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A REVIEW ON EMERGING TRENDS IN TARGETED DRUG DELIVERY SYSTEMS: EVENTS, APPROACHES AND SPECIFIC DRUG TARGETING

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Abstract: Recently, Targeted Drug Delivery System (TDDS) is an advanced tool towards innovation in the field of Pharmaceutical science. It targets a particular cell or tissue or organ rather than the whole body to deliver the drug through a carrier to achieve its therapeutic effectiveness. It has developed various advanced methods to deliver the drug in a certain amount for a prolonged period of time to target sites to treat chronic or lethal diseases in the body. The drug is delivered in a specific location that is the combination of fields like molecular biology, polymer science, biochemistry, pharmacology, microbiology etc. The need of TDDS is to overcome the problems associated with conventional drug delivery systems. Some problems are related with administration, distribution, metabolism and elimination of drugs and carriers. This approach helps to increase the drug therapeutic index and decreases the side effects of drugs during multiple interactions and non-targeted actions. In this review concept of TDDS, Study of its generation, types, Advantages over Conventional drug delivery systems, disadvantages and application was summarized. Events and biological processes involved in drug Targeting, delivery mechanisms through various biological processes were described briefly. Current approaches of drug to Tumor targeting and various approaches of drug to Brain specific targeting were studied through innovative techniques. This concept has great potential and challenge in future to serve mankind.

***Index Terms*-Targeted Drug Delivery System, Events and biological process involved in drug Targeting, Brain specific targeting, Tumor targeting, Biological events**

I. INTRODUCTION

TDDS is a self-contained, discrete drug delivery system, used for prolonging, localizing and targeting the damaged sites and also known as smart drug delivery system. The concept of targeting of the drug is based on some carrier based delivery to a specific site of action called “Magic bullet” to target (Muller RH. and Keck CM., 2004). These are biodegradable and non-toxic in nature. For example- Liposomes (Navneet Kumar Verma and Asha Roshan, 2015), Megnetic Microsphere (Amit Chandna et al, 2013), Polymeric micelles (M. Nakayama and T. Okano, 2006), Dendrimers (Madaan K et al, 2014), Lipoproteins (Mina Nikanjam et al. 2007), Nanoparticles (Rajesh Singh and James W. Lillard Jr. 2009) etc. This correlation of science shows a wider range of applications in the field of TDDS. The goal of the system is to manage pharmacokinetics, pharmcodynamics, immunogenicity,

toxicity and bio-recognition of active ingredients within the body through biological membrane absorption. Pharmacokinetics like low half life, high volume of distribution etc., Pharmacodynamics like low therapeutic index, low specificity, etc., Pharmaceuticals like low solubility, low stability etc., and Pharmacotherapeutics like high dose, low patient compliance, toxic effects etc (Vyas SP. and Khar RK., 2008). The principle of TDDS is to deliver a higher amount of drug to the target site of action and minimize the drug concentration in the vicinity of the target cell or tissues. Some bioenvironmental factors also affect the therapeutic effectiveness of drugs. These are enzymes, co-enzymes, structure of ligand, receptors, tissues, blood flow, active and passive diffusion etc. The design of such a delivery system is based on certain parameters including drug concentration, location of target site, molecular weight of drug and carrier, distribution, physicochemical properties of molecules, particle size, physiological environment, pH, electrical field, surface properties like charge, shape, density, stability of drug. Some biological parameters are also considered that includes rate of absorption of drug molecules through GIT, its volume of distribution, metabolic rate, elimination rate, peak drug plasma concentration, Half-life, pathological conditions, permeability and structure of capillary wall, bioavailability and toxic dose etc. For effective treatment of TDDS clinical enhanced permeability and retention effect (EPR), target heterogeneity (tumor targeting) and over expression properties are required with patient compliance. Developments in technology are increasing day by day in this area. There are five generations of drug delivery systems reported. It includes-

a. First generation (1G)- Conventional dosage form ex: Tablet, capsules, suspension, Emulsion, ointments, suppositories
b. Second generation (2G)- Modified action system ex: enteric coated tablets, prolonged action tablet, repeat action tablet
c. Third generation (3G)- Controlled drug delivery system ex: diffusion controlled, Osmotically controlled system, swelling controlled system
d. Fourth generation (4G)- Targeted Drug Delivery System ex: Modulated system, Self regulated system, Targeted system
e. Fifth generation (5G)- Nanorobots, Gene therapy, Long-term delivery system, Biologicals with advancements (Ghosh Tapash K. and Jasti Bhaskar R. 2009).

