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Anti Neoplastic Drugs Used in Cancer

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ABSTRACT

Cancer known medically as a malignant neoplasm, is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous. Benign tumors do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body. There are over 200 different known cancers that afflict humans.[1] Determining what causes cancer is complex. Many things are known to increase the risk of cancer, including tobacco use, certain infections, radiation, lack of physical activity, obesity, and environmental pollutants.[2] These can directly damage genes or combine with existing genetic faults within cells to cause the disease.[3] Approximately five to ten percent of cancers are entirely hereditary.

INTRODUCTION

Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests, or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample. Cancer is usually treated with chemotherapy, radiation therapy and surgery. The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment. While cancer can affect people of all ages and a few types of cancer are more common in children, the risk of developing cancer generally increases with age. In 2007, cancer caused about 13% of all human deaths worldwide (7.9 million). Rates are rising as more people live to an old age and as mass lifestyle changes occur in the developing world.[4]

1.1 Classification

Further information: List of cancer types and List of oncology-related terms:

Cancers are classified by the type of cell that the tumor cells resemble and are therefore presumed to be the origin of the tumor. These types include:

- Carcinoma: Cancers derived from epithelial cells. This group includes many of the most common cancers, particularly in the aged and include nearly all those developing in the breast, prostate, lung, pancreas and colon.

- Sarcoma: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve) each of which develop from cells originating in mesenchymal cells outside the bone marrow.

- Lymphoma and leukemia: These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively. Leukemia is the most common type of cancer in children accounting for about 30%.[5]

- Germ cell tumor: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

- Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue. Blastomas are more common in children than in older adults.

Chronic Lymphocytic Leukemia

B-cell chronic lymphocytic leukemia (B-CLL), also known as chronic lymphoid leukemia (CLL), is the most common type of leukemia. Leukemia's are cancers of the white blood cells (leukocytes). CLL affects B cell lymphocytes. B cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection by producing antibodies. B cells grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells. CLL is a stage of small lymphocytic lymphoma (SLL), a type of B-cell lymphoma, which presents primarily in the lymph nodes.[6] CLL and SLL are considered the same underlying disease, just with different appearances. CLL is a disease of adults, but, in rare cases, it can occur in teenagers and occasionally in children (inherited). Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men.

DNA analysis has distinguished two major types of CLL, with different survival times. CLL that is positive for the marker ZAP-70 has an average survival of 8 years. CLL that is negative for ZAP-70 has an average survival of more than 25 years. Many patients, especially older ones, with slowly progressing disease can be reassured and may not need any treatment in their lifetimes.[7]

CLL is usually first suspected by the presence of a lymphocytosis, an increase in one type of white blood cell, on a complete blood count (CBC) test. This frequently is an incidental finding on a routine physician visit. Most often the lymphocyte count is greater than 4000 cells per microliter (µl) of blood, but can be much higher. The presence of a lymphocytosis in an elderly individual should raise strong suspicion for CLL, and a confirmatory diagnostic test, in particular flow cytometry, should be performed unless clinically unnecessary.

CLL treatment focuses on controlling the disease and its symptoms rather than on an outright cure. CLL is treated by chemotherapy, radiation therapy, biological therapy, or bone marrow transplantation. Symptoms are sometimes treated surgically (splenectomy removal of enlarged spleen) or by radiation therapy ("de-bulking" swollen lymph nodes).

Initial CLL treatments vary depending on the exact diagnosis and the progression of the disease, and even with the preference and experience of the health care practitioner. There are dozens of agents used for CLL therapy.[21] An initial treatment regimen that contains fludarabine, cyclophosphamide, and rituximab (known as FCR) has demonstrated higher overall response rates and complete response rates.[8]

1.2 Non-Hodgkin Lymphoma

The non-Hodgkin lymphomas (NHLs) are a diverse group of blood cancers that include any kind of lymphoma except Hodgkin's lymphomas.[9] Types of NHL vary significantly in their severity, from indolent to very aggressive.

Non-Hodgkin lymphoma (NHL) is a cancer of a type of white blood cell called lymphocytes. Lymphocytes are part of the immune system that protects the body from infection and disease. NHL is a group of 30 or more cancers that begin in the lymphocytes.

These cancers are similar in some ways but have many differences in the way they affect people. They are all called non-Hodgkin lymphoma to distinguish them from another cancer of the lymphocytes called Hodgkin lymphoma.

