

A review on Targeted Drug Delivery system

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Abstract- Targeted drug delivery is an advanced method of delivering drugs to the patients in such a targeted sequence that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells) which in turn improves efficacy of treatment by reducing side effects of drug administration. Basically, targeted drug delivery is to assist the drug molecule to reach preferably to the desired site. The inherent advantage of this technique leads to administration of required drug with its reduced dose and reduced its side effect. This inherent advantage of targeted drug delivery system is under high consideration of research and development in clinical and pharmaceutical fields as backbone of therapeutics & diagnostics too. Various drug carrier which can be used in this advanced delivery system are soluble polymers, biodegradable microsphere polymers (synthetic and natural), neutrophils, fibroblasts, artificial cells, lipoproteins, liposomes, micelles and immune micelle. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue.

Keywords: Drug delivery; drug carrier system; therapeutics; diagnostics; cancer

INTRODUCTION

The conventional drug delivery system involves the absorption of the drug across a biological membrane, where as the targeted release system releases the drug in a dosage form. Targeted drug delivery is a special form of drug delivery system where the medicament is selectively targeted or delivered only to the site of action and not to the non-targeted organs or tissues or cells. The system is stand on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body and improves the efficacy and reduces the side effect. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue via the drug. Carriers used should be biodegradable or readily eliminated from the body without any problem. The preparation of the targeted drug delivery system should be simple, reproductive and cost effective. Targeted drug delivery has high solubility and more drug stability as compare to conventional drug delivery. Conventional drug have poor absorption, shorter half-life and require large volume of distribution, these problems are reduced in targeted drug delivery. [1, 15]

Type of Targeted drug delivery

As mentioned, directing a medicine to a particular location not only improves its therapeutic effectiveness. Additionally, it aims to lessen the drug's toxicity so that lower doses can be used during therapy. Two methods—also known as classification of drug is targeting—are frequently employed to satisfy such conditions [14, 17]

Passive Targeting

It describes the build-up of a medication or a drug-carrying system in a particular location, such as an anti-cancerous drug, whose cause may be related to physicochemical or pharmacological aspects of the illness. Therefore, in the case of cancer treatment, it is important to specifically control the size and surface properties of drug delivery nanoparticles to prevent uptake by the reticulo-endothelial system passive targeting is achieved by incorporating the therapeutic agent into a macromolecule or nanoparticle that passively reaches the target organ. In passive targeting, the drug's success is directly related to circulation time. This is achieved by cloaking the nanoparticle with some sort of coating... [14, 17]

Active Targeting

Active targeting refers to an intracellular localization that involves a particular ligand-receptor type interaction. Which only happens after extravasations and blood circulation. The three tiers of targeting that make up this active targeting strategy are as follows:

- 1) First order targeting is the constrained delivery of drug carrier systems to the capillary bed of a chosen target site, organ, or tissue, such as compartmental targeting in lymphatic's, the peritoneal cavity, multiple cavities, cerebral ventricles, the eyes, and joints.
 - 2) Second order targeting describes the selective administration of medications to particular cell types, such as cancer cells, as opposed to normal cells, as in the case of the selective administration of pharmaceuticals to suffer cells in the liver.
 - 3) Third order targeting is the practise of administering medication just to the intracellular place of cells that have been selected.
- [14, 17]

TARGETED DRUG DELIVERY COMPONENTS

A drug delivery system is essentially a Drug carriers or targets, as well as drug targets. A target organ, cell, or collection of cells that requires treatment in a chronic or acute illness. The route of administration involves the drug carrier as an important targeting moiety, and after its leakage from its carrier/markers to reach the drug to the specific or targeted site via biological metabolism with its clearance, as well as not to reach non-targeted sites to make this delivery system more site specific with reduced side effects of

drugs and their quantity. Carrier is a particular molecule or system that is needed for the successful transportation of loaded drugs to pre-determined places. These are vectors that have been engineered [5, 6]

VEHICLES FOR DRUGS DELIVERY

Drug delivery vehicles are also known as drug vectors, and they are the most crucial entity required. In order to transport the loaded drug successfully. Drug vectors transport and keep the drug so that it can be delivered within or near the target. They are created capable of executing such specialised duties that can be attributed to minor structural changes [3, 11, and 20]

IDEAL DRUG VEHICLE CHARACTERISTICS

In the case of tumour chemotherapy, an optimal drug vehicle should be able to penetrate blood-brain barriers as well as tumour vasculature. It must be recognised specifically and selectively by target cells while retaining the specificity of the surface ligands. The drug-ligand combination [must be stable in plasma, interstitial fluid, and other bio fluids. The drug vehicle employed Military (emtuzamabozogamicin) is an antibody-drug conjugate (ADC) that was approved by the US Food and Drug Administration (FDA) but was later withdrawn. Voluntarily exited the US [8, 32]

Liposomes

Liposomes are tiny, artificially created vesicles that range in size from 20 to 10,000 nm and are made of phospholipid bilayers all around. Numerous liposome formulations are quickly absorbed by macrophages, which can be used for either drug delivery to macrophages specifically or passive drug targeting, which allows drug release from these cells into the general circulation over time.

For use in non-viral vector mediated gene therapy, cationic liposomes and lipoplexes have been thoroughly studied [18, 21].

Monoclonal antibodies and fragments

The majority of strategies based on antigen recognition by antibodies have been developed for more specifically for cancer therapy. These strategies are mostly aimed at tumour associated antigens being present or in more specific term expressed by tumour cells. Antibody-drug conjugates (ADC) is complex of a drug with a monoclonal antibody which provides selective targeting for tumoral cell masses or lymphomas [21]. The drug is released by enzymatic cleavage of the linker under physiological conditions. An Example of: Antibody-drug conjugates (ADC) is Military (emtuzamabozogamicin) which was approved by the U.S. Food and Drug Administration (FDA), but later voluntarily withdrawn from the US market. Another ADC has been submitted for approval and at least 15 antibody conjugates are currently being investigated in clinical trials [16].

