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A Review on Enzymosome: Effective Tool for Tumor Targeting

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Abstract

Vesicular drug delivery system is a new era in Novel Drug delivery system. It can inhibit or neglect various drug related problems such as dosage problems, drug releasing property at the affected site, specific targeting property, prolonged release property and interaction property. Vesicular drug delivery system makes old drug in a new form and improves its therapeutic efficacy. Enzymosome is also under the vesicular drug delivery system. Enzyme is too much vital to stimulate a precursor for a target specific drug release at the affected area. There are some problems present for enzyme in the use of medication purpose such as the activity can be lost due to G.I.T degradation and enzyme has no any kind of own skin permeation property. To overcome the above problems, encapsulation of enzyme in a lipid-based vesicle is so important to make Enzymosome. Encapsulating the enzyme is essential for overcoming the alteration property, enhancing the half-life, increasing the site-specific targeting system and also helps to maintain the stability property etc. Enzymosome is established as a useful drug carrier in the medication of tumor treatment. This review helps to know about vesicular drug delivery system, its classification, preparation procedure of Enzymosome, its classification, uses in the medication purpose especially in targeted tumor therapy.

Keywords: Vesicular drug delivery, Enzymosome, Precursor, Preparation, Encapsulation, Tumor.

Introduction

In upcoming targeted drug delivery systems, the novel drug delivery has a special effect on sites of action [1]. There are various benefits are available of Novel drug delivery system (NDDS) in many industries like pharmaceutical, food and cosmetics etc [2]. According to our need, it helps to transfer the active ingredients of drug to the site of action because NDDS neglects the limitation of conventional drug delivery system [3]. A newly invented drug delivery system which is known as NDDS which helps to metamorphose many drugs and it also helps to conquer many drugs' related problems and to maintain extended release of active ingredients from the dosage form with controlled/regulated action [4]. Many drugs which are facing problems in bioavailability their vesicular carrier works as a smart vehicle and this carrier system is also useful in various platforms like genetic engineering, diagnosis tests, immunology techniques etc [5,6,7]. Vesicular drug delivery has a great role in cost reduction of clinical treatment and also in the improvement of pharmacodynamics effect of poorly wetting drugs [8]. In the prevalent chemotherapy, the vesicular drug delivery system is known as milestone for penetration of drug and cell permeation [9]. There are various types of organs, tissues; biological cell membranes are present inside a human body. All of the biological organs contain nucleic acid and genetic materials for reproduction and replication. Above all these are coming under the "SOMES" it's a Greek word [10]. There are some structural, physiochemical characteristics' similarity present in every organ's outlined cell membrane for this reason any kind of lipoidal and protein-peptide drugs can easily reach to the targeted area according to patient's need. Vesicle works as a drug carrier system in human body. It helps to transfer the drug molecules or the active ingredients in to the specific affected area. Vesicles are bio-compatible for human body because it is made up off lipid molecules [11]. Vesicle helps to encapsulate or protect the active ingredients of the dug in the core from the external environment and helps to maintain sustained or extended release of drug and to scale down the noxious effects [12]. Vesicular system is very essential to maintain the stability on the affected area. Vesicular system also has some great advantages in conventional medicines. Such as, to slash down the dose related adverse effects, to uphold the salubrious or salutary efficacy for extended period of time through jurisdiction the release of drug [13, 15]. Vesicles have amphiphilic characters because it can carry both hydrophilic and lipophilic drugs to the targeted area [14]. Both hydrophilic and lipophilic characters are present in the vesicular drug delivery system. So, it is amphiphilic in nature. In case of poorly soluble drugs, it helps to boost or recuperate the bioaccumulation of medication and slash down the cost of therapy [14]. A diverse range of amphiphilic building blocks helps to manufacture the vesicles. The main aim of vesicular drug delivery is to regulate the reduction of drug, obstruction of noxious or catastrophic effects and increase the concentration of drug at specific targeted site. Vesicular drug delivery system has more advantage than the conventional chemotherapy in the treatment of intracellular infections because it is effective for overcoming the various limitations [14].

Advantages

There are many benefits present for the vesicular drug delivery systems over the conventional drug delivery system like

- It helps to lengthen the time of presence for active ingredients of the drug in the blood and other organs. It also helpful to cut down the noxious effects of the drug while delivering to the site of action.
- It is very essential for enhancing the bio-availability of poorly soluble drugs.
- It helps to slow down the degradation of active ingredients from dosage form and this mechanism is known as controlled release systems.

Disadvantages

Beside the benefits vesicular drug delivery system also has some harmful or prejudice effects. Such as:

- Evasion or Escaping of drug or Dodging of drug can be seen from dosage form of vesicular drug delivery system in the time of preparation or manufacturing.
- Problems are also can be seen in the preservation.

- Problems may be occurred in the in vivo drug transportation process.
- The major problem is found in the stability of different ingredients of dosage forms and also limitation is present in their use.

