Review Article

Delivery of Biological Products

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ABSTRACT

The use of biologics or biological products as therapeutic agents is one of the rapidly emerging fields which present novel issues distinct from the traditional therapeutics. In the present study, data from several sources has been analyzed to recognize various modes of delivery of the biological products. As biologics have become a necessary alternative, in order to abolish certain ailments effectively it is essential to develop potential routes for their delivery. In the present era, therapeutics of biological origin such as vaccines, blood and blood products, allergenic extracts, human tissues and cells, recombinant therapeutic proteins, hormones, enzymes, etc. present a ray of hope for the patients. Better routes of delivery enable targeted delivery enabling the better patient compliance, greater efficiency, reduced toxicity, and reduced risk of side effects on the patient, greater residence time in the body, and hence reduced dosing frequencies. Therefore, devising an appropriate system of delivery for each of the specific biological product through various routes should be focused upon to improve the delivery of therapeutics. In the current study, various modes of biological delivery such as cell based drug delivery, depot delivery systems, delivery of injectable and non-injectable products, etc. have been considered. Thus, it should be ensured that both the formulation and delivery of the drug should be safe, pure, potent and effective. Hence, further studies in this field will enable the practitioners to improve the current treatments.

Keywords: Biologics, Biological Products, Delivery Systems, Biological Therapeutics.

INTRODUCTION

Presently, 'biological therapeutics', alternatively termed as 'biologics or biological products' are one of the rapidly emerging fields within the pharmaceutical industry. A differentiating factor involved in biological therapeutics is that they do not involve the traditionally produced synthetic chemical compounds; instead biologics are natural products which are derived from biological material. Any agent which is identical to the one that is normally present in the body is utilized as a therapeutic when it is administered exogenously, either when it is deficient and defective due to a disease or when it confers some beneficial effect to the body. They include a wide variety of products including vaccines, blood and blood products, allergenic extracts, human tissues and cells used for transplantations, gene and cellular therapies, recombinant therapeutic proteins, cytokines, hormones, immunosera, enzymes etc. Occasionally, some of these naturally occurring molecules can be used as a template in order to enhance the characteristics, as well as the binding properties of molecules. In addition, some biologics are designed such that they are analogous to natural products but have improved properties.[1]

The biological products have been differentiated from the traditional small drug molecules in the pharmaceutical industry by U.S. Food and Drug Administration. [1]

Center for Biologics Evaluation and Research (CBER) regulates the delivery of the biologics and the related products to the patients in order to guarantee their safety and effectiveness. The related products include blood and blood derived products, vaccines, tissues for transplantation, antitoxins and allergenic, as well as biological therapeutics that are derived biotechnologically. All of the these products cover almost the entire range of bioactive products which are obtained from living organisms in order to treat the ailments which are not yet treatable. The biological products also include therapeutic monoclonal antibody products, therapeutic synthetic peptides, therapeutic plasmid DNA products and therapeutic recombinant DNA products. [2]

The product quality, safety and consistency are predominantly focused by the regulatory bodies in order to bring the product from investigation phase to market. In order to market such a product, its licensing is necessary, for which, the manufacturers first ensure by demonstrating the data that the product is safe to use and is effective, then it undergoes the investigational new drug (IND) phase, premarket approval and post licensure phase. Recently, however the responsibility for the regulation of applications of biological products except those of blood and vaccines have been removed from CBER, and are now regulated by Center for Drugs Evaluation and Research (CDER) instead.[2]

NEED OF ALTERNATIVE DELIVERY SYSTEMS

The question that arises is that what is the need of delivery systems other than the conventional ones? In the recent times, advances in biotechnology have led to the replacement of the traditional drugs by therapeutics of biological origin, termed as 'biopharmaceuticals' in general. They are being replaced and supplemented by the biopharmaceuticals which are developed by recombinant DNA technology and molecular biology. Now, a number of severe illnesses are being treated by

the utilization of several biological products. However, there is a drawback that the delivery of these biologics is much more complicated than the conventional drugs because of the fact that the formulation and maintenance is quite challenging. Secondly, upon the administration to the patient, the formulation must protect the drug under degradative conditions such as the presence of enzymes in order to ensure the safe delivery. [3]

The administration of the modern biologics present many dilemmas including the frequency of dosing, volume, number of dosing, number of treatments and the delivery mechanism opted. For this purpose, there are ways to enhance the patience experience by modifying the technique and the formulation of the biologics for their delivery.[4]

