

# Comprehensive Investigation about Biotechnological Drug Delivery

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## Abstract

Drug delivery is a very vital field in medicine and treatment. Controlled drug delivery improves access to the drug by preventing untimely degradation, increasing drug intake, maintaining drug concentration during treatment by controlling the rate of drug release, and reducing side effects by targeting the drug to a specific site and cell. To reduce the rate of drug breakdown, prevent harmful side effects, increase drug availability and drug accumulation in the target area, various delivery and targeting systems are being developed. For continuous drug release, polymers must be used that release the drug at a controllable rate or are released over time by the decomposition of the polymer. Drug carriers include soluble polymers, micro particles composed of natural, insoluble and degradable synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes and micelles. Carriers can be degradable, inductive (sensitive to temperature and pH), and even targeted by specific antibodies against compounds in the target area. In this paper, we want to review and discuss some of the most generic methods in biotechnological drug delivery and compare these systems with each other and comprehensively review the pros and cons of each of the methods.

**Keywords:** Biotechnology, recombinant drugs, enzymes, antibodies

## 1. INTRODUCTION

The human body is a true pharmacopeia (prescription) of useful protein drugs. Body is a collection of endogenous enzymes, hormones and antibodies. They are responsible for maintaining homeostasis, wound stability, fighting infections, neutralizing toxins, keeping cancer cells in a stable state, and generally keeping alive only when we lose the function of certain enzymes, hormones, antibodies or when our bodies are overshadowed by certain types of trauma (blood loss, stroke, heart attack, widespread infection, or a heavy tumor burden). We need some supplements for our natural protein supplements. Enzymes are made by living organisms and act as biocatalysts in biochemical reactions. Enzymes are critical for the functioning of most cellular systems. Therefore, mutations, overexpression, overexpression or deletion can cause disease in living organisms, especially if a vital enzyme is damaged and can cause death (Dingermann,2008).

### Types of Drug Carriers

#### • **Michelle**

Micelles are formed by the accumulation of blocks of amphiphilic copolymers (5-50 nm) in the solution phase, which is a system of interest in drug delivery (Glick, 2017). Hydrophobic drugs are physically trapped in the center of the micelles and transported to the target site.

#### • **Liposomes**

Vesicles are made up of one, more, or more phospholipid layers (mostly phosphor lectin). Liposomes are the most common drug delivery system and using them as a drug delivery system reduces the need for high-dose drugs and

therefore Reduces the toxicity and side effects of the drug (Wink,2004). Liposomes can carry proteins and DNA. Liposomes are used to transmit amphotericin B against fungal and protozoan infections, doxorubicin is used to treat breast cancer, and hepatitis A and influenza vaccines are used as drug delivery systems.

#### • **Dendrimers:**

Nanometer particles are branched with symmetrical arrangement. They consist of a central core, branched units, and terminal functional groups. Ligand binding to the external surface is used to target dendrimers, and drug encapsulation, electrostatic interaction, or covalent bonding of the drug to the dendrimer is used to transfer the drug. Due to the small number of tests performed on this system, they are not yet a safe and non-toxic system (Hanlon, 2007). Reasons for the importance of dendrimers:

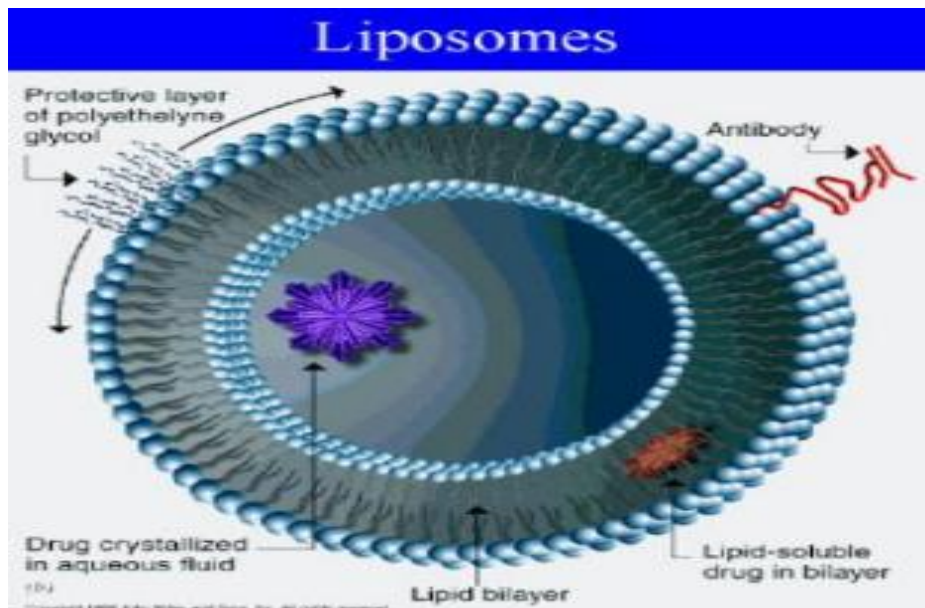
- The presence of multiple copies of the drug and possibly the induction of a multidimensional effect
- Increase the solubility of drugs and their availability in the body