Basic differences between all vesicular drug delivery systems

Liposomes: The name liposome is derived from two Greek words. One is "LIPO" and another one is "SOMA". Lipo means body and soma means body. It is basically a unilamellar vesicle which contains a single phospholipid bilayer sphere that encloses the aqueous solution, whereas multilamellar liposomes will exhibit multiple phospholipid bilayers.

Liposome is composed of two main structural parts:

- Phospholipid.
- Cholesterol.

Phospholipids: Phospholipids are the basic molecular building blocks of liposome. The cell wall of liposome mainly consists of natural substance lecithin which is a mixture of phospholipid that is also known as Predominantly Phosphatidylcholine (P.C). Phospholipid is a lipid which is amphipathic in nature. It consists of two main parts. Such as:

- Hydrophilic Polar head.
- Hydrophobic Tail.

The active ingredients of drug are encapsulated in the core of liposome. Liposome can cross or avoid the structural similarity between the cells and also it helps to reach the drug to the targeted specific site according to our need for the presence of both hydrophilic and hydrophobic parts. The hydrophilic active ingredients are present in the aqueous core section and hydrophobic/lipophilic active ingredients are present in the lipid bilayers.

Cholesterol: Cholesterol has some advantages, such as:

- It helps to stabilize the membrane.
- It works as a fluidity buffer.
- It inhibits the transformation of Trans to cis conformation.
- Unsaturated chain is responsible for oxidation purpose. So, antioxidant is very essential to protect the lipids from oxidation. Lipid exchange is occurred between the liposomes and HDLS, for this reason destabilization is occurred in the liposomes [18].

Niosomes: The structure and mechanism of action of noisome are almost as same as liposome but it overcomes the various limitations like physical stability of fusion, aggregation, sedimentation and leakage of storage. So, noisome is more useful than the liposome in delivery of drugs to the specific affected area. There is an issue present for noisome that is hydrolysis of encapsulated drug [19].

Pharmacosomes: Some interactions are occurred between the drug bi-layers which cannot influence the entrapment efficacy. The main benefit of Pharmacosomes is there is no need of extra time for abolishing or discharging the drug from formulation. The drug does not take place due to discharge from the dosage form and covalently linked with each other [20].

Ethosomes: This is also vesicular drug delivery system has a great role in Transdermal Drug delivery system because ethosome helps in the drug permeation through the skin and better stability than liposome. Some benefits are also can be seen in the stability for active ingredients of drug and encapsulation of raw ingredients [21].

Transferosomes: Transferosomes have susceptibility nature and procivity nature to the oxidative degradation. There should be a condition must be present to maintain the strength/balance of transferosome which is used as a specific drug delivery system. There is a difference present between the transferosome and liposome. Transferosome proved it 'self-more beneficial than the liposome, so it is more effective in the transdermal drug delivery system. There are some disadvantages present for the transferosomes such as:

- Sometime oxidative degradation is occurred in the transferosomes.
- Insufficient number of natural phospholipids [22].

Colloidosomes: Colloidosomes are also essential in the vesicular drug delivery system. There are some advantages/benefits present for the colloidosomes such as:

- It is biocompatible for our body.
- It is easily passable to the skin.
- It is easily capable to encapsulate the main active ingredients of the drug in the core
- The mechanical power is high.

But some problems are also present there:

Some unnecessary particles are formed at the time of manufacturing of colloidosomes and a large number of colloidosomes are lost during the time of transfer from organic to water medium [23].

Herbosomes: Herbosome is also an important part in vesicular drug delivery system because it has low adverse effects, biocompatible and chemical bonds are formed between the phytoconstituent and phosphatidylcholine molecule [24].

Sphingosomes: Sphingosome has structural similarity like the liposomes. The main structural component of sphingosome is sphingolipid. The mechanism of action of sphingsome and liposome is same but sphingosome is more stable than liposome. There is a issue present for sphingosome like low drug entrapment capacity [25].

The main advantages of sphingosomes are:

- It is more stable than liposomes and niosomes.
- Sphingolipid has high tumour loading efficacy in cancer therapy.
- Sphingosome has high in vivo circulation time [26].

Cubosomes: Cubosome has better physio-chemical stability than liposomes and easy manufacturing procedure but viscosity problem can be seen in the large-scale manufacturing [27].

A Brief Note on Enzymosome

Enzymosome is established as a beneficial drug carrier in the vesicular drug delivery system. Enzymosome is composed of two words. One is "Enzyme" and another one is "Somas" which means body. In enzymosome, enzyme is the main biological active compound which works as an energizer for a substrate that is encapsulated in a highly lipid-based cell. So, a newly modified liposome is formed through this process. The enzymes are attached on the surface of the lipid molecules in the liposomes. Here the liposomes are prepared for encapsulating the enzyme and helps to reach the targeted area [28].

We all know that liposome is amphiphilic in nature. There are two types of parts present in liposome. One is hydrophilic part and other one is lipophilic part. The hydrophilic active ingredients are present inside the aqueous section of liposome. The lipophilic drug substances are present outside the lipid bilayer membrane. Liposome is

established as a useful drug carrier to reach the drug at the specific targeted area for its amphiphilic characteristics [29].

