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TARGETED DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Targeted Drug Delivery System is a method of Delivery drugs to the patients at the targeted site or the site of action this improves efficacy of Treatment by reducing side effects of the drug administer. Targeted drug delivery, also known as smart drug delivery, is a method of treatment that involves the increase in medicament in one or few body parts in comparison to others. Basically, targeted drug delivery is to assist the drug molecule to reach preferably to the desired site. Research related to the development of targeted drug delivery system is now a day is highly preferred and facilitating field of pharmaceutical world. The various drug carriers which can be used in the advanced delivery system are Lipoprotein, Liposome's, Microspheres, and Nanoparticles. The present review deals with the targeted drug delivery system it's advantages, disadvantages, need of targeted drug delivery system and research update on targeted drug delivery system

INTRODUCTION

Targeted drug delivery, also known as Smart drug delivery is a method of treatment that involves the increase in medicament in one or few body parts in comparison to others. Targeted drug delivery system is based on a method that delivers a certain amount of therapeutic agent for a prolonged period of time to a Targeted diseased area within the body. It delivers the medication only to areas of interest within the body. These offer an improved efficacy of treatment and also reduce side effects. Greogoriadis, in 1981, described the use of novel drug delivery for drug targeting as 'old drug in new clothes.(Ref.no1.)

When implementing a Targeted release system, the following design criteria for the system need to take into account. The drug properties, side effects of the drugs, the route taken for the delivery of the drug, the targeted site, and disease.(2.)

There are four Principle requirements for a successful targeted drug delivery system retain, evade, target and release. i.e. There should be proper loading of the drug in to an appropriate drug delivery vehicle, it must possess an ability to escapes the body's secretions that may degrade it, leading to a long residence time in circulation and thereby reaching in site of interest and, should release the drug at the specific site within the time that calls for effective drug functioning. (Ref no1,3.) Ideally targeted drug delivery system should be biochemically inert (nontoxic), non-immunogenic, should physically and chemically stable in vivo and vitro Conditions, and should have Uniform capillary distribution. (4)

The targeted drug delivery system is preferred over a Conventional drug delivery system. Because the Conventional drug have low specificity and low therapeutic index as compared to targeted drug delivery system. Due to this reason Targeted drug delivery system is preferred over a Conventional drug delivery system. (2,5.) The concept of designing targeted delivery system has been originated from the Paul Ehrlich, who was a microbiologist, proposed the idea of drug delivery in the form of magic bullet.(6)

Types of targeted drug delivery:

There are six types of targeted drug delivery system

1] Active Targeting:

Active targeting means a specific ligand receptor type interaction of intracellular Localization which occurs only after blood circulation and extravasation. The interactions between a ligand and a receptor are possible only when the two are in close propinquity, (i.e. Less than about $0.5\mu\text{m}$)⁵.

The active targeting can further divided into three different targeting levels

A] First order targeting: it refers to restricted distribution of the drug carrier system to the capillary bed of a predetermined target site, organ or tissue.

For Example: IN case of lymphatic tissue, peritoneal cavity, pleural cavity, cerebral ventricles, eyes, joints etc.

B] Second order targeting: This is the targeting of drugs to specific sites such as the tumor cells and not to the normal cells.

For Example: Selective drug delivery to kupffer cells in the Liver.

C] Third order targeting: It is type of drug targeting wherein the drug is intracellularly localized at the target site via. Endocytosis or through receptor based ligand mediated entry.

(4,7.)

2] Passive Targeting:

This is based on the accumulation of Drug at areas around the site of interest, such as in case of tumor tissues. This is called Enhanced Permeability Retention (EPR) Effect. In these technique drug targeting occurs because of the body's natural response to physiochemical characteristics of the drug or drug carrier system. Passive targeting is actually a misnomer because it cannot really be described as a form a Selective Targeting.

