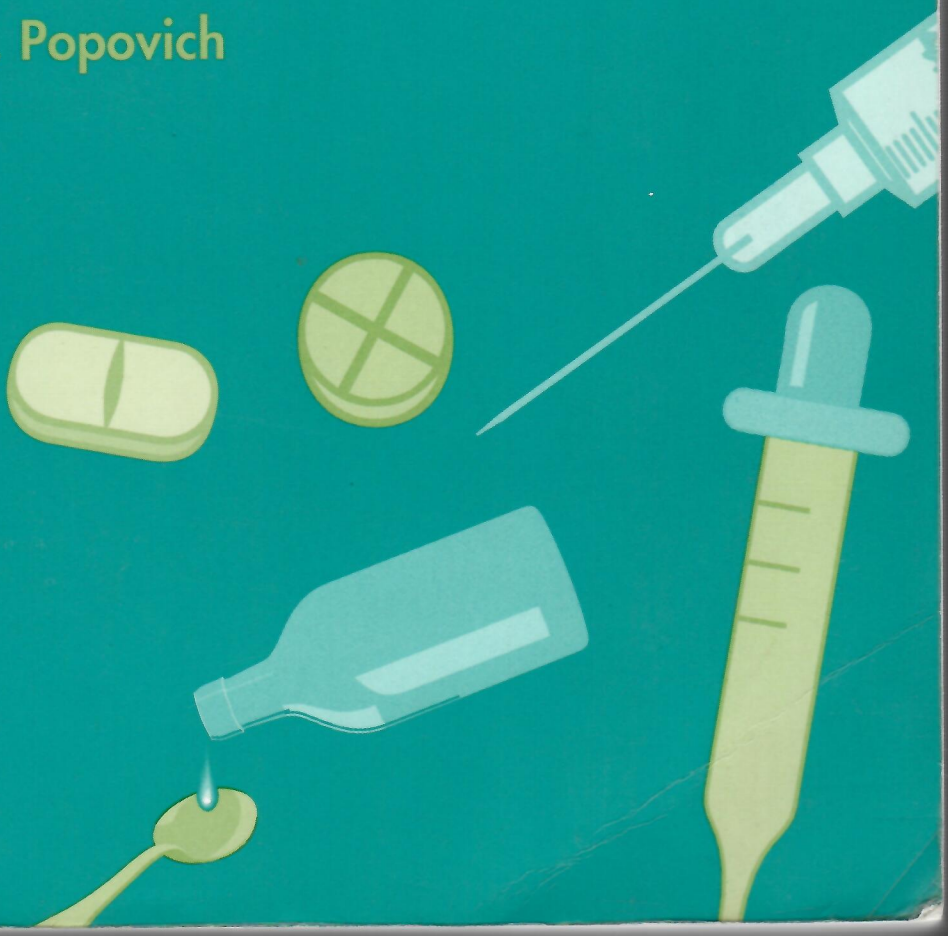
SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

Howard C. Ansel
Loyd V. Allen, Jr.
Nicholas G. Popovich



Pharmaceutical Dosage Forms and Drug Delivery Systems

SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

Howard C. Ansel, Ph.D.
Professor and Dean Emeritus
College of Pharmacy
The University of Georgia

Loyd V. Allen, Jr., Ph.D.
Professor Emeritus
College of Pharmacy
University of Oklahoma, and
Editor-in-Chief
International Journal of Pharmaceutical Compounding

Nicholas G. Popovich, Ph.D.
Professor and Associate Head
Department of Pharmacy Practice
School of Pharmacy and Pharmacal Sciences
Purdue University

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Editor: Donna Balado
Managing Editor: Jennifer Schmidt
Marketing Manager: Christine Kushner

351 West Camden Street
Baltimore, Maryland 21201–2436 USA

227 East Washington Square
Philadelphia, PA 19106

Printed in the United States of America

Library of Congress Cataloging-in-Publication Data

Ansel, Howard C., 1933–
Pharmaceutical dosage forms and drug delievery systems / Howard C. Ansel, Loyd V. Allen, Jr., Nicholas G. Popovich. — 7th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0–683–30572–7
1. Drugs—Dosage forms. 2. Drug delivery systems. I. Allen, Loyd V. II. Popovich, Nicholas G. III. Title.
[DNLM: 1. Dosage Forms. 2. Drug Delivery Systems. QV 785 A618i 1999]
RS200.A57 1999
615'.1—dc21
DNLM/DLC
for Library of Congress
99–17498
CIP

To purchase additional copies of this book call our customer service department at **(800) 638–3030** or fax orders to **(301) 824–7390**. International customers should call **(301) 714–2324**.

