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Review Article

A NOVEL EXPLORING APPROACH OF CANCER CHEMOTHERAPY BY MULTIPLE EMULSION SYSTEM

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ABSTRACT
Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells, leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) in 2008. Most common cancers are Lung, Liver, Colon, Rectum, Breast Ovarian & Prostate cause the most deaths each year. Lung cancer is the most frequent lethal cancer, 1.4 million cases per year by use of long-term exposure to tobacco smoke. Chemotherapy is the treatment of cancer with an antineoplastic drug or with a combination of such drugs into a standardized treatment regimen. Attempts to treat tumors with the single agents are often disappointing. A single drug usually kills the most sensitive population of cells in a tumor, leaving a resistant fraction unharmes and still dividing. Therefore, each time the same agent is readministered, the tumor becomes more resistant and the treatment less efficacious. The parenteral Sustained release dosage forms are most effective and common form of delivery for active drug substance & designed to achieve a prolonged therapeutic effect by continuously releasing medication over extended period of time after administration of single dose**.** For this reason whatever drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous not only in term of compliance but also for potential to improve the quality of the therapy. Such reduction in the frequency of drug is achieved, by the use of specific formulation technologies that guarantee that the release of the active drug substance happens in a slow and predictable manner. Multiple emulsions of w/o/w and o/w/o type are becoming popular since an additional reservoir is presented to the drug for partitioning which can effectively retard it release rate.
KEYWORDS: Cancer, Lung cancer, Chemotherapy, Multiple Emulsions

INTRODUCTION

Cancer

Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells[1]**.** It is one of the major causes of death in the developed nations. Cancer cells manifest, to varying degrees, four characteristics that distinguish them from normal cells. These are:

- Uncontrolled proliferation,
- Dedifferentiation and loss of function,
- Invasiveness and
- Metastasis.

There are three main approaches to treating established cancer-

- Surgical excision,
- Irradiation and
- Chemotherapy

KEY FACTS

- Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) in 2008.[2]
- Lung, stomach, liver, colon ovarian and breast cancer cause the most cancer deaths each year.
- The most frequent types of cancer differ between men and women.
- About 30% of cancer deaths are due to the five leading behavioral and dietary risks:
  - High body mass index,
  - Low fruit and vegetable intake,
  - Lack of physical activity,
  - Tobacco & alcohol use.

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs. This process is referred to as metastasis. Metastases are the major cause of death from cancer.[2]

The Problem: The main types of cancer patients are:

- Lung (1.4 million deaths)
- Stomach (740 000 deaths)
- Liver (700 000 deaths)
- Colorectal (610 000 deaths)
- Breast (460 000 deaths).

Figure: 1 and 2 showing graphical representation of different types of cancer patients

About 70% of all cancer deaths occurred in low-and middle-income countries. Deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030.[2]

The four most common are cancer of Lung, the Colon and Rectum, the Breast and Ovarian & the Prostate. Together, these four-five account for over half of all cancer cases. Lung cancer is the most frequent lethal cancer, with approximately 157,000 cases per year; it accounts death for over one fourth of all cancer death.[3]

The frequency of many kinds of cancer has remained relatively constant over the last fifty years, but some have changed significantly. The most striking change is in the frequency of lung cancer, which has increased more than ten-fold since1930. This continuing increase in the frequency of lung cancer accounts for the steady rise in the overall incidence of cancer in all over the world. There is a great variation in the prevalence of lung cancer in different geographical areas. Nearly 70% of all the new cases of lung cancer in the world occur in the developed countries. USA, Canada, New Zealand (Maori population) and Europe have the highest incidence (>50 per 105 population) followed by China, Ireland, Malta, Spain, Australia, and New Zeland (non - Maori population) with a moderate incidence (35-50 per

105 population) and low incidence (<35 per 105 population) countries include Utah (USA), Latin America, most Asian countries, lceland, Norway and Sweden. This is the most frequent tumour in males, and 2nd or 3rd most common in females. In the US alone, there were about 1,64,100 new cases in 2000, of which 70,000 were in the metastatic stage (stage IV) and another 70,000 were locally advanced (stage IIIA and IIIB disease). [4]

Lung Cancer

Lung cancer is a disease of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells. The most common symptoms are shortness of breath, coughing (including coughing up blood), and weight loss. It is leading cause of deaths in developed and also in developing countries causes 1 million deaths per year at present. The most common cause of lung cancer is long-term exposure to tobacco smoke. The occurrence of lung cancer in nonsmokers, who account for as many as 15% of cases, is often attributed to a combination of genetic factors, radon gas, asbestos, and air pollution, including secondhand smoke. Lung cancer may be seen on chest radiograph and computed tomography (CT scan). The diagnosis is confirmed with a biopsy. This is usually performed via bronchoscopy or CT-guided biopsy. Treatment and prognosis depend upon the histological type of cancer, the stage (degree of spread), and the patient's performance status. Possible treatments include surgery, chemotherapy, and radiotherapy.[5] Depending on the stage and treatment, the five-year survival rate is 14%. It is mainly of two types;

Non- small cell lung cancer - The non-small cell lung carcinomas (NSCLC) are grouped together because their prognosis and management are similar. There are three main sub-types: squamous cell lung carcinoma, adeno carcinoma and large cell lung carcinoma. Accounting for 25% of lung cancers, squamous cell lung carcinoma usually starts near a central bronchus. A hollow cavity and associated necrosis are commonly found at the center of the tumor. Well-differentiated squamous cell lung cancers often grow more slowly than other cancer types. Adenocarcinoma accounts for 40% of lung cancers. It usually originates in peripheral lung tissue. Most cases of adenocarcinoma are associated with smoking; however, among people who have never smoked ("never-smokers"), adenocarcinoma is the most common form of lung cancer. A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have different responses to treatment. It accounts for 70% of all lung cancer cases.