The ability of some colloid to be taken up by the reticulo Endothelial System (RES) especially in liver and spleen made then ideal substrate for passive hepatic Targeting of drugs. (1.)

3] Inverse Targeting:

This approach leads to saturation of Reticulo Endothelial Cell (RES) and suppression of defense mechanism. This type of targeting is effective approach to target drugs to non reticulo endothelialsystem (RES) Organs.

4] Dual Targeting:

In this targeting approach carrier molecule itself have therapeutic activity and thus increase the therapeutic effect of drug. For Example – a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.

5] Double Targeting:

Spatial placement relates to targeting drugs to specific organs tissues, cells or even subcellular compartment. When temporal and spatial methodologies are combined to target a

carrier system, then targeting may be called double targeting. Whereas temporal delivery refers to controlling the rate of drug delivery to target site

6] Combination Targeting:

These targeting systems are equipped with carriers, polymers and homing devices of molecular specificity that could provide a direct approach to target site. (2.)

Advantages of Targeted drug delivery:

- It reduces the side effects and Toxicity.
- Drug administration protocols may be simplified.
- It avoids the degradation of drug (First pass metabolism).
- No peak and valley plasma concentration.
- Drug bioavailability increase and fluctuation in concentration Decrease.
- Enhancement of the absorption of target molecules such as peptides and particulates.
- Selective targeting to infections cells that compare to normal cells.
- Dose is less compared to conventional drug delivery system.
- Drugs can be administered in a smaller dose to produce the desire effect.(2,8.)

Disadvantages of Targeted drug delivery;

- 1) Difficult to target the tumor cells.
- 2) Rapid clearance of target systems.
- 3) Advanced techniques and skilled persons are required.
- 4) Immune reactions against intravenous administered carrier systems.
- 5) It may causes toxicity and it is very difficult to maintain stability of dosage forms.
- 6) Insufficient Localization of target systems into tumor cells.
- 7) Requires highly sophisticated technology for the formulation.
- 8) Diffusion and redistribution of release drugs.
- 9) Drug loading is usually low. E.g. As in micelles.(2,8.)

Components of Targeted drug delivery:

Target:

Target means specific organ or cell or group of cells, which in chronic or acute condition need treatment.

Carrier or Marker:

Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre-selected sites. They are engineered vectors, which

retain drug inside or onto them either via encapsulation and or via spacer moiety and transport or deliver it into vicinity of target cells. (1,9.)

Characteristics of an ideal drug vehicle:

An ideal drug vehicle should be able to cross blood brain barrier. And in case of tumour chemotherapy tumour vasculature. After recognition, the carrier system should release the drug moiety inside the target organs, tissues or cells. Targeting moieties includes antibodies, lectins and other and other proteins, Lipoproteins, Hormones, Charged molecules, Polysaccharides and Low molecular weight ligands. The drug ligand complex should be stable in plasma, interstitial and other body fluids.

- **Liposome**
- **Monoclonal antibodies and fragments**
- **Modified (plasma) proteins**
- **Quantum dots**
- **Microsphere and Nanoparticles**
- **Lipoproteins**

Liposomes:

Delivery of Larger fraction of drug to the desired (diseased) site, by reducing the drug exposures to normal tissues can be achieved by site specific targeting.(2.)

Liposomes have generated a great interest because of their versatility and have played a significant role in formulation of potent drugs to improve therapeutics. The various problems like poor solubility, short half-life and poor bioavailability and strong side effect of various drugs can be overcome by employing the concept of liposomes especially in various disease like cancer etc. Liposomes are vesicular concentric structures, range in size from a nanometer to several micrometers, containing a phospholipids bilayer and are biocompatible, biodegradable and non-immunogenic.(10.) Encapsulating the drug in liposomes can be used for both Active and passive targeting of drugs in order to achieve a safer and Efficacious therapy. In Patients with Recurrent osteosarcoma, there was an enhanced tumoricidal activity of monocytes, when muramyl Peptide Derivatives were formulated as liposomes and administered systematically. On systemic administration, long circulating immunoliposomes are able to recognize and bind to target cells with greater specificity.(2,11,12.)