The basic prerequisite for the delivery of the biological products is that under optimal conditions, the formulation should ensure targeted delivery of the product to the site of action and the controlled release at the site. Thus, such a system enables the easy administration and high efficacy of the product. As the conventional therapeutics have a relatively short half-life within the body due to instability towards enzymes, hydrolysis and rapid clearance from the body, delivery systems should be designed such that the problem of stabilization can be overcome. In such systems, this problem of stabilization can be overcome by enhancing the biologic by complexing or encapsulation. For example, lipoplex formation or encapsulation in capsules such as liposomes or solid particles based on lipids or polymers is a promising technique to shield and protect the nucleic acid based biologics. Another prerequisite for the delivery is the maximization of the delivery of the products at the target site with a prolonged and controlled delivery time.[3]

CELL BASED DRUG DELIVERY

'Cell based drug delivery' is the technique used to deliver biological products to patients utilizing cells. The utilization of cells to deliver the therapeutic products is a physiologically favorable possibility in the pharmaceutical industry. The properties of biological products that make their utilization challenging is that their manufacture is difficult, they are expensive and need frequent administration to the patient as they degrade rapidly within the body. The most common approach of delivery is the polymeric drug formulation, where polymer-based implants are used to deliver products by the controlled release of the product from the delivery system by diffusion or by the timed degradation of the drug depot. A major advantage of using cell based drug delivery systems is that it would provide more concentration of therapeutics products steadily at a localized site in a manner that is triggered by cellular activity. This means that instead of injecting the medicine or taking pills, implantation or injection of cells can lead to the delivery of the desirable products as long as the cell functions. Using cell based system; we can also control the rate of release of product, which can also be varied as a function of regeneration of surrounding tissues, since the release is controlled by biological feedback. It is also very suitable for the long term delivery of a protein product such as growth factors as the release of the product can also be varied spatially, as a function of tissue remodeling. Thus, these systems provide a sustained release and specific delivery of biologics. [3]

Cell based systems have been declared as remarkable alternatives to particulate system of delivery. The cells that have been successfully used include genetically engineered stem and dendritic cells, bacterial ghosts, carrier erythrocytes, etc. Some of the successful applications include the use of genetically engineered stem and dendritic cells for cancer treatment and immunotherapeutic vaccines, respectively. Bacterial ghost cells have also been used for the delivery of anticancer drugs such as doxorubicin and vaccines. Additionally, carrier erythrocytes have been utilized for the delivery of enzymes such as L-asparaginase and drugs such as corticosteroids. The benefits of using carrier erythrocytes include minimal toxicity, decreased risk of pathogenic reactions against encapsulated agents and side effects, as well as, increased efficacy due to better patient compliance. In addition, mesenchymal stem cells (MSCs) have undergone a number of clinical trials because of their immunosuppressive properties and their chemotactic receptors which migrate to the sites of tissue injury enabling them to be used for the targeted delivery of therapeutics to the precise locations.[5, 6, 7]

Cell and Cell Products as Drug Sources

The elementary requirement for this type of delivery system is that the functional cells should be derived from appropriate sources, as obtaining cells from a source, cultivating them and manipulating them often hinders the use of this system. The simplest sources of such cells are either primary cells from humans, i.e. autologenic or allogeneic in origin, or from animals i.e. xenogeneic in origin. The examples of cells which have been used for cell based delivery include pancreatic islets, hepatocytes, kidney cells, parathyroid cells, chondrocytes and adrenal chromaffin cells. The major benefit of using primary cells for this purpose is that they are fully differentiated cells. Therefore, the biological therapeutics that are produced by the primary cells can be used readily without further processing such as viral design for efficient gene transfection, differentiation, production and purification. However, the disadvantages include the variation in cell number, cell quality, etc. [3]

The basic application of cell based therapies is the use of cells for the local delivery of therapeutic products by engineered cells at the site of transplantation. For example, baby hamster kidney cells were transfected with a human nerve growth factor fusion gene and were encapsulated in a semipermeable polymeric membrane and were transplanted into rat brains. Thus, the engineered cells continually secreted human nerve growth factor *in vivo*. [3]

Similarly, cells were engineered to release chemotherapeutic molecules. In order to inhibit the growth of blood vessels into tumors, BHK cells were transfected with human endostatin expression vector and encapsulated with alginate and poly (L-Lysine). Thus, endostatin which is an inhibitor of angiogenesis was continuously released from the microencapsulated engineered cells, more effectively reversing the growth of blood vessels feeding the tumor, as compared to injection of the same molecules.[3]