There are some advantages [30] present for the liposome Such as:

- It helps to slash down the volume of distribution.
- It inhibits drug clearance.
- It helps to enhance the drug permeability to the infected tissue according to our need.
- It also reduces the noxious effects related with biological tissues.
- So, liposomal enzyme proves it self an effective drug carrier system in Medical sciences. [30]

Enzymes are established itself as a site-specific effective biological compound. It has some great roles. Such as [31]:

- It has a great role in catalysis reaction.
- It is very beneficial for site-specific pharmacological action.
- It is proved as an activator for prodrug.

Enzyme has low lipid membrane permeability feature. If the outer surface of the liposome is enveloped by the enzyme then the deterioration and alcemization/metamorphose are minimized. This process helps to increase its half-life with the targeted action according to our need [31]. Enzymosome is worked as a novel drug carrier in vesicular drug carrier in vesicular drug delivery system. It helps to release the active ingredients from dosage form to site of action and boost up the uptake of active ingredients to the systemic circulation. Enzyme may be attached with the surface of the liposome through two ways: [32]

- Attaching with lipophilic part.
- Attaching with phospholipid part of liposomal layer.

We can enhance fruitfulness of the drug and slash down the side effects. It is also essential to send the drug at the particular target site. There Nano carriers are helpful in different medical sectors like: [33]

- Epilepsy or seizures a neuronal disorder.
- Encapsulate the drug in core and help to pass the drug through BBB for its lipophilic nature.

Here enzymes are acted as a therapeutic protein which is supplied through lipophilic enzymosome for increasing response. A vesicular drug delivery system has a great role in centrally acting drug delivery systems, target specific drug delivery and it's also having less toxicity [34]. Enzymosome is beneficial to exaggerate bio accumulate the drugs. The minimum amount of drug concentration is available for biological function to cut down the purchase cost [35]. The structural integrity and function of enzyme are found when enzyme is encapsulated in vesicle which is applied during in vivo and in vitro testing [36]. Upcoming modern developed models of enzymosomes are widely applicable in biotechnological research and recombinant protein research etc [37, 38].

Benefits of Liposomes Enzymes Conjugate [39]

- It lowers the hazardous effect of virulent drugs to the sensitive tissues.
- It helps to encapsulate the drug in the core and increases the balancing capacity.
- It increases the half-life and reduces the elimination of drug.
- It is biocompatible with body.
- Insusceptible to the fundamental and non-fundamental for administered doses.
- It has no any kind of noxious effect.
- It is totally mixed with our tissue or biodegradable in human body.
- Electrical properties are altered frequently.

Limitations

Though nanoparticles are very essential in medical sciences but the production cost of nanoparticles such as (Liposome, Niosome, Aquasome, Enzymosome, Electrosome etc.) chemical degradation may be occurred of phospholipids which are present in lipid vesicular structure. Biocompatibility may be decreased due low soluble ingredients and shorter half-life. Leakage or accidental release of active ingredients may be occurred [40, 41, and 42].

Lipid-Based Drug Carriers (Drug carrier which is made up of lipid)

There are various types of topical dosage forms are available like oral, parenteral and others. Above all of these are made from lipid/Triglyceride based drug carrier [43]. Lipid based enzymosome has a great role in safety and efficacy for the preparation of vaccines (attractive/interesting) preparations and modified treatment process. Lipid-based drug carriers are very essential for cost reduction and low toxicity purpose in various treatment, stability study, ultrasound treatment and identification of diseases etc [44].

Some advantages/benefits of lipid-based carrier are:

- It has risk but less than others.
- It increases the bioaccumulation and minor concentration.
- It has good characters and also capable of lipophilic excipients.
- Lipid-enzymosome is essential to detect the specific target area and helps to deliver the technology [45].

There various types of lipid-based carrier systems are available such as Liposome, Niosome, Aquasome, Mariosome, Phytosome, Transferosomes and Emulsions. Above all of these under the vesicular drug delivery system [46, 47]

There are some basic functional categories are present for the lipid-based drug carriers. Such as:

- Controlled or Modulated drug release.
- Physical and chemical stability maintaining.
- It helps to preserve the drug in the core from the deterioration.
- It is biocompatible with tissue in human body.
- Solid-lipid nanoparticles, lipid drug molecules help to prevent the cytotoxicity effect by preventing the polymer which used in making for nanoparticles. [48,49]

There are many scientific works are done on semisolids made nanoparticles to encapsulate the active ingredients for delivering it into systemic circulation [50]. Solid lipid nanoparticles, Self-emulsifying drug delivery systems, Nano emulsions and Pickering emulsions can be encapsulated or incorporated in the emulsions [51]. Enzyme is hooked up with liposomal compound to form the Enzymosome. It helps to protect the activity of enzyme and uphold the structural features of vesicles. Superoxide dismutase (SOD) is an enzyme that alternatively catalyses the dismutation of the superoxide radical into either ordinary molecular oxygen or hydrogen peroxide [52].

