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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

COMPOUNDING, STABILITY AND BEYOND-USE DATES

INTRODUCTION

Considerations in the extemporaneous compounding of prescriptions include stability and "beyond-use" dating. It should be noted that "Expiration Dates" are placed on commercially manufactured products and "Beyond-Use Dates" are used for compounded preparations. Prescriptions requiring extemporaneous compounding by the pharmacist generally do not require the extended shelf-life that commercially manufactured and distributed products do because they are intended to be utilized soon after receipt by the patient and are used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of their use and the compounding pharmacist must employ formulative components and techniques which will result in a stable product.

In years past, pharmacists were presented primarily with innocuous, topical prescriptions that required extemporaneous formulation. However, in recent years there has been a need to compound a wide variety of other drug delivery systems as well, including capsules, solutions, suspensions, emulsions, troches, injections, ophthalmics, nasals, otics, powders, ointments, creams, gels, etc. When presented with a prescription that requires extemporaneous compounding, the pharmacist is faced with a difficult situation because the potency and the stability of these prescriptions is a serious matter. Occasionally, the results of compatibility and stability studies on such prescriptions are published in scientific and professional journals. These are very useful; however, there are also prescriptions for which stability and compatibility information is not readily obtainable. In these instances it behooves the pharmacist to obtain whatever stability information might be available. There are numerous sources of information that can be utilized for determining an appropriate "beyond-use" date. This might include contacting a manufacturer of a commercial product if one is used as a source of drug or referring to the literature for published stability studies, or a compiled source of stability data. When evaluating stability studies in the literature, it is important that the products studied and reported be similar to what is to be prepared in drug concentration range, pH, excipients, vehicle, water content, etc., for the results to be applicable. Sources of such studies include manufacturers literature, Trissel's Stability of Compounded Formulations, the monographs in AHFS-Drug Information, the International Journal of Pharmaceutical Compounding, American Journal of Health-System Pharmacy, Lippincott's Hospital Pharmacy, other journals as well as published books on the subject. Generally, most pharmacists prepare/dispense small quantities of compounded products, recommend storage at cool or cold temperatures, and use a conservative "beyond-use" date.

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USP GUIDELINES: BEYOND-USE DATING FOR EXTEMPORANEOUS COMPOUNDED PRESCRIPTIONS

The USP provides guidelines on stability and the assignment of a "beyond-use" date for extemporaneous compounded formulations that, in the absence of other available stability information, are applicable to a specific drug and preparation. Unless published data is available to the contrary, the following are the maximum recommended beyond-use dates for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers when stored at controlled room temperature or as otherwise indicated.

Nonaqueous Liquids and Solid Formulations: If the source of the ingredient(s) is a manufactured drug product, the beyond-use date should be not later than 25% of the time remaining until the original product's expiration date, or 6 months, whichever is earlier. If the source of the ingredient(s) is a USP or NF substance, the beyond-use date is not later than 6 months.

Water-Containing Formulations: When prepared from ingredients in solid form, the beyond-use date should be not later than 14 days when stored at

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cold temperatures.
All-Other Formulations: The earlier of 30 days or the intended duration of therapy. If there is supporting valid scientific stability information appropriate to the specific preparation, the beyond-use date limits may be exceeded. The reader is referred to <1161> Pharmacy Compounding Practices in the USP/NF.

Also, when compounding on the basis of extrapolated information, it is best for the pharmacist to keep the formulation simple but use the necessary pharmaceutical adjuvants to prepare the prescription properly. In order to select the proper adjuvants for a preparation, it is important to consider the various types of stability and the general factors affecting stability.

TYPES OF STABILITY

Stability is the extent to which a product retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture. There are five general types of stability defined by the USP.
Chemical: Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical: The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic: The therapeutic effect remains unchanged.
Toxicological: No significant increase in toxicity occurs.