Small cell lung cancer – Small cell lung carcinoma (SCLC, also called "oat cell carcinoma") is less common. It tends to arise in the larger airways (primary and secondary bronchi) and grows rapidly, becoming quite large. The "oat" cell contains dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this an endocrine / para-neoplastic syndrome association. While initially more sensitive to chemotherapy, it ultimately carries a worse prognosis and is often metastatic at presentation. Small cell lung cancers are divided into limited stage and extensive stage disease. This type of lung cancer is strongly associated with smoking. It accounts for about 30% cases. Cancer cells are formed in the tissues of the lung. [5]

W.H.O Response

In 2008, WHO launched its Noncommunicable Diseases Action Plan.

WHO and the International Agency for Research on Cancer, the specialized cancer agency of WHO, collaborate with other United Nations organizations and partners in the areas of international cancer prevention and control to:

- Increase political commitment for cancer prevention and control;
- Generate new knowledge, and disseminate existing knowledge to facilitate the delivery of evidence-based approaches to cancer control;
- Develop standards and tools to guide the planning and implementation of interventions for prevention, early detection, treatment and care;
- Facilitate broad networks of cancer control partners at global, regional and national levels;
- Strengthen health systems at national and local levels;
- Provide technical assistance for rapid, effective transfer of best practice interventions to developing countries.
- Coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and develop scientific strategies for cancer prevention and control.

[1]**Globocan 2008, IARC, 2010**

Chemotherapy

Chemotherapy (sometimes cancer chemotherapy) is the treatment of cancer with an antineoplastic drug or with a combination of such drugs into a standardized treatment regimen.

Most commonly, chemotherapy acts by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that it also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles. This results in the most common side effects of chemotherapy: myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss).Newer anticancer drugs act directly against abnormal proteins in cancer cells; this is termed targeted therapy and is technically not chemotherapy.

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. Cancer is thought to be caused by the interaction between genetic susceptibility and environmental toxins.

In the broad sense, most chemotherapeutic drugs work by impairing mitosis (cell division), effectively targeting fast-dividing cells. As these drugs cause damage to cells they are termed cytotoxic. Some drugs cause cells to undergo apoptosis (so-called "self programmed cell death")

Combination Chemotherapy

Attempts to treat tumors with the single agents are often disappointing. A single drug usually kills the most sensitive population of cells in a tumor, leaving a resistant fraction unharmes and still dividing. Therefore, each time the same agent is readministered, the tumor becomes more resistant and the treatment less efficacious. This led, in the early 1960s, to the first use of a combination of drugs for treating testicular tumors. Due to its success, this “cocktail” approach was then rapidly extended to other tumor types and is still commonly uesd in clinical practice today.

As a rule, each drug included in a particular combination should be active as a single agent and have different toxic (dose limiting) side effects compare to the others. Multiple

drug therapy also enables the simultaneous attack of different biological targets, thus enhancing the effectiveness of treatment and they are less likely than older tumors to develop drug resistance.[9]

There are several fundamental approaches to treat cancer; these include surgery, radiotherapy, hormonal therapy, chemotherapy and immunotherapy. Generally, a combination of these approaches is adopted for cancer treatment. Surgery and radiotherapy can only be effective only if the tumor is localized. Moreover, surgery is a painful procedure and requires use of anesthetics. Radiation therapy, although painless, but carries a high potential of damaging tissues in the vicinity of the tumor. Chemotherapy forms a pivotal component out of these strategies wherein antineoplastic agents are employed to cure a particular cancer, to shrink the tumor prior to surgery, and to sensitize tumor to radiation therapy or as an adjuvant therapy. At present, chemotherapy is employed as a part of multimodality approach to the initial treatment of many types of tumors,[10] especially the use combination of more than two drugs simultaneously. The main aim of chemotherapy is to maximize the therapeutic effect and minimize the adverse effects but, because of various problems associated with the treatment, the goal is not achieved.[11] The complex of tumors like cell type and doubling time, tumor size heterogeneity, location and vascularization, uneven and slow blood flow within tumors, the leakiness of tumor vessels, etc. often limits the effectiveness of chemotherapy. In addition to the transport barriers, a second problem in cancer therapy is that the chemo- and radio- therapeutic agents are nonselective in there action: they are cytotoxic to both the healthy cells as well as tumor cells, which leads to undesirable side effects during anticancer therapy. If the dose decreased to alleviate undesirable side effects, this also reduces the efficacy of the therapy: conversely, increasing the dose, while more effective for controlling tumor growth, leads to increased toxicity of healthy tissues.[12]

Chemotherapeutic Agents

Cancer chemotherapy is now of established value and a highly specialized field. In addition to their prominent role in leukaemias and lymphomas, drugs are used in conjuction with surgery, radiotherapy and immunotherapy in the combined modality for many solid tumors, especially metastatic. The anticancer drugs either kill cancer or modify their growth. However, selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy. Small cell lung carcinoma is treated primarily with chemotherapy and radiation, as surgery has no demonstrable influence on survival. Primary chemotherapy is also given in metastatic non-small cell lung carcinoma.