The latest lymphoma classification, the 2008 WHO classification, largely abandoned the "Hodgkin" vs. "Non-Hodgkin" grouping. Instead, it lists over 80 different forms of lymphomas in four broad groups.[10]

A number of peer-reviewed health studies have shown a causal link between non-Hodgkin lymphoma and exposure to polychlorinated biphenyls (PCBs), a persistent organic pollutant now found throughout the natural environment.[11][12][13]

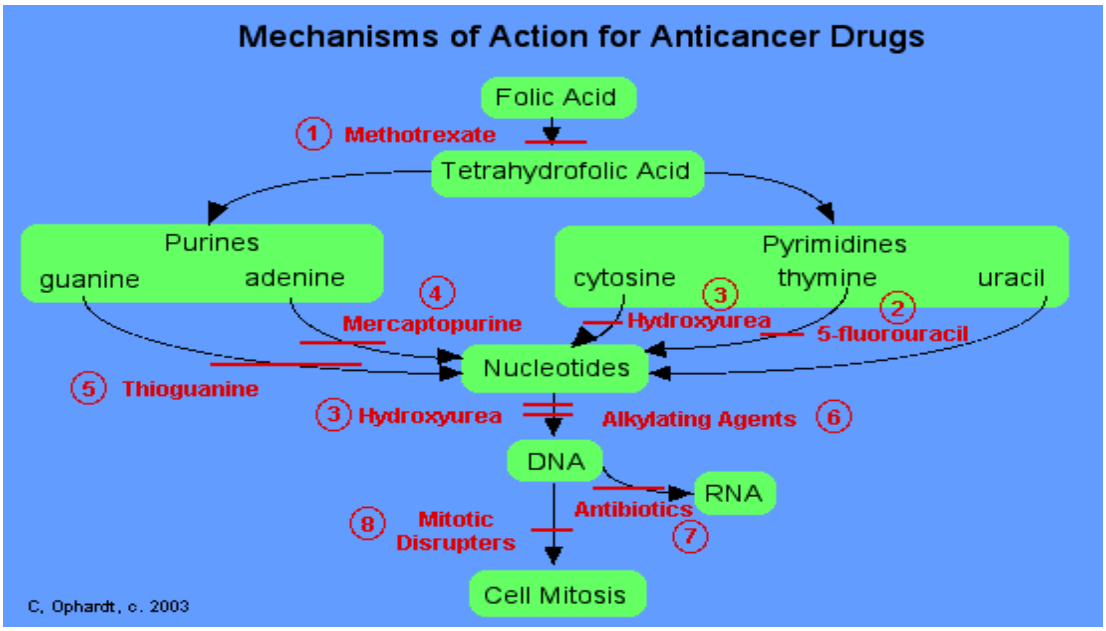

Figure No. 1: Mechanism of Action of some Anticancer Drugs [14]

Table No. 1: Antineoplastic Drugs Used in Cancer

Sl. No.	Category	Explanation	Drugs examples
1	Alkylating agents	Alkylating agents are so named because of their ability to alkylate many nucleophilic functional groups under conditions present in cells.	Cisplatin, Oxaliplatin and carboplatin
2	Anti-metabolites	Masquerade as purines which become the building-blocks of DNA. They prevent these substances from becoming incorporated in to DNA during the "S" phase (of the cell cycle), stopping normal development and division. They also affect RNA synthesis. Due to their efficiency, these drugs are the most widely used cytostatics	azathioprine, mercaptopurine or pyrimidines
3	Plant alkaloids and terpenoids	These alkaloids are derived from plants and block cell division by preventing microtubule function. Microtubules are vital for cell division, and, without them, cell division cannot occur. The main examples are vinca alkaloids and taxanes.	Vincristine, Vinblastine Vinorelbine &Vindesine Prototype taxane is the natural product paclitaxel, originally known as Taxol
4	Topoisomerase inhibitors	Topoisomerases are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling.	Irinotecan, Topotecan and etoposide and teniposide
5	Cytotoxic antibiotics [anthracyclines and actinomycins	A group of antibiotics that are used for the treatment of cancer because they interfere with DNA replication and protein synthesis	Anthracyclines: Doxorubicin, Epirubicin Actinomycin: Bleomycin and mitomycin
6	Nitrogen mustards	Are cytotoxic chemotherapy agents similar to mustard gas. Nitrogen mustards are nonspecific DNA alkylating agents	Melphalan and Bendamustine
7	Cytidine analogs [demethylating agents]	Are cytidine analogs that contain a nitrogen in place of the 5-carbon of the pyrimidine ring. Each enters the cell via nucleoside transporters, such as the confirmed human concentrative nucleoside transporter 1 (hCNT1) and equilibrative nucleoside transporter 1 (hENT1)	Azacitidine and decitabine
8	Proteasome inhibitor	Are drugs that block the action of proteasomes, cellular complexes that break down proteins, like the p53 protein. Proteasome inhibitors are being studied in the treatment of cancer, especially multiple myeloma.	Bortezomib and carfilzomib