99 00 01 02
1 2 3 4 5 6 7 8 9 10

perature, for many medicinal agents are destroyed at elevated temperatures, and the advantage of rapid solution may be completely offset by drug deterioration. If volatile solutes are to be dissolved or if the solvent is volatile (as alcohol), the heat would encourage the loss of these agents to the atmosphere and must therefore be avoided. Pharmacists are aware that certain chemical agents, particularly calcium salts, undergo exothermic reactions as they dissolve and give off heat. For such materials the use of heat would actually discourage the formation of a solution. The best pharmaceutical example of this type of chemical is calcium hydroxide, which is used in the preparation of Calcium Hydroxide Topical Solution, USP. This solute is soluble in water to the extent of 140 mg per 100 mL of solution at 25°C (about 77°F) and 170 mg per 100 mL of solution at 15°C (about 59°F). Obviously the temperature at which the solution is prepared or stored can affect the concentration of the resultant solution.

In addition to, or instead of, raising the temperature of the solvent to increase the rate of solution, a pharmacist may choose to decrease the particle size of the solute. This may be accomplished by the *comminution* (grinding a solid to a fine state of subdivision) of the solute with a mortar and pestle on a small scale or industrial micronizer on a large scale. The reduced particle size causes an increase in the surface area of the substance exposed to the solvent. If the powder is placed in a suitable vessel (as a beaker, graduate cylinder, or bottle) with a portion of the solvent and is stirred or shaken, as suited to the container, the rate of solution may be increased due to the continued circulation of fresh solvent to the drug's surface and the constant removal of newly formed solution from the drug's surface.

Most solutions are prepared by simple solution of the solutes in the solvent or solvent mixture. On an industrial scale, solutions are prepared in large mixing vessels with ports for mechanical stirrers to effect solution (Fig. 12.1). When heat is desired, thermostatically controlled mixing tanks may be used.

Oral Solutions and Preparations for Oral Solution

Solutions intended for oral administration usually contain flavorants and colorants to make the

Fig. 12.1 *Large scale pharmaceutical mixing vessels. (Courtesy of Schering Laboratories.)*

medication more attractive and palatable for the patient. When needed, they may also contain stabilizers to maintain the chemical and physical stability of the medicinal agents and preservatives to prevent the growth of microorganisms in the solution. The formulation pharmacist must be wary of chemical interactions which may occur between the various components of a solution which may result in an alteration in the preparation's stability and/or potency. For instance, it has been demonstrated that esters of p-hydroxybenzoic acid (methyl-, ethyl-, propyl-, and butylparabens), frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils (4). This partitioning effect could reduce the effective concentration of the preservatives in the aqueous medium of a pharmaceutical product below the level needed for preservative action.

Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 mL (one teaspoonful), 10 mL, or 15 mL (one tablespoonful). A few solutions have unusually large doses, as Magnesium Citrate Oral Solution, USP with a usual adult dose of 200 mL. On the other hand many solutions used in pediatric patients are given by drop, utilizing a calibrated dropper usually furnished by the manufacturer in the product package.

Dry Mixtures for Solution

A number of medicinal agents, particularly certain antibiotics, have insufficient stability in aqueous solution to meet extended shelf-life periods. Thus, commercial manufacturers of these products provide them to the pharmacist in dry powder or granule form for reconstitution with a prescribed amount of purified water immediately before dispensing to the patient. The dry powder mixture contains all of the formulative components including drug, flavorant, colorant, buffers, and others, except for the solvent. Once reconstituted by the pharmacist the resultant solutions remain stable when stored in the refrigerator for the labeled periods, usually from 7 to 14 days depending upon the preparation. This is a sufficient period of time for the patient to complete the volume of medication usually prescribed. However, if medication remains after the patient completes the course of therapy, instructions should be explained to discard the remaining portion which would be unfit for use at a later date.

Examples of dry powder mixtures intended for reconstitution to oral solutions are the following:

Cloxacillin Sodium for Oral Solution, USP (Teva); an antiinfective antibiotic

Oxacillin Sodium for Oral Solution, USP [Prostaphlin (Teva)]; an antiinfective antibiotic

Penicillin V Potassium for Oral Solution, USP [Pen-Vee K (Wyeth-Ayerst)]; an antiinfective antibiotic

Potassium Chloride for Oral Solution, USP [K-LOR (Abbott)]; a potassium supplement

Oral Solutions

In the practice of pharmacy, the pharmacist may be called on to dispense a commercially prepared oral solution; dilute the concentration of a solution, as in the preparation of a pediatric form of an adult product; prepare a solution through the reconstitution of a dry powder mixture; or extemporaneously compound an oral solution from bulk components.

In each instance, the pharmacist should be sufficiently knowledgeable of the dispensed product to expertly advise the patient of the proper use, dosage, method of administration, and storage of the product. Knowledge of the solubility and stability characteristics of the medicinal agents and the solvents employed in the commercial products is useful to the pharmacist in informing the patient of the advisability of mixing the solution with juice, milk, or other beverages upon administration. Information regarding the solvents used in each commercial product appears on the product label and in the accompanying package insert. Table 12.5 presents examples of some oral solutions. Some solutions of special pharmaceutical interest are described later in this chapter.