Proteins that have been modified (plasma)

Because of their solubility and low molecular weight, modified plasma proteins can be used as intelligent drug vehicles for drug delivery. They are a suitable mechanism of drug delivery because they may be easily changed by the attachment of other molecules such as peptides, sugars, and other ligands to transport the medications of interest. In the instance of liver cell targeting, significant changes to protein backbones such as albumins have been performed to ensure optimal drug delivery [2, 19].

Nanoparticles and microspheres

Microspheres and nanoparticles are made of biocompatible materials and fall under one of two categories: or the carriers of the particle type. Dextrans, fiscal, sepharose, or poly-L-lysine have all been created as the major drug carriers in HPMA polymeric backbone carriers. Nanoparticles may have a lower drug loading capacity than soluble polymers because they are smaller (0.2–0.5 m) than microspheres (30–200 m). Depending on the physicochemical properties of the drug, drug formulation into nanoparticles might take place at the surface of the particles or in the nucleus. The drug's release rate from the particle is strongly influenced by the place of inclusion. They swiftly disperse to the target site following systemic administration or transportation, and the cells of the phagocytic system then internalise them [26]

Lipoproteins

LDL and HDL are examples of lipid particles that contain both an Apo protein and a lipid moiety.

It is possible to include lipophilic pharmaceuticals or lipophilic pro-drugs using natural targeted liposomes and their core; covalent bonding with the drug is not necessary. New targeting moieties can be added through modifications at the glycolipid inclusion level. Most studies on the usage of LDL and HDL particles have focused on and made improvements to medication delivery systems that target the liver. [2]

DRUG TRANSPORTATION USING A TRANSDERMAL APPROACH

Typically applied transdermal medication delivery method patches that provide medication for systemic effects at a predetermined and controlled rate are used to give the medication. A transdermal drug delivery device or vehicle, which may be active or passive in nature, offers a different method for delivering a medicine to a particular spot and delivers the drug across the skin barrier as well[21].

Targeting Folates

A technique used in biotechnology for drug delivery is foliate targeting. It entails the process through which medication and the nutrient folate (folic acid) are joined to create folate conjugate. Based on the fact that folate naturally has a high affinity for the folate receptor protein (FR), which is frequently expressed on the surface of cancer cells, and that folate-drug conjugates likewise strongly bind to the FR, which in turn causes cellular uptake via endocytosis. It is also known that the folate receptor protein (FR)

functions as a tumour-antigen or biomarker. The use of folate receptor protein (FR) in diagnostic and therapeutic procedures, particularly for the treatment of cancer, takes use of this natural characteristic [10, 27, and 28]

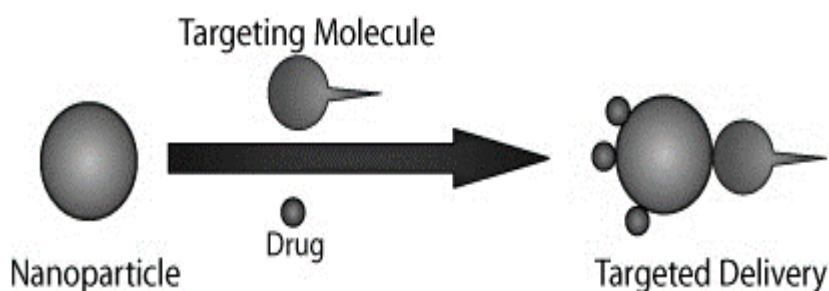
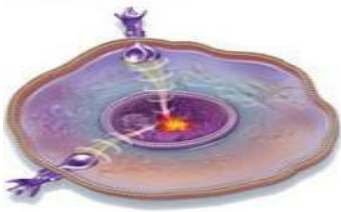



Fig. 1 Targeting Molecule

Sr. no	Normal cell	Cancer cell
	Normal cell are Small uniformly shaped nuclei.	Cancer cell are variable shaped nuclei.
2	It contains large cytoplasmic volume.	It contains small cytoplasmic volume.
3	It has low level of dividing cells.	It has high level of dividing cell.
4	Normal cell have definite size and shape.	Cancer cell have variation in their size and shape.
5	Normal cells are arranged in discrete tissues.	Cancer cell show disorganized arrangement of cell.
6	It contains single nuclei.	It contain multi nuclei.
7	It contains normal chromosomes.	It contains abnormal chromosomes.
8	Normal pH	Low intracellular Ph.
9	Lymphatic drainage developed in normal cell.	Impaired lymphatic drainage developed in cancer cell.
10	<p>Normal cell</p> 	<p>Example of one type of abnormal or cancerous cell</p> 

[25]

Table 1 Difference between normal cell and cancer cell

Ideal characteristics of Targeted drug delivery system are

- It should be non-toxic and Non-immunogenic
- It should be physically and chemically stable in vivo and in vitro.
- They control the drug distribution to target cells or tissues or organs.
- Must have uniform capillary distribution.
- Convenient and predicate rate of drug release.
- Drug release does not influence the drug action.
- Curative amount of drug release.
- Minimal drug leakage during transfer.
- Carriers used must be bio-degradable or readily eliminated from the body without any problem and no carrier induced modulation of diseased state.
- The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective. [12,19,23]

Advantages of Targeted drug delivery system

- Drugs deliver / releases over extended period of time
- Intermittent dosing can be avoided
- Improve patient compliance.
- Reduce inter and intra-patient variability.
- Drug can be administered in a smaller dose to produce the desired side effect.
- No peak and valley plasma concentration.
- Toxicity is reduced by delivering drug at the targeted site.
- Self-administration is possible.
- Enhance absorption of drug.[22,28]