Newer and Experimental Approaches

Isolated Infusion Approaches

Isolated limb perfusion (often used in melanoma), or isolated infusion of chemotherapy into the liver or the lung have been used to treat some tumours. The main purpose of these approaches is to deliver a very high dose of chemotherapy to tumor sites without causing overwhelming *systemic* damage. These approaches can help control solitary or limited metastases, but they are by definition *not* systemic, and, therefore, do not treat distributed metastases or micrometastases.

Targeted Delivery Mechanisms

Specially targeted delivery vehicles aim to increase effective levels of chemotherapy for tumor cells while reducing effective levels for other cells. This should result in an increased tumor kill and/or reduced toxicity. Specially targeted delivery vehicles have a differentially higher affinity for tumor cells by interacting with tumor-specific or tumor-associated antigens.

In addition to their targeting component, they also carry a payload - whether this is a traditional chemotherapeutic agent, or a radioisotope, or an immune-stimulating factor. Specially targeted delivery vehicles vary in their stability, selectivity and choice of target, but, in essence, they all aim to increase the maximum effective dose that can be delivered to the tumor cells. Reduced systemic toxicity means that they can also be used in sicker patients and that they can carry new chemotherapeutic agents that would have been far too toxic to deliver via traditional systemic approaches.

Nanoparticles

Nanoparticles have emerged as a useful vehicle for poorly soluble agents such as paclitaxel.[15] Protein-bound paclitaxel (e.g., Abraxane) or nab-paclitaxel was approved by the U.S. Food and Drug Administration (FDA) in January 2005 for the treatment of refractory breast cancer. This formulation of paclitaxel uses human albumin as a vehicle and not the Cremophor vehicle used in Taxol. Nanoparticles made of magnetic material can also be used to concentrate agents at tumour sites using an externally applied magnetic field.

Electro-chemotherapy

Electro-chemotherapy is the combined treatment in which injection of a chemotherapeutic drug is followed by application of high-voltage electric pulses locally to the tumor. The treatment enables the chemotherapeutic drugs, which otherwise cannot or hardly go through the membrane of cells (such as bleomycin and cisplatin), to enter the cancer cells. Hence, greater effectiveness of antitumor treatment is achieved. Clinical electro-chemotherapy has been successfully used for treatment of cutaneous and subcutaneous tumors irrespective of their histological origin.[16][17][18][19][20][21][22]. The method has been reported as safe, simple and highly effective in all reports on clinical use of electrochemotherapy. According to the ESOPE project (European Standard Operating Procedures of Electro-chemotherapy), the Standard Operating Procedures (SOP) for electrochemotherapy were prepared, based on the experience of the leading European cancer centers on electrochemotherapy.[23] Recently, new electro-chemotherapy modalities have been developed for treatment of internal tumors using surgical procedures, endoscopic routes or percutaneous approaches to gain access to the treatment area.[24][25]

PARENTERAL DOSAGE FORMS: [26, 27,28,29 30]

The term "parenteral" is applied to preparations administered by injection through one or more layers of skin tissue. The word is derived from the Greek words, para and enteron, meaning outside of intestine and is used for those dosage forms administered by routes other than the oral route.

MERITS OF PARENTERAL ADMINISTRATION:

The increasing use of parenteral administration is due in part to the number of advantages it offers:

An immediate physiologic response can be achieved if necessary, which can be of prime consideration in clinical conditions such as cardiac arrest, asthma and shock.

Parenteral therapy is required for drugs that are not effective orally or that are destroyed by digestive secretions, such as insulin, other hormones and antibiotics. Drugs for uncooperative, nauseous, or unconscious patients must be administered by injection.

When desirable, parenteral therapy gives the physician control of the drug, since the patient must return for continued treatment. Also, in some cases, the patient cannot be relied upon to take oral medication. Parenteral administration can result in local effects for drugs when desired, as in dentistry and anesthesiology.

