of water and volatile alcohols subsequent to permeation of plastic polymers in syringes and infusion solution bags causes increasing drug concentrations in otherwise stable, compatible solutions. In the case of aqueous fluids in flexible PVC bags, up to 15% weight loss as water occurred over 84 days at 25 °C and 2% loss resulted at 4 to 8 °C.[93] The extent of water loss decreases with increasing fill volume to plastic surface area ratios, as would be expected for a diffusion-controlled phenomenon.[93]

4. Adsorption. The loss of drug molecules and ions from solution via adhesion to solid surfaces is adsorption. London dispersion and other electrostatic or van der Waals intermolecular forces are the mechanism of adsorption. Most adsorption studies on drugs from aqueous solutions featured insulin, which adsorbs under various conditions to plastic[94, 95] and glass[96] intravenous infusion components. Perusal of the literature[94–96] will permit estimates to within approximately 20% of the dose that can be delivered from most insulin intravenous admixtures.

5. Complexation. Tetracyclines can form insoluble chelates with ions including Al^{+3}, Ca^{+2}, Fe^{+2}, and Mg^{+2}, depending on concentrations and solution pH.[56] Sequestering agents such as disodium EDTA and citrates can potentially impair the efficacy of intravenous calcium and trace minerals.[97] Hydrogen-bonded complexes of hydroxy compounds (phenol derivatives, alcohols, and polyols) and starch derivatives and nonionic surfactants, as well as drug–albumin binding, represent potential physical compatibility problems. Antibacterial preservatives apparently form poorly soluble complexes with erythromycin gluceptate and amphotericin B, which is one reason why these antibiotics should be dissolved in nonbacteriostatic sterile water for injection.[11, 21, 22]

6. Salting Out.[98–101] This term refers to the decreased solubility of nonelectrolytes and weakly hydrated organic ions in the presence of strong electrolytes, e.g., NaCl, KCl, and $CaCl_2$, and highly hydrated organic ions, e.g., $citrate^{-2}$. Nonionized organic drugs such as diazepam are salted out as solid precipitates, but salts of bases may separate as water-immiscible, viscous, dense liquids consisting of undissociated, solvated ion pairs.[101] The ability of anions and cations to cause salting out follows the lyotropic or Hofmeister series.[98–100] This phenomenon is related to salt and drug concentrations, temperature, and pH. It has been observed in intravenous admixtures of chlor-

Figure 13. Schematic illustration showing solution equilibria between ionized and neutral drug species and the sorption (heavy arrows) of neutral drug species by flexible PVC plastic.



[b] *Bis (2-ethylhexyl) phthalate or DOP.*

promazine hydrochloride in normal saline and Ringer's injections[102] and in concentrated solutions of erythromycin gluceptates in electrolyte solutions.[21, 22] Ampholytes are least soluble at the pH of their isoelectric points, IEP, where they are neutral dipolar ions, $^{+}I^{-}$. The IEP values of ampicillin, human serum albumin, insulin, and lorazepam are 4.9, 4.7, 5.7, and 6.4, respectively. Albumin can precipitate from hyperalimentation or TPN solutions, impairing flow through inline filters.

7. Salting In. This term refers to the increased solubility of one solute in the presence of another. Although amino acids enhance the solubility of some organic drugs, the requirement of chloride ion to prevent cisplatin precipitation is an interesting clinical example of salting in.[103]

8. Dissolution Rate and Surfactant Effects. Antibiotics and other proteinaceous injectable drug powders can form translucent, adhesive masses that are hydrated, but incompletely dissolved, when initially reconstituted with aqueous solutions. The problem can be exacerbated by vigorously agitating the containers; such agitation causes foaming, further impairing visual confirmation of complete dissolution. Considering the mechanism of action and pharmacokinetics of most of these types of drugs, spending a few more minutes to assure their complete solution with minimal foam is unlikely to compromise patient prognoses. Moreover, the injection of potentially emboli-inducing particles and underdosing caused by drug adherence to ampuls, vials, needles, and syringes will be avoided.

9. Polymorphism.[3] Changes from the soluble metastable to the less soluble stable polymorphic crystalline forms of some drugs can cause precipitate development in injectable solutions. This problem is most likely to occur when solutions such as antibiotics are stored frozen at −20 °C and colder for long durations. If the crystals do not completely dissolve upon thawing, agitation, and gentle warming, polymorphic transformation can be the reason. Precipitation elicited by polymorphic changes should not be confused with that caused by decreased temperature; the latter reversibly decreases the solubility of endothermic solutes.

III. Conclusion

To avoid local irritation and transient excessive blood concentrations that can seriously impair neuromuscular, central nervous system, cardiovascular, and respiratory functions, most commercial injectable drugs are further diluted prior to intravenous administration, e.g., as piggybacks.[104] Diluting and combining injectable drugs in parenteral fluids in clinical practice render pharmacists responsible for the stability, compatibility, safety, and effectiveness of these medication orders. There are three professional bases upon which pharmacists can recognize, predict, control, and avoid physicochemical phenomena adversely affecting injectable drugs: (1) judgment gleaned from personal experience, (2) practical comprehension of physicochemical determinants of drug incompatibility and instability, and (3) reference to the pertinent literature (Table 1).