Their relatively large size, increased shelf life and induced EPR effect (Kreuzer,1996)

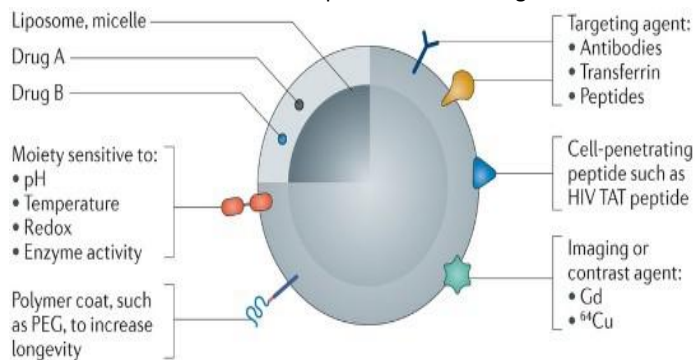
## 2. Polymer particles

They consist of two classes of nanoparticles and micro particles composed of natural or synthetic polymers (Prevost, 1998) . High stability, good biocompatibility and multi functionality, and slow and continuous release of the drug, make them suitable carriers for drug delivery. Suitable carriers for the delivery of a variety of drugs for the treatment of infectious diseases have been successful

examples.

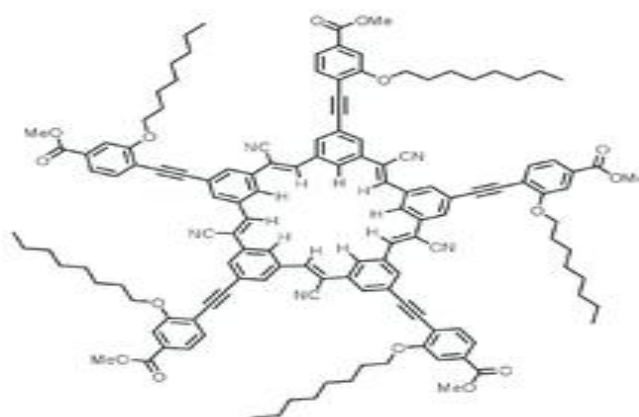


**Figure 1.** A liposome is a spherical vesicle having at least one lipid bilayer. The liposome can be used as a vehicle for administration of nutrients and pharmaceutical drugs.



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**Figure 2.** Liposomes can be prepared by disrupting biological membranes (such as by sonication).

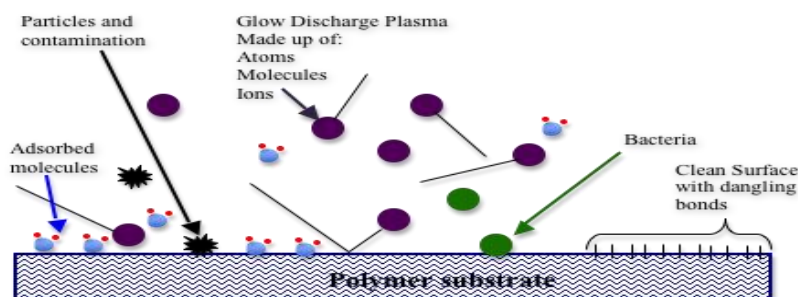


**Figure 3.** Dendrimers are repetitively branched molecules. The name comes from the Greek word δένδρον (dendron) which translates to "tree". Synonymous terms for dendrimer include arborols and cascade molecules.

### 3. Nanoparticles

Nanoparticles (including spherical particles and Nano capsules with a size between 10-200 nm) are in solid state and in the form of crystals or amorphous and include all types that are able to absorb or encapsulate the drug and thus protect it against chemical and enzymatic degradation.

In recent years, nanoparticles with degradable polymers because of their potential for controlled drug release, in targeting specific organs or tissues, as DNA carriers in gene therapy, and because of their ability to transport proteins, peptides, (Dempster,1995) and genes from Oral are considered.



**Figure 4.** Polymers range from familiar synthetic plastics such as polystyrene to natural biopolymers such as DNA and proteins that are fundamental to biological structure and function.