1.1 Characteristics of TDDS

- The system should be *in-vivo* and *in-vitro* physically and chemically stable.
- The system should be non immunogenic and biochemically inert.
- The system should pass and absorb through biological membranes.
- Carrier should deliver the sufficient amount of drug at the site of action.
- Carrier should be non-toxic and biodegradable.
- Release of drugs should be prolonged in a controlled manner to achieve the target.
- The system should be biocompatible.
- The system recognition should be avoided by the host's defense mechanism.
- The system should be easy to adopt by body and eliminate from body.
- The system should be reproductive and cost effective.

1.2 Advantages of TDDS over Conventional drug delivery systems

- It targets diseased tissue or specific parts of the body without affecting healthy tissue.
- Drugs are released in a controlled way for a longer period of time that reduces fluctuation in drug-plasma level.
- Dose intervals can be manageable due to uniform drug effect at target site.
- Reduction in dose and side effects is possible.
- Avoidance of the first pass metabolic pathway is possible to increase its efficacy.
- Due to selecting targeting infectious cells than normal cells improves therapeutic effectiveness.
- Reduce inter and intra- patient variability that increases the patient compliance.
- Small dose of drug is effective to produce the desired effect.

1.3 Disadvantages of TDDS

- Complex manufacturing processes, administration and storage need advanced techniques.
- Skilled people are required to handle and control the delivery to the site of action.
- A Challenge specific to carriers, receptors and ligands.
- Cost of such products is higher than conventional drug delivery systems.
- Sometimes it is difficult to manage stability and uniform release rate of drugs within the dosage form.
- Sometime may cause toxicity due to accumulation of higher concentration at the target site.
- Rapid clearance of drugs is required to avoid side effects at site of action (Aman Kumar et al, 2017).

II. Types of Targeting

2.1 Active targeting

It is the receptor mediated targeting that targets systemic circulation through drug-carrier system and extravasation. It is based on accumulation of drug to site of action via ligand-receptor interaction. Surface modification of the target molecule is possible. It can be achieved by coating through bio-adhesive, non-ionic surfactants, tissue antibodies, albumin proteins, any specific cell etc. It is widely used in tumor targeting in cancer therapy. It is further classified as first, second, third and fourth order targeting. First order targeting includes limitation in drug distribution for the drug-carrier system to the capillary bed of the target site of action. Mostly present in organ compartmental targeting in peritoneal cavity, pleural cavity, lymphatic cavity etc. Second-order targeting includes the selective provision of drugs towards specific types of cells (tumor cells). It is also called cellular targeting.

Ex. Specific delivery to kupffer cells of liver.Third order targeting targets intracellular sites specifically. Fourth order targeting is targeting of drug macromolecules (DNA and proteins) (Anarjan FS, 2019).

2.2 Passive targeting

It targets the body's natural immune system of systemic circulation. Passive diffusion is possible through the EPR mechanism without altering the surface of drug-loaded carriers. The common techniques used to achieve passive targeting are nano-sizing and PEGylation. Sometimes the blood brain barrier mechanism has been disrupted. It is possible by ultrasound and magnetic resonance methods. It is mostly used in tumor targeting via nanoparticles approach (Bazak Ret al. 2014).

2.3 Local targeting

It is a non-invasive target strategy that delivers the drug to local cell or tissue sites for management of local pathologies. Sometimes it creates side effects in local areas.

2.4 Systemic targeting

It is an invasive target strategy that delivers the drug to systemic circulation through an intravenous route of drug administration. Accumulation of higher dose at site of action may cause side effects.

2.5 Biological targeting

It is used to target areas through the use of antibodies, peptides, proteins, or other biomolecules that bind with receptors, sites, or other biological targets in a specific and controlled manner.

2.6 Chemical targeting

It is used to target areas through the use of site-specific prodrugs, enzymes or chemical reactions. By the help of this the targeting of a vehicle or the controlled release or action of the agent can occur.

2.7 Physical targeting

This system targets the site of action via some charecteristics of environment changes. It includes pH, size, composition, temperature, light intensity, ionic strength, stimuli (glucose concentration) etc. This concept is not suitable for tumor and cytocolic drug delivery of loaded drug carriers to sites of interest.