The engineered cells should be derived from cell sources with lower immunogenicity and greater capacity for *in vivo* survival. The problems associated with the engineered cells include the gene transfection efficiency, risk of viral vectors, related efficiency and multiple purification processing. However, with the advances in genetic engineering, application of genetically modified cells for the purpose of therapeutic delivery is improving and promising.[8]

On the other hand, stem cells are quite important for their use in therapeutic delivery systems as they can differentiate into almost all somatic cell types, as well as, due to the fact that there is unlimited donor source for the stem cells and flexibility to a wide range of genetic manipulations. For example, intracerebral implants of cells engineered to release adenosine were utilized for their antiepileptic ability to control seizures in rats. [8]

Another example includes the use of bone marrow stem cells transplants in thousands of patients as a part of cancer treatment each year. BMSC transplants allow the cancer patients to survive potentially lethal doses of chemotherapy and radiation, as high doses of these drugs are cytotoxic and hence kill the hematopoietic stem cells. Each source of stem cells has certain advantages and disadvantages; therefore, it is necessary to select proper cell sources in different diseases, therapeutic efficacy and long term safety.[8]

Cell Encapsulation for Therapeutic Delivery Machinery

Cell encapsulation is the primary machinery for cell based therapeutic delivery systems, of which, the most preferable system is cell microencapsulation. Cell encapsulation is basically the enclosing of cells capable of producing a desired substance, in a semipermeable non-immunogenic sheath, to restore a lost function. It can be used in both organ replacement and the continuous, as well as, controlled release of a product. Thus, this technique involves enclosing the biological material within a polymeric matrix surrounded by a semipermeable membrane which is designed to prevent immune rejection. [8]

The capsule membrane allows the bidirectional flow of nutrients, oxygen and waste, as well as, the secretion of the therapeutic product. Thus providing the advantage that it prevents the income of antibodies and other immune cells that may destroy the enclosed cells.[8, 9]

An example of application of encapsulation is the delivery of large molecular weight proteins such as insulin, contrary to the methods of direct injection. Thus, the insulin is produced inside the transplanted cells and the insulin is delivered in response to the blood glucose levels. Cell based therapy has been successfully applied for the treatment of human diseases including neurological disorders, renal failures, cancer and liver diseases.[8]

Other applications include the immobilization of stem cells releasing various therapeutic factors in polymeric scaffolds made of alginate microcapsules. One of the ideal tools for microencapsulation is the immobilization of stem cells and alginate is an ideal biomaterial for obtaining a desirable result. [10]

A basic consideration is the material for cell encapsulation, which should be designed and selected for each therapeutic device. As the permeability of membrane function is dependent on both the material of the membrane and thermodynamic properties, which depend upon both on the solute population and the material used for the formulation of the membrane. [8]

The mass transport properties of a membrane are critical as the influx rate of the molecules is essential for cell survival and the outflow rate of metabolic waste ultimately determines the viability of entrapped cells. The membrane permeability is normally determined by the molecular weight cut off (MWCO) of membranes, which is application dependent. The MWCO should be high enough to permit the inflow of nutrients but low enough to reject antibodies and other immune molecules. [8]

Thus, cell encapsulation provides protection to the cell against the host by being isolated, as well as, maintains the phenotype by providing a proper 3D environment and thus, enhancing the release of therapeutic biologics from the encapsulated cells. Further modification is the co-encapsulation, which increases the duration of viability and function of cells. For instance, co-encapsulation of hepatocytes with BMSC, thus resulting in increased viability of the hepatocytes in vivo and in vitro along with lowering of systemic bilirubin levels in rats. [8]

Cell Based Protein Factory

Cells can be manufactured which function as a protein factory ensuring a controlled release of the biologic in the body, in order to release a therapeutic protein *in vivo*. One of the applications of cell based protein factories includes the manipulation of cells to deliver growth factors. Thus, it ensures the incorporation of the growth factors within a cell within the growth matrix in such a way that its release is controlled by the local enzymatic activity which is associated with the tissue regeneration. Thus, it was experimentally determined that by placing an enzymatically degradable linker between the cross-linking substrate and the growth factor domain in a fusion protein, growth factors can be delivered in an active form in response to cell regulated process. [9]