Oral Rehydration Solutions

Rapid fluid loss associated with diarrhea can lead to dehydration and ultimately death in some patients, particularly infants. More than five million children younger than 4 years of age die due to diarrheal illnesses each year worldwide (5). Diarrhea is characterized by an increased frequency of loose, watery stools, and because there is an intensive fluid loss, dehydration can be an outcome. During diarrhea, the small intestine secretes far above the normal amount of fluid and electrolytes, and this simply exceeds the ability of the large intestine to reabsorb it. This fluid loss occurs mostly from the body's extracellular fluid compartment and can lead to a progressive loss of blood volume culminating in hypovolemic shock.

Table 12.5. Examp

Oral Solution
Antidepressants
Nortriptyline HCl Or Solution
Fluoxetine HCl
Antiperistaltic
Diphenoxylate HCl and Atropine Sulfa Oral Solution
Loperamide HCl Oral Solution
Antipsychotics
Haloperidol Oral Solution
Perphenazine Oral Solution
Thiothixene HCl Oral Solution
Bronchodilator
Theophylline Oral Solution
Cathartics
Magnesium Citrate Oral Solution, USP
Sodium Phosphate Or Solution

Table 12.5. Examples of Oral Solutions by Category

Oral Solution	*Some Representative Commercial Products*	*Concentration of Commercial Product*	*Comments*
Antidepressants			
Nortriptyline HCl Oral Solution	Pamelor Oral Solution (Novartis)	10 mg nortriptyline/5 mL	Tricyclic antidepressant
Fluoxetine HCl	Prozac Liquid (Dista)	20 mg fluoxetine/5 mL	Used in the treatment of depression and for obsessive-compulsive disorder.
Antiperistaltic			
Diphenoxylate HCl and Atropine Sulfate Oral Solution	Lomotil Liquid (Searle)	2.5 mg of diphenoxylate HCl and 0.025 mg of atropine sulfate/5 mL	This preparation is indicated in the management of diarrhea. Diphenoxylate is related structurally and pharmacologically to the narcotic meperidine. Atropine sulfate is added to the solution in subtherapeutic amounts to discourage (by virtue of side effects) deliberate overdosage.
Loperamide HCl Oral Solution	Imodium A-D Liquid (McNeil Consumer Products)	1 mg of loperamide HCl per 5 mL	This preparation is indicated for the treatment of diarrhea for both adults and children 6 years of age and older. Loperamide is structurally related to haloperidol.
Antipsychotics			
Haloperidol Oral Solution	Haldol Concentrate (Ortho-McNeil)	2 mg haloperidol/mL	These solutions are used primarily in severe neuropsychiatric conditions when oral medication is preferred and other oral dosage forms (as tablets and capsules) are considered impractical. The concentrated solutions are employed by adding the desired amount of the concentrate by calibrated dropper to soup or a beverage as tomato or fruit juices, milk, coffee, tea or carbonated beverages.
Perphenazine Oral Solution	Trilafon Concentrate (Schering)	16 mg perphenazine/5 mL	
Thiothixene HCl Oral Solution	Navane concentrate (Pfizer)	equivalent of 5 mg thiothixene/mL	
Bronchodilator			
Theophylline Oral Solution	Theophylline Oral Solution (Roxane)	80 mg of theophylline per 15 mL	This alcohol-free solution is used for the treatment of bronchial asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.
Cathartics			
Magnesium Citrate Oral Solution, USP	—	amount of magnesium citrate equivalent to between 1.55 g and 1.9 g/100 mL of magnesium oxide	Discussed in text
Sodium Phosphate Oral Solution	Phospho-Soda (Fleet)	2.4 g monobasic sodium phosphate and 0.9 g dibasic sodium phosphate per 5 mL.	Works as laxative within 1 hour when taken before meals or overnight when taken at bedtime. Usual dose is 10 to 20 mL of solution, best taken diluted with one-half glass of water and followed with a full glass of water.