2.8 Inverse targeting

This approach targets the site of action by avoiding passive uptake of colloidal carriers by the ReticuloEndothelial system (RES). RES action is suppressed by pre-injection of a larger amount of macromolecules or blank colloidal carriers like dextrin sulphate. It is achieved by saturation of macromolecules at that area, which reduces the defense mechanism. This method is most suited for targeting non-ERS organs in the body.

2.9 Dual targeting

This approach helps the delivery of such carrier molecules that have their own therapeutic activity. It works on the synergistic effect of the drug that increases therapeutic effectiveness at site of interest. The dual combined methodologies- temporal and spatial are used for better efficacy of drugs (Xin H et al. 2011).

2.10 Double targeting

It is based on a combination of temporal and spatial methods for targeting a carrier system. Spatial placement is used to targeting the drugs to specific organs, tissues, cells and sub-cellular compartment whereas temporal delivery is used to control the rate of drug delivery to the target site of action.

2.11 Combination targeting

It is a direct targeting method by the help of polymers, homing devices and some carriers having molecular specificity to deliver the drug to target sites.

2.12 Location based targeting

This is the location specific drug targeting approach that targets the specific cell, organs and organelles. Some examples are as follows-

a. Intracellular targeting, achieved through protein, antibodies, nano carries based on protein, antibodies, nanocarrier based drug delivery.

b. Brain targeting, achieved through polymer-based drug delivery (dopamine-liposome conjugates).

c. GIT targeting, achieved by floating drug delivery of antifungal, antiviral etc. drugs, oral controlled drug delivery for abdomen, small intestine, lymph nodes etc**.**

2.13 Disease-based targeting

It is site-specific targeting tumors and other targetable infectious diseases. It can be possible by using nano-drug delivery systems like nano-vaccines, nano-particles etc. to achieve advanced targeting and improved cellular responses.

2.14 Ligand-based targeting

The carrier surface groups are called ligands,that selectively direct the carrier to a pre-specified site of the receptor. Mostly these are colloidal in nature and recognize the target. Some examples of ligands are Folate, Transferrin, galactosamine etc (Kleinstreuer C et al, 2014).

III. COMPONENTS OF DRUG TARGETING

3.1 Target

Any specific organ or cell or tissues that need to be cured either acute or in chronic condition is known as ‘Target’.

3.2 Carrier

A special molecule or system that is required for effective transportation of loaded drugs up to the site of target is known as ‘carrier’. It may be liposomes, microsphere (Ankita NY et al, 2022 and Nirav R. Patel et al, 2011), nano-particles, quantum dots (Wang Y et al. 2015), nano-erythrocytes, resealed erythrocytes, polymers, microcapsules etc.

IV. EVENTS AND BIOLOGICAL PROCESS INVOLVED IN DRUG TARGETING

A molecule targeted at the site of action needs some biological process to reach systemic circulation for effectiveness of the drug. These steps are as follows-

4.1 Cellular uptake and processing

It is the first biological process of cellular uptake of molecules through the plasma membrane of a cell. Mostly low molecular mass are passed the cell wall and plasma membrane simply by diffusion method. This is not possible for macromolecules having larger molecular mass. In this condition some other methods like 'Endocytosis' is used for cellular uptake rather than diffusion.

Endocytosis involves two steps-

a. Ingestion of solid molecules through plasma membrane (Phagocytosis).

b. Engulfment of extracellular fluid content into the cell (Pinocytosis).

Macromolecules when comes in contact with the plasma membrane of a cell, a pseudopodium-like structure of cell wall is created to engulf the macromolecule. The plasma membrane now attends a vacuole called 'Phagosome' after complete ingestion of macromolecules. The process is known as 'Phagocytosis'.

The molecules which are present in extracellular fluid when comes in contact with the plasma membrane of a cell entered with fluid by the formation of a vesicle called 'cytoplasm'. The process is known as 'Pinocytosis'. (Fig.1) This process does not require external stimuli and is a universal process. It involves fluid phase and adsorptive pinocytosis that is slower than the phagocytosis process and depends on factors like concentration of molecules, size, temperature of environment etc (Saha, K et al. 2013).