Disadvantages of targeted drug delivery system

- Requires a skill in manufacturing storage, administration.
- Diffusion and redistribution of drug release.
- Rapid clearance of targeted systems.
- Maintaining stability of dosage form is difficult.
- Highly sophisticated technology requires for formulation.
- Expensive.
- Yields comparatively very less. [22,28]

Limitation of TDDS: -

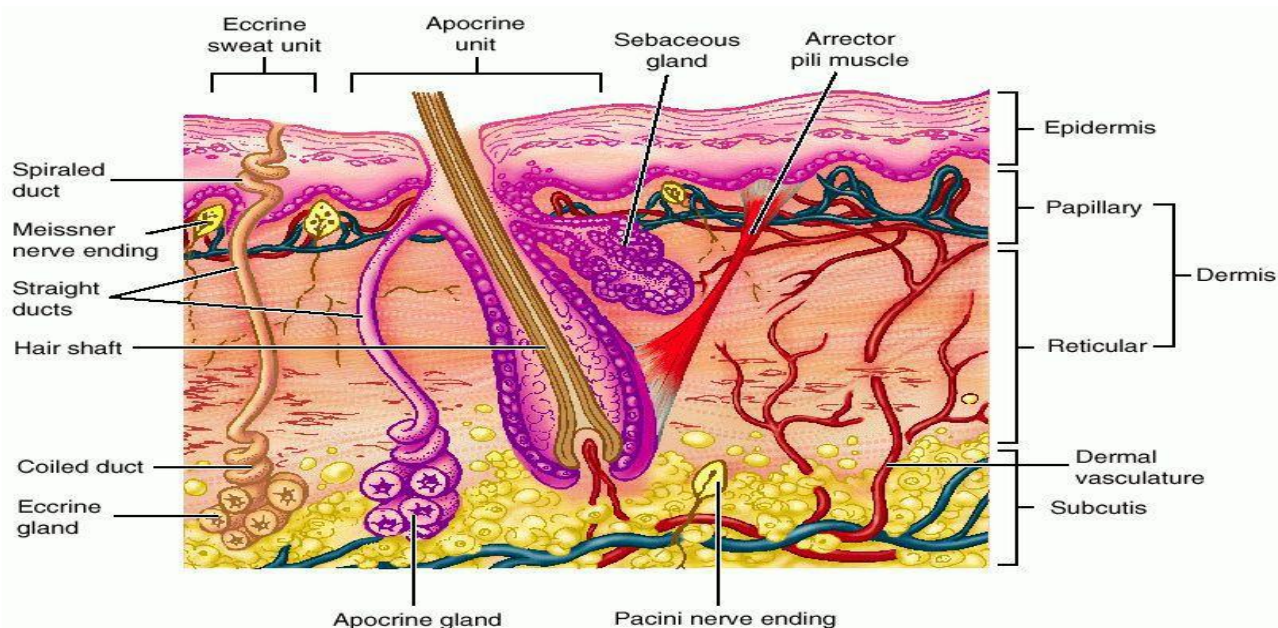
- TDDS cannot deliver ionic drugs.
- High dosage will not be achieved through this program.
- It will not develop a cellular drug.
- TDDS is unable to deliver medication in a way that affects the heart.
- TDDS cannot develop if the drug or texture causes irritation to the skin.
- Skin rejuvenation function changes from place to place, from person to person and up to 6years.
- Transdermal drug delivery system limited to strong drug [11]

ANATOMY AND PHYSIOLOGY OF SKIN:

The skin has evolved into an extremely efficient barrier, which prevents both excessive water loss from the body and the ingress of xenobiotic. It enables us to withstand a considerable range of environmental challenges. The reasons for this are manifold and may be summarized simply for the purposes of this chapter. The outer layer of the skin, the stratum cornea, forms the rate-controlling barrier for diffusion for almost all compounds. It is composed of dead, flattened, keratin-rich cells, the coenocytes. These dense cells are surrounded by a complex mixture of intercellular lipids. They comprise ceramists, free fatty acids, cholesterol, and cholesterol sulphate. Their most important feature is that they are structured into ordered bilayer arrays. The predominant diffusional path for a molecule crossing the stratum cornea appears to be intercellular².

The penetration across epithelial borders is a slow process due to the effect of the barrier properties. The skin, in particular the stratum cornea, possesses a barrier to drug penetration due to its high density (1.4 g/cm² in dry state), its low hydration of 15 to 20%. The barrier function is further facilitated by the continuous replacement of stratum cornea, thereby limiting the topical & transdermal bioavailability. Therefore, in recent years, numerous studies have been conducted in the area of penetration enhancement³. Limitations include slow penetration rates, lack of dosage flexibility and a restricted to relatively low dosage drugs. Human skin comprises of three distinct but mutually dependent tissues:

- a) The stratified, a vascular, cellular epidermis.
- b) Underlying dermis of connective tissues.
- c) Hypodermis. [4, 29, 32]



[31]

Figure: 2 Anatomy of Skin

Basic elements of transdermal Drug Delivery Systems:

1. Compound matrix
2. The drug
3. Permeation enhancers
4. Different excipients

1) Polymer Matrix:

The chemical compound controls the release of the drug on the wire. The following conditions must be met for the polymer to be applied to transdermal patches.

- (i) The polymer should be stable.
- (ii) The polymer must be non-toxic
- (iii) The polymer should be easily made
- (iv) The polymer should be inexpensive

Polymers that can be useful for stratum devices are:

Natural Polymers: Gelatine from Cellulose, Wax, Natural Rubber, Starch etc. Synthetic Elastomers: e.g., polybutadiene, Hydrant rubber, Polysiloxane, synthetic rubber, Nitrile, propenonitrile, synthetic rubber,

Styrenebutadiene rubber, synthetic rubber etc. Synthetic Polymers: e.g., polyvinyl alcohol, PVC, synthetic resin, plastic, Polyacrylate, Polyamide, Polyurea, Polyvinyl Pyrrolidone, Polymethylmethacrylate, Epoxy Etc. The chemical compound controls the release of the drug on the wire. The following conditions must be met for the polymer to be applied to transdermal patches.

