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FORMULATION DEVELOPMENT

The formulation of a sterile product involves the combination of one or more ingredients with a medicinal agent to enhance the convenience, acceptability, or effectiveness of the product. Rarely is it preferable to dispense a drug singly as a sterile dry powder unless the formulation of a stable liquid preparation is not possible.

Therapeutic Agent

A therapeutic agent is a chemical compound subject to the physical and chemical reactions characteristic of the class of compounds to which it belongs. Therefore, a careful evaluation must be made of every

combination of two or more ingredients to ascertain whether or not adverse interactions occur, and if they do, of ways to modify the formulation so that the reactions

are eliminated or minimized. The formulation of sterile products is challenging, with respect to the knowledge and ingenuity of the persons responsible.

The amount of information available to the formulator concerning the physical and chemical properties of a therapeutic agent, particularly if it is a new compound, is often quite meager. Information concerning basic properties must be obtained, including molecular weight, solubility, purity, colligative properties, and chemical reactivity, before an intelligent approach to formulation can begin. Improvements in formulation are a continuing process, since important properties of a drug or of the total formulation may not become evident until the product has been stored or used for a prolonged time. However, because of the extensive test documentation required by the US Food and Drug Administration (FDA), only outstanding formulations can be justified for continuance to the state of a marketed product.

Vehicles or Solvent System

Aqueous Systems: the most frequently employed vehicle for sterile products is water, since it is the vehicle for all natural body fluids.

One of the most inclusive tests for the quality of water is the total solids

content, a gravimetric evaluation of the dissociated and un-dissociated organic and inorganic substances present in water.the 10 ppm total solids officially permitted for Water for Injection may be much too high when used as the vehicle for many products. Water shall contain a minimal amount of organic compounds. Such compounds are undesirable for two main reasons: they may be toxic, and/or they may serve as sources of nutrition for microorganisms. In practice, Water for Injection normally should not have a conductivity of more than 1micromho (1 megohm, approximately 0.1 ppm NaCl) and total organic carbon (TOC) not more than 500 ppm. Non-aqueous and Mixed Solvents:

In the formulation of sterile pharmaceutical products, it is sometimes necessary to eliminate water entirely or in part from the vehicle, primarily because of solubility factors or hydrolytic reactions.

Water-immiscible solvents include fixed oils, ediyl oleate, isopropyl myristate, and benzyl benzoate. The most frequently used non-aqueous solvents are polyediylene glycol, propylene glycol, and fixed oils.

Solvent selection: A parenteral therapeutic agent is given by preference as a solution. If aqueous, the solution is physiologically compatible with body tissues, and the biologic response elicited should be reasonably predictable. The high dielectric constant of water makes it possible to dissolve ionizable electrolytes, and its hydrogen bonding potential brings about the solution of such organic substances as

alcohols, aldehydes, ketones, and amines. Conversely, water is a poor solvent for nonpolar compounds, such as alkaloidal bases, which require non-polar solvents. Since therapeutically active compounds given by injection range in property from highly polar to non-polar, solvents having complementary properties must be employed if a solution is to be achieved. Adding to the complexity of solvent selection, is the requirement that solvents to be injected must be of low toxicity to body tissues. Ether is a solvent for testosterone, but is highly irritating to body tissues and cannot be used alone as a solvent for an injectable preparation. Frequently, the desired solubility can be achieved with mixed solvents, e.g. the use of approximately 40% ethanol in water to solubilize the digitalis glycosides.

Compounds that are dissolved in water are often subject to degradativereactions, such as hydrolysis, oxidation, decarboxylation, and racemization.Formulation must be designed, in such cases, to minimize the degradative effects. Often, these reactions are markedly affected by the pH of the solution. Epinephrine in solution undergoes racemization and oxidation, but if the pH is maintained at 3.0 or less, little reaction occurs. The oxidation reaction can be further reduced by displacing atmospheric oxygen with an inert head space gas and adding 0.1% (w/v) sodium metabisulfite as an antioxidant. Atropine sulfate rapidly hydrolyzes in solution, but if the pH is maintained with a buffer

system at about 3.5 to 4.0, hydrolysis does not occur at a significant rate.