The combination regimen depends on the tumor type. Non-small cell lung carcinoma is often treated with Cisplatin or Carboplatin, in combination with Gemcitabine, Paclitaxel, Docetaxel, Etoposide, or Vinorelbine. In small cell lung carcinoma, Cisplatin and Etoposide are most commonly used. Combinations with Carboplatin, Gemcitabine, Paclitaxel, Vinorelbine, Topotecan, and Trinotecan are also used. In extensive-stage small-cell lung cancer Carboplatin may safely be combined with Etoposide phosphate/ topotecan hydrochloride, this combination showed improves outcomes.[6, 7] Table 1 showing different types of drugs used in cancer as a chemotherapy.

Lung Cancer - Chemotherapy

Chemotherapy uses powerful medicines to kill cancer cells. Chemotherapy is the most effective therapy for small cell lung cancer. It can help control the growth and spread of the cancer, but it cures lung cancer in only a small number of people. Chemotherapy also may be used to treat more advanced stages of non-small cell lung cancer. Chemotherapy is called a systemic treatment because the medicines enter your bloodstream, travel through your body, and kill cancer cells both inside and outside the lung area. Some chemotherapy drugs are taken by mouth (orally), while others are injected into a vein (intravenous, or IV).

Lung Cancer - Clinical Trials

Major drug companies continually research and develop new medications and treatments, which must be shown to be safe and effective before doctors can prescribe them to patients. Through lung cancer clinical trials, researchers test the effects of new drugs on a group of volunteers with lung cancer. Following a strict protocol and using carefully controlled conditions, researchers evaluate the investigational drugs under development and measure the ability of the new drug to treat lung cancer.

Ovarian Cancer - Chemotherapy

Chemotherapy is used to shrink and slow cancer growth. Chemotherapy is recommended for most women after the initial surgery for ovarian cancer.

Choices of medications

Different chemotherapy drugs are given in different ways. Some are taken by mouth (oral), some are injected into a vein (intravenous, or IV), and others are injected through a thin tube into the belly (intraperitoneal, or IP). Oral and IV chemotherapy is called a systemic treatment because the medicines enter the bloodstream, travel through the body, and kill cancer cells both inside and outside the ovaries. In intraperitoneal chemotherapy, the drug is put into the body in the same area as the cancer. It is not a systemic treatment, but a little of the medicine still gets into the bloodstream.

Recommendation for Ovarian Cancer

Recurrent or Persistent Ovarian Epithelial Cancer Treatment Overall, approximately 80% of patients diagnosed with ovarian epithelial cancer will relapse after first-line platinum-based and taxane-based chemotherapy and may benefit from subsequent.

Extensive research and clinical trials have studied the different chemotherapy medicines used to treat ovarian cancer. There are several drugs to treat ovarian cancer. Some are used alone, and some are combined with other drugs. Chemotherapy is recommended after surgery for most women with ovarian cancer. The number of cycles of treatment will depend on the stage of your disease. The side effects will depend on the medicines that are used and how the medicines are given.

Some of the chemotherapy medicines used for ovarian cancer include:

Carboplatin. Cisplatin. Paclitaxel. Docetaxel.

Other medicines that may be used if ovarian cancer recurs include:

Cyclophosphamide. Doxorubicin. Gemcitabine. Topotecan. Oxaliplatin.

Drug delivery system

Rationale of controlled drug delivery

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and

physiological parameter inherent in selected route of administration. It is desirable that the duration of drug action become more a designed property of a rate controlled dosage form and less or not at all, a property of the drug molecules inherent kinetic properties.

Thus, optimal design of controlled release systems requires a thorough understanding of pharmacokinetics and pharmacodynamics of drug. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patients compliance. This is achieved by;

- Better control of plasma drug levels and less frequent dosing. For conventional dosage forms, only the dose (D) and dosing interval (C) can vary and for each drug, there exists a therapeutic window of plasma concentration, below which, therapeutic effect is insufficient and above which undesirable or toxic side effects, are elicited.
- In general, the dosing interval may be increased either by modifying the drug molecule to decrease the rate of elimination (Kcl) or by modifying the release rate of a dosage form to decrease the rate of absorption (Ka).[14]

Factors influencing the design and performance

To establish criteria for the design of controlled release products a number of variables must be considered,

- Drug properties
- Routes and drug delivery
- Target sites
- Acute or chronic therapy
- The disease

Sustained release dosage form

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over extended period of time after administration of single dose. The term "sustained release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. Products of this type have been formulated for oral, inject able and topical use, and include inserts for placement in body cavities as well. In the case of injectable dosage form; this period may vary from days to month.[15]

Advantages of sustained release dosage form

- Frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- Blood level oscillation characteristic of multiple dosing of conventional dosage form is reduced. Because more even blood level achieved.
- Total amount of drug administration can be reduced, thus maximizing availability with minimum dose.
- Incident of both local and systemic adverse effect can be reduced in sensitive patient.

IMPLEMENTATION OF DESIGN

Two general sets of methods have been developed for implementation of practical sustained release dosage form design.

- Approaches based on drug modification.
- Approaches based on dosage form modification.

Approaches based on drug modification

The physicochemical properties of drug may be altered through complex formation, drug adsorbate preparation, or prodrug synthesis. The principal advantage of this approach to sustained release is that it is independent of dosage form design.

Drug complexes

In the case of drug complexes, the release rate is a function of two processes:

- The rate of dissolution of solid complex into the biological fluids.
- The rate of dissociation of complex in solution, in general the dissolution step may be described by the following expression:

$$Rate\ dissolution = Ks(solubility)(surface\ area)$$

Where ks is the dissolution rate constant, a function of the hydrodynamic state as well as factor influencing the diffusion process. The formulator has the option of altering surface area through particle size control and solubility of drug complex through selection of the complexing agent.