- **Functional carbon nanotubes**

A member of the family of biomaterials and as a new tool for the transfer of peptides, proteins, nucleic acids, vectors, non-coding RNA, antibiotics to mammalian cells and other therapeutic agents - due to low toxicity and lack of immune responses - case Attention is drawn.

- **Nano erythrocytes**

Examples are ghost cells and vesicles with an average diameter of 0.1 microns that release erythrocytes that carry a variety of proteins, enzymes, (Dudzinski,2005) and

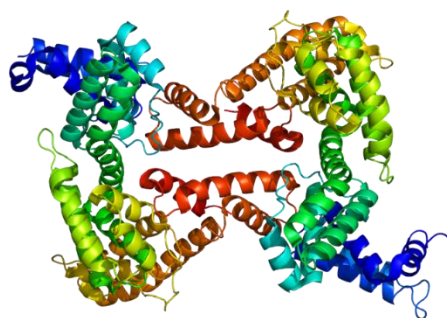
macromolecules and are used in the treatment of liver tumors, parasitic diseases and enzymatic diseases.

- **Albumin**

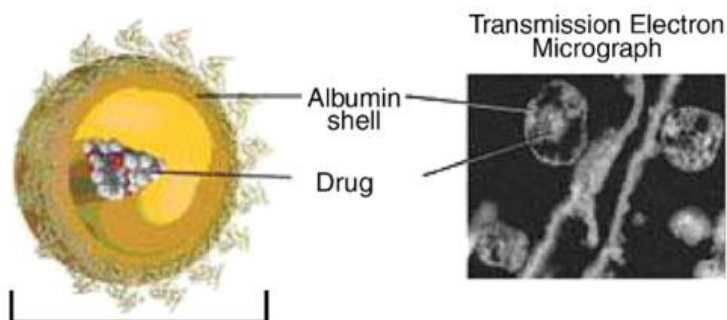
Albumin is very important as a drug carrier in the treatment that the drug is delivered in three ways.

Combining low weight drugs with endogenous or exogenous albumin

- Conjugation of active proteins (Dudzinski,2005)
- Encapsulation of the drug with albumin nanoparticles



**Figure 5.** Albumin is a family of globular proteins, the most common of which are the serum albumins. All the proteins of the albumin family are water-soluble, moderately soluble in concentrated salt solutions, and experience heat denaturation.



**Figure 6.** Albumins in a less strict sense can mean other proteins that coagulate under certain conditions. See Other albumin types for lactalbumin, ovalbumin and plant "2S albumin".

- **Lipoproteins**

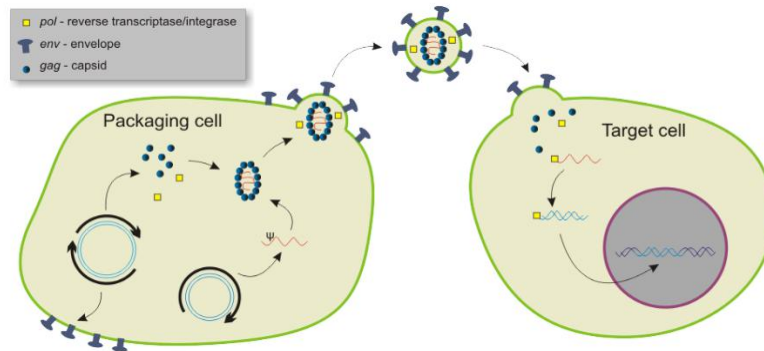
In the treatment (Pohlscheidt,2018) of tumors, the lack of specificity of drugs and the development of drug resistance are two problems that scientists face. For treatment, a variety of antibodies and liposomes can be used, but antibodies due to immunogenic responses and liposomes due to stability. They are left out and lipoproteins, especially HDL, are now considered suitable candidates.

#### 4. Gene-Based Drugs

Gene transfer is one of the most challenging topics in the treatment of genetic disorders. In connection with gene transfer, various physical, chemical and plasmid DNA methods are used. Advantages of using plasmid DNA: Ability to transmit long sequences of target gene, cheap and stable, low immunogenicity of plasmid DNA.