Method of Preparation

Preparation of Enzymosomes of Surface-Exposed Superoxide

Binding the enzymosome with the lipid molecule or liposome is called Enzymosome. Formation of enzymosome is very important in immune-mediated diseases or antibody treatment. This new developed therapeutic model is known as SOD (Super Oxide Dismutase) [53]. Various enzymes like Cu, Zn-superoxide dismutase are very beneficial to define an inborn resistance technique. Which helps to cut down / slash down the malformation/teratogenic effect developed by noxious free radicals. It starts a process of simultaneous oxidation and reduction process for harmful superoxide radical anion 02 to 02 and water. Superoxide dismutase is used as an important alternative compound for traditional anti-inflammatory therapies. We should avoid the side effects during the use of anti-inflammatory drugs [54].

At the previous time, the enzyme has shorter half-life and low skin or tissue permeation capability. So, at this time it was not accepted for clinical trials. Many researches work and studies were done for developing or modifying the drug carrier where enzyme should be incorporated/loaded with increased half-life and higher penetration capability for clinical trials in various diseases like type 2 DM and obesity etc [55].

There are some applications available for intracellular SOD (Superoxide dismutase). Such as

It helps to reach the drug to cell penetrating peptides (CPPs) or Protein transduction domains (PTDs). Proteins are established/proved beneficial for biological research and regulating the delivery of these peptides. New upcoming contemporary/latest development of incorporating procedure introduced for its captivating/delightful use in treatment of various medical issues [56].

Blueprint of Immune-Enzymosomes Which Have the Ameliorated Enzyme Desideratuming Capability and Cell Attaching Properties

There are some hyper efficient conventional anticancer medicines present for chemotherapeutic agents who are used in cancer treatment due to the insufficient difference between normal cell and cancer cell. There are many scientists established some valid documents for immune-enzymosomes which can be used as a target drug carrier in cancer treatment. We know that liposome is amphiphilic in nature. The hydrophilic and hydrophobic both type of categories are present in liposome. Liposome can cross or inhibit the structural similarity between the cell wall and helps to reach the entrapped drug to the targeted site-specific affected area [57]. When Anthracycline Glucuronide prodrugs attach on the surface of immune liposomes then this combined system is very helpful as an essential effective drug in the cancer treatment of ovary (OVACAR-3). Two important compounds like enzyme and Beta-glucuronidase are accomplished for vitalizing the anthracycline glucuronide prodrugs. The functional activity of immune-enzymosome formulation is increased when Beta-glucuronidase (GUS) is attached with the ovarian cancer cell [58]. The mechanism of action of immunoliposome is as same as liposome. Being an amphiphilic drug carrier immunoliposome can go every place in human body through neglecting the cellular characteristics or similarity. It is established as a conventional drug carrier for enclosing the chemotherapeutic agent inside and target specific drug release [59].

Least possible resistance activity must be presented in the immune liposome with the help of non-noxious prodrug, the antibody-enzyme complex can be injected in human body. Its determinate from blood and tissues when it makes a complex form with cancerous cell. Enzyme's action is very essential for proper targeting purpose. At first prodromus into active anti-neoplastic drug molecule within the synchronicity of malignant cell, some essential benefits of immune-enzymosomes are present in the diagnosis field, such as: [59]

- A large number of streptodomase or enzyme moieties could be attached in one addressed carrier system.
- Increasing the concentration of enzyme on the outer covering area of cell surface helps in the transformation of prodromus within the cell.
- Enzyme (GUS) or Glucuronidase enzyme is privileged for its superiority over the enzyme which is present in cellular organ.

Some low resistance power is present here, such as:

- Energizing of hydrophilic glucuronide drugs are limited circumspection.
- They have low permeable power.
- This system also diminishes the resistance problem.

Manufacturing & Construction of Alkaline Enzymosomes weighted With Bacillus Fastidious

There is same research works were completed by Tan. Q et.al to find out the auspicious action of novel alkaline enzymosome for discharging the enzyme, Bacillus fastidious which releases a particular enzyme uricase and embroider its biological functions, curative use and posological properties [60]. Urease is a vital enzyme which works as an active catalyst in oxidation this reaction is very beneficial to maintain the uric acid level in blood [61].

After performing many researches and studies a documented data is proved that UBF loaded Alkyl Enzymosome has more advantage than the Normal UBF to maintain the proper balance of uric acid level in blood [62, 63].

From the studies, ESUBFs is very essential for supplying and maintaining the quantity of UBF. Emphatically enhance the AUC, half-life and catalyst activity as well as its bio-chemical and pharmacological features [64]. Through this process ESUBFs is made it 'self an essential exclusive 2nd choice mixture solution for inhibitors like gout and hyperuricemia. [65] In vivo uricolytic action has a great advantage in clinical applications. But some side effects are still present such as the normal dosage of UBF formulation can affect. It can be inhibited through conjugation process [66].