Drug adsorbates

It is represent a special case of complex formation in which then product is essentially insoluble. Drug availability is determined only by the rate of dissociation, and therefore, access of the adsorbent surface to water as well as the effective surface area of the adsorbate.

Prodrug

Produrg is therapeutically inactive drug derivatives that regenerate the parent drug by enzymatic or nonenzymatic hydrolysis. The solubility, specific absorption rate and elimination rate constant of an effective prodrug should be significantly lower than that of the parent compound.

Approaches based on dosage form modification

Two general principles are involved in retarding drug release from most practical sustained release formulation involving dosage form modification. These are

- Embedded matrix
- Barrier principle

In the embedded matrix the drug is dispersed in a matrix of retardant material, which may be encapsulated in particulate form. Release is controlled by a combination of several physical processes. These include,

- Permeation of the matrix by water
- Leaching (extraction or diffusion) of drug from matrix
- Erosion of matrix material

In the barrier concept of control release implies that a layer of retardant material is imposed between the drug and elution medium. Drug release results from the diffusion of drug through the barrier, permeation of the barrier by moisture and erosion of the barrier. In addition to barrier composition and physicochemical properties, thickness and integrity of the barrier are important variables in controlling drug release. [15]

Novel Sustained Release Parenteral Drug Delivery

The parenteral administration route is most effective and common form of delivery for active drug substance with metabolic bioavailabilities drug for which the bio availabilities is limited by high first pass metabolism effect of other physicochemical limitation and for drugs with a narrow therapeutic index. For this reason whatever drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous not only in term of compliance but also for potential to improve the quality of the therapy. Such reduction in the frequency of drug is achieved, in practice, by the use of specific formulation technologies that guarantee that the release of the active drug substance happens in a slow and predictable manner**.** [16]

For the development of new injectable drug delivery system has receive considerable attention over the few year. This interest has been sparked by the advantages the delivery system possesses, which include ease of application, localized delivery for a specific action. Prolonged delivery period, decreasing body drug dosage with concurrent reduction in the possible undesirable side effect common to most form of systemic delivery and improved patient compliance and comfort.

Advantage of Parenteral Sustained Release

- Convenience
- Compliance potential for controlled release
- Avoiding the peaks (risk of toxicity) and troughs (risk of ineffectiveness)
- Reducing the dosing frequency
- Increasing patient compliance
- Improved drug delivery

There are several approaches to achieve sustained drug delivery via parenteral route; the release is being controlled by dilution, diffusion, dissociation, and partitioning or bio erosion. The systems can be broadly classified as;

Classification

Colloidal Carriers

- Solutions
- Dispersions
- Microspheres and Microcapules
- Nanoparticles and Niosomes
- Liposomes
- Resealed Erythrocytes

Implants

Infusion Devices

- Osmotic pumps
- Vapour Pressure Powered Pump
- Battery Powered Pumps

Colloidal Carriers

Solutions

Both aqueous as well as oily solutions may be used for sustained/controlled drug release. With aqueous solutions (given i.m), the drug release may be controlled in three ways;

- By increasing the viscosity of vehicle by use of methyl cellulose, CMC or PVP & thus, decreasing molecular diffusion & localizing the injected drug.
- By forming a complex with macromolecules like methyl cellulose or PVP from which the drug dissociates at a controlled rate (only free drug will get absorbed).
- By forming complexes that control drug release not by dissociation by reducing the solubility of parent drug.

Oil solutions control the release by partitioning the drug out of the oil in the surrounding aqueous biofluids. Vegetable oils like arachis oil, cottonseed oil are used for such a purpose. The method is applicable only to those drugs, which are oil soluble & have an optimum partition coefficient.

Dispersion

Dispersed systems like emulsions or suspensions can be administered by i.m, s.c or i.v routes. Among emulsions the o/w have not been used successfully since absorption of drug incorporated in the oil phase is rapid due to large inter facial area & rapid partitioning. Similarly, few w/o emulsions are water soluble drugs have been tried to controlled release. Multiple emulsions of w/o/w and o/w/o types more correctly, double emulsions are becoming popular since an additional reservoir is presented to the drug for partitioning which can effectively retard it release rate. Control of drug release from suspensions is easier and predictable. Drug dissolution and subsequent diffusion are the main rate controlling step. Release of water soluble drugs can be retarded by presenting it as oil suspension and vice versa for oil soluble drugs. Factors to be considered in the formulations such systems include.

- Solid content: should be ideally in the range 0.5 to 5.0%.
- Particle size: this factor is very important since larger the particle size, slower the dissolution; however, larger particle have their own disadvantages like causing irritation at the injection site (size should be therefore be below 10 microns), poor syringability and injectability and rapid sedimentation latter problem can be overcome by use of viscosity builders which also retard drug diffusion.

Microspheres and Microcapsules

Microsphere are free flowing powders consisting of spherical particles of size ideally less than 125 microns that can be suspended in a suitable aqueous vehicle and injected by an 18 to 20 number needle. Each particle is basically a matrix of drug dispersed in a polymer from which release occurs by a first order process.

Microcapsules differ from microspheres in that the drug is centrally located within the polymeric shell of finite thickness and release may be controlled by dissolution, diffusion or both. Quality microcapsules with thick walls generally release their medicaments at a zero order rate. Steroids, peptides and antineoplastics have been successfully administered parenterally by use of controlled release microcapsules.