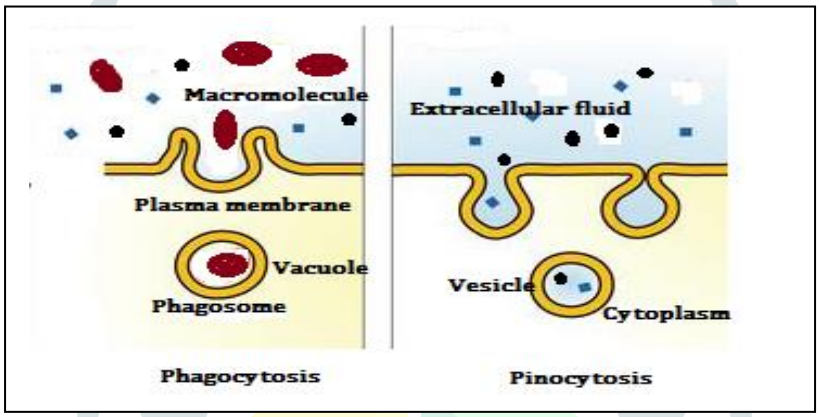

Fig. 1 Cellular uptake through Phagocytosis and Pinocytosis

4.2 Transport across the epithelial barrier

This is the second line cellular uptake in which molecules have to cross the epithelial barriers present in the body. These layers are mostly present in the cavities of buccal, oral, vaginal, rectal, nasal etc. Biologically it has three layers- Epithelia, Lamina propria and Basal lamina. When a low mass molecule comes in contact with the epithelial cell, transport occurs by diffusion process. Higher mass molecules or drug loaded carriers or macromolecules are transported through Endocytosis. A different property of different kinds of molecules also affects the transport via epithelial barriers. Some are as follows-

- Polar nature of molecules can cross the epithelial barrier more easily than non-polar molecules through tight-junction of epithelial cells.
- Positively charged molecules can cross the epithelial barrier more frequently than negatively charged molecules through epithelial cells.
- Passive transport is possible from damaged mucosa of epithelial cells.
- Active transport is possible in the structure integrity of the epithelial cells.
- Transcellular and Paracellular absorption mechanisms occur via buccal mucosa of epithelial cells effectively.

Some common types of epithelial tissues like Squamous, Cuboidal, Columnar and Stratified are found as inner lines inside the body cavities (Fig.2). For example the transport of different molecules through intestinal epithelial barriers are shown in Fig.3