In the different work and research studies, Alkaline UBF enzymosomes were converted into a developed one which is established for its beneficial performances in bio-chemical, biological and pharmaceutical sectors and helps in exploit of hyperuricemia effects that is happened for an enzyme urease that is secreted from Bacillus Fastidious. Uricase is essential to reduce the uric acid level in hyperuricemia rat model in experimental work [67].

Uricase enzyme proved it's self as a very beneficial to increase the target specific drug delivery system and rapid action of active ingredients in this sector. Enzymosome has a positive advantage to keep enzyme protected inside the core and helps to release the active

ingredients. After completing various research works, we can know that UBF included novel alkaline enzymosome (ESUBFs) is worked as a catalyst through in-vitro drug administration at optimum ph. ESUBFs have larger drug plasma concentration curve (AUC) comparing with the UBF and it is also known for its longer circulation half-life [68, 69]. ESUBFs is essential for different types of enzyme deficit diseases such as Hurler syndrome, Niemannpick disease (Babies develop liver enlargement, difficulty in feeding and nerve damage) etc [70].

Functions of CD39 Enzymosomes in Antiplatelet movement

The active essential component of an endothelial cell is an enzyme which is CD39/NTD Dase-(I) that is arises on the opening side of the cell. It is capable of consumption for ATP, ADP, AMP and it also has a great role in diminution of platelet sensitivity to the major agonists. Enzymosome can keep CD39 compound which is essential for anti-platelet activity. The function of the CD39 enzyme is totally controlled according to the domains of transmembrane [71].

A yeast expression system is essential in human body to form CD39. Here, yeast expression system is a vital model which is sterilised and reconstructed within a proper lipid vesicle according to our perfection [72]. At the time of reconstruction of CD39 enzymosome within a lipid membrane, the reaction enhancing activity can be determined through the dephosphorylation and formation of ADP & ATP [72]. Formation of ADP and ATP are taken as measuring parameter. Here platelet aggregometry method is very essential for describing the collagen and thrombin. ADP has a great role in prevailing on platelet activation. Which is hindered by lipid vesicles having CD39, thromboembolism is vital process which is persuaded by a Murine model of Thromboplastin [72]. This Thromboembolism is proved as a process to find out the proper biological benefits, useful activity and pharmacological activity of CD39 enzymosome through I.V route in limiting platelet consumption and death. The devaluation of Km value and contemporary increasing of both ADPase and ATPase impetus efficiency are happened during reconstruction of human CD39 enzymosome in lipid vesicles [72]. Medication with CD39 enzymosome and further studies on this topic are very helpful to stop the devaluation of platelet counts which is functioned by thromboplastin. During the correction of solubilized counterpart, the consolidation of enzyme into the lipid bilayer helps to enhance the functional activity of CD39 enzymosome. For this above process, the death rate of animal model and platelet consumption can be decreased. To complete anti-platelet medication, the CD39 enzymosome proved it' self as a vital option through thrombus manufacturing process [73].

Layout and Personation of Enzymosomes with Surface Exposed Superoxide Dismutase

SOD (Cu, Zn Superoxide dismutase) is a legitimate the defence system which decreases noxious effects of oxygen-derived free radicals. Here, SOD is first discovered by Mc Cord and Fridovich in 1969 [74]. Its impetus the dismutation of O2 plus H2O2 from toxic superoxide radical anion which inhibits the biological inflammatory process under controlled by free radical [75] there are too many chances of noxious effects, adverse effects and interaction effects may be present during the treatment of conventional anti-inflammatory therapies such as non-steroidal anti-inflammatory drug. To avoid these kinds of side effects, we have to use the SOD enzymosomes as a standard optimized tool in the treatment of inflammatory pathology. These kinds of side-effects generally occurred in G.I.T tract of human body [76].

Through the short half-life time in bloodstream, permeation property into the cellular organs and target specific activity are poor or low in case of enzyme. For this above some particular reasons, there are some researches studies are done to improve the activity of enzymes such as

A particular covalent attachment of SOD (Cu, Zn superoxide dismutase) with some catalytic chemical compounds such as Polyethylene glycol (PEG), Dextran, Albumin, incorporation of liposomes and application with Ficoll etc [77, 78, 79, 80, 81, 82, 83, 84]. Nakaoka et al. first investigated that when the SOD is attached with PEG, the distribution behaviour is not changed in various organs such as spleen, lungs, heart and G.I.T [85]. Turrens et al. first investigated that when SOD (Cu, Zn superoxide dismutase) is encapsulated within the liposomal compartment then the half-life and activity of SOD is increased. There are some problems can be faced like low incorporation efficiencies due to liposomal preparation [86]. In current situation higher liposomal embodiment productiveness were found currently [87, 88, 89]. The amount of enzyme release and quantity from SOD liposomes at the infected site determines the curative activity of SOD liposomes. The release of enzyme at specific targeted site is proved more beneficial when SOD is present on the surface area of liposome not in the core section of it. Formation of dative bond of palmitic acid with (-NH2) groups of SOD is very effective in acylation of enzyme. A lipophilic enzyme is formed from the acylation procedure. This enzyme helps to enhance the penetration capability through liposomal bilayers. This whole process is conjectured by research team [90, 91, and 92]. Through placing the SOD on the upper surface area of liposome is very helpful for targeting to the specified targeted site.