Compounding pharmacists are interested in all five types of stability but the compounding process emphasizes observations that can be done related to the chemical, physical and microbiological.

Chemical stability is important for selecting storage conditions (temperature, light, humidity), selecting the proper container for dispensing (glass vs. plastic, clear vs. amber or opaque, cap liners) and for anticipating interactions when mixing drugs and dosage forms. Stability and expiration dating/beyond-use dating are based on reaction kinetics, i.e., the study of the rate of chemical change and the way this rate is influenced by conditions of concentration of reactants, products, and other chemical species that may be present, and by factors such as solvent, pressure, and temperature

MECHANISMS OF DEGRADATION

Chemically, the most frequently encountered destructive processes include hydrolysis and oxidation. Hydrolysis is a solvolytic process in which drugs react with water to yield breakdown products of different chemical composition. For example, a molecule of aspirin combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid.

The process of hydrolysis is probably the most important single cause of drug decomposition because many drugs are esters or contain such other groupings as substituted amides, lactones, and lactams, which are susceptible to the hydrolytic process.

Another destructive process is oxidation. The oxidative process is destructive to many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils. Chemically, oxidation involves the loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, causing the reduction of the recipient molecule. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element--for example, ferrous (+2) oxidizing to ferric (+3). In organic chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. The oxidative process frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, as molecular (atmospheric) oxygen and free hydroxyl. These radicals tend to take electrons from other chemicals, thereby oxidizing the donor.

Many of the oxidative changes in pharmaceutical preparations are "autoxidations" which occur spontaneously under the initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly as the process continues. It is a type of chain reaction beginning with the union of oxygen with a drug molecule and continuing with a free radical of this oxidized molecule participating in the destruction of other drug molecules.

In pharmaceutical compounding, steps should be taken to reduce or prevent the occurrence of drug substance deterioration due to hydrolysis, oxidation, and other processes. These techniques of doing this will be discussed later.

FACTORS AFFECTING STABILITY

Formulation and stability difficulties arise less frequently with solid dosage forms than with liquid pharmaceutical preparations; this is one reason many new drugs first reach the market as tablets or dry-filled capsules. The stability of a drug and its dosage form is affected by a number of various factors, including pH, temperature, solvent, light, air (oxygen, carbon dioxide, moisture), humidity, particle size and others.

pH is one of the most important factors in the stability of a product. Many pH:stability profiles are published or can be obtained and can be used to determine the pH of maximum stability of a drug. After the pH range is determined, buffers can be prepared to maintain the pH for the expected shelf-life or duration of therapy of the product.

Temperature affects the stability of a drug by increasing the rate of reaction speed about two to three times with each 10ºC rise in temperature. This effect on temperature was first suggested by Arrhenius as:
where k is the specific reaction rate, A is the frequency factor, Ea is

$$k = Ae^{-Ea/RT}$$

or

$$\log k = \log A - \frac{Ea}{2..303\ RT}$$

the energy of activation, R is the gas constant (1.987 calories/deg mole), and T is the absolute temperature. As is evident from these relationships, an increase in temperature will result in an increase in the specific reaction rate, or the degradation rate of the drug. Temperature effects can be minimized by selecting the proper storage temperature, whether this is room, refrigerated or freezing.

Solvent: In a liquid preparation, the effect of the solvent is important. The solvent affects the solubility, pH and the solubility parameter of the active ingredient; solvents should not be indiscriminately changed in products if stability may be compromised.

Light may provide the activation energy required for a degradation reaction to occur. Many light-activated reactions are zero order, or constant reactions. Light effects can be minimized by packaging in light resistant containers and covering the products that are light-sensitive during administration with aluminum foil or an amber plastic overwrap.

Air (oxygen) can induce degradation by oxidation. This can be minimized by decreasing the headspace in a container by filling as full as practical, or by replacing the headspace with nitrogen.