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**Figure 6.** Gene therapy (also called human gene transfer) is a medical field which focuses on the utilization of the therapeutic



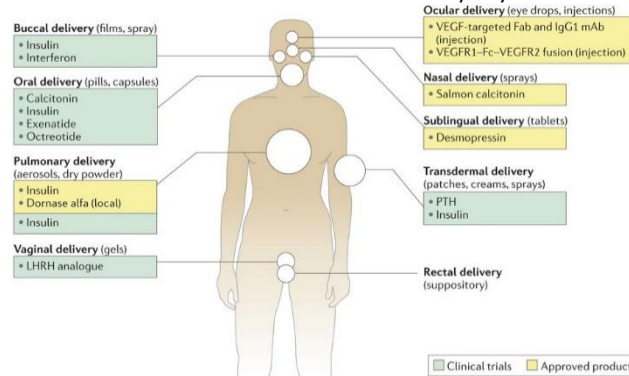
delivery of nucleic acids into a patient's cells as a drug to (Bucke,2001) treat disease.

### 5. Directions for taking the drug

The choice of drug delivery mechanism is influenced by the patient's acceptance of the drug, drug characteristics such

as solubility, access to the disease site and its effectiveness in relation to a particular disease. The most (Ramanathan, 1997) important system for drug delivery is the oral route.

**Figure 7.** Drug's effects. Follow the directions on the medicine label carefully. If you don't understand the directions, ask your



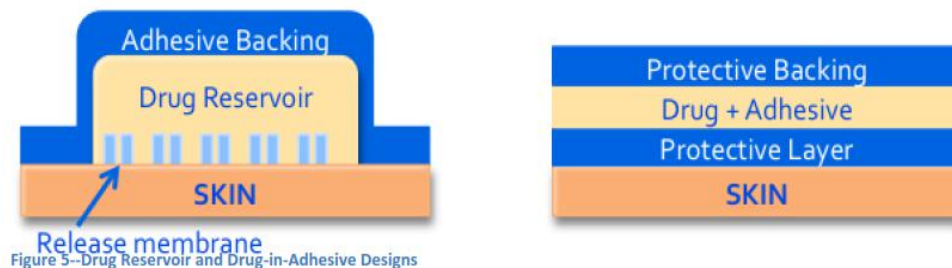
doctor, nurse, or pharmacist to explain them to you.

#### • Oral routes:

The most important and common system for drug delivery, including tablets, polymers and hydrogels. Parenteral routes (injection): include intravenous, intramuscular, subcutaneous injection. The only (Evens,1993) commercially available Nano system (liposome) is intravenously. Nanoscale drugs have great potential for improving drug delivery through the nasal and sublingual pathways to areas such as the eyes, brain, and intracellular cavities that are difficult to access. nasal and pulmonary routes (pulmonary system): One of the most important routes of drug delivery and is done through aerosols, powders and solutions

(sprays). All of which may include nanostructures such as liposomes, micelles, nanoparticles (Ducor, 1998) and dendrimeric aerosol products for pulmonary transport. This system makes up 30% of the drug delivery system. Transdermal Drug delivery system: In this system, the drug is transported by diffusion. The drug delivery system prevents problems such as gastrointestinal irritation, drug metabolism, fluctuations in transfer rate, and food-drug interference. This system is also suitable for patients with low consciousness. Its limitations include (Frost,2005) slow penetration rate, inability to change the dose much, and its limitation in the use of low-dose drugs.

**Figure 8.** Backing Dosage information listed on the Drugs.com website should be used as a guideline only. Always consult your



doctor or healthcare specialist before changing the dosage of any medicines.

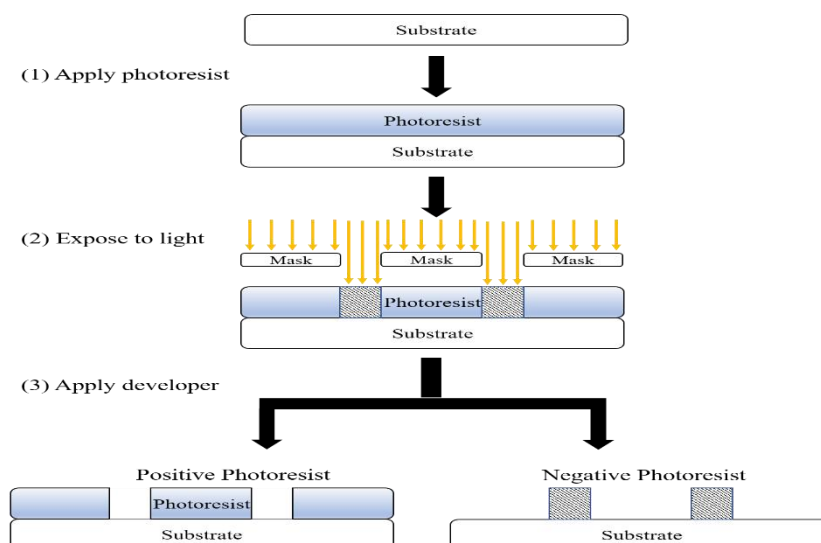
### 6. Introduction of micro and nano-drugs in pharmaceutical biotechnology

Important micro fabrication techniques include:

#### • Photolithography:

A light-sensitive polymer is used to transfer a user-created shape to a material through selective exposure. This technique is used to study surface structure patterns as well

as the ability to organize the transport properties of biocompatible skeletons.