Nanoparticles and Niosomes

Nanoparticles are also called as nanospheres or nanocapsules depending whether the drug is in polymer matrix or encapsulated in a shell. They differ from microspheres in having submicron particles in the nanometer size range- 10 to 1000nm. The polymers used are the usually biodegradable ones. The main advantage of this system it can be stored for upto 1 year. Like nanoparticles, niosomes are inexpensive alternatives to liposome. They are closed vesicles formed in aqueous media from nonionic surfactants with or without the presence of cholesterol or other lipids.

Liposomes

The term liposomes (meaning lipid body) were derived on the basis of names of subcellular particles like liposome and ribosome. It is defined as a vesicle of lipid by layers enclosing an aqueous compartment. The lipid most commonly used is phospholipids. Sphingolipids, glycolipids and sterols have also been used to prepare liposomes. Their size ranges from 25 to 5000 nm.

Resealed Erythrocytes

Drug loading in body's own erythrocytes when used to serve as controlled drug delivery systems have several advantages. They are fully biodegradable and biocompatible, nonimmunogenic, can circulate intravascular for days (act as circulatory drug depots) and follow large amounts of drug to be carried. The drug need not to be chemically modified and is protected from immunological detection and enzymatic inactivation. Drug loading can be done by immersing the cells in buffered hypotonic solution of drug which causes them to rupture and release hemoglobin and trap the medicament. On restoration of isotonicity and incubation at 37°C, the cells reseal and are ready for use. Damaged erythrocytes are removed by the liver and spleen. These organs can thus be specifically targeted by drug loaded erythrocytes. [17]

Nevertheless, efforts and endeavors to this end continue but it still remains an unreciprocated issue particularly in the treatment of appalling diseases like cancer wherein lot many drug related problems are drawn in.

In spite of the fact that cancer is one of the most explored diseases and an appreciable number of synthetic and natural anticancer agents of established therapeutic activity are available, it still persist as an incurable menace for the society. The reason lies in the inefficacy of the existing delivery systems which poses a challenge in the treatment. Thus, the need of the hour is to develop the novel strategies not only in terms of modulated therapy but also encompassing novel delivery systems with a functional role in delivering the drug molecule.

Multiple Emulsions

Multiple emulsion/ Liquid membrane system / Double emulsion systems are novel development in the field of emulsion technology and are more complex type of dispersed systems.

Multiple emulsion systems are novel development in the field of multiple emulsion technology and are more complex type of dispersed systems. Multiple emulsions are the emulsion systems in which the dispersed phase contain smaller droplets that have the same composition as the external phase. This is made possible by double emulsification hence the systems are also called as double emulsion. These systems have been extensively studied from both academic and practical application point of view.

Multiple emulsions have been termed as also liquid membrane system in which the liquid film which seperates the liquid phases acts as a thin semi permeable film through which solute must diffuse in order to traverse from one phase to another,

Further moving ahead, this challenge is taken up with the help of dispersed drug delivery systems to provide adequate systems which can play a functional role and thus improve the efficacy of the system as a whole. Dispersed systems have been undergoing tremendous advancements since the last decade in terms of suspensions, emulsions and micro emulsions. As the efficacy of lipophilic drugs is often hindered due to their low aqueous solubility, toxicity, poor absorption and bio-distribution. Their aqueous-based formulations are expected to function better *in vivo*. Development of drug delivery systems with low toxicity and high therapeutic index is thus needed. The multiple emulsions are considered to be promising drug delivery systems by virtue of their thermodynamic stability, macroscopic homogeneity, ease of preparation and small droplet size.[18] Lipophilic compounds, dissolved and encapsulated in the dispersed nano-sized oil pools in multiple emulsions are expected to be transported easily through the circulating blood stream, without capillary blockage and thereby readily absorbed in the organs. It is a suitable carrier system for both hydrophilic and lipophilic compounds. Multiple emulsions are complex systems, termed "emulsions of emulsions", i.e. the droplets of the dispersed phase contain even smaller dispersed droplets themselves. Each dispersed globule in the double emulsion forms a vesicular structure with single or multiple aqueous compartments separated from the aqueous phase by a layer of oil phase compartments.[19]

The emulsion was discovered as long ago as 1925 by Herbert. He found that the standard w/o emulsion system used as a vaccine adjuvant was highly viscous and difficult to inject, and therefore decided to re-emulsify the system. Not only was the resultant w/o/w emulsion easier in administration but also the antibody titer was higher than for the w/o system. Since then many others have used the w/o/w emulsion system as a vaccine adjuvant, as well as for the delivery of various pharmacological agents and the entrapment of enzymes. More detailed study has been done on them recently only in the past 20 years. Now a day's double emulsion consider as a suitable vehicle to provide sustained release.[20-27] Multiple emulsions are categorized into two major types which are water-oil-water (w/o/w) and oil-water-oil (o/w/o) double emulsions. There are two main ways in which multiple emulsions are prepared. These are one step (Phase inversion technique) and two step emulsification process. Double emulsions contain two surfactants of which one is lipophilic (low HLB) and one is hydrophilic (high HLB) and type and concentration of surfactants affects the long-term stability, hence the composition of double emulsion is of great importance.[28-31]

Various possible mechanisms through which materials can be transported across the oil phase in the w/o/w systems have been proposed and discussed such as diffusion mechanism, micellar transport, thinning of the oil membrane, rupture of oil phase, facilitated diffusion, photo-osmotic transport, solubilisations of internal phase in the oil membrane.[19]

Stability is always problem of emulsion, w/o/w are thermodynamically unstable. A lot of work has been done to overcome the stability problem of multiple emulsions. In practice multiple emulsion having relatively large droplets, cannot be stable on storage for long time and usually release the entrapped matter in an uncontrolled manner, therefore they have very short shelf life. The presence of two thermodynamically unstable interfaces is the major cause of instability. Table2 showing different types of formulation system developed for anticancer drugs.