continued

Table 12.5. Examples of Oral Solutions by Category

Oral Solution	*Some Representative Commercial Products*	*Concentration of Commercial Product*	*Comments*
Corticosteroid			
Prednisolone Sodium Phosphate Oral Liquid	Pediapred Oral Solution (Medeva)	5 mg prednisolone (as sodium phosphate) per 5 mL	Synthetic adrenocortical steroid with predominantly glucocorticoid properties indicated in the treatment of endocrine, rheumatic, collagen, allergic, and other disorders.
Dental Caries Protectant			
Sodium Fluoride Oral Solution	Pediaflor Drops (Boss)	0.5 mg/mL	Prophylaxis of dental caries; intended for use when community water supplies are inadequately fluoridated.
Electrolyte Replenisher			
Potassium Chloride Oral Solution	KaoChlor 10% Liquid (Savage)	20 mEq of KCl/15 mL, in a flavored aqueous vehicle	Used in conditions of hypopotassemia (low level of potassium in the blood). Condition may be prompted by severe or chronic diarrhea, a low level of potassium intake in the diet, increased renal excretion of potassium, and other causes. The solution is diluted with water or fruit juice before taking.
Fecal Softener			
Docusate Sodium Solution	Colace Syrup (Roberts)	10 mg docusate sodium/mL	Usually 50 to 200 mg of the drug is measured by calibrated dropper and mixed with milk, fruit juice, or other liquid (to mask the taste) before administration. The drug softens the fecal mass by lowering the surface tension, thus permitting normal bowel habits, particularly in geriatric, pediatric cardiac, obstetric, and surgical patients. Dosage is taken for several days or until bowel movements are normal.
Hematinic			
Ferrous Sulfate Oral Solution	Fer-In-Sol Drops (Mead Johnson Nutritional)	15 mg ferrous sulfate/ 0.6 mL	Used for prevention and treatment of iron deficiency anemias. Usual prophylactic dose of 0.3 or 0.6 mL measured by calibrated dropper and mixed with water, fruit juice, or vegetable juice before administration. Dosage form intended primarily for infants and children.
Histamine H_2 Antagonist			
Cimetidine HCl Liquid	Tagamet HCl Liquid (SmithKline Beecham)	300 mg of cimetidine HCl per 5 mL	This preparation is indicated to treat peptic ulcer disease and pathological hypersecretory conditions, e.g., Zollinger-Ellison syndrome.
Narcotic Agonist Analgesic			
Methadone HCl Oral Solution	Methadone HCL (Roxane)	1 or 2 mg/mL	For relief of severe pain; detoxification and maintenance treatment of narcotic addiction.
Vitamin D Source			
Ergocalciferol Solution	Calciferol Drops (Schwarz)	8,000 units/mL	A solution of water-insoluble ergocalciferol (vitamin D_2) in propylene glycol. The usual prophylactic dose of ergocalciferol is about 400 units and the therapeutic dose may be as high as 200,000 to 500,000 units daily in treating rickets.

Diarrhea is a norm
to rid itself of a noxiou
tavirus, Escherichia c
proach is to allow the
to terminate it too qui
fluid and electrolytes
dration. The loss of fl
panied by a depletion
carbonate ions, whi
mentioned, in hypovo
sis, hyperpnea and v
of vomiting and diarr
well. Consequently, t
water with an oral re
nutritional foods su
bran.

Oral rehydration so
treatment of patients
5 to 10% of body we
the-counter, are relati
has diminished the in
ciated with parente
solutions. Therapy wi
the observation that
from the small intesti
rhea. This active tra
geous because it is co
Almost like in domir
promotes anion abso
water absorption to
produce maximal ab
studies have demons
trations of glucose ar
tion are 110 mM (2
sodium ion, respectiv
ions are also includec
rect the subsequent
caused by diarrhea ar

A typical oral reh
mEq Na^+, 20 mEq K
and 25 g of dextrose
available in liquid or
stitution. It is import
cific amount of wate
forms. Further, these
with or given with o
uids, such as milk or
no method to calcu
patient actually rec
ready-to-use oral e
dehydration or achi
alyte Solution (Ro
(Ross). These produc
cose. Ricelyte Oral
tains electrolytes in

Diarrhea is a normal physiologic body response to rid itself of a noxious or toxic substance, e.g., *Rotavirus, Escherichia coli.* Thus, the treatment approach is to allow the diarrhea to proceed and not to terminate it too quickly, but promptly replace the fluid and electrolytes that are lost to prevent dehydration. The loss of fluid during diarrhea is accompanied by a depletion of sodium, potassium and bicarbonate ions, which if severe can result, as mentioned, in hypovolemic shock, as well as acidosis, hyperpnea and vomiting. If continuous, bouts of vomiting and diarrhea can cause malnutrition as well. Consequently, the goal is to replace lost fecal water with an oral rehydration solution and utilize nutritional foods such as soybean formula and bran.

Oral rehydration solutions are usually effective in treatment of patients with mild volume depletion of 5 to 10% of body weight. These are available over-the-counter, are relatively inexpensive and their use has diminished the incidence of complications associated with parenterally-administered electrolyte solutions. Therapy with these solutions is based on the observation that glucose is actively absorbed from the small intestine, even during bouts of diarrhea. This active transport of glucose is advantageous because it is coupled with sodium absorption. Almost like in domino fashion, sodium absorption promotes anion absorption which in turn promotes water absorption to short circuit dehydration. To produce maximal absorption of sodium and water, studies have demonstrated that the optimal concentrations of glucose and sodium in an isotonic solution are 110 mM (2%) glucose and 60 mEq/L of sodium ion, respectively. Bicarbonate and/or citrate ions are also included in these solutions to help correct the subsequent metabolic acidosis which is caused by diarrhea and dehydration.