The use of a mixed solvent system often reduces degradative reactions.Barbituric acid derivatives hydrolyze readily in water, particularly at a lowpH. It has been shown, however, that pentobarbital sodium is soluble and stable in a vehicle containing 60% polyethylene glycol 400 and 10% ethanol in water at a pH of 8.

The aforementioned reactions do not occur in an anhydrous, non-polar vehicle, such as fixed oil, although the presence of a

small amount of water may permit slight reactions. Oleaginous injections are subjected, however, to the disadvantages of being viscous (thus difficult to administer, particularly in cold weather) and of involving frequent incidence of pain upon injection.

Solutes

The physical and chemical purity of solutes used for sterile preparations must also be exceptional. Obviously, the contaminants entering a product with a solute have the same effect as if they entered via the vehicle. Even small traces of contaminants may be detrimental to products, necessitating purification of the solute. For a few substances (for example, ascorbic acid and calcium gluconate), special parenteral grades are commercially available.

In addition, solutes should be free from microbial and pyrogenic contamination. This entails not only proper quality of the chemical as

procured, but also storage conditions designed to prevent contamination, particularly after a container has been opened. Preferably, production lots should be designed to use the entire contents of packages of chemicals whenever possible.

Added Substances

Substances added to a product to enhance its stability are essential for almost every product. Such substances include solubilizers, antioxidants, chelating agents, buffers, tonicity contributors, antibacterial agents, antifungal agents, hydrolysis inhibitors, antifoaming agents, and numerous other substances for specialized purposes. At the same time, these agents must be prevented from adversely affecting the product. In general, added substances must be nontoxic in the quantity administered to the patient. They should not interfere with the therapeutic efficacy or with the assay of the active therapeutic compound. They must also be present and active when needed throughout the useful life of the product. Therefore, these agents must be selected with great care, and must be evaluated as to their effect upon the entire formulation.

Antibacterial agents: Antibacterial agents in bacteriostatic concentration must be included in the formulation of products packaged in multiple-dose vials, and are often included in formulations to be sterilized by marginal processes or made by aseptic manipulation.

Antioxidants: Antioxidants, included in many formulations to protect a therapeutic agent susceptible to oxidation, particularly under the accelerated conditions of thermal sterilization, may function in at least two ways., i.e. (1) by being preferentially oxidized (reducing agents), and thereby gradually used up, or (2) by blocking an oxidative chain reaction in which they are not usually consumed.In addition, certain compounds have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those blocking oxidative reactions. A fourth group of compounds are useful in this connection in that they complex with catalysts that otherwise would accelerate the oxidative reaction. Because of the differences in action, combinations of these agents are sometimes used. **Antioxidants (reducing agents)**

Ascorbic acid Sodium bisulfite

Antioxidants (blocking agents)

Ascorbic acid esters Butylated hydroxytoluene (BHT) **Synergists**

Ascorbic acid Citric acid

Chelating agents

Ethylenediaminetetraacetic acid salts

It should also be mentioned that for those products in which oxygen enters into a degradative reaction, an antioxidant effect can be achieved by displacing oxygen (air) from contact with the product. Usually, this is accomplished by saturating the liquid with either nitrogen or carbon

dioxideand sealing the final container after displacing the air above the product with the gas. *Buffers:*

Buffers are added to maintain the required pH for many products, as change in pH may cause significant alterations in the rate of degradative reactions. Changes in pH may occur during storage as a result of the dissolution of glass constituents in the product, release of constituents from rubber closures or plastic components in contact with the product,dissolution of gases and vapours from the airspace in the container and diffusion through the rubber or plastic component, or reactions within the product. Buffers must have the capacity to maintain the pH of the productagainst these influences, but not enough to prevent the body fluids from over whelming the buffer ollowing administration. In most cases, the biologic effectiveness of the drug is maximum at or near the biologic fluid pH rather than at the stabilizing pH of the injected product.