Drugs held and delivered by liposomes have significantly improved pharmacokinetics properties such as the Therapeutic index. Liposomal drugs are among the first nanotechnology products used as therapeutic agents to get the approval of FDA for the clinical use. DOXIL R (doxorubicin liposomes) was approved in 1995 as a Medicament for Kaposi's sarcoma related AIDS. Liposomes can be coated with polyethylene glycol, besides other polymers, resulting in an increased half-life.(1.)

Preparation of Liposomes:

There are many ways of preparing liposomes. Some of the important methods are:

- 1) Ultra sonication
- 2) French pressure cell
- 3) Hydration of lipids in presence of solvent
- 4) Solvent injection method
 - a) Ethanol injection
 - b) Ether injection method
- 5) Detergent removal detergent can be removed by
 - a) Bio-beads
 - b) Dialysis
 - c) Column chromatography
- 6) Reverse phase evaporation technique
- 7) High pressure extrusion
- 8) Miscellaneous Methods
 - a) Removal of chaotropic ions
 - b) Freeze- Thawing. (6.)

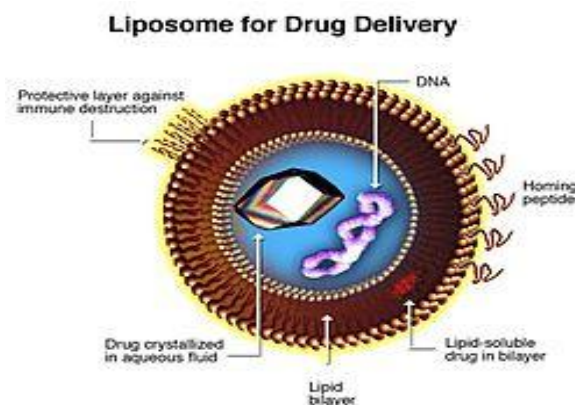


Fig.1 Liposomes for drug deliver

Monoclonal antibodies and Fragments:

Monoclonal antibodies Production Somatic Cell Fusion or Hybridoma technology was introduced by Kohler and Milsteil in 1975. The technique's involves fusing a normal antibody producing B cell with a myeloma cell to produce a hybrid cell or hybridoma.(6.) The use of Monoclonal antibodies (mAbs) as therapeutic agent is gaining importance in the treatment of various conditions such as cancer, cardiovascular disease and viral infections. In addition to Monoclonal antibodies the target tumors have been conjugated to radioisotopes, chemotherapeutic agents, bacterial toxins, cytokines and enzymes in order to potentiate their cytotoxic effects.(13.) In concert with their clinical acceptance, monoclonal antibodies have become commercially viable drugs.(14.) Recently monoclonal antibodies are developed as antitumor agents.15. Adalimumab (HUMIRA) is the first human monoclonal antibody approved for human use.(2.)

Therapeutic monoclonal antibodies (TMAs) have mainly found use as naked antibodies. There are now twelve registered TMAs for cancer therapy out of which five are used for hematological cancers. These antibodies are Orthoclone OKT3[®], Rituximab(Rituxin[®]/Mabthera[®]), Trastuzumab (Herceptin[®]), Alemtuzumab (Campath[®]/Mabcampath[®]), Ibritumomab tiuxitan (Zevalin[®]), Tositumomab (Bexxar[®]), Cetuximab (Eribix[®]), Bevacizumab (Avastin[®]), Pembrolizumab (Vectibix[™]), Ofatumumab (Arzerra[™]), Ipilimumab (Yervoy[™]), Pertuzumab (Perjeta[™]). The first TMA cancer therapy approved by the Food and Drug Administration (FDA) was Orthoclone OKT3[®]. This was in September 1992. The most recent one is Pertuzumab that was approved in 2012. Since then, mAbs have been gradually implemented in cancer therapy.(1.)