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2) The Drug:

Because of the success of the drug delivery system, the drug must be selectively charged. The following is a list of the attractive features of stratum Delivery [22].

Physiochemical properties

- (a) A drug must have a molecular weight of less than 1000 Dalton.
- (b) The drug should be compatible in both lipophilic and hydrophilic phases.
- (c) The drug should have a low melting point. [22]

Biological properties

- (a) The drug should be intensified with a daily dose of a few mg / days.
- (b) The life span ($t_{1/2}$) of a drug should be short.
- (c) Medication should not cause allergies. [22]

3) Permeation Enhancers:

These compounds promote skin porosity by altering the skin as a barrier to the flow of desired Penetration. The dehydrator is thought to have touched one or more of these layers to achieve Improved skin penetration. A large number of computers have been investigated for their ability To improve stratum cornea permeability. [22]

4) Different Excipients

A. Solvents:

These compounds increase Inflammation almost by inflammation of the polar pathway and / or by excretion of lipids. Examples accept liquid alcohol - wood and ethanol; radical alkyl sulfoxides - Dimethyl sulfoxide, radical homologs of alkyl sulfoxide dimethyl amide and dimethyl form amide; paroled-Ones- a pair of pyrrolidone, N-methyl, 2-purrolidone; Laurocapram (Atone), Solvents — Propylene glycol, glycerol, Sloane liquid, Isopropyl palmitate. [22]

b. Surfactants

These compounds are expected to improve the transport of the polar pathway, especially fluid drugs. The power of the top acting agent to change the input can be the function of a cool head unit and consequently the length of the integrated biological chain.

Anionic Surfactants: egg,

Dioctylsulpho-Succinate, Na lauryl salt, Decodecyl-Methyl sulphoxide etc[22]

c. Nonionic Surfactants:

e.g., Plutonic F127, Plutonic F68, etc. Bile Salts:

e.g., Na mstaurocholate, Na Deoxycholate, Na tauroglycocholate.

d. Bile salt:

Sodium taurocholate, sodium deoxycholate.

e) **Various Chemicals:** These include urea, hydrating and catalytic agent

□ It should be easily removed. [22]

PRINCIPLES OF TRANSDERMAL PERMEATION:

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimetre of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum cornea.
3. Sorption by stratum cornea and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ. [30]

KINETICS OF TRANSDERMAL PERMEATION:

Knowledge of skin permeation kinetics is vital to the successful development of transdermal therapeutic systems. Transdermal permeation of a drug involves the following steps:

1. Sorption by stratum corneum.
2. Penetration of drug through epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physiochemical properties. The rate of permeation across the skin is given by:

$$dQ/dt = P_s (C_d - C_r)$$

Where C_d and C_r are the concentration of the skin penetrant in the donor compartment i.e. on the surface of stratum corneum and in the receptor compartment i.e. body respectively. P_s is the overall permeability coefficient the skin tissue to the penetrant. This permeability coefficient is given by the relationship:

$$P_s = D_s K_s / h_s$$

Where K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and h_s is the overall thickness of skin tissues. As K_s , D_{ss} and h_s are constant under given conditions the permeability coefficient P_s for a skin penetrant can be considered to be constant. From above equation it is clear that a constant rate of drug permeation can be obtained only when $C_d \gg C_r$ i.e. the drug concentration at the surface of the stratum corneum C_d is consistently and substantially greater than the drug concentration in the body C_r . The equation becomes:

$$DQ/dt = P_s C_d$$

The rate of skin permeation is constant provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant the drug should be released from the device at a rate RR i.e. either constant or greater than the rate of skin uptake R_a i.e. $RR \gg R_a$. Since $R_r \gg R_a$, the drug concentration on the skin surface C_d is maintained at a level

equal to or greater than the equilibrium solubility of the drug in the stratum corneum C_s i.e. $C_d \gg C_s$. Therefore a maximum rate of skin permeation is obtained and is given by the equation:

$$(dQ/dt)_m = P_s C_s$$

From the above equation it can be seen that the maximum rate of skin permeation depends upon the skin permeability coefficient P_s and is equilibrium solubility in the stratum corneum C_s . Thus skin permeation appears to be stratum corneum limited [12, 21, and 31].

BIOPHARMACEUTICAL PARAMETERS IN DRUG SELECTION FOR TRANSDERMAL PATCH:

Dose should be low i.e. <20mg/day.

Half-life should be 10 h or less.

Molecular weight should be <400.

Partition coefficient should be Log P (octane-water) between 1.0 and 4.

Skin permeability coefficient should be <0.5 X 10⁻³cm/h.

Drug should be non-irritating and non-sensitizing to the skin.

Oral bioavailability should be low.