In cases in which prolonged drug action is wanted, parenteral forms are available, including the long acting steroids injected intra-articularly and the long-acting penicillin's administered by deep intramuscular injection.

Parenteral therapy provides the means of correcting serious disturbances of fluid and electrolyte balances. When food cannot be taken by mouth, total nutritional requirements can be supplied by the parenteral route.

DEMERITS OF PARENTERAL ADMINISTRATION:

Regardless of the parenteral route of administration, a number of disadvantages are inherent in parenteral procedures.

The dosage forms must be administered by trained personnel and require more time than those administered by other routes. Parenteral administration requires strict adherence to aseptic procedures and some pain on injection is inevitable. Once a drug has been given parenterally, it becomes more difficult to reverse its physiologic effect.

Finally, because of the manufacturing and packaging requirements, parenteral dosage forms are more expensive than preparations given by other routes.

ROUTES OF ADMINISTRATION:

Each route of administration calls for products with special qualities. Three primary routes of parenteral administration are commonly employed

They are:- **Hypodermic (Subcutaneous):** injection under the dermis, into the subcutaneous tissues. Volume of the injection rarely exceeds 1.0 ml.

Intramuscular: injection into the muscles of the shoulder, thigh or buttock. Volume rarely exceeds 2.0 ml. Aqueous or oily suspensions and oily solutions are given by this route. A very popular route for administration of large number of injectables.

Intravenous: injection into the median basilic vein, near the anterior surface of the bow. The volume of such injection can vary from 1.0 - 500 ml.

Sometimes it is more than 500 ml. Certain anesthetics, fluids, electrolytes, continuous nutrition and IV admixtures of several drugs for diseases which require prompt administration are done by this route.

These three routes satisfy to a large extent the four principal reasons for administering parenterals: for therapy (definitive or palliative), for prevention, for diagnosis & for temporarily altering tissue functions in order to facilitate other forms of therapy.

FORMULATION OF SMALL VOLUME PARENTERALS:

Vehicles:

A. Water

By far the most frequently employed vehicle for sterile products is water since it is the vehicle for all natural body fluids. The superior quality required for such use is described in the monograph on water for injections in the U.S.P. Requirements may be even more stringent for some products

B. Non Aqueous Solvents:

A non-aqueous solvent must be selected with great care for it must not be irritating, toxic, or sensitizing, and it must not exert any adverse effect on the ingredients of the formulation.

The screening of such a solvent must therefore include an evaluation of its physical properties, such as density, viscosity, miscibility, polarity, stability, solvent activity and toxicity.

Solvents that are miscible with water, and that usually used in combination with water as the vehicle, include dioxolanes, dimethylacetamide, N(Beta-hydroxy ethyl) lactamide, butylene glycol, polyethylene glycol 400 and 600, propylene glycol, glycerine and ethyl alcohol. The most frequently used non-aqueous solvents are propylene glycol, polyethylene glycol and fixed oils.

Water immiscible solvents include fixed oils, ethyl oleate, isopropyl myristate and benzyl benzoate. A number of vegetable oils are used as solvents, including soybean, peanut, cottonseed, corn, olive and sesame oil. Oils of mineral origin or hydrocarbons, cannot be used since these materials are not metabolized by the body.

An oily vehicle may be necessary if the medicament is insoluble or only slightly soluble in water, when a depot effect is desired and when an oily medium is more suitable for diagnostic procedure. Oily injection suffer from the disadvantages, they may be too viscous in cold weather, they often cause pain on injection, they make the syringe and needle difficult to clean and they must be injected with great care to avoid accidental intravenous injection which could lead to thrombosis.

Added Substances:

Substances added to a product to enhance its stability are essential for almost every product. Such substances include solubilizers, antioxidants, chelating agents, antifungal agents, hydrolysis inhibitors, anti-foaming agents and numerous other substances for specialized purposes.

A. 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.

B. 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., by preferentially getting oxidized and thereby gradually used up, or 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 which otherwise would accelerate the oxidation reaction.

Because of the differences in action, combinations of these agents are sometimes used lists the most commonly employed antioxidants in sterile products.

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 by saturating the liquid with either nitrogen or carbon dioxide and sealing the final container after displacing the air above the product with the gas.

C. Buffers:

Buffers are added to maintain a required pH for many products to avoid any significant alteration in the rate of degradative reactions. Acetates, citrates and phosphates are the principal buffer system's 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.