Thus, rather than expressing a therapeutic protein in cultured cells and then purifying them into patients, it would make it easier for implanting the patients with the cells directly once or few times a year rather than taking a pill or injection daily.[9]

Table 1: The cells and materials that are commonly used for encapsulation:

Cells	Functions	Material
Human & Animal primary cells		
Pancreatic Islets	Diabetes	Alginate-poly(L-lysine) alginate Alginate-poly(L-ornithine)
Hepatocytes	Liver transplantation	Alginate- chitosan Hydroxyethyl methacrylate- methyl methacrylate
Kidney cells	Erythropoietin	Alginate-poly(L-lysine) alginate
Parathyroid cells	Parathyroid hormones	Alginate
Chromaffin cells	Catecholamines	Alginate-poly(L-lysine) alginate
Chondrocytes	Chondrocyte transplantation	Alginate
Hybridomas	Antibody production	Alginate-agarose
Stem Cells		
BMSC	Improve hepatocyte survival	Alginate-poly(L-lysine) alginate
Embryonic Cells	Epilepsy	Polyethersulfone hollow fiber
Mesenchymal Stem Cells	Tissue repair	Collagen-agarose
Genetically Engineered Cells		
BHK Cells	hNGF	Poly (Acrylonitrile-vinyl chloride)
BHK Cells	VEGF	Polysulfone hollow fiber
BHK Cells	Human ciliary neutrophic factor	Polyethersulfone
Myoblasts	Mouse growth hormone	Alginate-poly(L-lysine) alginate
Mouse C_2C_{12} Myoblasts	Adenosine	Polyethersulfone

DELIVERY OF INJECTABLE PROTEIN AND PEPTIDE DRUGS

Although there are a various biological products which are being utilized as therapeutics, with a number of delivery systems, yet emphasis has been laid on proteins and peptide drugs due to their importance and numerous applications in the pharmaceutical industry. [11]

The protein and peptide drugs are one of the most important therapeutic that is being used nowadays, accounting for about more than 100 products used in the pharmaceutical industry. Due to their intrinsic properties such as physical and chemical instability, large molecular size and poor permeability, protein and peptide drugs are normally administered parenterally. Although this method ensures the fast mode of action and high efficacy, yet it is invasive in nature, as they have short plasma half-life and they need to be administered frequently and have low patient compliance. In order to improve patient compliance, non-invasive routes such as oral, pulmonary, nasal and transdermal delivery are ideal, but are often disappointing due to low bioavailability. Thus, in order to improve the delivery of peptide and protein therapeutics, it is necessary to modify them either chemically at a specific position or to design a specific delivery system. [11]

Modifications of Protein and Peptide Drugs

The properties of the protein and peptide biologics can be modified in several ways, for instance, by mutating one or more amino acids, using either natural or unnatural amino acids, by PEGylation, by acylation or by designing specific drug delivery systems. However, the efficacy and the potential side effects must be taken into consideration when designing such a delivery system and a drug delivery system or a chemical modification in the biologic product cannot be taken into consideration until the effects on the stability of the product have not been studied thoroughly. [11]

Some of the proteins and peptide drugs have been modified by the coupling of polyethylene glycol (PEG) to the protein by first activating PEG and converting one of its termini to functional groups capable of reacting with the amino acids or functional groups on the surface of the protein. Many of such drugs are now being marketed, including, *Oncaspar, Somavert* etc. thus, it renders the protein increased stability for long term storage and easier purification.[11]

Acylation is another chemical modification that renders the therapeutic proteins or peptides extended serum half-lives and increased stability, due to the attachment of such a modified protein to human serum albumin

through its fatty acid binding site, e.g., *Detemir* which is an acylated insulin analogue thus extending the action time and reducing the injection frequency. Some of the insulin analogues such as *Humalog, NovoRapid, Lantus*are recombinant insulin analogues which have 24 hour lasting effect. They have been modified by amino acid substitution in the primary structure of the protein in order to bring about an altered pharmacokinetic profile *in vivo.* Thus, they have slower rate of release and faster mode of action as they have low solubility at physiological pH and form a slow dissolving depot of hexameric insulin at the subcutaneous injection site. Another example is that of recombinant human interleukin-2 (IL-2), commercially available as *Proleukin*. [11]