As beneficial carrier for localization at the infected site, after doing so many researches, an information is come that is if long circulating liposomes (LCL) is administered in human body through I.V route, it goes to the affected area preferentially [93, 94, 95, 96].

As a result, liposomes can easily penetrate the inflammation area. From this, we can say that LCL is very essential as a targeted drug delivery carrier for AC-SOD. Through this study, we can give an importance for a comparison study of physiochemical properties between SOD and AC-SOD also related to the reciprocal liposomal formulations. There are 2 types of liposomes such as LCL (Long Circulating Liposomes) which is coated with PEG and non-PEG coated liposome having Stearylamine. Some essential characteristics such as zeta- potential, enzymatic activity, highly exposed enzymatic activity, highly exposed enzymatic activity and pharmacological effectiveness should be showed by both liposomes.

Treatment of Tumour by Enzymosomes

Small particles of crude drug are encapsulated in the Nanomedicine which is administered to the specific affected area through different powers such as heat, light and other sources. Nanoparticles are manufactured in laboratories in sufficient amount that is enough for medication within low-scale of measurement [97]. There are various types of impetus enzymes are available such as alkaline phosphate, carboxypeptidase, beta-glucosidase and beta-lactamase. Above all of these works as dominant of antitumor drugs, this enzyme activity works as a precursor at the tumour site, in this mechanism liposome has a great advantage or established as a beneficial carrier because it

can go any organ of our human body through avoiding the structural similarity between the cells. It helps to reach the encapsulated enzyme to the specific affected site (Tumour site) [98]. Today's modern pharmaceutical technology, the transmission system of enzyme is divided into 2 major categories [99]:

- Shipment of genes that conceal prodrug-stimulating enzymes into specific affected tumor sites such as GDEPT 'Gene–Directed-Enzyme-Prodrug-Therapy' and VDEPT 'Virus-Directed-Prodrug-Therapy'.
- Consignment of stimulated enzymes onto tumour tissues (Antibody-Directed-Enzyme-prodrug-Therapy).

Here antineoplastic drugs and virazole agents are very important for specific targeting to the infected site by antibody enzyme conjugates, this whole mechanism is known as prodrug activation Therapy (ADEPT or Antibody Directed Catalysis) [100].

Lack of precision to the tumour cells restricts the cancer chemotherapy. A substitute medication of cancer is ADEPT technology [101]. Enzyme attaches with antibody and increases its synergistic effect; this enzyme-antibody combination is very essential and important for proper tumour targeting therapy. A prodrug is converted into a parent neoplastic drug when a consecutive amount of prodrug is administered in human body. The discipled prodrug is proved as a beneficial drug for proper killing to the targeted tumour cells but also the neighbouring tumour cells also [102].

The enzyme stimulating prodrug medication in tumour treatment has 2 steps:

- At first, the essential drug catalyst enzymes are selected.
- Non-noxious precursor is known as pristine of exogenous enzyme which is appeared in tumours and it is applied by parenteral route. [103]

The counterbalance action of serum enzymes has not any kind of effect on small noxious species which are made from the prodrug stimulation and it may have standard slaughtering effect. In 1992 Rowlinson-Busza created the cyanide generation system (Antibody Guided Enzyme Nitrile Therapy) [104].

Monoclonal Antibodies (Mab), Cytokinase Immune- toxins, Tumour antigens (Vaccine) and normal antibodies are proved as beneficial medicated therapy for tumour treatment. Mab-guided medication is very useful to carry the enzymes to the specific targeted area to sidestep the amalgamate effects. There are various prodrugs which are converted into activated new drug through coupling the antigen/antibody with enzymes [105]. These responsible enzymes are carboxypeptidase G2, beta- lactamase, beta-galactosidase, Alkaline Phosphatase, V-amidase, Cytosine Deaminase, Nitroreductase, Carboxypeptidase and Catalytic antibodies etc. Release of active ingredients of drug at the affected site is depended upon the function of the enzymes. At last, antigen-negative cells are escaped from the tumour medication due to appearance of heterogeneous/conglomerate substance [105].

The main aim of this article is to upgrade and reformed the enzymosomes. Long dissemination time in blood is important for proper targeting to the tumour site to control function of enzyme in its stimulated form. Here, the main objective of this article is to release of enzyme from enzymosome at the specific targeted site and release of active ingredients of drug from liposomal bi-layer at the infected site [106].