For achieving long stability of double emulsion two different emulsifiers one is lipophilic for the w/o interface and second one is hydrophilic are necessary. Polymeric surfactants have a beneficial effect on stability of double emulsion because they make them resistant to shear, thus protect against coalescence. Also polymeric emulsifier, colloidal solid particles and macromolecular amphiphiles (proteins, polysaccharides) have ability to stabilize outer and inner emulsion of multiple emulsion system by forming rigid and strong film at the interface. According to the previous studies, the monomeric emulsifiers, if used alone are not sufficient to provide proper stability but it was concluded that if we used monomeric lipophilic surfactant with polymeric surfactant, shows better results by forming an interracial complex with polymeric surfactant and formed a thick strongly gelled film that produces "resistance to rupture" of the inner droplets. This film reduces the coalescence rates and imparts good mechanical and steric stability. Also, it was suggested that that this elastic film in the oil phase lowers the formation of reverse micelles and stabilize the double emulsion by reduces the transfer of electrolyte via the reverse micellar mechanism. In comparison of conventional non-ionic surfactants regarding the physical stability of double emulsion, the polymeric surfactants proved to be superior. Polymeric surfactants in combination with the conventional small molecular-weight emulsifiers are suggested as the future emulsifiers for double emulsions. The use of polymeric surfactants in combination of conventional small molecular-weight emulsifiers is very helpful in improving shear resistance with excellent stability and shelf-life.[32-34] Figure 3 showing structure of double emulsion.

Fat Emulsion

Fat emulsions are used as dietary supplements for patients who are unable to get enough fat in their diet, usually because of certain illnesses or recent surgery or chemotherapy. Fats are used by the body for energy and to form substances needed for normal body functions.[36]

A preparation of 10% fat administered into a vein to help maintain the weight of an adult patient or the weight and growth of a younger patient. Such fat emulsions are prepared from refined soybean oil and egg-yolk phospholipids and may contain such major fatty acids as linoleic, oleic, palmitic, and linolenic acids. The IV fat emulsion is isotonic and may be administered into a peripheral vein, but it is not mixed with other solutions used in parenteral alimentation. IV fat emulsions are often administered when hyperalimentation is not sufficient to maintain adequate treatment of a patient or when the patient needs calories but cannot tolerate the high percentage of dextrose contained in hyperalimentation solutions. Such emulsions may also be administered to patients who need more essential fatty acids than are contained in hyperalimentation solutions or who need general nutritional improvement, especially postoperative patients, severe hepatic diseases, blood coagulation defects caused by decreased blood-platelet counts, pulmonary diseases, lipoid nephrosis, hepatocellular damage, or bone marrow dyscrasia or to those being treated with anabolic inhibitory drugs. If possible, the IV fat emulsion is usually administered during the day so that the patient may follow a normal eating pattern with rest during the night and lower nocturnal urinary flow. Once the primary IV line has been established, IV fat emulsions are usually administered with the aid of an electronic control device to maintain an even flow rate and prevent fatty-acid overload. The patient's fluid intake and output are regularly measured during the delivery of such an emulsion, and daily blood studies are conducted to determine the level of free-floating triglycerides. Hepatic function tests are performed if the patient receives consecutive IV fat emulsion infusions over a long period. Immediate adverse reactions or those that may occur up to 2½ hours after the onset of the infusion may include less temperature rise, flushing, sweating, pressure sensations over the eyes, nausea, vomiting, headache, chest aend back pain, dyspnea, and cyanosis.[37]

Types

Liposyn II (Intravenous Fat Emulsion) is a sterile, nonpyrogenic fat emulsion for intravenous administration. It is supplied in both a 10% and 20% concentration.

Liposyn II (intravenous fat emulsion) 10% contains 5% safflower oil, 5% soybean oil, up to 1.2% egg phosphatides added as an emulsifier and 2.5% glycerin in water for injection. May contain sodium hydroxide for pH adjustment. pH 8.0 (6.0 — 9.0). Liposyn II (intravenous fat emulsion) 10% has an osmolarity of 276 mOsmol/liter (actual). The total caloric value of Liposyn II (intravenous fat emulsion) 10% including fat, phospholipid and glycerol is 1.1 kcal/mL. Of this total, approximately 0.6 kcal/mL is supplied by linoleic acid.

Liposyn II (intravenous fat emulsion) 20% contains 10% safflower oil, 10% soybean oil, 1.2% egg phosphatides and 2.5% glycerin in water for injection. May contain sodium hydroxide for pH adjustment. pH 8.3 (6.0 _ 9.0). Liposyn II (intravenous fat emulsion) 20% has an osmolarity of 258 mOsmol/liter (actual). The total caloric value of Liposyn II (intravenous fat emulsion) 20% including fat, phospholipid and glycerol is 2 kcal/mL. Of this total, approximately 1.2 kcal/mL are supplied by linoleic acid.