Endocardial Delivery of Biologics for Cardiac Regeneration

Various systems have been recognized to ensure an accurate delivery of stem cells and other therapeutics through the use of catheters to the myocardium. Several routes have been adopted for this purpose, including intramyocardial (IM), intra coronary (IC) and intravenous. The retention time of the biologics also varies in different organs through different routes. However, there may be certain drawbacks of these routes including the fact that the biologics that are delivered directly into the myocardium have the capability of entering the vascular system and hence, migration to remote organs. [1]

The intracardial delivery of biologics depends on a number of factors the cell adhesion on the endothelial layer, trans endothelial passage and migration and the availability of chemo attractive agents in the myocardium. These methods of delivery have been opted for patients with myocardial infarction, chronic myocardial ischemia and ischemic left ventricular dysfunction. The coronary transfer of cells has an advantage over other methods in that they lead to homogenous distribution of cells in the subtended territory. Whereas, the epicardial delivery of biologics is considered as the most reliable method of delivery since the biologics are injected to the epicardium which is highly accessible by surgical incision. [12]

DEPOT DELIVERY SYSTEMS

Depot delivery systems are those which are designed to extend or prolong the effect of the protein or peptide drugs without the need to chemically modify the biological product. Such systems ensure the continuous delivery of the product after a single administration and thus reduce the need of injection frequency, decreasing adverse side effects, saving cost and increasing patient compliance. Currently, there are three main types of depot delivery systems which provide a sustained release of the biologic *in vivo,* these include micro- and Nano particulate systems, *in situ* depot forming systems (gels) and implant systems. However, relatively few such products have been marketed. Thus, for designing rational depot delivery systems for proteins and peptides, it is important to understand the physicochemical properties, pharmacokinetics, pharmacodynamics of the biologic and the characteristic of the depot system such as the release mechanism and the properties of the carriers.[11]

Micro- and Nano particulate Systems

In the near future, it is expected that the nanotechnology will contribute significantly and effectively in the therapeutics. Although, the US FDA has multiple guidance documents for the administration of novel drugs, nanoparticles represent issues that are not normally encountered in case of small drug molecules. In the past few years, the primary type of parenteral control release protein and peptide products marketed are those involving the micro- and nano particulate systems. They can be either injected subcutaneously or intramuscularly for its systemic effect or injected into a particular body site for the localized treatment. They can be injected intravenously, in order to achieve the long term circulation in blood, due to their micron and submicron size. [11, 13]

Based on the type of material that is used, they are of following two types:

Polymeric Micro- and Nano particulates

Micro- and Nano- particulates should be made of polymers which are biodegradable and biocompatible due to their non-retrievable nature on their administration. There are a number of synthetic and naturally occurring biodegradable polymers which are available for protein delivery. The most commonly employed is poly (lactic-co-glycolic acid (PGLA) and its derivatives. The first approved protein i.e., recombinant human growth hormone loaded PGLA microspheres was Nutropin Depot. It sustained the release of the biologic over the period of 2 to 4 weeks. PGLA based particles are more efficient in delivering the smaller sized peptide drugs including luteinizing hormone releasing hormone agonist, the release of which can be enhanced from a period of 1 month to 4 months.[11]

Besides PGLA, other synthetic biodegradable polymers that have also been used include polycaprolactone, polyanhydride, polyorthoesters, polyphosphazenes and other natural biodegradable polymers such as gelatin, albumin, dextran, etc. but not so many of these particulate formulations have gained clinical or commercial success yet. A number of techniques can be used to fabricate the micro and nano particles, for instance, by spray drying, double emulsion method, phase separation technique, spray freeze drying, ink jet technology, etc. [11]

Implant System

"Research teams are developing implants that directly distribute medicine to target cells instead of taking the indirect route offered by other drug-delivery methods, like intravenous injection or oral pills. The implants are actually drug-laden electronic chips which may be of biological origin that are only activated to release their

medicine once at the target site. The implants are not only able to maneuver into hard-to-reach locations, including those occupied by some inoperable tumors, but they can also cross the blood-brain barrier, which often makes impossible the distribution of traditionally delivered medicines to locations in the brain."[14]

"In addition, the researchers are further enhancing the implants to sense their environment and only discharge the medicine if certain conditions exist. For example, several strategically placed chemotherapy implants that would work in conjunction with a sensing system, such as early ultrasound detection, and only activate if the system detects the presence of trace cancerous cells. Scientists and clinicians foresee the use of a small, but highly targeted dose to eliminate the malignant cells very early and extremely efficiently while sparing the patient the side effects associated with the high doses of cancer drugs currently used."[11]