Now days, enzymes are very important for prodrug activation with antigen/antibody which is shown under this table:

Antibody/ Antigen	Enzyme	Prodrug	Active drug
MAbs W14A and SBIO/ chorionic onadotropin	Carboxypeptidase G2	Benzoic acid mustards-glutamic acid	Benzoic acid mustards
No antibody in study	β-Lactamase	Vinca-cephalosporin	Vinca alkaloid
MAb L6 (against a carbohydrate antigen on human carcinomas)	Penicillin amidase	Doxorubicin-phenoxyacetamide Melphalan-phenoxyacetamide	Doxorubicin Melphalan
MAb BW431/26/ Carcinoembryonic Antigen (CEA)	Alkaline phosphatase	Etoposide phosphate	Etoposide
MAb 323/A3 (against a pan-carcinoma membrane glycoprotein)	β-Glucuronidase	Epirubicin-glucoronide	Epirubicin
MAb KS1/4/ UCLA-P3 human lung adenocarcinoma	Carboxypeptidase A	Methotrexate-alanine	Methotrexate

There are various techniques are available for enhancing the efficacy of carrier mediated delivery of therapeutic proteins. Such as:

- It's application into polymeric carriers.
- Placing of aqueous space of lipid.
- Incorporation of detergent or lipid-detergent vesicles.
- Incorporation of hydrophobic/lipophilic bilayer vesicles.

Here a technology is come for enhancing the performance of antibodies through the attachment on the upper surface area of liposomes. From the different publication sources, we can know that when the enzymes are attached with the upper surface of Nano-carrier then it can be used for active targeting. Superoxide–Dismutase (SOD) is very important for treating Rheumatoid Arthritis and Reperfusion diseases.

Here the main aim is to improve the blood circulation time, enhancing the biological properties and increasing the specificity to the tumour cells. Above these processes are helpful to enhance the functions of all enzymes in its activated form. Here two main characters such as specific targeting property and stable capability are should be present in enzymes. Liposome and noisome are very useful for their excellent biocompatibility and biodegradable property to encapsulate the drug inside the lipid vesicles to overcome immunogenicity properties [107]

Benefits of Enzyme Prodrug Medication Which is Under Controlled by Antibody

A huge number of precursors can be manufactured from a single enzyme. These precursors are used as a therapeutic agent for cytotoxic

drugs. Here, the strength of drugs is not affected through this process. Noxious effects such as radiation from radioactive materials and enzyme-antibody convolution do not deteriorate the whole systemic circulation when they are situated inside it. All the obstacles of antigenic amalgamate and tumour accessibility is inhibited by the function of radionuclide [108].

Limitation of Enzyme Prodrug Medication Which Is under Controlled by Antibody ADEPT has noxious effects on normal cells. If:

- The precursors are disciple into antineoplastic agent by the enzymes which is secreted from the body.
- There is a residual quantity of enzyme-antibody complex present in systemic circulation of human body.
- The cropped antineoplastic agents can go to the system circulation from tumour site.
- The tumour unambiguous antibody has many benefits like It helps to convey the enzyme to the normal tissue and cross responsive with cell surface antigens of normal cells. [109]

Future Prospective Of Enzymosome in Treatment for Tumour

Enzymosome is proved as a beneficial drug carrier for site-specific drug delivery system because there is a suitable biocompatible and small capsule like environment present inside the enzymosome where the enzyme can present easily and attach with the outer surface area of lipids. Basically, enzymosome is a lipid constructed drug carrier. The active ingredients which are encapsulated within enzymosome can easily reach to the affected site [110]. Enzymosome is proved as a remarkable vesicular drug delivery system to neglect the noxious

Side effects and biocompatibility problems, it is so flexible with the drug formulation related

Problems the active ingredients of drug are encapsulated in enzymosome which can easily Permeable through BBB and helps to reach the drug to the CNS for the medication of malignant tumour [111].

There are various precursors, their complex forms and charged proteins can be transported through enzymosome to the CNS by enhancing the amount of drug. Drug carrier nucleus has some limitations such as some damages are occurred due to oxidation process and stress & strain damages also. It's main function in proper selection and site-specific targeting. It also brings newer technologies to the vesicular drug delivery system [112].

There various modern techniques such as blotinylation, pegylation are newly come for targeted drug delivery system. Both lipoidal and non-lipoidal vesicular carriers are used as a biocompatible drug carrier in sustained drug release and cellular targeting. Not only the enzymosome, there are more lipid-based drug carriers such as ethosome, transferosome, pharmacosome, virosome besides non-lipoidal carriers such as noisome and aquasomes are also enlisted under vesicular drug delivery system [113].

After doing various research studies, documented evidence is proved that PEG-SOD enzymosome is widely used for its therapeutic action. We know that liposome is a very effective drug carrier because both hydrophilic and lipophilic capabilities are present in it. It can carry the encapsulated drug to any part of human body by overcoming the structural similarity between the cells. On the other side, low–water soluble drug molecules can be incorporated in emulsion. Enzymosome is defined as a new generation flexible drug carrier for further use in future. Also, some different strategies are come for protein drug delivery purpose. The required enzyme is attached at the hydrophilic area of lipid vesicles and lipophilic compounds are assembled in hydrophobic portion. When an enzyme is made a conjugation with a lipid vesicle then it is known as enzymosome. The basic characteristics of enzymosome are to encapsulate the active ingredients of drug to maintain its bio-compatibility and overcome the noxious effects etc. Till now, there many studies are done to achieve the targets like increasing the site-specific targeting and rate controlling drug delivery at the affected site. Above all of these essential characters are present in enzymosome for tumour therapy. So, enzymosome is established as a novel vesicular drug delivery system.