**Figure 9.** Photolithography, also called optical lithography or UV lithography, is a process used in microfabrication to pattern parts (Morboli,2016) on a thin film or the bulk of a substrate (also called a wafer).

• **soft lithography:**

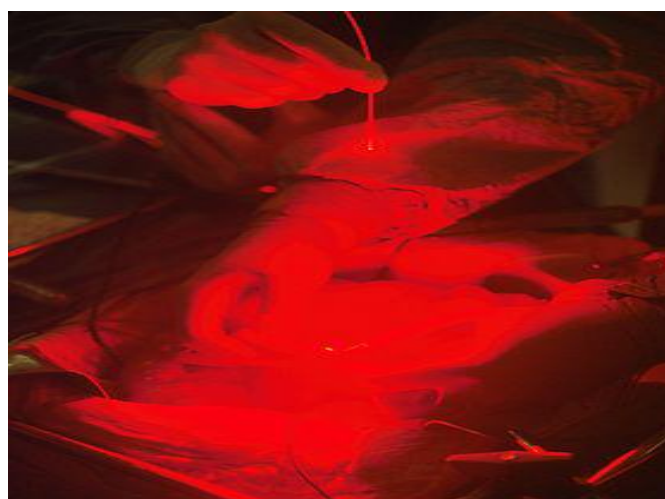
Soft lithography consists of three different techniques, (Audretsch,2003) all based on the production and use of a microstructure (Hefferon,2020) without poly (dimethyl siloxane).

- film deposition: involves the formation of micron-thick films on the bed surface
- Etching: Selective removal of materials from the surface of microdermabrasion by chemical or physical processes (Black,1834-1844)
- Bonding: Bonding substrates with or without the use of interface layers

**7. Important Nanofabrication techniques:**

• **Photodynamic therapy (PDT)**

Light therapy as a non-invasive, effective and modern treatment for about two decades has opened its place in the treatment of some cancer and non-cancer diseases. This method is based on the interaction (Audretsch, 2003) of two factors, the first factor of light-sensitive substance (Ps), which has two basic characteristics. The first characteristic is the ability to selectively absorb in atypical cancer cells (tumor tissue),while in adjacent healthy cells, absorption is almost non-existent (or so low that it is not considered) and the second characteristic is the formation of photo biochemical interactions due to long-term radiation. It is a specific wave (depending on the type of Ps material) of radiation (mainly laser) that forms the basis of occupational therapy. Appropriate wavelength (as a second factor).



**Figure 10.** Photodynamic therapy (PDT) is a form of phototherapy involving light and a photosensitizing chemical substance, used in conjunction with molecular oxygen to elicit cell death (photo toxicity).

PDT is popularly used (DiMasi,2007) in treating acne. It is used clinically to treat a wide range of medical conditions, including wet age-related macular degeneration, psoriasis, atherosclerosis and has shown some efficacy in anti-viral treatments, including herpes. It also treats malignant cancers including head and neck, lung, bladder and particular skin. The technology has also been tested for

treatment of prostate cancer, both in a dog model and in human prostate cancer patients.

**8. Magnetic nanoparticles**

**Applications of magnetic nanoparticles in medicine include the following:**

Targeted transfer (Qing-jun,2006) of the desired compound

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including genes, drugs, stem cells, proteins and antibodies to the target tissue (Nasim,2003) and cell.

- Magnetic resonance imaging.
- Treatment of cancer with hyperthermia.
- Isolation of cells and macromolecules and cell purification.
- Application in biosensors
- Ability to track particles (Barkstrom,1985) in vitro and in vivo through magnetic resonance imaging (MRI)
- Immuno-cyto-chemical tests

Solid lipid nanoparticles (SLNs) were first introduced in 1991 as an alternative to conventional colloidal carriers such as emulsions and polymeric polymer nanoparticles.

- Targeted drug release
- Proper biocompatibility
- Increase the stability of drug formulations
- Increase drug content
- Easy to sterilize prepared formulations

### 9. Chemical protection of the substance in solid lipid nanoparticles

Preparation through (Frew,2007) conventional emulsion preparation methods

Long-term stability

### • Michelles

Micelles are densities of surfactant molecules dispersed in a colloidal liquid in which these ionic surfactants have (Schmidt, 2006) an electrostatic attraction to the ions that surround them in solution (later known as cross-ions).