Acetates, citrates and phosphates are the principal buffer systems used, but buffer systems making use of other ingredients in the formulation are often used to reduce the total number of ingredients in the product.

Tonicity contributors:

Compounds contributing to the isotonicity of a product reduce the pain of injection in areas with nerve endings. Various agents are used in sterile products to adjust tonicity. Simple electrolytes

such as sodium chloride or other sodium salts and non electrolytes such

as glycerin and lactose are most commonly used for this purpose.

Chelating agents:

Chelating agents may be added to bind, in nonionizable form, trace amounts of heavy metals, which if free, would catalyze degradative changes. The chelating agent most commonly used is the trisodium or calcium disodium salt of ethylenediamine tetra-acetic acid in a concentration of about 0.05% (w/v). *Inert gases:*

These have been used to displace oxygen from a solution and reduce the possibility of oxidative changes in the formulation. Inert gases may be used to stabilize solutions in other ways. For

example, sodium bicarbonate injection decomposes, particularly during autoclaving, to produce sodium carbonate, carbon dioxide, and water. Saturation of the solution with carbon dioxide inhibits this reaction and stabilizes the solution. *Protein stabilizers:*

A number of ingredients have been shown to stabilize proteins, both in the dry and solution state. Serum albumin competes with therapeutic proteins for binding sites in glass and other surfaces and minimizes the loss of the protein caused by surface binding.A number of different types of substances are used as **cryoprotectants** and **lyoprotectants** to minimize protein denaturation during freeze-drying. Antioxidants, buffers and chelating agents are also used to stabilize proteins in solution when necessary.

CONTAINERS

Glass containers traditionally have been used for sterile products, many of which are closed with rubber stoppers. Interest in plastic containers for parenterals is increasing, and such containers are being used for commercial ophthalmic preparations and IV solutions.

Plastic Containers:

The principal ingredient of the various plastic materials used for containers is the thermoplastic polymer. Although most of the plastic materials used in the medical field have a relatively low amount of added ingredients, some contain a substantial amount of plasticizers, fillers, antistatic agents, antioxidants, and other ingredients added for special purposes. These ingredients are not usually chemically bound in the formulation and, therefore, may migrate out of the plastic and into the product under the conditions of production and storage. Considerable variability also has been encountered in the purity of the commercially available polymers. Plastic containers are used mainly because they are light in weight, are non-breakable, and, when low in additives, have low toxicity and low reactivity with products. Tissue toxicity can occur from certain polymers, but additives are a more common cause. Reactivity due to sorption(absorption and/or adsorption) has been found to occur most frequently with the polyamide polymers, but additives leached from any of the plastic materialsmay interact with ingredients of the product.

Glass Containers

Glass is still the preferred material for containers for injectable products.The two general types of glass are soda-lime and borosilicate. The glass that is most resistant chemically is composed almost entirely of silicon dioxide, but it is relatively brittle and can only be melted and molded at high temperatures. The USP provides the Powdered Glass and the Water Attack tests for evaluating chemical resistance of glass. The test results are measures of the amount of alkaline constituents leached from the glass by purified water under controlled elevated temperature conditions; the Powdered Glass test is performed on ground, sized glass particles, and the Water Attack test is performed on whole containers.On the basis of the results from the official tests, glass compounds are classified into four types. The greatest chemical resistance is provided by Type I, and the least by NP (non-parenteral) glass. It should be noted, however, that within these types, as well as Types II and III. Type I glass is preferred for most sterile products, but Types II and III may be used when the product has a non-aqueous vehicle or the period of contact with the aqueous vehicle is brief, as with dry powders reconstituted just prior to use, or if the non reactivity between the glass and product has been established. *Physical Characteristics*

The protection of light-sensitive products from the degradative effect of ultraviolet rays may be one of the important physical characteristics

of a glass container. Ultraviolet rays can be completely filtered out by the use of amber glass. Container use Considerations

Single-dose containers are intended to provide sufficient drug for just one dose, the integrity of the container being destroyed when opened so that it cannot be reclosed and used again. Single-dose containers may range from liter bottles of IV solutions to 1 ml, or smaller, cartridges. The desire for further reduction in the risk of contamination, both bacterial and viral, and an increased control over the administration of drugs, particularly in a hospital, have led to the recent development of single-dose, disposable administration units. For most of these units, the product container is a glass cartridge with plastic and metal fitments separated from immediate contact with the product.