In situ depot forming systems

In situ depot-forming systems are usually viscous solutions or suspensions containing both biodegradable carrier and drug. They are also called phase sensitive *in situ* gel forming drug delivery systems. These systems are made by phase sensitive polymers and water miscible organic solvents. The phase sensitive polymers used in these systems have high solubility in organic solvents but poor solubility in water. Once the solution formulation is injected in the body, water soluble organic solvents dissipate and water penetrates into organic phase which leads to polymer precipitation and phase separation. These two processes control the quick formation of gel depot at injection sites. It has advantages in prolonging the release of peptides and proteins, but faces problems such as denaturation and biocompatibility issues with of peptides and proteins with the organic solvents.[15]

"The development of new injectable drug-delivery systems has unique advantages over traditional ones, which include ease of application, localized and prolonged drug delivery. In the past few years, an increasing number of such systems have been reported in the literature for various biomedical applications, including drug delivery, cell encapsulation, and tissue repair. These are injectable fluids that can be introduced into the body in a minimally invasive manner prior to solidifying or gelling within the desired site. For this purpose both natural (chitosan, alginates) as well as synthetic polymers (PEGylated polyesters, ricinoleic acid-based polymers) have been utilized. These systems have been explored widely for the delivery of various therapeutic agents ranging for anti-neoplastic agents like paclitaxel to proteins and peptides such as insulin, almost covering every segment of the pharmaceutical field."[15]

DELIVERY OF NON-INJECTABLE PEPTIDES AND PROTEINS

Over the last few decades, pharmaceutical scientists have been trying to find alternative ways of administering peptides and proteins other than injection. Many efforts have been made to investigate the feasibility of nasal, pulmonary, buccal, transdermal, ocular, rectal, sublingual, and vaginal and controlled release oral drug delivery systems for the administration of proteins and peptides. These non-invasive routes have lower peptide degrading enzyme abilities. [11]

Intranasal Delivery of Peptides and Proteins

CNS diseases are usually challenging because of the blood brain barrier which prevents the entry of all molecules other than small and non-polar molecules. However, a possible alternative route is the intranasal delivery as it is a non-invasive mode of drug delivery capable of allowing the direct access to the CNS bypassing the BBB. CNS disorders like Parkinson's disease, Alzheimer's disease, stroke, multiple sclerosis, epilepsy, psychiatric disorders, etc. can be treated possibly through the administration of high molecular weight biologics like proteins, stem cells and vectorsintranasally. [16]

The intranasal route has also been attracting a lot of attention as an alternative to parenteral injections of peptides and proteins drugs. This is due to special organization of the nasal mucosae including, a highly vascularized epithelium mucosae, a relatively large surface area and lower enzymatic activity than the gastrointestinal tract. More importantly, the nasal mucosa is rich in lymphoid tissues, which is named as nasal associated lymphoid tissue (NALT) which will ease vaccination and allows the vaccine to be transported over a shorter distance after it gains access to the lymphoid tissue. There has been an increased research on the nasal pathway for CNS drug delivery. Improved delivery to the brain via the intranasal route has been reported for therapeutic peptides and proteins, such as insulin, vascular endothelial growth factor and intestinal vasoactive peptides. This is due to the fact that intranasal administration offers non-invasive alternative routes to the central nervous system for drug delivery as it effectively by passes the blood brain barriers. [11]

The intranasal delivery systems have been further enhanced by the use of bio adhesive microsphere delivery systems as the ciliary beating leads to rapid clearance. Hence, in order to prolong the residence time, different kinds of microspheres have been used in intranasal delivery of peptides and proteins. Example includes insulin cross linked with dextran microspheres, starch microspheres and aminated gelatin microspheres. Due to the bio adhesive nature of microspheres, they adhere to the intranasal cavity for a prolonged time. Other modes of intranasal delivery include the use of liposomes and microemulsions. Microemulsions are optically isotropic and thermodynamically stable systems of water, oil, surfactants and co-surfactants which are used for drug delivery. [11]

The inhaled route for drug delivery has been used not only for respiratory diseases, but also for other systemic diseases such as diabetes mellitus. Apart from the approved inhaling agents currently in market, other

therapies such as systemic inhaled chemotherapy in lungs is also being evaluated currently. For this purpose, specialized 'Nano carriers' and 'Nano complexes' are being utilized to in order to effectively exploit the characteristics of the nanoparticles to deliver the biological products to the site of interest. [17]