Both Liposyn II (intravenous fat emulsion) 10% and Liposyn II (intravenous fat emulsion) 20% contain emulsified fat particles of approximately 0.4 micron in diameter, similar to naturally occurring chylomicrons.[38]

Liposyn III **(**Intravenous Fat Emulsion) is a sterile, nonpyrogenic fat emulsion for intravenous administration. It is supplied in both a 10% and 20% concentration.

Liposyn III (intravenous fat emulsion) 10% contains 10% soybean oil, up to 1.2% egg phosphatides added as an emulsifier and 2.5% glycerin in water for injection. Sodium hydroxide has been added for pH adjustment. pH 8.3 (6.0 to 9.0). Liposyn III (intravenous fat emulsion) 10% has an osmolarity of 284 mosmol/L (approx.) and a specific gravity of 0.995. The total caloric value of Liposyn III (intravenous fat emulsion) 10% including fat, phospholipid and glycerol is 1.1 kcal/mL. Of this total, approximately 0.5 kcal/mL is supplied by linoleic acid.

Liposyn III (intravenous fat emulsion) 20% contains 20% soybean oil, 1.2% egg phosphatides and 2.5% glycerin in water for injection. Sodium hydroxide has been added for pH adjustment. pH 8.3 (6.0 to 9.0). Liposyn III (intravenous fat emulsion) 20% has ean osmolarity of 292 mOsmol/L (approx.) and a specific gravity of 0.988. The total caloric value of Liposyn III (intravenous fat emulsion) 20% including fat, phospholipid and glycerol is 2.0 kcal/mL. Of this total, approximately 1.0 kcal/mL is supplied by linoleic acid.

Both Liposyn III (intravenous fat emulsion) 10% and Liposyn III (intravenous fat emulsion) 20% contain emulsified fat particles of approximately 0.4 micron in diameter, similar to naturally occurring chylomicrons.[38]

Table 3 showing marketed preparation of lipid emulsion.

Applications of lipid emulsions

Lipid emulsions as a drug delivery system have been applied to the development of several commercially marketed products, Abbott, Baxter, Elkins-Sienn and others manufacture the drug

Diazepam in the US. Propofol emulsions are also available in the US from Baxter and alprostadil in Japan by Taisho as Palux. Over time, drugs eventually come off patent, which manifests in a generic line extension that erodes the sales from the drug innovator. New opportunities for drug compounds could be evaluated for improvements in the original formulation or the pursuit of new indications as a lipid emulsion. Studies performed in our laboratory evaluated Phenytoin as a model drug for applicability in a lipid emulsion that was first approved by the US Food and Drug Administration (FDA) in 1939 as an injectable solution.

CONCLUSION

The forgoing review shows different aspects related for the treatment of different types of cancer with the multiple emulsion system approaching a exploring approach for drug delivery by itself a dispersion system. In this exploring approach sustained release Parenteral W/O/W multiple emulsion might be prepared with optimized ratio of two different surfactant (hydrophilic and lipophilic) and oil phase for stable formulation of multiple emulsion for chemotherapy of cancer with incorporation of two anticancer drugs and its derivatives of drugs (combination of two hydrophilic drug or combination of hydrophilic lipophilic drug) for pulmonary drug delivery system. From above discussion we can thought, as such fat emulsion is giving in patient for total parenteral nutrition (TPN) and to maintain the weight of body, due to

which a lipid fat emulsion is giving to patient. By infusion of fat emulsion patient may can not weak after surgery/ chemotherapy. Patients may / will get as a nutritional supplement from oil phase by releasing of drug by sustained release formulations of multiple emulsion system. So after surgery it play a vital role to deliver of two different drug by sustained release formulations to achieve better therapeutic action. Inspite of certain drawbacks, the dispersed drug delivery systems still play an important role in the selective target in sustained delivery of various drugs. Researcher are implementing their efforts in improving the design of dispersing system by making them steady in nature,. As their flexibility in globule design posses a wide range of potential, its application must be explored throughout the world by encouraging the participation of researcher in the field of multiple emulsion drug delivery system

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TABLE 1: AN OVERVIEW OF ANTICANCER DRUGS FOR DIFFERENT TYPES OF CANCER.[8]

TABLE SHOWING; MOSTLY MEDICINES/ DRUGS USED IN DIFFERENT TYPES OF CANCER						
S.NO	Common chemotherapy	Lung		Liver	Ovarian	Breast
		NSCLC	SCLC			
1	Carboplatin	Docetaxel	Bevacizumab	Cisplatin	Cisplatin	Anastrozole
2	Cisplatin	Gefitinib	Erlotinib	Doxorubicin	Carboplatin	Capecitabine
3	Docetaxel	Gemcitabine	Etoposide	Dacarbazine	Cyclophosphamide	Docetaxel
4	Erlotinib	Gemcitabine	Etoposide phosphate	Sorafenib	Docetaxel	Exemestane
5	Etoposide	Gefitinib	Topotecan hydrochloride	-	Doxorubicin	Epoetin alfa
6	Gemcitabine	Vinorelbine	-	-	Etoposide	Fulvestrant
7	Irinotecan	Paclitaxel	-	-	Gemcitabine	Filgrastim
8	Paclitaxel	Porfimer sodium	-	-	Oxaliplatin.	Gemcitabine
9	Pemetrexed	Pemetrexed	-	-	Paclitaxel	Ixabepilone
10	Vinorelbine	-	-	-	Taxol	Pegfilgrastim
11	-	-	-	-	Topotecan	Paclitaxel
12	-		-	-	Vinorelbine	Pamidronate disodium
13	-	-	-	-	-	Trastuzumab
14	-	-	-	-	-	Zoledronic acid

TABLE 2: AN OVERVIEW OF THE POTENTIAL OF MULTIPLE EMULSIONS FOR ANTICANCER DRUGS.