Rubber Closures

Rubber closures are used to seal the openings of cartridges, vials, and bottles, providing a material soft and elastic enough to permit entry and withdrawal of a hypodermic needle without loss of the integrity of the sealed container.

Ideally, closures should be completely nonreactive with the product with which they are in contact. No such ideal compound exists; therefore, each rubber compound should be tested for compatibility with each preparation with which it is to be used. Two general compatibility problems exist, namely, the leaching of ingredients from the rubber compound with subsequent reaction with ingredients of the product, and the removal of ingredients from the product by sorption by

the rubber compound or by vapour transfer through the closure. Several properties of rubber closures are significant, particularly elasticity, hardness, and porosity. Rubber closures must be sufficiently elastic to provide a snug fit between the closure and the neck and lip of the glass container.

Devices

Devices associated with sterile products include the following: Administration sets for large volume parenterals (LVPs) Filter needles

Hypodermic needles

Hypodermic syringes

In-line filters

Plastic irrigating solution bottles

Plastic LVPs containers

Plastic ophthalmic dropping bottles

Transfer needles

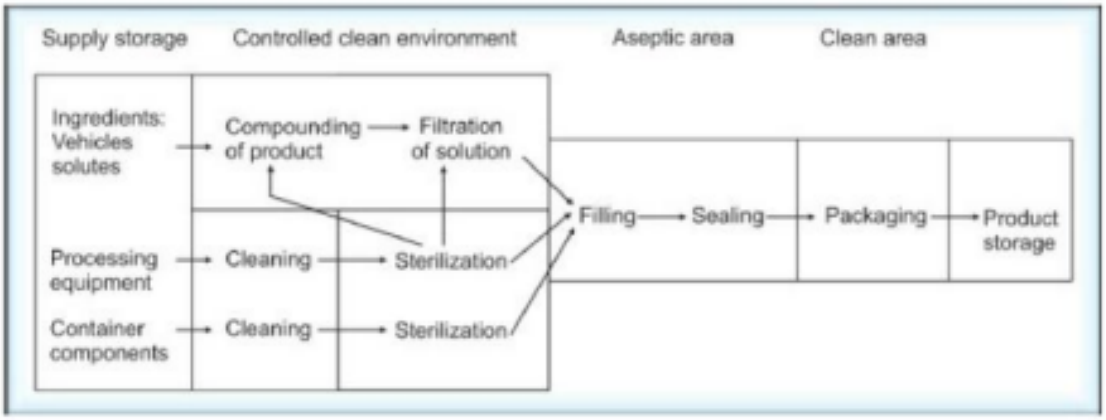
Transfer sets

Although the contact time of the product with the device is usually brief, it is intimate; therefore, compatibility between the device and the product must be evaluated. For example, it has been shown that insulin can be adsorbed by PVC tubing during the time of contact for administrative of an IV solution, approximately 6 h.

PRODUCTION

The production process includes all of the steps from the accumulation and combining of the ingredients of the formula to the enclosing of the

product in the individual container for distribution. Intimately associated with these processes are the personnel who carry them out and the facilities in which they are performed. The most ideally planned processes can be rendered ineffective by personnel who do not have the right attitude or training, or by facilities that do not provide an efficiently controlled environment. To enhance the assurance of successful manufacturing operations, all process steps must be carefully reduced to writing after being shown to be effective.