Modified Plasma Proteins:

Modified plasma proteins can be intelligent drug vehicles for drug transportation due to their solubility and having relatively small molecular weight. In the case of liver cell targeting, extensive modification of protein backbones such as albumin have been carried out for effective delivery of the drug. They can easily be modified by the attachment of different molecules like peptides, sugar, and other ligands to transport the drug of interest makes them a suitable mode of drug delivery.(Ref.no.2,16.) Soluble synthetic polymers have been extensively researched as versatile drug carrier systems. For cancer therapy, the well-established N (-2-

hydroxypropyl)Meth acrylamide (HMPA) polymer have been extensively studied. It provide a solution for selective and targeted chemotherapy.(Ref.no. 4,17.)

Quantum dots:

A quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes or bound pairs of conduction band electrons and valence band holes in all three spatial directions. The optical properties (fluorescence emission) of Quantum dots can be fine-tuned by the quantum dots size and is calculated using conventional techniques like scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Atomic force microscopy (AFM), or more preferably scanning tunneling microscopy (STM) And dynamic light scattering (DLS) Studies. Quantum dots are particularly significant for optical application due to their theoretically high quantum yield.Besides these technique use field flow fractionation was also successfully employed an excellent complement to characterization of water soluble quantum dots by the conventional tools. Optical characterization of quantum dots is usually done by UV-VIS and photoluminescence spectroscopy, which offer fast, non-destructive and contactless option.(2,4.)

Microsphere and Nanoparticles:

Microsphere and nanoparticles consist of biocompatible polymers and belong either to the soluble or the particle type carriers. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200mm. Nanoparticles are smaller (0.2-0.5mm) than microspheres (30-200mm) and may have a smaller drug loading capacity than the soluble polymers. This is the important approach in delivery therapeutic substance to the target site in sustained and controlled release fashion. Formulation of drugs in to the nanoparticles can occur at the surface of the particle and in nucleus, depending on the physicochemical characteristics of the drug.Nanoparticles can modify or imitate the process occurring in living organisms. After systemic administration or transportation, they quickly distribute to the target sit and subsequently become internalized by the cells of the phagocytic system. Besides, microspheres and a nanoparticle which are mostly used for cell selective delivery of drugs, they have more recently been studied for their application in oral delivery peptides and

peptidomimetics. The main goal designing nanoparticles as a delivery system are to control size of particle, surface characteristics and discharge of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.(Ref.no.2,4,6.)

Preparation of Microspheres:

The various methods of preparations are:

- 1) Solvent evaporation method
 - a) Single emulsion technique
 - b) Double emulsion technique
- 2) Polymerization method
- 3) Spray drying and spray congealing method
- 4) Coacervation phase separation method

Preparation of Nanoparticles:

Nanoparticles can be prepared from a variety of materials such as polysaccharides, proteins and synthetic polymers.

Preparation of Nanoparticles from polymerization of monomers;

- a) Emulsion
- b) Mini Emulsion
- c) Micro Emulsion
- d) Interfacial polymerization
- e) Controlled/living radical polymerization

Preparation of Nanoparticles from Dispersion of Performed Polymers:

It is a common technique used to prepare biodegradable nanoparticles for poly (Lactic acid) (PLA), poly (D, L-lactide-co-glycolide) (PLGA), Poly (D, L-glycolide) (PLG).

These can be accomplished by different methods described below.

1. Dialysis
2. Solvent evaporation
3. Salting out
4. Nano precipitation
5. Super critical fluid technology (SCF)
6. Emulsification/solvent diffusion

Ionic gelation or coacervation of hydrophilic polymers. (Ref.no.6.)