D. Tonicity Contributors:

Compounds contributing to the isotonicity of a product reduce the pain of injection in areas with nerve endings. Buffers may serve as tonicity contributors as well as stabilizers for the pH. Other added substances also contribute to the colligative properties of the preparation. Whenever possible such dual activity is desirable.

STERILIZATION:

Sterilization is the process designed to produce a sterile state. Sterile state or sterility is defined as the total absence of viable life forms. The concept of sterility is absolute and acknowledges no boundaries. In real terms, sterility is therefore a descriptive and limited concept. A sterile item is one that does not contain, carry, or harbor any viable life forms. The sterile item must be protected from contamination from the general environment, otherwise, it becomes non-sterile.

Filtration:

Filtration may be used for the removal of particles, including microorganisms, from solutions and gases without the application of heat. This process depends upon the physical removal of organism by passage through a bacteria proof filter, it is used for the sterilization of thermo-labile solutions, useful process for sterilization of large volume solutions and gases including

air.

Membrane filters are composed of various types of cellulose and cellulose esters. A vast range of grades and pore sizes are available. They are very thin and need careful handling. The pore size most often used for sterilization is 0.22 micron. For clarification sometimes 0.45 micron filters are used. They are sterilized by autoclaving, in the holder or packed between thick filter pads to prevent curling.

Advances in Aseptic Processing Technology;

1. In Clean Room Design:

A conventional class 100 cleanroom technology has advanced in design compared to clean room in the microelectronics field. Class 1 cleanrooms used in microelectronic manufacturing are superior to contemporary pharmaceutical clean rooms in controlling nonviable particulates. To maximize the laminarity of the airflow the entire floor may be perforated to serve as return air duct.

Elimination of personnel from the aseptic manufacturing i.e., operation by robots would make further improvements in air quality in obtaining quantitative improvement in sterility assurance levels (SAL).

2. Gowning:

Full shield length helmet covering entire head with full vision face shield with an ancillary portable High Efficiency Particulate air HEPA filter is being developed. Air conditioned suits - a complete single piece garment with a separate helmet having integral cooling to maintain the operator comfortable, at the same time presenting complete barrier to passage of microorganisms and particulates are being used. These are made up of polyvinyl chloride (PVC) and functions as individual barrier system.

3. Absolute Barriers:

They are used in USA and UK for vial/ampoule filling. They are made of either flexible PVC or rigid plastic composites. Operators have access to their work stations by means of partial bodysuits made of clear flexible plastic with integral sleeves and gloves. The sleeves and gloves may be used alone for access to machine adjustments or critical setup, or changeover

locations.

Absolute barriers are cold sterilized by using hydrogen peroxide, per acetic acid or formaldehyde. With absolute barrier technology coming into vogue, the total elimination of personnel contamination should make SAL greater than 10^{-6} achievable.

4. Automation and Robotics:

Filling and stoppering equipment are becoming more and more automated. Remote computer control is used for adjustments, fill volume settings, weight checking and automation of lyophilizers to reduce the need of employee intervention.

Robots are used for loading of partially stoppered vials, automatic loading and unloading of lyophilizers, material handling - loading stoppered bowls and automated vision systems which in conjunction with robots can detect and remove damaged, unstoppered or empty containers.

5. Electrophoretic Air Systems:

In this, charged particles move toward a positive or negative pole in an electric field. It is used to remove particulate materials from air in submarines, space vehicles and microelectronics clean rooms. These systems can remove both inorganic and organic particulate material including microorganisms.

These can remove particles ranging from 0.01 mcg to greater than 100 mcg. The ability of electrophoresis to remove very small particles with a range of 0.01 micrometer indicates the potential to remove virus particle from air.

LYOPHILIZATION [31, 32, 33, 34, 35, 36, 37, 38.]

Lyophilization or Freeze drying fills an important need in pharmaceutical manufacturing technology by allowing drying of heat-sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation, or a change of phase from solid to vapor without passing through the liquid phase. The most common application of pharmaceutical freeze drying is in the production of injectable dosage forms, the process is also used in the production of diagnostics and, occasionally, for oral solid dosage forms where a very fast dissolution rate is desired.

Freeze drying of pharmaceutical solutions to produce an elegant stable powder has been a standard practice employed to manufacture many marketed pharmaceutical injectable products. There are several characteristics of the freeze dry process that make it desirable over other drying methods.