For persons to whom "a picture is worth a thousand words," Table 4 illustrates several physicochemical incompatibility and instability problems that are convincingly visibly evident. Example 7 also reinforces the author's "iceberg rule":[34, 49, 105] The fact that most or all of the evidence of instability is not visible neither proves the problem to be nonexistent nor *per se* qualifies the injectable drug as safe and efficacious.

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Table 4. Examples of Visually Evident Incompatibility and Instability Problems with Drugs in Intravenous Admixtures

Example	Admixture Preparation	Phenomenon Demonstrated	Result Expected	Approximate Developing Time, hr
1a	Dilute 4 ml of diazepam injection (5 mg/ml) in 25 ml of normal saline in a glass bottle	Low aqueous solubility of diazepam[81,82]	Yellow precipitate[a]	0.25
1b	As in 1a using a flexible PVC bag	Sorption of diazepam by flexible PVC[82,89]	Solution[a]	0.25
2a	Dilute 1 ml of phenytoin sodium injection (50 mg/ml) to 10 ml with 5% dextrose (D5W)	Precipitation of nonionized phenytoin from acidic D5W[42-46,b]	Needle-like crystals	1.0
2b	As in 2a with normal saline (NS)	Solubility of phenytoin anion in less acidic NS	Solution	1.0
3	Combine 1 ml of heparin sodium (10 units/ml) and 2 ml of tobramycin sulfate (40 mg/ml)	Insoluble salt of anionic heparin and cationic tobramycin	Fine white precipitate or turbidity	0
4	Combine 20 ml of sodium bicarbonate (1 mEq/ml) and 10 ml of calcium gluconate or chloride (10% w/v) in 50 ml of D5W or NS	Low solubility of calcium carbonate	White precipitate and turbidity	0
5a	Dissolve 50 mg of sodium nitroprusside in 250 ml of D5W. Store 50 ml in an amber glass bottle about 1 m from an illuminated fluorescent light	Prevention of photodegradation by amber glass that does not transmit ultraviolet light	Colorless solution	12 to 96
5b	Store 50 ml of the solution from 5a in a clear, colorless glass bottle	Photodegradation caused by ultraviolet light[105]	Pale brown solution	12 to 96
6	Combine 1 ml of 1:1000 epinephrine and 5 ml of aminophylline (25 mg/ml) in 250 ml of D5W. Store under ambient conditions	Autoxidation of phenolic hydroxy groups to quinones and other products[31,48]	Pink to brown tinted solution	8 to 24
7a	Dilute 125 mg of ampicillin sodium to 100 ml in D5W; store at room temperature for 24 hr. To 10 ml of this, add 4 ml of 0.02 *N* iodine and store in the dark at room temperature for 30 min; then add two drops of starch indicator solution	Invisible hydrolysis of ampicillin to aldehydes that reduce iodine (I_2) to iodide (I^-)[28,107,108]	Pale amber color when iodine is added; no color change when starch is added	25[c]
7b	As in 7a but using freshly prepared ampicillin solution	Invisible difference between hydrolyzed and intact ampicillin solutions	Dark amber color when iodine is added; blue-black or purple color when starch is added	0.5[c]
8a	Add 1 ml of hydralazine HCl (20 mg/ml) to 50 to 100 ml of D5W	Reaction of hydrazine group of hydralazine with aldehyde C=O group of dextrose[109,110]	Solution turns progressively yellow	0.1 to 2
8b	As in 8a but using NS instead of D5W	No reaction or incompatibility	Colorless solution	0.1 to 2
9a	Dilute 250 mg of tetracycline HCl for injection to 250 ml in D5W; store under fluorescent light at room temperature	Stabilizing effect of pH 2 to 3 from ascorbic acid buffer on tetracycline epimerization	Yellow solution Amber solution Dark amber solution with scanty dark precipitate	24 to 50 50 to 80 80 to 120
9b	As in 9a but also adding 10 ml of aminophylline (25 mg/ml)	Catalysis of tetracycline epimerization by pH > 4	Amber solution Dark amber solution with scanty dark precipitate Dark amber solution with more dark precipitate	24 to 50 50 to 80 80 to 120
10a	Dilute 5 ml of lorazepam injection (4 mg/ml) to 50 ml in D5W in a clear, colorless glass container	Higher solubility of lorazepam in D5W	Colorless solution	0.1 to 6
10b	As in 10a but using NS instead of D5W	Lower solubility of lorazepam near its IEP in NS[111]	Cloudy solution[d]	0.1 to 6

[a] *Samples of each admixture should be examined in clear glass containers at 15 minutes after their preparation.*
[b] *The pK_a of phenytoin, a weak acid, is about 8.3.*
[c] *Extensive ampicillin hydrolysis in D5W requires 24 hours, but the starch–iodine reaction is instantaneous.*
[d] *Fine crystals may develop during storage for several days.*

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