Therapeutic index should be low. [31, 33]

APPROACHES USED IN DEVELOPMENT OF TRANSDERMAL PATCH5:

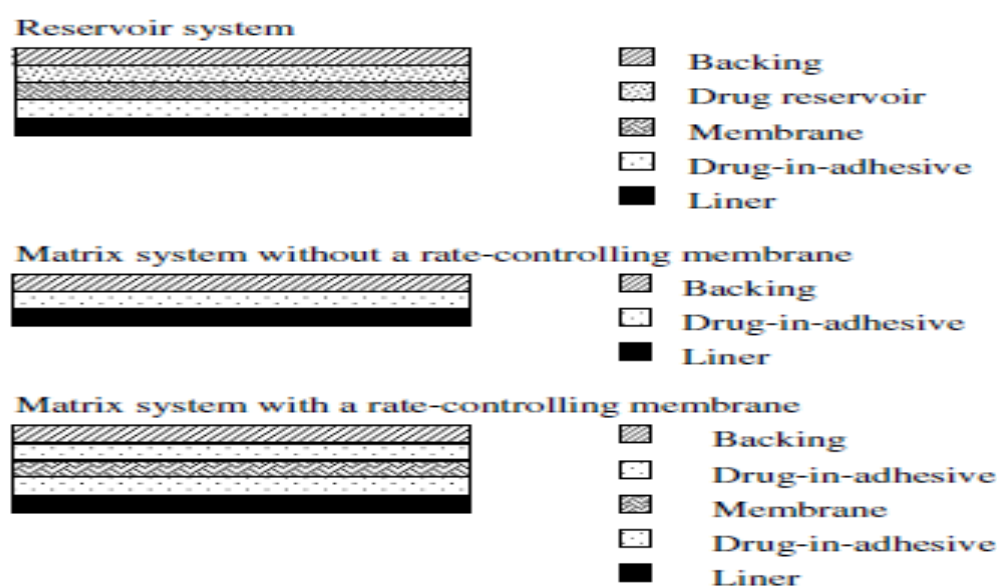


Figure: 3 Types of TDDS.

Membrane moderated systems:

In this, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unreachable, viscous liquid medium e.g. silicon fluid. The rate controlling membrane can be micro

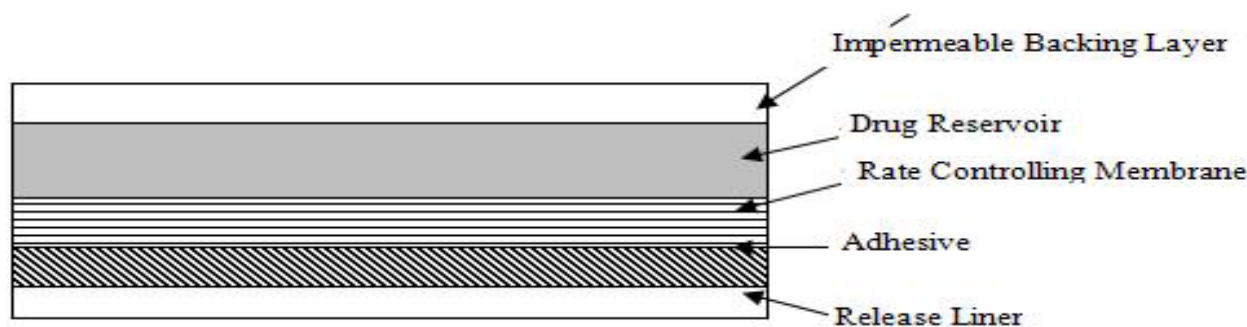
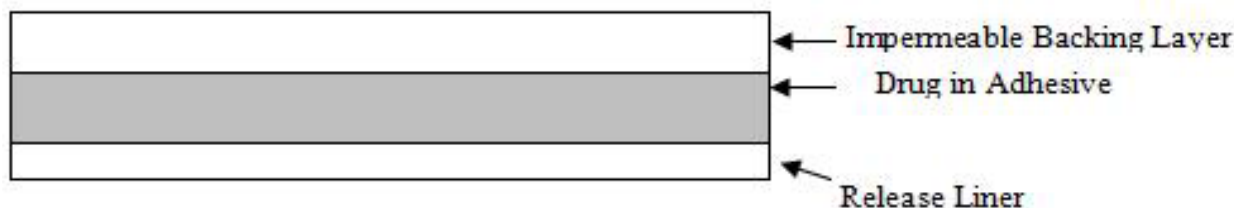
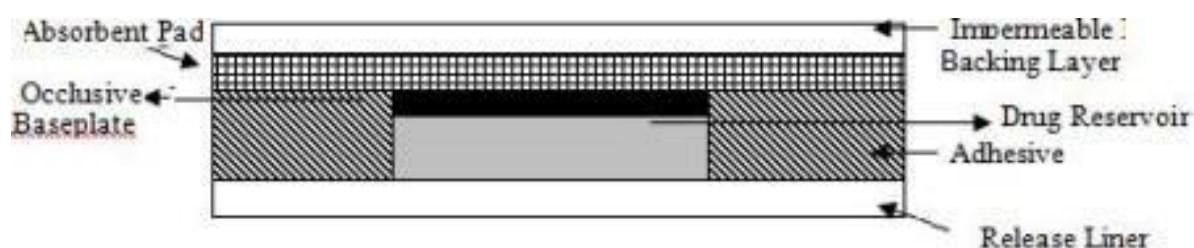


Figure: 4 Representation of Membrane moderated systems

porous or nonporous polymeric membrane e.g. ethylene vinyl acetate co-polymer on the external surface of the polymeric membrane, a skin layer of drug, compatible hypo allergic adhesive polymer may be applied to achieve an intimate contact of TDDS with skin surface. Marketed systems: Transdermal-Nitro system for once a day; Transderm-Scop system- 3 days medication; Cat après- TTS – for weekly treatment [31, 33]