Pulmonary delivery of peptides and proteins

Pulmonary delivery of peptide and protein drugs have certain advantages over nasal route as lungs have greater surface area of absorption, i.e., 100 m^2 as compared to 180 cm^2 administered through nasal route. In addition good vascularization and the ultra-thinness of the alveolar epithelium can also increase the rapid uptake and absorption of the drug. In order to increase the efficiency of absorption through this route, protease inhibitors and permeation enhancers, which increase the absorption of macromolecular drugs, are used. Some of the absorption enhancers include bile salts and bile acids, fatty acids, surfactants, acylcarnitines, phospholipids etc. mechanism of actions include disruption of membranes, opening tight junctions, enzyme inhibition, mucolytic activity, increasing the fluidity of the phospholipid membranes and perturbation of intercellular lipid domains. [11]

Buccal Administration of Peptides and Proteins

The buccal mucosa has an expanse smooth muscle which is relatively immobile and has abundant vascularization, thereby providing a direct entry into the systemic circulation. Thus, it avoids the hepatic first pass effect and the degradation in the gastrointestinal tract. It also offers ease of administration and the termination of delivery easily, when required. For effective buccal adhesive drug delivery system design, a surface area of 1-3 cm^2 is needed. Maximal duration of approximately 4 to 6 hours of contact time is general.[11]

Nanosized delivery systems-an overview

The term nanomaterial refers to the material which has atleast one of the dimensions measuring 100 nm or less. Normally, the size of therapeutic nanoparticle ranges from 2 to 1000 nm. Targeted nanodelivery is possible through the use of dendrimers, liposomes, polysomes and micelles [17]

"Nanotechnology and nanomedicine provide platform for advanced therapeutic strategies of various infectious diseases, as nanomedicine, due to small size and targeted designed Nano sized particles, permit passage through many previously impermeable biological membranes, often resulting in targeted delivery of antimicrobials. In particular, specific properties of nanomaterials and nanodelivery systems enable their closer and more efficient interactions with pathogen membranes and cell walls.[18]

For the effective delivery of the low molecular weight drugs and new biologic molecules such as siRNA, which have poor solubility, shorter half-life period due to rapid degradation, poor bioavailability, potentially side effects to the non-targets requires a delivery system which is targeted and effective. Thus, research has been conducted on nano-carriers. One of the advantages of nanoparticles is that they offer a large surface area due to their small size. They tend to improve the efficiency and the bioavailability of the drug by encapsulating and delivering more drugs. These systems can be further modified by the surface modification of nanoparticles to make them targeted to a particular tissue or cell. They are more suitable for use as they exhibit low toxicity, high patient compliance and they protect the bioactive material from degradation. [19]

After a long period of research and trials, liposome formulated drugs have now entered clinics to treat cancers and systemic fungal infections, mainly because they are biologically inert and biocompatible. For the delivery of genetic material such as DNA, ribozymes, DNAzymes, oligonucleotides and small interfering RNAs, the liposomes, in particular lipid- DNA complexes termed as lipoplexes are now competitive with viral gene delivery systems. Nanoparticles, nanospheres, polymerosomes, nanogels, micelles, dendrimers and virosomes are the other main types of nanocarrier systems that are used for the delivery of drugs and biologics. These delivery systems vary in their chemical compositions, their carrying capacity, shape, sizes, as well as, their organ or tissue targeting properties. [19]

Iron oxide and Gold Nanoparticles

Recently, a novel kind of nanoparticles termed as hybrid nanoparticles due to their organic and inorganic nature simultaneously has emerged to formulate theranostic systems. For instance the utilization of superparamagnetic iron oxide particles (SPIONS) and plasmonic gold nanoparticles (Au-NPs) are being extensively studied for cancer treatment, such as, the anticancer doxorubicin. They can not only be used for magnetic drug targeting, but also be used in thermal therapy [20]

Lipid Nanosystems

Another class of nanoparticles that have raised great expectations in medicine is the use of solid lipid nanoparticles (SLN). "The use of SLN for antineoplastic agents has been underexplored when compared to the encapsulation of the same agents in polymeric particles. The preparation and efficacy assessment of a SLN platform as drug delivery carrier for anticancer agents, herein proposed as a strategy to find innovative formulations, could dramatically improve the outcome of cancer therapy.[21]

CONCLUSION

Currently, a number of new biologics are being tested for their use as effective drugs, and for this purpose, novel systems of targeted delivery to the desired site is being experimented. However, the primary concern of CBER is that the manufacturers can develop a safe, pure, potent and effective biological product and then market it. For

this purpose, critical evaluation at each step of the manufacturing process is imperative in order to optimize both the production and the delivery of the desired product.