Freeze drying as a practical commercial process was introduced around the time of the Second World War and found its first application in preservation of blood plasma, followed by manufacture of penicillin and other antibiotics. Application of freeze drying has continued to grow to include vaccines, steroids, vitamins and a wide range of diagnostic products. The relative importance of freeze drying in pharmaceutical science will continue to expand with the development of the next generation of therapeutic agents from discovery research through clinical trials, FDA approval and market introduction.

Many of these new products are proteins that are chemically or physically unstable in aqueous solution and depend on maintenance of the proper secondary, tertiary and even quaternary structure for biological activity.

Formulation and manufacture of injectable dosage forms of these agents present a challenge to the pharmaceutical scientist, and freeze drying will be a necessary tool for the development of these products.

Lyophilization or freeze drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase.

The advantages of Lyophilization Include:

- Ease of processing a liquid, which simplifies aseptic handling
- Enhanced stability of a dry powder
- Removal of water without excessive heating of the product
- Enhanced product stability in a dry state
- Rapid and easy dissolution of reconstituted product

Disadvantages of Lyophilization Include:

- Increased handling and processing time
- Need for sterile diluent upon reconstitution
- Cost and complexity of equipment

The process consists of three separate, unique, and interdependent processes;

1. Freezing,

2. Primary drying (sublimation), and

3. Secondary drying (desorption).

FREEZING PROCESS/ PRINCIPLE OF LYOPHILIZATION:

Freezing is a critical step, since the microstructure established by the freezing process usually represents the microstructure of the dried product. The product must be frozen to a low enough temperature to be completely solidified. Since freeze drying is a change in state from the solid phase to the gaseous phase, material to be freeze, dried must first be adequately pre-frozen. The method of pre-freezing and the final temperature of the frozen product can affect the ability to successfully freeze dry the material.

Rapid cooling results in small ice crystals, useful in preserving structures to be examined microscopically, but resulting in a product that is more difficult to freeze dry. Slower cooling results in larger ice crystals and less restrictive channels in the matrix during the drying process.

Of all pharmaceutical unit operations, drying processes contribute the most to the manufacturing cost. Lyophilization is the most expensive of all drying operations both in capital investment and in operating expense. The high cost and commercial value per production batch demands careful attention to process design and process control. The heat input during the lyophilization process must be well controlled to insure that the product temperature does not become too high. The structure of the product deteriorates at too high temperatures and the final quality of the product becomes unacceptable.

Lyophilization stabilizes the formulation by slowing the kinetic clock of the degradation process. it alters the clock by removing the solvent component or components to levels that never support chemical reactions or biological growth.

THE PRIMARY DRYING PROCESS (SUBLIMATION)

Sublimation of ice is not an inherently slow process. Sublimation, the change of phase from a solid to a vapor at constant temperature, is a relatively fast process and is not the rate-limiting factor in freeze drying.

Transfer Operations in Primary Drying

Freeze drying involves transfer of heat and mass to and from the product under preparation, conceptually, all transfer operations such as heat and mass transfer are described as a flow rate, or flux, being determined by a driving force divided by a resistance. The overall drying rate is determined by driving forces (temperature differences or pressure differences) divided by the sum of a series of resistances to either heat or mass transfer.

Heat Transfer in Primary Drying

Transfer of heat from the heat source usually a heated shelf to the product is often the rate-limiting step in the freeze drying process There are three basic mechanisms for heat transfer:

1. Conduction

2. Convection

3. Radiation

Conduction is the transfer of heat by molecular motion between differential volume elements of a material.

Convection is the transfer of heat by bulk flow of a fluid, either from density differences (natural convection) or because an external force Is applied (forced convection). Heat transfer by natural convection has been shown to be negligible at the low pressures encountered in freeze drying.

Heat transfer by thermal radiation arises when a substance, because of thermal excitation, emit radiation in an amount determined by its absolute temperature.

Mass Transfer in Primary Drying

Mass transfer in primary drying refers to the transfer of water vapor from the product through open channels, created by the prior sublimation of ice, to the condenser.

SECONDARY DRYING:

The secondary drying process reduces the free water in the product. After primary freeze drying is complete and all ice has sublimed, bound moisture is still resent in the product. The product appears dry, but the residual moisture content may be as high as 7-8%. Continued drying is necessary at the warmer temperature to reduce the residual moisture content to optimum values.

This process is called isothermal desorption as the bound water is desorbed from the product.

The desorption phase or secondary drying starts when ice is being distilled away and a higher vacuum allows the progressive extraction of bound water at above zero temperatures.