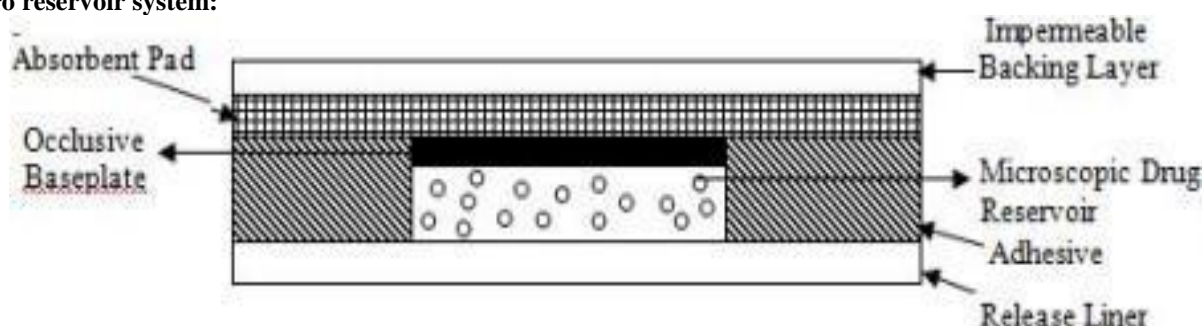
B. Adhesive diffusion controlled system:**Figure: 5 Representation of Adhesive diffusion controlled system**

It is the simplest version of the membrane moderated drug delivery systems. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting onto a flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On the top of the reservoir layer, layers of non-medicated rate controlling adhesive polymer of constant thickness are applied. Drug -in -adhesive patch may be single layer or multi-layer. The multi-layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane. Characteristics of drug in adhesive patch may account for improved patient compliance due to ease of remembering once weekly patch application, improved cosmetic acceptance and better adhesion. Marketed devices: Chimera®; Nicotrol; Deposit®

C. Matrix dispersion:**Figure: 6 Representation of Matrix dispersion**

Here the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and medicated polymer is then moulded into disc with defined area and thickness. This is glued onto an occlusive base plate on the surface of the disc, the adhesive polymer is spread along the circumference to form a stripe of adhesive rim around the disc. Advantages of matrix patches include absence of dose dumping, direct exposure of polymeric matrix to the skin and no interference of adhesive.

Marketed System: Nitro-Door®

D. Micro reservoir system:**Figure: 7 Representation of Micro reservoir system**

These are considered as combination of reservoir and matrix dispersion type. In this the drug reservoir is formed by first suspending the drug solids in an aqueous solution of water soluble polymer and then dispersing the drug suspension homogeneously in lipophilic polymer, by high shear mechanical force to form unreachable microscopic spheres of drug reservoir. This dispersion is stabilized immediately by cross-linking the polymer chains which produces a medicated disc with constant surface area and thickness. Marketed system: Nitro disc® [32]

Biological processes and events involved in drug targeting

- Cellular uptake and processing □ Transport across the epithelial barrier.
- Extravasation.
- Lymphatic uptake.

Cellular uptake and processing

Macromolecular assemblies hence cannot enter by such simple process hence take up by a process called endocytosis. Cellular uptake and processing involve two Steps are

- Internalization of the plasma membrane,
- Concomitant with engulfment of extracellular material.

Pinocytosis is universal phenomenon as compared to phagocytosis. Fluid phase pinocytosis capture's molecule is comparatively slower as compare to phagocytosis and it is directly proportional to the concentration as well as size. [1]

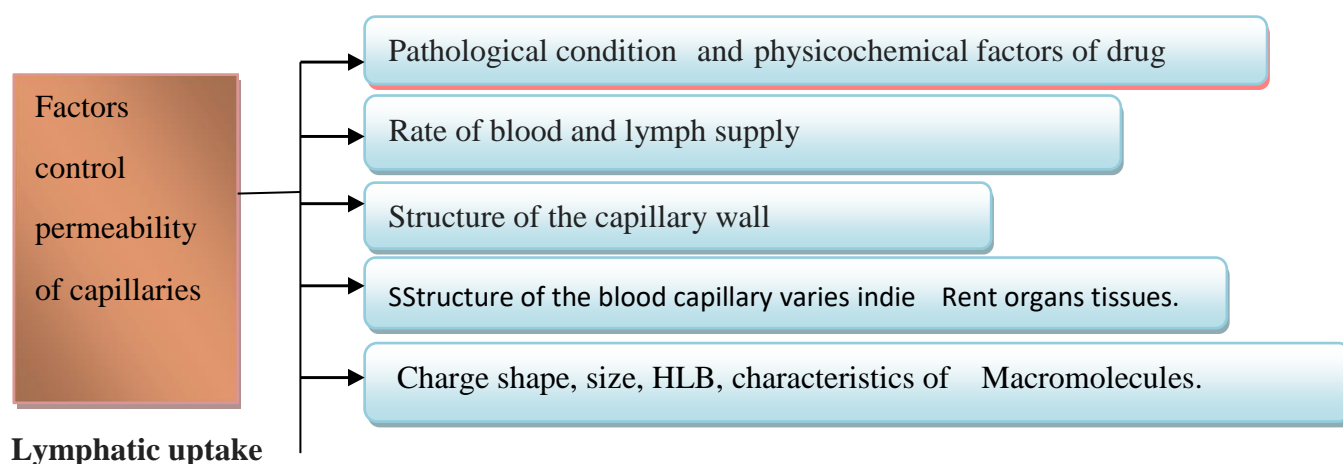
Transport across the epithelial barrier.

One or more layers of epithelial cells lined internally in the oral, buccal, nasal, vaginal and rectal cavities. Low molar mass drug cross epithelial barrier by passive diffusion and selective and non-selective endocytosis. Polar material diffuse through tight junction of epithelial cells. Passive transport is usually higher in injured mucosa where as active transport depends on structural integrity of epithelial cells. [17]

Extravasation:-

Dysfunction of cells located outside the cardiovascular system leads to many diseases therefore a drug to exert its therapeutic effects it must depart from the central circulation this process of trans vascular exchange is called Extravasation which is governed by blood capillary walls.