REFERENCES

1. Ekins S, Xu JJ, Drug Efficacy, Safety, and Biologics Discovery: Emerging Technologies and Tools, John Wiley and Sons, New Jersey, 2009.
2. Medina C, Compliance Handbook for Pharmaceuticals, Medical Devices, and Biologics, CRC Press, 136, 2004.
3. Atala A, Lanza R, Thomson J, Nerem J, Principles of Regenerative Medicine,1,Academic Press, Burlington, 2008, 960-63.
4. Burgess EB, Optimizing Drug Delivery for Modern Biologics, 5, 2012, 30-32.
5. Millán CG, Gandarillas CIC, Marinero MLS, Lanao JM,Cell-based drug-delivery platforms, Therapeutics Delivery, 3, 2012, 21-45.
6. Magnani M, Pierigè F, Rossi L, Erythrocytes as a novel delivery vehicle for biologics: from enzymes to nucleic acid-based therapeutics, Therapeutics Delivery, 3, 2012, 405-14.
7. Greco SJ, Rameshwar P, Mesenchymal stem cells in drug/gene delivery implications for cell therapy, 3, 2012, 997-1004.
8. Yaszemski MJ, Trantolo DJ, Lewandrowski KU,Hasirci V, Altobelli DE, Wise DL,Tissue Engineering and Novel DeliverySystems, CRC Press, 2003, 460-89.
9. Atala A, Lanza R, Thomson, JA, Foundations of Regenerative Medicine: Clinical and Therapeutic Applications, 1, Academic Press, 2010, 518-30.
10. Garate A, Murua A, Orive G, Hernández RM, Pedraz JL,Stem cells in alginate bioscaffolds, Therapeutic Delivery, 3, 2012, 761-74.
11. Jorgensen L, Nielson HM,Delivery Technologies for Biopharmaceuticals: Peptides, Proteins, Nucleic Acids, 1, John Wiley and Sons, West Sussex, 2009 11-25.
12. Dib N, Menasche P, Bartunek JJ, Zeiher AM, Terzic A, Chronos NA, Henry TD, Peters NS, Avilés FF, Yacoub M, Sanborn TA,DeMaria A, Schatz RA, Taylor DA, Fuchs S, Itescu D, Miller LW, Dinsmore JG, Dangas D, Popma JJ, Hall L, Holmes DR, Recommendations for Successful Training on Methods of Delivery of Biologics for Cardiac Regeneration, JACC: Cardiovascular Interventions, 3,2010, 265–75.
13. Sadrieh N, Tyner KM, Nanotechnology and therapeutic delivery: a drug regulation perspective, Therapeutic Delivery, 1, 2010, 83-9.
14. http://www.ssim.eng.wayne.edu/implants/drug_delivery.asp
15. Chitkara D, Shikanov A, Kumar N, Domb AJ, Biodegradable injectable in situ depot-forming drug delivery systems, Macromolecular Biosciences, 6, 2006, 977-90.
16. Locchead JJ, Thorne RJ, Intranasal delivery of biologics to the central nervous system Adv. Drug Deliv. Rev. 64(7), 2012, 614-28.
17. Zarogoulidis P, Gialeli C, Karamanos NK,Inhaled chemotherapy in lung cancer: safety concerns of nanocomplexes delivered, 3, 2012, 1021-23.
18. Basnet P, Skalko-Basnet N, Nanodelivery Systems for Improved Topical Antimicrobial Therapy, 2013, Current Pharmaceutical Design.
19. Gad SC, Handbook of Pharmaceutical Biotechnology, John Wiley and Sons, New Jersey, 2007.
20. Gautier J, Allard-Vannier E, Munnier E, Souce M, Chourpa I, Recent advances in theranosticnanocarriers of doxorubicin based on iron oxide and gold nanoparticles,Journal of Controlled Release, 2013.
21. Vidiera MA, Arranja AG, Gouveia LF, Experimental design towards an optimal lipid nanosystem: A new opportunity for paclitaxel-based therapeutics, European Journal of Pharmaceutical Sciences, 49, 2012, 302-310.

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