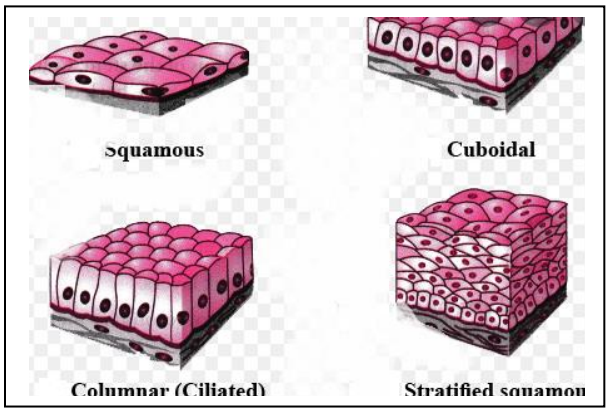

Fig. 2 Common types of Epithelial tissues

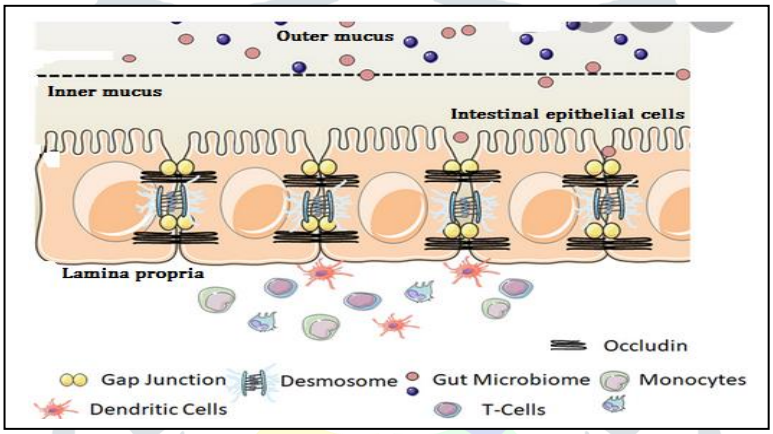

Fig. 3 Transport of molecules through intestinal epithelial barriers

4.3 Extravasations

It is a process of transport of drug molecules outside from the blood capillaries and accumulated in the vicinity of vessels, called 'Extravasations'. It is the biological process seen in the cardiovascular system at the time of dysfunction of cells or disease conditions. The factors that influence the extravasations are capillary permeability and structure, rate of blood flow, physicochemical properties of drug and carriers, pathological conditions etc. Morphology and continuity of epithelial cells in capillaries are varied according to the condition. Mainly these are three types- continuous, Fenestraded and sinusoidal. The process of extravasations involved following steps to complete the biological process. It includes- Step-1;Rolling, Step-2;Activation, Step-3;Adhesion to epithelial cells or arrest, Step-4; Migration, Step-5;Transendothelial migration (TEM) or Diapedesis. The drug or carrier molecules or cells, when flow inside the systemic circulation inside the blood capillary. It crosses the barrier of endothelial cells present on both sides of the capillary. At this time molecules undergo transient rolling type of interaction with the endothelium by the influence of shearing force produced by flow of blood mediated by selectins, cell surface lectins that help in adhesion (Step 1). These interactions activate chemokines-dependent stimulation in molecules or cells (Step 2). As a result binding of molecules occurs with the epithelial cell firmly and the process is called 'arrest'. This process is mediated by the cell surface to epithelial cell adhesion molecules (Step 3). After that molecule or cell spreads, polarizes and migrates over the epithelial cell surface and tries to penetrate from it. The process is called 'migration' (Step 4). Finally, molecules or cells crossed the epithelial barrier through paracellular or transcellular transport mechanisms and entered the interstitium (outer area from capillary). This process is called 'Transendothelial migration or Diapedesis' (Step 5) (Vande Broek et al, 2008). The steps involved during extavasation are shown in Fig.4.

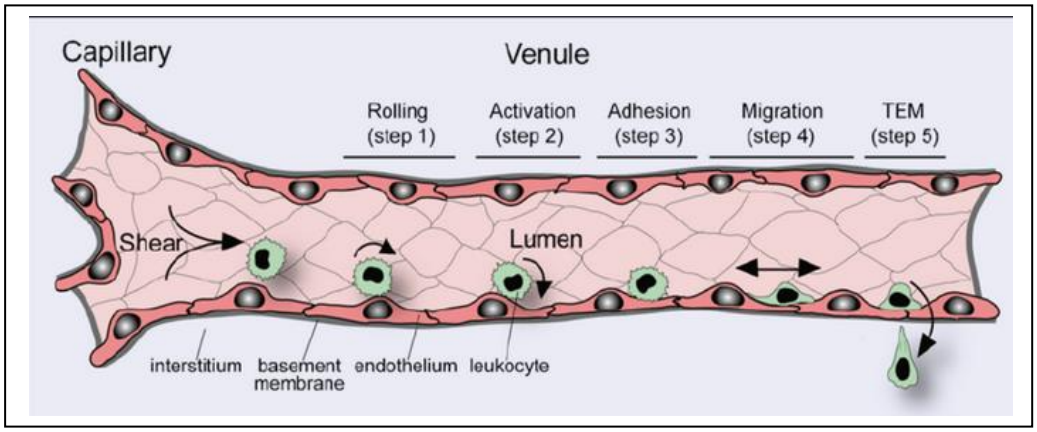

Fig. 4 Steps involved during Extravasations

4.4 Lymphatic uptake

Lymphatic system is a closed system broadly divided into two parts- The conducting system and lymphoid tissue. The conducting system carries lymph and tubular vessels that consist of lymph capillaries, lymph vessels, and the right and thoracic ducts. Lymphoid tissues are concerned with the immune system of the body that works against infections. It consists of connecting tissues and lymphocytes. These may be primary, secondary and tertiary depending upon stages of maturation. After extravasations drug molecules either reabsorb into blood circulation directly or enter through the lymphatic system. Most drugs enter directly into systemic circulation but some highly lipophilic drugs are transported via the intestinal lymphatic system to the bloodstream. Ex-Vitamin derivatives, Cyclosporine etc. It avoids hepatic first pass metabolism of drug molecules and is a suitable route for absorption of macromolecules (Avani KS et al. 2022).