Secondary drying is normally continued at a product temperature higher than ambient but compatible with the sensitivity of the product. All other conditions, such as pressure and collector temperature, remain the same. Because the process is desorptive, the vacuum should be as low as possible (no elevated pressure) and the collector temperature as cold as can be attained. Secondary drying is usually carried out for approximately 1/3 to 1/2 the time required for primary drying.

Process Overview

Vials are aseptically filled with the solution to be freeze dried and are usually partially stoppered with a special slotted rubber closure that allows escape of water vapor when the stopper is inserted halfway into the neck of the vial. Vials are transferred under aseptic conditions, generally in metal trays, to the freeze dryer.

Trays of product are placed on shelves containing internal channels allowing circulation of silicone oil or another suitable heat transfer fluid. Shelves may be pre-chilled or not, depending on the solution stability of the product. The tray will have a removable bottom, which allows the vials to rest directly on the shelf, thus eliminating one resistance to heat transfer. A temperature-measuring device may be placed in several vials spaced throughout the chamber

prior to freezing and connected to an external device for process monitoring and sequencing of the freeze dry cycle.

The product is first frozen to a low enough temperature to allow complete solidification of the contents of each vial, then the chamber is evacuated until the pressure is less than the vapor pressure of ice at the temperature of the product.

After this pressure is reached, heat is applied to the shelves to provide the energy required for sublimation of ice. As drying proceeds, a receding boundary can be observed in the vial as the frozen layer decreases in thickness and the thickness of the partially dried solids increases. This phase is called primary drying. When the ice is gone, additional drying time is required to remove water adsorbed to, or trapped by, the solid matrix. This is called secondary drying when the product is sufficiently dry, the vials are usually stoppered in place within the dryer by hydraulic compression of the shelf stack, which pushes the stoppers to the fully inserted position, either under a full vacuum or by backfilling the chamber with an inert gas.

The most important objective in developing a freeze dried product is to assure that quality requirements are met not only initially but throughout the shelf life of the product. Examples of critical requirements are recovery of the original chemical or biological potency after reconstitution, rapid and complete dissolution, appropriate residual moisture level, and acceptable cake appearance.

Of all pharmaceutical unit operations, drying processes contribute the most to manufacturing cost of all drying operations, freeze drying is the most expensive, both in capital investment and in operating expense.

PROCESS MONITORING

The high cost per production lot of many therapeutic agents demands careful attention to process monitoring. One freeze dryer load of some of the newer biotechnology-derived therapeutic agents may represent millions of dollars in sales. This cost may not be recoverable if product is damaged during freeze drying. Product temperature during freeze drying is determined by the relative rates of heat and mass transfer, which is governed by both the shelf temperature and chamber pressure. Thus, both shelf temperature and chamber pressure are critical process variables. The observed value of these variables depends on the method used for measurement. This is particularly true for pressure measurement.

FREEZE DRY EQUIPMENT

A freeze drying system for production of pharmaceutical dosage forms consists of a chamber containing shelves through which a heat transfer fluid can be circulated; a system for pumping, heating, and cooling the fluid; a vacuum pumping system; a condenser for trapping water vapor; and a refrigeration system for cooling the condenser.

In recent years, a system for sterilization of the chamber/condenser has also become mandatory. In addition to these essential components, pharmaceutical freeze dryers may also incorporate systems for stoppering vials within the chamber, automatic clean-in- place (CIP) equipment and, more recently, sophisticated mechanisms for automatic loading and unloading of vials.

Computerized monitoring and control of freeze dryers has become widespread in the last 10 years. A modern pharmaceutical freeze dryer requires a large capital investment, with the cost of large production units approaching $1 million each. On the other hand, the value of a batch of product has increased drastically with the development of therapeutic proteins derived from recombinant DNA technology.

The value of one freeze dryer load of a product such as tissue plasminogen activator or erythropoietin may well be more than the cost of the equipment itself; thus, it is important to design freeze dryers with adequate redundancy in both equipment and control systems.

IMPORTANT EQUIPMENTS USED IN FREEZE DRYING

A. Vacuum System

By far the most common type of vacuum pump in freeze drying is the rotary oil pump. The pump consists of a steel cylinder rotating eccentrically within a round casing. The gas being pumped is admitted into the casing via an inlet valve, compressed and forced out a discharge valve. Oil serves both as a lubricant and as a sealant to prevent back diffusion of gas past the rotating cylinder.