Carbon dioxide can result in insoluble carbonates forming in the solid dosage form which results in a decrease in the disintegration and dissolution of the product. It can be minimized by packaging in tight containers and filling them as full as reasonable. Humidity, or moisture, can result in hydrolysis reactions and degradation of the drug product. This can be minimized by working in a dry environment and by packaging the product with a desiccant packet added.

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Particle size can have an important effect on the stability of a product. The smaller the particle size, the greater the reactivity of the product. When working with poorly stable drugs in solid dosage forms such as powders and capsules, it may be advisable to use a larger particle size as appropriate.

Other factors affecting drug stability include ionic strength and dielectric constant. Some paths of physical instability include the formation of polymorphs, crystallization, vaporization and adsorption.

Polymorphs are different crystal forms of the same chemical compound and differ in their crystal energies. They may exhibit differences in such properties as solubility, compressibility and melting point. The occurrence of polymorphs can be minimized by being aware of the causative factors and preventing them. For example, heating and shock-cooling can cause the formation of polymorphs.

Crystallization of particles in suspension can result in a different particle size distribution of the particles. This occurs often by temperature fluctuations; increasing temperatures result in greater solubility (often with the smaller particles dissolving faster) and decreasing temperatures result in some drug in solution crystallizing out on particles that are already present. This cycling will decrease the proportion of smaller particles and increase the proportion of larger crystals present.

Vaporization is loss of solvent which is increased at higher temperatures. With a loss of solvent, or liquid, the resulting concentration of the product will increase. This may lead to overdosage when administered. Also, with a loss of solvent, precipitation of the drug may occur if the solubility of the drug in the remaining vehicle is exceeded.

Adsorption of the drug or excipients is rather common and may lead to a loss of the drug available for exerting its effect. Drugs may adsorb to filters, the container, tubing, syringes, or other materials which it contacts. This may be of special importance to low dose drugs. Sorption can often be minimized by pre-treating equipment/containers with silicone and the sorption of some materials can be minimized by the addition of albumen or similar material to the vehicle prior to adding the drug.

OBSERVATION OF INSTABILITY

Drug instability in pharmaceutical formulations may be detected in some instances by a change in the physical appearance, color, odor, taste or texture of the formulation whereas in other instances chemical changes may occur which are not self-evident and may only be ascertained through chemical analysis. Evidence of instability in dosage forms in many cases can be observed by the pharmacist. For example, the following physical observations of different dosage forms can be made.

Capsules: A change in the physical appearance or consistency of the capsule or its contents, including hardening, brittleness or softening of the shell. Also, any discoloration or expansion/distortion of the gelatin capsule.

Powders: Dry powders and granules should remain free flowing. Physical instability may be indicated by caking or discoloration. Upon opening the container, if there is a release of pressure, this may be indicative of bacterial or other degradation resulting in a release of carbon dioxide. Powders should have a uniform color and, if appropriate, a characteristic odor.

Solutions/Elixirs, Syrups, etc.: Solutions should be free of precipitates, discoloration, haziness, gas formation and microbial growth. They should be clear and of the appropriate color and odor.

Emulsions: Emulsions should have a reasonably uniform globule size distribution and viscosity. They should not exhibit breaking, creaming, gas formation, discoloration or microbial growth.

Suspensions: Suspensions should not exhibit caking, difficulty in resuspending, crystal growth, discoloration or microbial growth. They should have reasonably uniform particle size distribution and viscosity.

Ointments: Ointments should have a uniform appearance and, as appropriate, a characteristic odor. They should not change in consistency or demonstrate a separation of liquid, if contained, or the formation of granules or grittiness, or dryness.

Creams: Creams should have a uniform appearance and, as appropriate, a characteristic odor. They should not exhibit emulsion breakage, crystal growth, shrinking due to evaporation or water, gross microbial contamination, discoloration or inappropriate odor.

Suppositories: Suppositories should remain uniform in appearance. They should not exhibit excessive softening, drying, hardening, shriveling. There should be no evidence of oil stains on the packaging.