A typical oral rehydration solution contains 45 mEq Na^+, 20 mEq K^+, 35 mEq Cl^-, 30 mEq citrate, and 25 g of dextrose per liter. These formulations are available in liquid or powder/packet form for reconstitution. It is important that the user add the specific amount of water needed to prepare the powder forms. Further, these products should not be mixed with or given with other electrolyte-containing liquids, such as milk or fruit juices. Otherwise, there is no method to calculate how much electrolyte the patient actually received. Commercially available, ready-to-use oral electrolyte solutions to prevent dehydration or achieve rehydration include Pedialyte Solution (Ross), and Rehydrate Solution (Ross). These products also contain dextrose or glucose. Ricelyte Oral Solution (Mead Johnson) contains electrolytes in a syrup of rice solids. The rice-based formula produces a lower osmotic effect than the dextrose- or glucose-based formulas and is thought to be more effective in reducing stool output and shortening the duration of diarrhea. The pharmacist must discourage the production of homemade versions of electrolyte solutions. The success of the commercial solutions is based on the accuracy of the formulation. If prepared incorrectly, homemade preparations could cause hypernatremia or cause the diarrhea to worsen.

Oral Colonic Lavage Solution

Traditionally, the preparation of the bowel for procedures such as a colonoscopy have consisted of the administration of clear liquid diets for 24 to 48 hours preceding the procedure, the administration of oral laxatives, e.g., magnesium citrate or bisacodyl, the night before, and cleansing enemas administered 2 to 4 hours prior to procedure commencement. Typically, to circumvent the cost of having to hospitalize the patient the night before the procedure, patients were allowed to perform this regimen at home. However, while the results have been satisfactory, that is, the bowel is cleared for the procedure, poor patient compliance with and acceptance of this regimen can cause problems during the procedure. Further, additive effects of malnutrition and poor oral intake prior to the procedure can cause more patient problems.

Consequently, an alternative method to prepare the gastrointestinal tract has been devised. This procedure requires less time and dietary restriction and obviates the need for cleansing enemas. This method involves the oral administration of a balanced solution of electrolytes with polyethylene glycol (PEG-3350). Prior to its dispensing to the patient, the pharmacist reconstitutes this powder with water creating an iso-osmotic solution having a mildly salty taste. The polyethylene glycol acts as an osmotic agent within the gastrointestinal tract and the balanced electrolyte concentration results in virtually no net absorption or secretion of ions. Thus, a large volume of this solution can be administered without a significant change in water or electrolyte balance.

The formulation of this oral colonic lavage solution is as follows:

Polyethylene Glycol 3350	236.00 g
Sodium Sulfate	22.74 g
Sodium Bicarbonate	6.74 g
Sodium Chloride	5.86 g
Potassium Chloride	2.97 g

In 4800 mL disposable container.

The recommended adult dosage of this product is 4 L of solution before the gastrointestinal procedure. The patient is instructed to drink 240 mL of solution every 10 minutes until about 4 L are consumed. The patient is advised to drink each portion quickly rather than sipping it continuously. Usually, the first bowel movement will occur within 1 hour. Several regimens are utilized, and one method is to schedule patients for a midmorning procedure, allowing the patient 3 hours for drinking and a 1-hour waiting period to complete bowel evacuation.

To date, this approach to bowel evacuation has been associated with a low incidence of side effects, primarily nausea, transient abdominal fullness, bloating, and occasionally, cramps and vomiting. Ideally, the patient should not have taken any food 3 to 4 hours before beginning the administration of the solution. In no case should solid foods be taken by the patient for at least 2 hours before the solution is administered. No foods, except clear liquids, are permitted after this product is administered and prior to the examination. The product must be stored in the refrigerator after reconstitution, and this aids somewhat in decreasing the salty taste of the product.

Magnesium Citrate Oral Solution

Magnesium citrate oral solution is a colorless to slightly yellow, clear, effervescent liquid having a sweet, acidulous taste and a lemon flavor. It is commonly referred to as "Citrate" or as "Citrate of Magnesia." It is required to contain an amount of magnesium citrate equivalent to between 1.55 and 1.9 g of magnesium oxide in each 100 mL.

The solution is prepared by reacting official magnesium carbonate with an excess of citric acid (equation 1), flavoring and sweetening the solution with lemon oil and syrup, filtering with talc, and then carbonating it by the addition of either potassium or sodium bicarbonate (equation 2). The solution may be further carbonated by the use of carbon dioxide under pressure.

$$(1)\ (MgCO_3)_4 \cdot Mg(OH)_2 + 5H_3C_6H_5O_7 \rightarrow 5MgHC_6H_5O_7 + 4CO_2 + 6H_2O$$

$$(2)\ 3KHCO_3 + H_3C_6H_5O_7 \rightarrow K_3C_6H_5O_7 + 3CO_2 + 3H_2O$$

The solution provides an excellent medium for the growth of molds, and any mold spores present during the manufacture of the solution must be killed if the preparation is to remain stable. For this reason, during the preparation of the solution the liquid is heated to boiling (prior to carbonation), boiled water is employed to bring the solution to its proper volume, and boiling water is used to rinse the final container. The final solution may be sterilized.