### • Applications of micelles/Imaging

Ligand-modified micelles can detect overexpressed receptors on tumor cells and bind specifically to them, and by chelating or combining the imaging component, micelles can be tracked in vivo for biodistribution studies. In the 1990s, pharmaceutical nanocrystals attracted the attention of pharmaceutical researchers. Drug nanocrystals are colloidal dispersions less than micrometers in size that contain approximately 100% of the active drug substance and are stabilized with the help of small amounts of stabilizers such as polymers or surfactants.

### 10. Advantages of nanocrystals:

#### Increase dissolution rate

As the particle size decreases, the contact surface between the particle and the environment increases, resulting in a dissolution rate (which is related to the contact surface area).

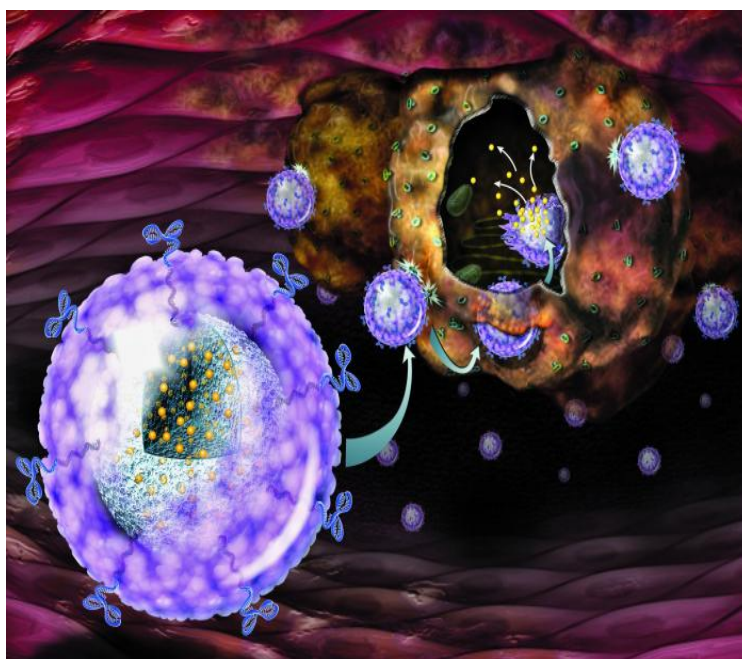


Figure 11. More than 3,000 human enzymes have been identified and named.

Enzyme Committee (EC) (Courtois, 2003) The International Union of Molecular Biochemistry and Biology (IUBMB) divides enzymes into six groups based on catalytic reactions:

1. Oxidoreductases
2. Transferases

3. Hydrolases
4. Liases
5. Isomers
6. Ligases

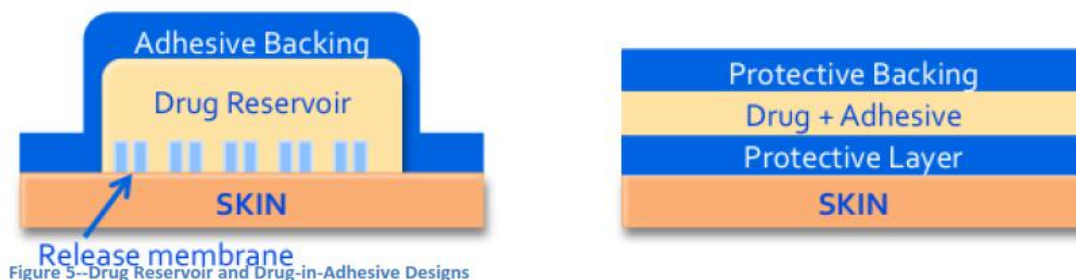


Figure 12. The dynamic characteristics of the membrane-moderated controlled release with an excess active agent dispersed in the core zone are presented for both isothermal and non-isothermal systems. Effects of the void fraction, membrane thickness, concentration dependence of diffusivity, and step change in the temperature of the environment on the rate of release are comprehensively studied.

**11. Enzymes as medicine**

Most pharmaceutical enzymes belong to the group of hydrolase. Medicinal enzymes are divided into two categories in terms of use (Ezan,2008) for various diseases:

1. For rare diseases
2. For common diseases such as cancer and heart attack

- Enzymes market

Enzymes market: US \$ 4 million in 2015

Pharmaceutical Enzyme Market: US \$ 800 million

- Summary of the history of medicinal enzymes:

The first enzyme with medicinal properties: lysozyme of 1960  
 activase: the first recombinant enzyme in 1987, the second recombinant drug protein to be used: heart attacks due to clogged coronary arteries.  
 adagen: The first medicinal enzyme for rare diseases in 1990, a type of adenosine deaminase treated with PEG, used: SCID disease.