Gels: Gels should have a uniform appearance and, as appropriate, a characteristic odor. They should not exhibit any shrinkage, separation of liquid from the gel, discoloration or microbial contamination.

Troches: Troches should exhibit a uniform appearance and, as appropriate, a characteristic odor. They should not exhibit any softening or hardening, crystallization, microbial contamination or discoloration.

Sterile products

All sterile products must maintain sterility and, as appropriate, their nonpyrogenicity.

Ophthalmic preparations: Ophthalmic preparations should exhibit a uniform appearance, color, consistency, clarity (solutions), particle size and resuspendibility (suspensions, creams, ointments), strength, and sterility.

Small-volume parenterals: Small-volume parenterals should exhibit a uniform appearance, color, be free from particulate matter, be easily dispersed (suspensions), and show no signs of change of closure integrity.

Large-volume parenterals: Large-volume parenterals should exhibit a

uniform appearance, color, clarity, be free from particulate matter, and show no signs of change of closure integrity.

ENHANCING STABILITY OF DRUG PRODUCTS

Many pharmaceutic ingredients may be utilized in compounding a dosage form. Some of these may be used to achieve the desired physical and chemical characteristics or to enhance its appearance, odor, and taste. Others may be used to increase stability, particularly against hydrolytic and oxidative processes. In each instance, the added pharmaceutic ingredient must be compatible with and not detract from the stability of the drug substance in the particular dosage form prepared.

There are several approaches to stabilizing pharmaceutical preparations containing drugs subject to deterioration by hydrolysis, including the elimination of water from the pharmaceutical system. Even solid dosage forms containing water-labile drugs must be protected from the humidity of the atmosphere by applying a waterproof protective coating over tablets or by enclosing and maintaining the drug in tightly closed containers. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

Storage under refrigeration is advisable for most preparations considered unstable due to hydrolytic causes. Together with temperature, pH is a major determinant in the stability of a drug prone to hydrolytic decomposition. The hydrolysis of most drugs is dependent upon the relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolyzable drugs the pH of optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through judicious use of buffering agents, the stability of otherwise unstable compounds can be increased.

Pharmaceutically, the oxidation of a susceptible drug substance is most likely to occur in the presence of oxygen, exposure to light, or combined in a formulation with other chemical agents without proper regard to their influence on the oxidation process. Oxidation of a chemical in a preparation is usually accompanied by an alteration in color. It may also result in precipitation or a change in the odor.

The oxidative process is minimized in the presence of antioxidants, which react with one or more compounds in the drug to prevent continuation of the chain reaction. In general, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Among those more frequently used in aqueous preparations are sodium sulfite, sodium bisulfite, hypophosphorous acid, and ascorbic acid. In oleaginous preparations, alpha-tocopherol, butylhydroxytoluene, butylhydroxyanisole, and ascorbyl palmitate are used.

Trace metals originating in the drug, solvent, container, or stopper can be a constant source of difficulty in preparing stable solutions of oxidizable drugs. The rate of formation of color in epinephrine solutions, for instance, is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions. Great care must be taken to eliminate these trace metals from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process. These agents are referred to as chelating agents and are exemplified by calcium disodium edetate and ethylenediamine tetra-acetic acid.

Light can also act as a catalyst to oxidation reactions. As a precaution against the acceleration of the oxidative process, sensitive preparations are packaged in light-resistant or opaque containers. Also, since most drug degradations proceed more rapidly with an advanced temperature, it is also advisable to maintain oxidizable drugs in a cool place.