Quality Control

The three general areas of quality control are incoming stock, manufacturing (processing), and the finished product. For sterile products, incoming stock control encompasses routine tests on all ingredients as well as special evaluations such as pyrogen tests on WFI, glass tests on containers, and identity tests on rubber closures. It also may be necessary to perform microbial load (bioburden) tests to determine the number and types of microorganisms present. Process control in the manufacture of sterile products involves all of the innumerable tests, readings, and observations made throughout the manufacturing process of a product, including conductivity measurements during the distillation of WFI, confirmation of volume

of fill in product containers, recording of cycle time and temperature for thermal sterilization of the product, and confirming the count and identity of labels for the product. The production control includes all of the final assays and tests to which the product is subjected. In addition to the usual chemical and biologic tests, a sterile product is subjected to a leak test (when applicable), a clarity test, a pyrogen test (when applicable), and a sterility test. Leak Test

Ampoules are intended to provide a hermetically sealed container for a single dose of a product, thereby completely

barring any interchange between the contents of the sealed ampoule and its environment.

The leak test is intended to detect incompletely-sealed ampoules so that they may be discarded. Tip-sealed ampoules are more likely to be incompletely sealed than are those that have been pull-sealed. In addition, small cracks may occur around the seal or at the base of the ampoule as a result of improper handling. Vials and bottles are not subjected to such a leak test because the rubber closure is not rigid; however, bottles are often sealed while a vacuum is being pulled so that the bottle remains evacuated during its shelf-life.

Clarity Test

Clarity is a relative term, the meaning of which is markedly affected by the subjective evaluation of the observer. Unquestionably, a clean solution having a high polish conveys to the observer that the product is of exceptional quality and purity. It is practically impossible,

however, to prepare a lot of a sterile product so that every unit of that lot is perfectly free from visible particulate matter, i.e. is, from particles that are 30 to 40 μm and larger in size.

Although particulate matter is of primary concern in products given intravenously, all parenteral products should be free from insoluble particles.

Suspensions, emulsions, or dry solids, in addition to solutions, should be compounded and processed under clean conditions to minimize the presence of foreign particles.

The visual inspection of a product container is usually done by individual human inspection of each externally clean container under good light, baffled against reflection into the eyes, and viewed against a black and white background, with the contents set in motion with a swirling action, since a moving particle is much easier to see than one that is stationary.

Pyrogens and Pyrogen Test

Water used in parenteral and irrigating solutions should be free of pyrogens. To achieve this, proper controls must be maintained in the preparation and storage of water. Pyrogens are products of metabolism of microorganisms. Most bacteria and many molds and viruses have been reported as producing pyrogens. The gram-negative bacteria produce the most potent pyrogenic substances as endotoxins. Chemically, pyrogens are

lipid substances associated with a carrier molecule, which is usually a

polysaccharide but may be a peptide.

About 1 h after injection into man, pyrogens roduce a marked rise in body temperature, chills, body aches, cutaneous vasoconstriction, and a rise in arterial blood pressure. Antipyretics eliminate the fever, but not the other systemic effects of pyrogens.

The fever response to pyrogens in rabbits is the basis for the official pyrogen test.

Sterility Test

All products labeled "sterile" must pass the sterility test, having been subjected to an effective process of sterilization. The test for sterility is intended for detecting the presence of viable form of microbes in pharmacopoeial preparations.

Method A: Membrane Filtration

A suitable unit consists of a closed reservoir and a receptacle between which a properly supported membrane of appropriate porosity is placed. A membrane suitable for sterility test has a nominal pore size not greater than 0.45 μm, diameter of approximately 47 mm and whose effectiveness to retain

microorganisms has been established. Cellulose nitrate filters, for example, are used for aqueous, oily, and weakly alcoholic solutions; and cellulose acetate filters, are used for strongly alcoholic solutions. Specially adapted filters may be needed for certain products such as antibiotics.

Method B: Direct Inoculation

Apart from testing oily solutions, creams, ointments and solid products, direct inoculation method is utilized particularly for surgical devices, sterile devices, surgical dressings and sutures, in case where membrane filtration method appears difficult. In this test, the quantity of the preparation to be examined is transferred directly into the culture medium so that the volume of the product is not more than 10% of the volume of the medium, unless otherwise prescribed.