Conclusion

There are various drug delivery carriers present under the vesicular drug delivery system. Enzymosome is important to encapsulate the active ingredients inside the core safe, to maintain the biocompatibility, to maintain rate-controlled drug delivery at affected area and to overcome the noxious effects. Above all of these basic essential categories must be present in enzymosome to be a novel, conventional and effective drug carrier. Enzymosome has a great role in bringing new life to old drugs.

Figure 1: Diagrammatic representation of structure of lipoid bilayer.

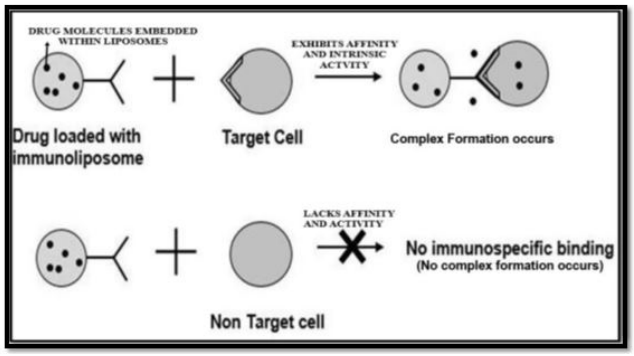


Figure 2: Schematic of three loading methods for preparing protein/Nano carrier composites.

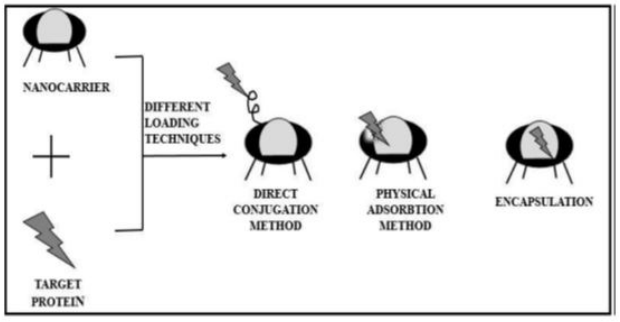


Figure 3: Specificity of immuno-enzymosomes to target cells.

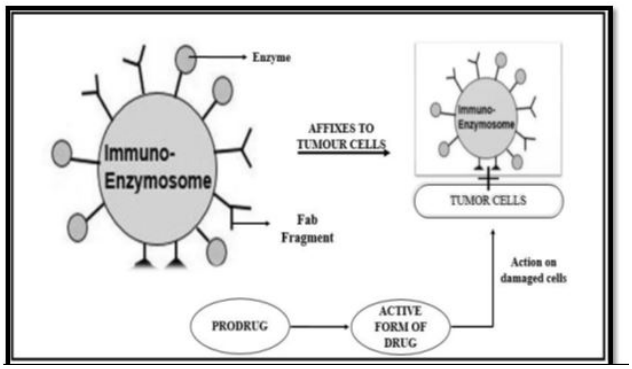


Figure 4: Enzyme bound drug targeting tumor cells.

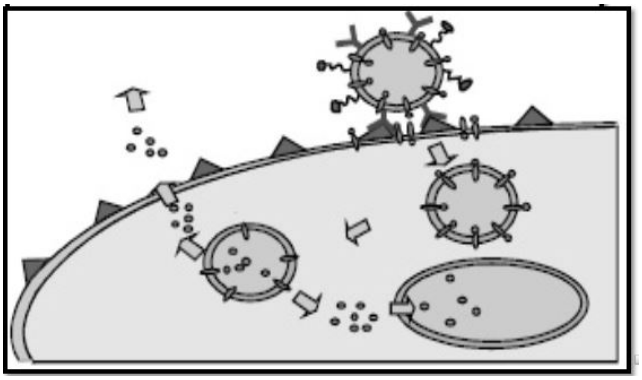
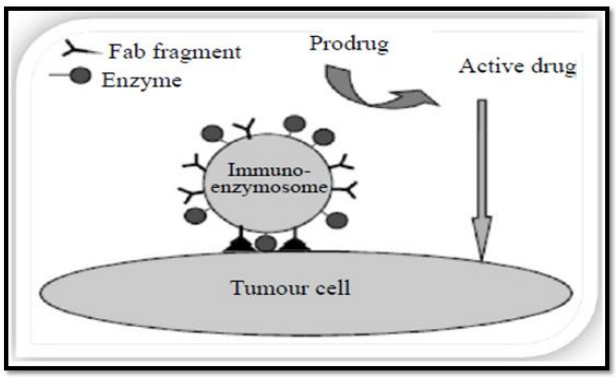


Figure 5: Prodrug converted in to active drug by enzymes.



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