Q_{10} METHOD OF PREDICTING SHELF-LIFE STABILITY

The Q_{10} method of shelf-life estimation can provide the compounding pharmacist a tool to quickly calculate a beyond-use date for a drug product that is going to be stored or used under a different set of conditions than what might be customary. The Q_{10} approach, based on Ea, is independent of reaction order and is described as:

$$Q_{10} = e^{[(Ea/R)[(1/T+10)-(1/T)]}$$

where Ea is the energy of activation, R is the gas constant, and T is the absolute temperature.
Actually the expression "Q_{10}" is simply a ratio of two different reaction rate constants defined as follows:

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$

where K_T is the reaction rate constant at a specific temperature, T, and $K_{(T+10)}$ is the reaction rate constant at a temperature 10° higher. Values of "Q" that are commonly used are 2, 3 and 4 and are related to different energies of activation, 12.2, 19.4 and 24.5 kcal/mol, respectively. For practical purposes, if the Ea is not known a median value of "3" has been used as a reasonable estimate since the energy of activation of many drugs is in the range of 18-20 kcal/mol.
The actual equation that is used for estimating shelf-life is:

$$t_{90}(T2) = \frac{t_{90}(T1)}{Q_{10}^{(\Delta T/10)}}$$

where $t_{90}(T2)$ is the estimated shelf-life, $t_{90}(T1)$ is the given shelf-life at a given temperature T1, and ΔT is the temperature difference between T1 and T2.

Looking at this relationship, it is apparent that increasing the expression ($\Delta T/10$) positively will decrease the shelf-life and decreasing the expression will increase the shelf-life of the drug.

Example 1

As an example, if a preparation that is normally stored at room temperature (25°C) with an expiration date of 1 week is stored in the refrigerator (5°C), what will be the approximate new shelf-life of the product?

$$t_{90}(T2) = \frac{t_{90}(T1)}{Q_{10}^{(\Delta T/10)}} = \frac{1}{3^{(-20/10)}} = 9 \text{ weeks}$$

because 25° down to 5° is 20° in the negative direction, -20°. The increase in shelf-life will be about 9 times for a decrease in the storage temperature of -20°. This is assuming an energy of activation of about 19.4 kcal/mol.

Example 2

Considering the opposite situation, if a preparation that is normally stored at refrigeration temperature (5°) with a shelf-life of 9 weeks is stored at room temperature (25°), what will be the approximate decrease in the shelf-life of the product?

$$t_{90}(T2) = \frac{t_{90}(T1)}{Q_{10}^{(\Delta T/10)}} = \frac{9}{3^{(20/10)}} = 1 \text{ week}$$

because 5° up to 25° is in the positive direction +20°. This is also assuming an energy of activation of about 19.4 kcal/mol.

It should be noted that this method works for products for which a specific shelf-life has been determined and the only variation is in the storage temperature, not in altering any of the formulation.

Example 3

An antibiotic solution has a shelf-life of 48 hours in the refrigerator (5°C). What is its estimated shelf-life at room temperature (25°C)?

Using a Q value of 3, we set up the relationship as follows.

$$t_{90}(T2) = \frac{t_{90}(T1)}{Q_{10}^{(\Delta T/10)}} = \frac{48}{3^{\{(25-5)/10\}}} = 5.33 \text{ hours}$$

Example 4

An ophthalmic solution has a shelf-life of 6 hours at room temperature (25°C). What would be the estimated shelf-life if stored in a refrigerator (5°C)?

$$t_{90}(T2) = \frac{t_{90}(T1)}{Q_{10}^{(\Delta T/10)}} = \frac{6}{3^{\{(5-25)/10\}}} = 54 \text{ hours}$$

In summary, the Q_{10} method of shelf life estimation is based upon the number 3 raised to a certain power, either positive or negative. The power is simply the difference in storage temperatures divided by 10. Generally, one is using "3" raised to the first, second or third power, either positive or negative; meaning the numbers 3, 9 and 27 are commonly used. If the temperature increases, the shelf life is divided by 3, 9 or 27 and if the temperature decreases, the shelf life is multiplied by 3, 9 or 27. Pharmacists should keep in mind that these are estimates, and actual energies of activation can be often be obtained from the literature for more exact calculations.

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