V. VARIOUS APPROACHES FOR DRUG TARGETING

5.1 Tumor targeting

Tumor is the result of abnormal growth of normal cells raised from a faster rate of cell division than normal. Soft tissues are feeling like painful bumps or hard masses. Most common types of tumor are benign tumors, which are non-cancerous in nature and malignant tumors, which are cancerous. These are treated by some approaches like chemotherapy, use of radiation and conventional surgery etc. These practices couldn't control the metastasis steps of the tumor. Chemotherapy is the therapy with antitumor drugs that circulates in the blood of the whole body and as a result it is painful and affects the healthy tissues too. Some undesirable side effects are developed. By considering the effectiveness and its limitations of these clinical practices nowadays alternative targeting methods are developed to treat localized tumors. Various innovative techniques have been developed for tumor targeting by researchers. Some of them are as follows-

- Development of Multifunctional polymeric micelles with cancer-targeting capability through $\alpha_v\beta_3$ integrins was found to be an effective way to target tumors. In this approach Doxorubicin and a cluster of super paramagnetic iron oxide nanoparticles loaded micelle core was used to target tumorous cells. The presence of cRGD on the micelle surface resulted in the cancer-targeted delivery to $\alpha_v\beta_3$-expressing tumor cells (Norased Nasongkla et al. 2006).
- Development of A novel single-walled carbon nanotube -based tumor-targeted drug delivery system. This approach was conjugated with prodrug of an anticancer agent taxoid with a cleavable linker and this was attached to tumor-recognition modules biotin and a spacer to the nanotube surface. This showed higher potency towards tumor cells (Jingyi Chen et al. 2008).
- Nanocarriers loaded molecules as a targeting approach have been developed. These molecules are peptides, antibodies, ligands, nucleic acids that enhance their recognition and internalization by the target. These have enhanced permeability and retention effects (Emily Gullotti and Yoon Y. 2009).
- Development of bortezomib pH-sensitive polymeric carrier to target the cancer cells through cell surface receptor-mediated mechanisms to increase cellular uptake (Jing Su et al. 2011).
- Development of ligand directive polymeric nanoparticles for targeting approach to tumor tissues. Specific tumor-homing ligands are antibody, antibody fragments, peptides, aptamers, polysaccharides, folic acid worked on the surface stealth of nanoparticles , that lead to increase the retention time and accumulation of nanoparticles in the tumor vasculature. It helps in selective and effective internalization by target tumor cells (Yinan Zhong et al. 2014).
- Development of multifunctional envelope type mesoporous silica nanoparticles for tumor targeting (Jing Zhang et al. 2013).
- Development of rod shaped gold nanocrystals with ligands for tumor targeting (Xiaohua Huang et al. 2010).

Recently, different mechanisms and approaches have been used to treat cancer cells or tissues. These are involved in tumor therapy. Targeting the cell membrane, endoplasmic reticulum system, lysosomes, mitochondria, cell nucleus, change in the tumor cell environment etc. are effective approaches used in tumor targeting.

5.2 Brain targeting

Brain, a part of the central nervous system controls various functions and activities in our body. It regulates emotions, temperatures, feelings, anger, hunger, thinking power, vision, hearing, motor skills, learning, speech etc. It is a vital organ made up of about 60% fat and 40% in combination of water, salt, protein and carbohydrates. It receives and sends the electrical and chemical signals throughout the body to control all above activities in coordination with nerve cells, neurons, spinal cord, messengers etc. Any

imbalance in coordination and regulation leads to disorders or diseases. Most common are CNS malignancy, brain tumor, multiple sclerosis, mania, schizophrenia, abscess etc. The efficacy and safety of conventional drugs in brain delivery to treat these disorders or diseases was found to be less by researchers as compared to targeted drug delivery systems. Targeted brain drug delivery system was designed and developed to overcome difficulties to cross blood brain barriers (BBB) by drugs. The various approaches have been proposed and succeed with advantages like reduction in the toxicity, increment in bioavailability, dose reduction, concentration fluctuation, permeability enhancements etc. Some disadvantages are also associated with these approaches like stability, targeting particular cells or tissues, need of skilled people for delivery, need of advanced techniques and equipment etc. The aim of brain targeting is to cross the BBB, blood- tumor barrier, blood- cerebrospinal fluid barrier and tight junction of epithelial cells for macromolecules, proteins and carriers. The carriers like liposomes, nanoparicles, dendrimers, prodrugs, niasomes, carbohydrates etc. are found suitable for brain targeting (Guo L., Ren J. and Jiang, X. 2012). Some approaches are as follows-

5.2.1 Lipophilic approach

This approach was developed for increasing the permeability of low molecular weight substances at physiological pH. It was observed that lipophilic drug has faster penetration from BBB than hydrophilic nature of drug. For example; heroin (lipophilic drug) has faster crossing ability than morphine (hydrophilic drug) through BBB (Takalani F et al. 2020).