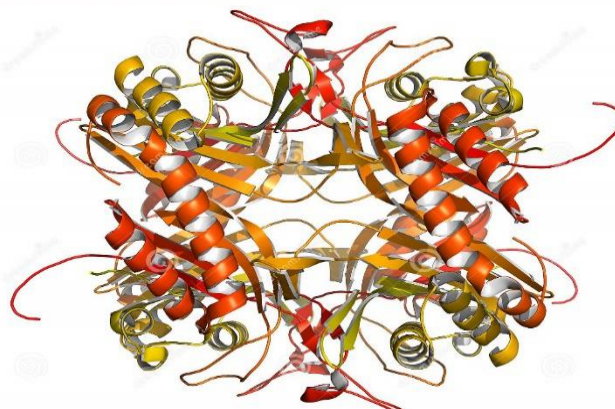
**12. Types of pharmaceutical applications of enzymes:**

1. Oral or inhaled therapeutic enzymes

**13. Some recombinant drug enzymes:**

Recombinant human superoxide dismutase	Oxsodro
Human acid precursor $\alpha$ -glucosidase, recombinant	Pompase
Recombinant human acid $\alpha$ -glucosidase	Myozyme
N-Acetylgalactosamine-4-sulfatase, recombinant human	Aryplase
Recombinant human highly phosphorylated acid $\alpha$ -glucosidase	TBD
Recombinant urate oxidase	Fasturtec

Figure 13. Rasburicase (recombinant urate oxidase) can be used when uric acid levels cannot be lowered sufficiently by standard



approaches. Rasburicase is useful in cases of hyperuricemia and has been shown to be safe and effective in both pediatric and adult patients. It also has a more rapid onset of action than allopurinol.

**14. A review of drug marketing from the past, present and future-biotechnology**

The pharmaceutical industry is one of the most strategic

industries in the world, which at the same time has a direct relationship with human lives. The pharmaceutical industry refers to the industries that refer to the sale and supply of

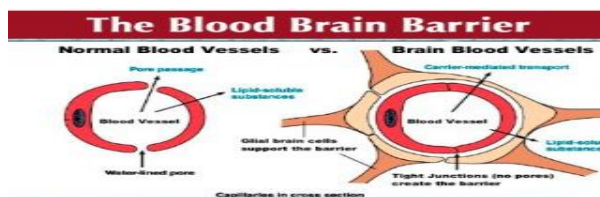
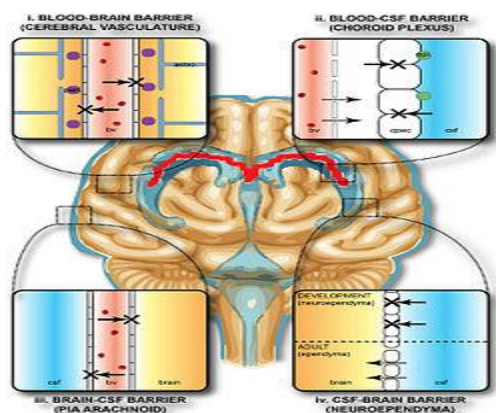
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drugs, so that (Muller,2004) today the percentage of the global economic market is higher than other industries in the pharmaceutical industry refers to the significant turnover in the world and also in our country . It is at the top of the world market table, which is 14.4%. And this industry in the fields of life sciences after the production of veterinary and medical equipment and diagnostics are in the ranking table. If it grows at this rate, it will reach \$ 1.6 trillion in the year 2020 is coming. It is the best database for the pharmaceutical industry (Database) (INDST), Industrial Statistics and the European System of Accounts (ESA). In general, pharmaceutical products can be divided into two categories: Ethical and OTC drugs. Each of these categories is also divided into two categories: Generic and originators. They market a drug. In this way, many large companies have devoted a level of revenue to research and development that produces drugs with new compounds and have the exclusive right to sell these drugs under the name of Originators drugs. After twenty years, other companies can buy drugs under the name of Generics by purchasing protocols and working methods from the company of origin. And because these drugs have no cost for research and development, they are usually cheaper than the original drugs. Ethical drugs are drugs. Which is sold in pharmacies under the supervision of a doctor and only with a license or (Drews,1960-1964) so-called prescription, while OTC drugs are also available to the public in other stores . The US Food and Drug Administration (FDA) says that generic drugs in terms of dosage The prescription, safety, potency, quality, mode of action, mode of absorption, and mode of use are similar to those of the brand name drug . In other words, the difference is less than 20%. Generic pharmacists are