Magnesium citrate solution has always been troublesome because it has a tendency to deposit a crystalline solid upon standing. Apparently this is due to the formation of some almost insoluble, normal magnesium citrate (rather than the exclusively dibasic form as in equation 1). The cause of the problem has largely been attributed to the indefinite composition of the official magnesium carbonate, which by definition is "a basic hydrated magnesium carbonate or a normal hydrated magnesium carbonate" (see equation 1). It contains the equivalent of 40 to 43.5% of magnesium oxide. Apparently, solutions prepared from magnesium carbonates with differing equivalents of magnesium oxide vary in stability, with the most stable ones being prepared from samples of magnesium carbonate having the lower equivalent of magnesium oxide. The formula for the preparation of 350 mL of magnesium citrate solution calls for the use of 15 g of official magnesium carbonate, which corresponds to approximately 6.0 to 6.47 g of magnesium oxide.

In carbonating the solution, the bicarbonate may be added in tablet form rather than as a powder in order to delay the effervescence resulting from its contact with the citric acid. If the powder were used, the reaction would be immediate and violent, and it would be virtually impossible to close the bottle in time to prevent the loss of carbon dioxide or solution. The solution may be further carbonated by the use of CO_2 under pressure. Most of the magnesium citrate solutions prepared commercially today are packaged in the same type of bottles as "soft drink" carbonated beverages. The solution is packaged in bottles of 300 mL. Since the solution is carbonated, it loses some of its character if allowed to stand for a period of time after the container has been opened. Magnesium citrate solution is stored in a cold place, preferably in a refrigerator, keeping the bottle on its side so the cork or rubber liners of the caps are kept moist and swollen, thereby maintaining the airtight seal between the cap and the bottle.

The solution is employed as a saline cathartic, with the citric acid, lemon oil, syrup, carbonation, and the low temperature of the refrigerated solution all contributing to the patient's acceptance of the large volume of medication. For many patients

it represents a pleasant way of taking an otherwise bitter saline cathartic.

Sodium Citrate and Citric Acid Oral Solution

This official solution contains 100 mg of sodium citrate and 67 mg of citric acid in each mL of aqueous solution. The solution is administered orally in doses of 10 to 30 mL as frequently as four times daily as a systemic alkalinizer. Systemic alkalinization is useful in patients having conditions in which long term maintenance of an alkaline urine is desirable, such as patients with uric acid and cystine calculi of the urinary tract. The solution is also a useful adjuvant when administered with uricosuric agents in gout therapy since urates tend to crystallize out of an acid urine.

Syrups

Syrups are concentrated, aqueous preparations of a sugar or sugar-substitute with or without added flavoring agents and medicinal substances. Syrups containing flavoring agents but not medicinal substances are called *nonmedicated* or *flavored vehicles* (syrups). Some official, previously official and examples of commercially available nonmedicated syrups are presented in Table 12.6. These syrups are intended to serve as pleasant-tasting vehicles for medicinal substances to be added in the extemporaneous compounding of prescriptions or in the preparation of a standard formula for a *medicated syrup*, which is a syrup containing a therapeutic agent. Due to the inability of some children and elderly people to swallow solid dosage forms, it is not unusual today for a pharmacist to be asked to prepare an oral liquid dosage form of a medication available in the pharmacy only as tablets or capsules. In doing so, considerations of drug solubility, stability, and bioavailability must be considered case by case (6,7). The liquid dosage form selected for compounding may be a solution or a suspension, depending upon the chemical and physical characteristics of the particular drug and its solid dosage form. Vehicles are commercially available for this purpose (7).

Medicated syrups are commercially prepared from the starting materials; that is, by combining each of the individual components of the syrup, as sucrose, purified water, flavoring agents, coloring agents, the therapeutic agent, and other necessary and desirable ingredients. Naturally, medicated syrups are employed in therapeutics for the value of the medicinal agent present in the syrup.

Syrups provide a pleasant means of administering a liquid form of a disagreeable tasting drug. They are particularly effective in the administration of drugs to youngsters, since their pleasant taste usually dissipates any reluctance on the part of the child to take the medicine. The fact that syrups contain little or no alcohol adds to their favor among parents.

Any water-soluble drug that is stable in aqueous solution may be added to a flavored syrup. However care must be exercised to ensure the compati-

Table 12.6. Examples of Nonmedicated Syrups (Vehicles)

Nonmedicated Syrup	*Comments*
Cherry Syrup	A sucrose-based syrup containing about 47% by volume of cherry juice. The syrup's tart and fruit flavor is attractive to most patients and the acidic pH of the syrup makes it useful as a vehicle for drugs requiring an acid medium.
Cocoa Syrup	This syrup is a suspension of cocoa powder in an aqueous vehicle sweetened and thickened with sucrose, liquid glucose, and glycerin, and flavored with vanilla and sodium chloride. The syrup is particularly effective in administering bitter tasting drugs to children.
Orange Syrup	This sucrose-based syrup utilizes sweet orange peel tincture, and citric acid as the source of flavor and tartness. The syrup resembles orange juice in taste and is a good vehicle for drugs stable in an acidic medium.
Ora-Sweet and Ora-Sweet SF (Paddock Laboratories)	Commercially available vehicles for the extemporaneous compounding of syrups. Both vehicles have a pH between 4 and 4.5 and are alcohol free. Ora-Sweet SF syrup is sugar free.
Raspberry Syrup	A sucrose-based syrup containing about 48% by volume of raspberry juice. It is a pleasantly flavored vehicle used to disguise the salty or sour taste of saline medicaments.
Syrup	This is an 85% solution of sucrose in purified water. This "simple syrup" may be used as the basis for the preparation of flavored or medicated syrups.