5.2.2 Prodrug approach

This approach has been designed with a drug that covalently attached to an inert chemical moiety. This moiety activates after cleaving by hydrolytic enzyme inside the cell and lipoidal nature of the drug has been increased. It helps to cross BBB for low molecular masses. For example; chemical modification of some drugs by amidation, carboxylation, esterification of chemical groups. Acetylated morphine, a form of prodrug, has faster intake through BBB than morphine (Rautio J et al, 2008).

5.2.3 Liposomal loaded drug approach

Liposomes are bilayer vesicles having hydrophilic and lipophilic character. These are commonly made up with phospholipid (Phosphalidylcholine), cholesterol etc. These have the surface affinity to ligands, peptides, polymers etc. This approach has been developed to target brain delivery in which drug particles have been loaded inside the liposomal cavity and delivered to target site. It reduces loss of drug in the vicinity of target cells (Chen Y et al 2004).

5.2.4 Polymeric micelles loaded drug approach

This is the structure developed by combination of amphiphilic co-polymers that have both hydrophilic and lipophilic character. The suitable size range of micelles was found to be in the range of 1-100nm to cross the barriers. Surfactants are biodegradable and biocompatible molecules. For example drug loaded micelles, consisting of polyethylene glycol, polypropylene glycol, poloxamer etc. were found effective in the brain drug delivery system.

5.2.5 Dendrimer approach

These are polymer molecules having complex branches that have a central core loaded with drug molecules. These have in small size range 1.5-14.5nm suitable for faster uptake through epithelial cells of the brain. Example; poly- amidoamine (PAMAM) dendrimer.

VI. Miscellaneous Approaches

6.1 Invasive techniques

Intra ventricular infusion, BBB disruption, Intra cerebral implant, Intra cerebro ventricular infusion, Use of polymer, convectional enhanced drug delivery etc.

6.2 Non-Invasive techniques

6.2.1 Physiological approach

Transport mediated delivery, Receptor mediated delivery, Insulin receptor mediated transcytosis, adsorptive mediated transcytosis, transferring receptor mediated transcytosis etc.

6.2.2 Biological approach

It includes Molecular Trojan horses approach, conjugation of drug with antibody, autonomic nervous system approach, use of genomics etc.

6.2.3 Chemical approach

It includes Chimeric peptides approach, P-Glycoprotein inhibition approach, cationic protein approach etc.

6.2.4 Colloidal approach

It includes use of vesicular systems, nanocarrier systems, self micro emulsifying systems, and lipid based drug delivery systems, emulsions, nanosuspensions etc.

6.2.5 Others

It includes Focused ultrasound delivery, Intra nasal delivery, Intra arterial delivery, Iontophoretic delivery etc.

VII. FUTURE PERSEPECTIVES

In the recent novel era of advanced developments and high technology equipment, TDDS has great potential to cure diseases. It will be possible through gene therapy, BBB genomics, use of recombinant proteins as neurotherapeutics and neurodiagnostics. Some approaches like BBB active efflux transporter, BBB carrier mediated transporter, Enzymatic BBB, continued development of next generation medicines etc. may become tools to manage such conditions. Due to the biocompatible, non-toxic, biodegradable character of carriers, mediated drug delivery has been preferred over conventional drug delivery systems to target tumor cells or brain cells to cross BBB. These approaches are challenges and can serve mankind in future.

VIII. CONCLUSION

TDDS has been developed with various approaches, techniques and mechanisms that are found suitable to reach the drug to the target site to maintain the disorders or diseases. These deliveries were found to be safe to mankind by approved authorities after clinical evaluation. Targeting of drug molecules to a specific site is most prominent and a challenge to researchers. This review concise different techniques, strategies and its applications used to design the TDDS.

IX. CONFLICTS OF INTEREST

Conflicts of interest declared none.

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