increasing to 84 % Reached in 2012.OTC drugs include aspirin and other non-steroidal anti-inflammatory drugs, acetaminophen, anticonvulsants, cough medicines, and more. It takes 15-10 years and \$ 1.2 billion to develop a drug on the market. Only 2-10 drugs in recent years have been able to reach the cost of selling. The four main criteria that should be considered in the selection and use of drugs are effectiveness, safety, quality and economic evaluation. The steps that are taken to certify a drug entering the market under FDA supervision can be summarized as follows:  
 Basic Research/Drug Development  
 Pre-Clinical/Translational Research  
 Phase 1 Clinical Trial  
 Phase 2 Clinical Trial  
 Phase 3 Clinical Trial  
 FDA Review/Manufacturing  
 Phase 4 Clinical Trial/Post-Market Surveillance/Report  
 Adverse Events

**Figure 14.** How the Global Pharmaceutical Industry is doing.

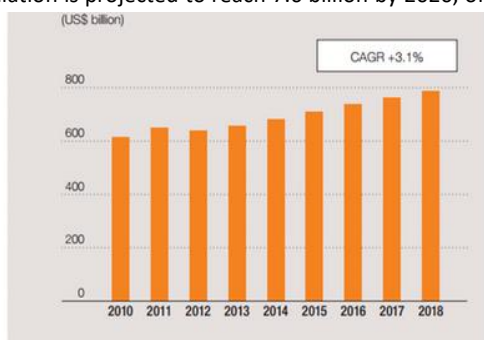
The United States is at the top of the pharmaceutical market table with 41%, followed by Europe and Japan with 27.4% and 9.7%, respectively, in second and third place among European countries.Germany, France and Italy also have the largest share, as well as China and India, which are ahead of the rest of the E7 or developing countries. In diseases such as AIDS, cancer, and heart disease, the mortality rate from over-the-counter drugs has dropped significantly. According to the report, the highest percentage of diseases in Europe is assigned to cardiovascular diseases with 39.2%, acute neoplasms with 25.9% and respiratory systems with 7.6% in



required to perform tests that prove that the amount of effective substance absorbed into the bloodstream from the prescriptions made by them is equal to the amount absorbed by the original brand-name drugs and should be The average variance between branded and generic drugs is about 3.5%, which in practice reaches 10%. Statistics show that the market share of generic drugs in recent years is

**Figure 16.** The blood–brain barrier (BBB) is a highly selective semipermeable border of endothelial cells that prevents solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the central nervous system where neurons reside.

It has doubled its condition from 2004 to 2020.The world's population is projected to reach 7.6 billion by 2020, of which



the second and third ranks. The highest rates of prostate cancer have been reported in developing countries. Although the United States is still projected to be at the top of the list in 2020, countries like China are much faster than the United States, and the US pharmaceutical economy is growing at a very steady pace.

more than 30% will be physically inactive or more than 20% will be obese and overweight, and more than 13% will be older. They will be 60 years old. So it can be predicted that in 2020, heart disease, diabetes and cancer will continue to occupy the top of the table of the share of the economic market of medicine as well as the share of non-communicable diseases compared to 2010, 15 % Has increased to an estimated 44 million deaths worldwide . In the field of health, in 2007 the most focus was on



emergency care and causal rooms, known as secondary care, and the share of OTC drugs was very small. Preventive self-care of patients with OTC drugs should be allocated to reduce the cost of diagnosis and treatment and surgery among the challenges ahead in the field of drug market can be 1-reducing innovation in production 2- and regulating strict rules and conditions of the two bodies FDA and EMA 3-

increasing costs in the field of health and also spending exorbitant costs for development and research. However, it is the only factor that is leading the way in the pharmaceutical industry, despite all the obstacles and factors, and that is the capitalist system or the capitalist system.



Figure 16. The most sustainable health models around the world have a mutually reinforcing setup of state-funded protection with individual accountability toward well-being.

## 15. CONCLUSION

Developing new drugs is a time-consuming and costly process. The relative improvement of the effect of the drug is being accomplished by various methods; For the past 20 years, researchers have based their research on nanotechnology to improve drug delivery and targeting methods. Improving delivery techniques that reduce the toxicity and increase the effectiveness of the drug has created great benefits for patients and a new market for drug production and delivery companies. Another approach to drug delivery is to cross specific physical barriers, such as the blood-brain barrier, or to find acceptable routes for the delivery of protein drugs instead of the digestive tract, where the drug is broken down.

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