Additional Considerations

Ophthalmic solutions must be sparkling clear and free of all particulate matter for patient comfort and safety. The formulation of an ophthalmic suspension may be undertaken when it is desired to prepare a product with extended corneal contact time, or, it may be necessary when the medicinal agent is insoluble or unstable in an aqueous vehicle.

Drug particles in an ophthalmic suspension must be finely subdivided, usually micronized, to minimize eye irritation and/or scratching of the cornea. The suspended particles must not associate into larger particles upon storage and must be easily and uniformly redistributed by gentle shaking of the container prior to use.

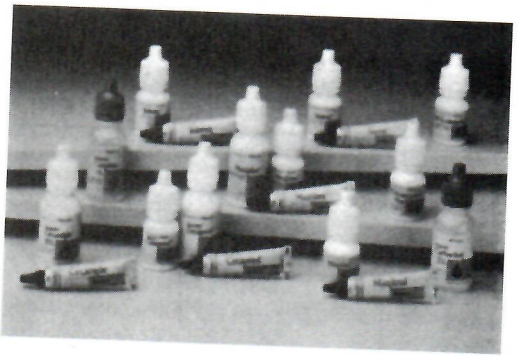


Fig. 16.4 *Examples of ophthalmic product packaging. Liquids are in 5-mL and 15-mL Drop-Tainer dispensers and ointments are in tubes containing 3.5 g of product. (Courtesy of Alcon.)*

Packaging Ophthalmic Solutions and Suspensions

Although a few commercial ophthalmic solutions/suspensions are packaged in small glass bottles with separate glass or plastic droppers, the vast majority are packaged in soft plastic containers having a fixed, built-in dropper (Figs. 16.3, 16.4). The latter type of packaging is preferred both to facilitate administration and to protect the product from external contamination. Ophthalmic solutions and suspensions are commonly packaged in containers holding 2, 2.5, 5, 10, 15, and 30 mL of product.

Patients must exercise care in protecting an ophthalmic solution/suspension from external contamination. Obviously, the fixed dropper containers are less likely to acquire airborne contaminants than the screw-type bottles which are fully opened when in use. However, each type is subject to contamination during use by airborne contaminants and by the inadvertent touching of the tip of the dropper to the eye, eyelids or other surface.

Ophthalmic solutions used as eye washes are generally co-packaged with an eye cup which should be cleaned and dried thoroughly before and after each use.

Fig. 16.3 *Commercial package of an ophthalmic solution in a plastic container with built-in dropper device. (Courtesy of Alcon.)*

Proper Administration of Ophthalmic Solutions and Suspensions

Prior to the administration of an ophthalmic solution or suspension, the patient or caregiver should be advised to wash his/her hands thoroughly. If the ophthalmic drops are supplied with a separate dropper, the patient should inspect the dropper to make sure it has no chips or cracks. Ophthalmic solutions should be inspected for color and clarity. Out of date or darkened solutions should be discarded. Ophthalmic suspensions should be shaken thoroughly prior to administration to evenly distribute the suspensoid.

The cap of an eye-drop container should be removed immediately prior to use and returned immediately after use. The combined dropper-container as shown in Figure 16.3 is used by holding it between the thumb and middle finger with the index finger on the bottom of the container. One or more drops are delivered by gently squeezing the container. A product packaged with a separate dropper is used by holding the dropper between the thumb and forefinger then drawing up and discharging the medication drop-wise in the usual and familiar manner.

To instill eye drops, the patient should tilt his/her head back and with the index finger of the free hand gently pull downward the lower eyelid of the

filtration (3). In this process, a pressurized stream of water is passed *parallel to* the inner side of a filter membrane core. A portion of the feed water, or influent, permeates the membrane as filtrate, while the balance of the water sweeps tangentially along the membrane to exit the system without being filtered. The filtered portion is called the *permeate* because it has permeated the membrane. The water that has passed through the system is referred to as the *concentrate,* because it contains the concentrated contaminants rejected by the membrane. Whereas, in *osmosis,* the flow through a semi-permeable membrane is from a less concentrated solution to a more concentrated solution, the flow in this crossflow system is from a more concentrated to a less concentrated solution—thus the term *reverse osmosis.* Depending on their pore size, crossflow filter membranes can remove particles defined in the range of *microfiltration* (0.1 to 2 microns, e.g., bacteria); *ultrafiltration* (0.01 to 0.1 microns, e.g., virus); *nanofiltration* (0.001 to 0.01 microns, e.g., organic compounds in the molecular weight range of 300 to 1000); and *reverse osmosis* (particles smaller than 0.001 microns). Reverse osmosis removes virtually all virus, bacteria, pyrogens, organic molecules, and 90–99% of all ions (3).