Table: 2 Factors control permeability of capillaries



After extravasation drug molecules can either reabsorb into the blood stream directly or enter into the lymphatic system and arrival with the lymph to the blood circulation. Also drugs administered by subcutaneous intracellular transdermal peritoneal routes can reach the systemic circulation by lymphatic system. It is directly related difference between the hydrostatic as well as osmotic forces. Formulation medium and its composition.

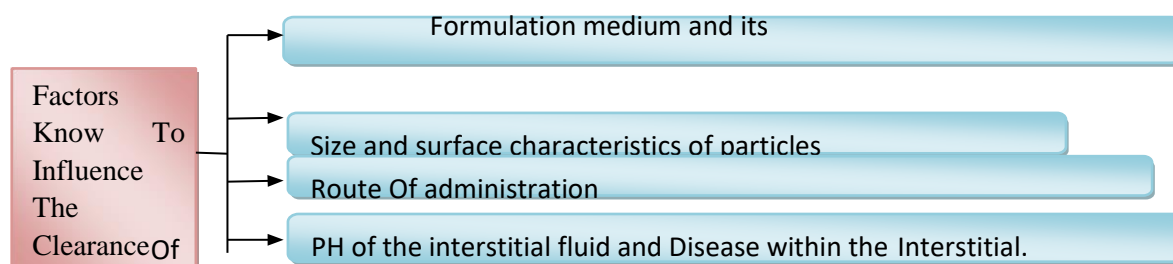


Table: 3 Factors Known to influence the clearance of

Brain targeted drug delivery system^{10, 11, 12}

The brain is the most versatile and sophisticated organ in the body and is protected by a very effective barrier as Blood Brain Barrier (BBB) and Blood Cerebrospinal Fluid Barrier (BCSFB). More than 98% of small molecular weight drugs and practically 100% of large molecular weight drugs like peptides and proteins developed for CNS pathologies do not readily cross the BBB. In the treatment of diseases or situation that results from the lack of simple hormones and peptides administration of drugs in a controlled manner provides effective managing of disease and therapy. In case of treating fatal CNS disease, such as brain tumours, HIV encephalopathy, epilepsy, cerebrovascular disease and neurodegenerative disorders is particularly challenging because a variety of difficult obstacles often delay drug delivery to brain and spinal cord. So drug targeting to brain is essential to increase treatment efficacy and it also reduces toxicity due to localizing drug at the desired site of action. [10,11,12,]

Barriers to CNS Drug Delivery

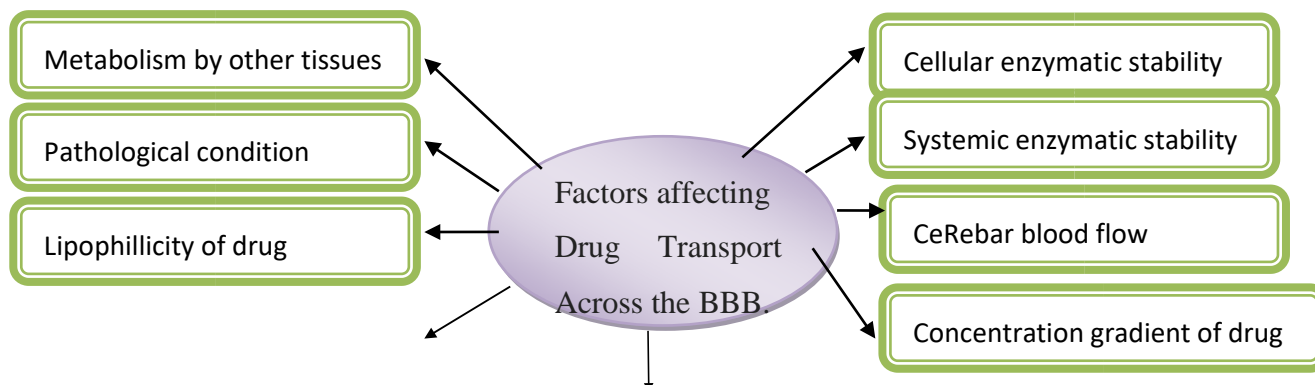
The failure of drugs in the effective treatment of many CNS diseases can be rationalized by considering a number of barriers that inhibits drug delivery to the CNS are Blood Brain Barrier (BBB) BBB consist of Basal membrane and brain cells, such as pericytes and astrocytes, surrounding the endothelial cells which maintain enzymatic and physical barrier of brain. Capillaries of the vertebrate brain and spinal cord lack pore and are lined with a layer of special endothelial cells that lack fenestrations and are sealed with the tight junctions.

Blood-Cerebrospinal Fluid Barrier (BCSFB)

The epithelial cells have an arrangement in such a manner that it prevents the entry of molecules. The CSF freely exchange molecules with the extracellular fluid of brain, parenchyma, delivering drugs into the CSF could theoretically result in therapeutic CNS drug concentrations.

Factors affecting drug transport across the BBB.

Table: 4 Factors affecting drug transport across the BBB



Approaches to CNS drug delivery

A. Invasive approaches or neurosurgical approaches

- Intra cerebra ventricular (ICV) infusion
- Convection-enhanced delivery (CED)
- Intra-cerebral injection or implants
- Disruption of the BBB.

B. Non-invasive

• Chemical techniques

- a. Prodrug
- b. drug conjugate

• Colloidal Techniques

- a. Nano particles
- b. Liposome

C. Miscellaneous techniques a. Intranasal delivers [22, 24, and 27]

A. Invasive approaches or neurosurgical approaches

It involves placement of a biodegradable chemotherapeutic impregnated pellets into tumour restriction area. Drug added to polymer and compressed to form pellets. These are implanted intracranial through which drug bypass the BBB and release drug molecule locally to the brain in the sustained fashion.

Intra-cerebroventricular (ICV) infusion

Intra cerebra ventricular infusion one strategy for bypassing BBB intra-ventricular infusion of drug directly into the CSF. Drug solution can be subcutaneously injected into the implanted reservoir and delivered to the ventricles manual compression of the reservoir through the scalp.