There is generally a trade-off between pumping speed and attainable vacuum—the higher the attainable vacuum, the lower the pumping speed. For this reason, pumps with very high attainable vacuum, such as diffusion pumps, are backed by one or more "roughing" pumps that discharge directly to the atmosphere.

The exhaust from a rotary oil pump contains a fine mist of oil droplets. Since the vacuum pump is critical to the integrity of the freeze drying operation, redundant equipment is important. Since the main vacuum pump is usually a rotary oil pump, an extra pump should be designed into the system as a "live" spare.

B. Refrigeration

Refrigeration is required both for cooling the shelves during freezing of product and for cooling the condenser during drying. The condenser is generally cooled by direct expansion of the refrigerant, usually a fluoro-hydrocarbon, in the condenser coils.

The refrigerant evaporates in the condenser coils, withdrawing the latent heat of sublimation from the condenser.

Vapor is drawn from the freeze drying condenser by a compressor and pumped to a condenser at a higher pressure. In the condenser, cooling water causes the compressed vapor to liquefy, and the condensed refrigerant is collected in a receiver. The liquid refrigerant is returned to the cooling coils via an expansion valve and the cycle is repeated.

C. Heat Transfer Fluid

The most common types of heat transfer fluid are silicone oil, Trichloro-ethylene (TCE), and Lexol, an oil similar to kerosene. Silicone oil is by far the most common Trichloroethylene has been phased out, for the most part, due to safety concerns.

D. Condenser Design

There are two basic types of condenser configuration—internal and external. For the internal design, condenser plates or coils are mounted either along the sidewalls of the chamber or in the bottom of the chamber. In the external arrangement, a separate condenser chamber, again containing either refrigerated plates or coils, is connected to the dryer chamber by means of a very short, large diameter pipe containing a valve to isolate the chamber from the condenser.

E. General Construction Considerations

Pharmaceutical freeze dryer chambers and condensers are usually constructed of type 304 or 316 stainless steel and should be pressure-rated vessels to accommodate steam sterilization. Internal surfaces should be mechanically polished (320 grit) for cleanability and passivated

for improved corrosion resistance.

All internal surfaces should be free draining to eliminate standing water after either cleaning or steam sterilization. Most freeze dryers have hydraulically movable shelves to insert lyostoppers into vials after drying is complete (internal stoppering). Several designs are available, including a single piston that enters the chamber from either above or below to push the shelves together. Shelves may also be drawn together by pulling shelf support rods out of the chamber from above. Regardless of the design used, it is important that no nonsterile element be allowed to enter the sterile chamber while product is present.

F. Sterilization of Freeze Dryers:

The most common method of sterilization of freeze dryers is steam under a pressure of about 15 psi, which corresponds to a temperature of about 121°C. Some units are sterilized by Ethylene oxide (EtO), These units are generally sanitized by a chemical sanitizing agent. The principal objection to the use of chemical sanitization is that many internal surfaces are not easily reached by manual application of a disinfectant solution. Also, the piping for introduction of air or nitrogen is not easily sanitized.

Inspection guidelines concerning freeze dryers state the following:

1. Freeze dryers should be steam sterilized prior to every lot, including both the chamber and condenser.

2. Validation of freeze dryer sterilization should follow the same approach as validation of an autoclave.

3. Two independent temperature recording systems should be used—one to monitor and control temperature, and the other to monitor the cool point in the system.

4. Provisions should be made to sterilize the lines used for introduction of air, nitrogen, or other gas.

5. Provisions should be made for sterilization and integrity testing of vent filters.

6. Sterilization should include the shelf support rods.

Thus Freeze drying provides a valuable tool to the pharmaceutical scientist by permitting

dehydration of heat-sensitive drugs and biologicals at low temperature. The final product is quickly and easily reconstituted, and the process is compatible with aseptic operations. Modern pharmaceutical freeze dryers are well suited to GMP operations, including sanitary design concepts, cleanable surfaces, and sterilization capability.

Critical system performance criteria include lowest attainable vacuum, ability to hold a vacuum, uniform shelf temperature distribution, redundancy of vacuum pumps and refrigeration compressors, and ability to sterilize the chamber, condenser, and piping used for introduction of air or inert gases. Lyophilization has been an effective approach for large scale production of dried pharmaceutical [39].

CONCLUSION

The introduction part gave over the overall understandings of Bendamustine hydrochloride and its physical, chemical and biological properties. Also, the introduction part has the details of introduction on parenteral dosage forms and lyophilization process.

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