Preparation of Solutions

Most pharmaceutical solutions are unsaturated with solute. Thus the amounts of solute to be dissolved are usually well below the capacity of the volume of solvent employed. The strengths of pharmaceutical preparations are usually expressed in terms of % *strength,* although for very dilute preparations, expressions of *ratio strength* may be used. These expressions and examples are shown in Table 12.4.

The term %, when used without qualification (as with w/v, v/v, or w/w) means % weight-in-volume for solutions or suspensions of solids in liquids; % weight-in-volume for solutions of gases in liquids; % volume-in-volume for solutions of liquids in liquids; and weight-in-weight for mixtures of solids and semisolids.

Some chemical agents that may be soluble in a given solvent are only slowly soluble and require an extended time for dissolving. To hasten the dissolution process, a pharmacist may employ one or several techniques; such as applying heat, reducing the particle size of the solute, utilizing a solubilizing agent, or subjecting the ingredients to rigorous agitation during the preparation of the solution. Normally, most chemical agents are more soluble in solvents at elevated temperatures than at room temperature or below because an endothermic reaction between the solute and the solvent utilizes the energy of the heat to enhance the dissolution process. However, elevated temperatures cannot be maintained for pharmaceuticals, and the net effect of heat is simply an increase in the *rate* of solution rather than an increase in solubility. An increased rate is satisfactory to the pharmacist, because most of his solutions are unsaturated anyway and do not require the presence of solute above the normal capacity of the solvent at room temperature. Pharmacists are reluctant to use heat to facilitate solution, and when they do, they are careful not to exceed the minimally required tem-

Table 12.4. Common Methods of Expressing the Strengths of Pharmaceutical Preparations

Expression	*Abbreviated Expression*	*Meaning and Example*
Percent weight-in-volume	% w/v	number of grams of a constituent in 100 mL of preparation (e.g., 1% w/v = 1 g of constituent in 100 mL of preparation).
Percent volume-in-volume	% v/v	number of mL of a constituent in 100 mL of preparation (e.g., 1% v/v 1 mL of constituent in 100 mL of preparation).
Percent weight-in-weight	% w/w	number of grams of a constituent in 100 g of preparation (e. g., 1% w/w = 1 g of constituent in 100 g of preparation).
Ratio strength, weight-in-volume	——:—— w/v	number of grams of constituent in stated number of mL of preparation (e.g., 1:1000 w/v = 1 g of constituent in 1000 mL of preparation).
Ratio strength, volume-in-volume	——:—— v/v	number of mL of constituent in stated number of mL of preparation (e.g., 1:1000 v/v = 1 mL of constituent in 1000 mL of preparation).
Ratio strength, weight-in-weight	——:—— w/w	number of grams of constituent in stated number of grams of preparation (e.g., 1:1000 w/w = 1 g of constituent in 1000 g of preparation).

perature, for many medicinal agents are destroyed at elevated temperatures, and the advantage of rapid solution may be completely offset by drug deterioration. If volatile solutes are to be dissolved or if the solvent is volatile (as alcohol), the heat would encourage the loss of these agents to the atmosphere and must therefore be avoided. Pharmacists are aware that certain chemical agents, particularly calcium salts, undergo exothermic reactions as they dissolve and give off heat. For such materials the use of heat would actually discourage the formation of a solution. The best pharmaceutical example of this type of chemical is calcium hydroxide, which is used in the preparation of Calcium Hydroxide Topical Solution, USP. This solute is soluble in water to the extent of 140 mg per 100 mL of solution at 25°C (about 77°F) and 170 mg per 100 mL of solution at 15°C (about 59°F). Obviously the temperature at which the solution is prepared or stored can affect the concentration of the resultant solution.

In addition to, or instead of, raising the temperature of the solvent to increase the rate of solution, a pharmacist may choose to decrease the particle size of the solute. This may be accomplished by the *comminution* (grinding a solid to a fine state of subdivision) of the solute with a mortar and pestle on a small scale or industrial micronizer on a large scale. The reduced particle size causes an increase in the surface area of the substance exposed to the solvent. If the powder is placed in a suitable vessel (as a beaker, graduate cylinder, or bottle) with a portion of the solvent and is stirred or shaken, as suited to the container, the rate of solution may be increased due to the continued circulation of fresh solvent to the drug's surface and the constant removal of newly formed solution from the drug's surface.

Most solutions are prepared by simple solution of the solutes in the solvent or solvent mixture. On an industrial scale, solutions are prepared in large mixing vessels with ports for mechanical stirrers to effect solution (Fig. 12.1). When heat is desired, thermostatically controlled mixing tanks may be used.

Oral Solutions and Preparations for Oral Solution

Solutions intended for oral administration usually contain flavorants and colorants to make the

Fig. 12.1 *Large scale pharmaceutical mixing vessels. (Courtesy of Schering Laboratories.)*