S.no	Type	Drug incorporated	Route of administration / Model used / Studied investigated.	Reference
1.	w/o/w	Cytarabine	In-vitro analysis	Kim C. K et-al, 1995
2	w/o/w	5-fluorouracil	In-vitro release analysis	Fukushima et-al , 1983
			Intramuscular administration in rats	Omotosho, J.A., 1989
3	o/w/o	Lipiodol (lymphographic agent)	Intra-arterial	Fukushima et-al , 1986
4	w/o/w	Doxorubicin hydrochloride	In – vitro sustained release behavior and tissue distribution function in Sprague Dawley rats.	Lin, S.Y. et-al , 1992
5	w/o/w	Etoposide	In-vitro analysis	Tao. T. Ma. Jing-long et-al 1993.
6		Methotrexate	In-vitro characterization	Tao. T. Ma. Jing-long et-al 1992.
7	w/o/w	Famorubicin	In-vitro release	Hino T , et-al 2000
8		Tegafur	In-vitro release	Oh, I. Kang, et-al 1998

TABLE 3: COMMERCIALLY MARKETED PREPARATION OF AVAILABLE INJECTABLE LIPID EMULSIONS

S.no	Trade Name	Drug	Indication	Manufacturer	Market
1	Diazemuls	Diazepam	Sedative	Pharmacia	Worldwide
2	Diprivan Worldwide	Propofol	Anaesthetic	Astra Zeneca	Worldwide
3	Limethason	Dexamethasone palmitate	Steroid	Mitsubishi Pharmaceutical	Worldwide
4	Liple Ja	Alprostadil	Vasodilator, platelet inhibitor	Mitsubishi Pharmaceutical	Worldwide
5	Ropion	Flurbiprofen axetil	Non-steroidal analgesic	Kaken Pharmaceuticals	Worldwide
6	Vitalipid	Vitamins A, D, E, K	Parenteral nutrition	Fresenius Kabi	Worldwide

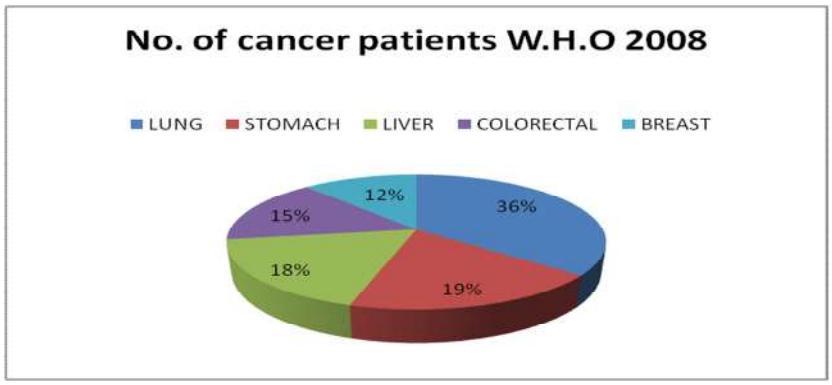


Figure 1: Pie Chart Shows Number of Different Types of Cancer patients as Per W.H.O2008

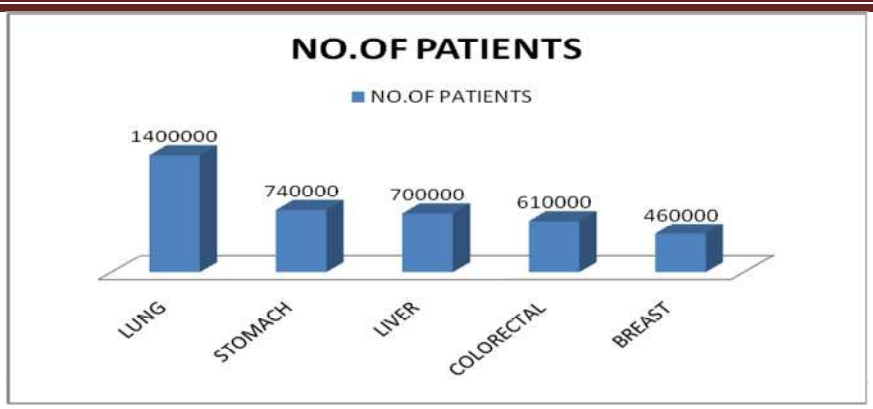


Figure 2: Chart Shows Actual Number of Different Types of Cancer patients as Per W.H.O2008

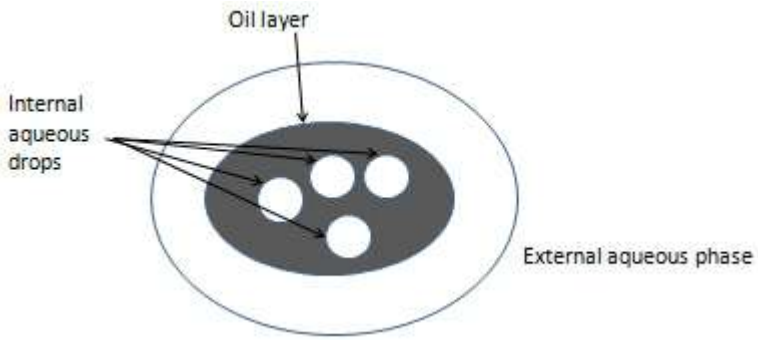


Figure 3: Double emulsion (w/o/w)