BBB Disruption: - disruption makes tight junction between the endothelial cells of the brain capillaries leaky. The BBB can be transiently disrupted by a variety of techniques such as osmotic disruption technique. MRI guided focused ultrasound BBB. [21, 24, 28]

Convection enhanced delivery: - it involves insertion of a small calibre catheter into the brain parenchyma. Through this catheter, drug is actively pumped into the brain parenchyma and penetrates in the interstitial space. [28]

B. Non-invasive techniques:-

This technique usually interrelated to drug manipulation which may include alteration as prodrugs, lipophilic analogues, chemical drug delivery, carrier mediated drug delivery, receptor mediated drug delivery etc. [29]

• **Chemical techniques:** - it improves some deficient physiological property such as membrane permeability. Chemical methods involve the chemical transformation of drugs by changing the various functionalities.

Prodrug¹³: - Prodrug which is lipid soluble and can cross the BBB. Prodrug is pharmacologically inactive compounds that results from transient chemical modification of biologically active species. It is metabolized within the brain and converted to the parent drug. Prodrug is used to improve gastrointestinal tolerance, increase in systemic availability, and improve solubility, taste and shelf life.

Examples levodopa, GABA, Nillumbik acid, valproate. [13]

Drug conjugates: - it involves caging of compounds within glycol, maltose, diglucosyl and dimaltosyl derivatives of cyclodextrin. The therapeutic complexes comprise of an omega 3-fatty acid such as alpha linolenic acid, eicosapentaenoic acid and their derivatives. [13]

Colloidal Techniques

Nano particles¹⁴: - Nano particles are micronized solid colloidal particles prepared of polymeric materials ranging in size from 1-1000 nm. It is used as carrier systems in which the drug is dissolved, entrapped, encapsulated, adsorbed or chemically linked to the surface. Systems in CNS targeted drug therapy supply better penetration of therapeutic and diagnostic agents, and a reduced risk in comparison to conventional treatments. Nano particles are used to deliver drugs through oral, nasal, parenteral, intra-ocular etc. Through Nano particles particle size can be easily altered resulting in attaining both active and passive drug targeting after parenteral administration became the most advantageous in the treatment of many chronic diseases. [14]

Liposome¹⁵: - liposomes are colloidal, vesicular structures composed of one or more lipid bilayer surrounding an equal number of aqueous compartments. A free drug injected in blood stream typically achieves therapeutic level for short duration due to metabolism and excretion. Drug encapsulated liposome achieves therapeutic level for long duration. Liposomes are biodegradable and essentially nontoxic vesicles can encapsulate both hydrophilic and hydrophobic materials and are utilized as drug carrier in drug delivery system. Many liposome-based DNA delivery systems have been described, including molecular components for targeting given cell surface receptors or for escaping from lysosome compartment. [15]

Tumour targeting drug delivery

A specific interaction between drug and its receptor at the molecular level. A rapidly growing tumour requires various nutrients and vitamins. Tumour cells express many tumour specific receptors which can be used as target to deliver cytotoxic agent into tumours. Tumour targeting improve the drug chemotherapeutic index by

- Preferentially localizing its pharmacological activities at the site of action cellular concentration.
- Recognition and interaction with target cell.
- Achieving cellular concentration so as to exhibit therapeutic response.

Tumour targeting is classified in different ways by pioneers of the area. It is classified as active and passive targeting. [20]

Application of targeted drug delivery system

- Targeted drug delivery is utilized to treat many diseases, such cardiovascular diseases and diabetes. Regenerative technique is developed to cure various diseases. The development of a number of regenerative techniques in recent year for curing heart diseases.
- Targeted drug delivery is also used in the stem cell therapy. This therapy helps to regenerate myocardium tissue and return the contractile function of heart by creating a microenvironment before myocardial infarction.
- Liposome is used in the treatment of tuberculosis. Chemotherapy is used for treatment of tuberculosis but it is not effective. Liposome shows better microphages penetration and optimum concentration at the targeted site.
- It is also used in 3D printing to investigate how to target cancerous tumour. By printing a plastic 3D shape of tumour and filling it with drug and show therapeutic effect at a targeting location of the drug.
- Detection of proteins
- Bio detection of pathogens.
- Tissue engineering.
- MRI contrast enhancement.
- Drug and gene therapy.
- Probing of DNA structure.
- Drug discovery [29]

CONCLUSIONS

Delivery of drug molecule to reach its specific site is itself a difficult task in the complex cellular network of an organism. Finally, targeted drug delivery is coming forward as one of the brightest advanced technique in the medical sciences in the diagnosis and treatment of couple of lethal diseases. It has crossed the infancy period and now touching height of growths in research and development in clinical and pharmaceutical fields. Overall, it may be concluded with the vast database of different studies, the science of site specific or targeted delivery of these drugs has become wiser and intelligent with time and the advancement of scientific technology. Manifestation of all these strategies and advanced technologies in clinical field leads to new era of therapeutic and diagnostics in future. Many problems which appeared during the development of drug targeting strategies for clinical application for different types of therapies have been identified, analysed and solved especially in the treatment of cancer. Several such preparations have entered the phases of clinical testing or trials have now been marketed. However, such strategies should be subjected to continuous evaluation in the light of advances in the understanding of the numerous processes occurring in response

to administration of the carriers or vehicles with drugs of interest with site specificity. New strategies under investigation should periodically undergo evaluation, taking advantage of the 'bench to bed-side' experience available today. Furthermore, in the coming years, combining expertise in the drug targeting field with the technological developments in molecular biology and molecular medicine will facilitate the elucidation of the cellular and molecular processes underlying disease [1, 9]

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