Lipoproteins:

Modification at the level of glycolipid incorporation can be used to introduce new targeting moieties. Lipid particles such as LDL and HDL containing a lipid and an Apo protein moiety is termed as a natural targeted liposomes and its core can be used to incorporate lipophilic drugs or lipophilic pro-drugs and it does not required covalent bonding with the drug. The majority of the research on the use of LDL and HDL particles has been done and improved at the level of targeting the drugs to the liver.(Ref.no.2,18.)

Approaches:

1. Transdermal Approach In Drug Transportation:

Transdermal drug delivery system is topically administered medicaments in the form of patches that delivers drugs for systemic effects at a predetermined and controlled rate. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. In theory, transdermal patches work very simply. These device allow for pharmaceuticals to be delivered across the skin barrier. There is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Through a diffusion process, the drug enters the bloodstream directly through the skin.(Ref.no.4,10,19.)

2. Folate Targeting:

Folate targeting is a method utilized in biotechnology for drug delivery purposes. It involves the attachment of the vitamin, folate (folic acid), to a molecule/drug to form a “folate conjugate”. Based on the natural high affinity of folate for the folate receptor protein (FR) which is commonly expressed on the surface of cancer cells and folate – drug conjugates also bind tightly to the folate receptor protein (FR) which in turn, trigger cellular uptake via endocytosis. The folate receptor protein is also a recognized tumor antigen/biomarker. Because of this inherent property of folate receptor protein, exploits its use in diagnostic and therapeutic methods especially for the treatment of cancer.(Ref.no.4.)

3. Brain Targeted Drug Delivery Systems:

The brain is a delicate organ, and evolution built very efficient ways to protect it. The major challenge to CNS drug delivery is the blood- brain barrier (BBB), which limits the access of drugs to the brain substance. The delivery of drugs to central nervous system (CNS) is a

challenge in the treatment of neurological disorders. Drugs may be administered directly in to the CNS or administered systematically (e.g. by intravenous injection) for targeted action in the CNS. Various strategies that have been used for manipulating the blood brain barrier for drug delivery to the brain include osmotic and chemical opening of the blood brain barrier as well as the use of transport/carrier systems. It is important to consider not only the net delivery of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS. Various pharmacological agents have been used to open to BBB and direct invasive methods can introduce therapeutic agents into the brain substance. Various route of administration as well as conjugations of drugs e.g. liposomes and nanoparticles are considered.(Ref.no.10.)

Applications of Targeted Drug Delivery System:

- 1) The most important application of targeted drug delivery is to treat cancerous tumours.
- 2) Targeted drug delivery can be used to treat many diseases, such as cardiovascular disease and diabetes.
- 3) The delivery of the drugs works intravenously and by inhalation.
- 4) The liposome delivery systems allows for better microphage penetration and better builds a concentration at the infection site.
- 5) Liposomes can be used as drug delivery for the treatment of tuberculosis. The traditional treatment of TB is skin to chemotherapy which is not overly effective, which may be due to failure of chemotherapy to make a high enough concentration at the infection site.(Ref.no.2.)

Ideal properties of Targeted drug delivery system:

- 1) Its preparation should be easy or reasonably simple, reproductive and cost effective.
- 2) Carrier used must be biodegradable or readily eliminated from the body without any problem.
- 3) Minimal drug leakage during transit.
- 4) Controllable and predictable rate of drug release.
- 5) Restrict drug distribution to target cell or tissue or organ.
- 6) Non Toxic, biocompatible and the physiochemical stable in – vivo and in-vitro.
- 7) Drug release should not Effect drug action.

- 8) Therapeutic amount of drug release.
- 9) No carrier induced modulation of disease state.
- 10) It should have uniform capillary distribution. (Ref.no.8.)

Devices based on Nanotechnology:

Nano carriers –

- 1) **Nanotubes-** They are hollow cylinder made of carbon, atoms. Help to identify DNA changes associated with cancer cells. Which can be filled and sealed for potential drug delivery.

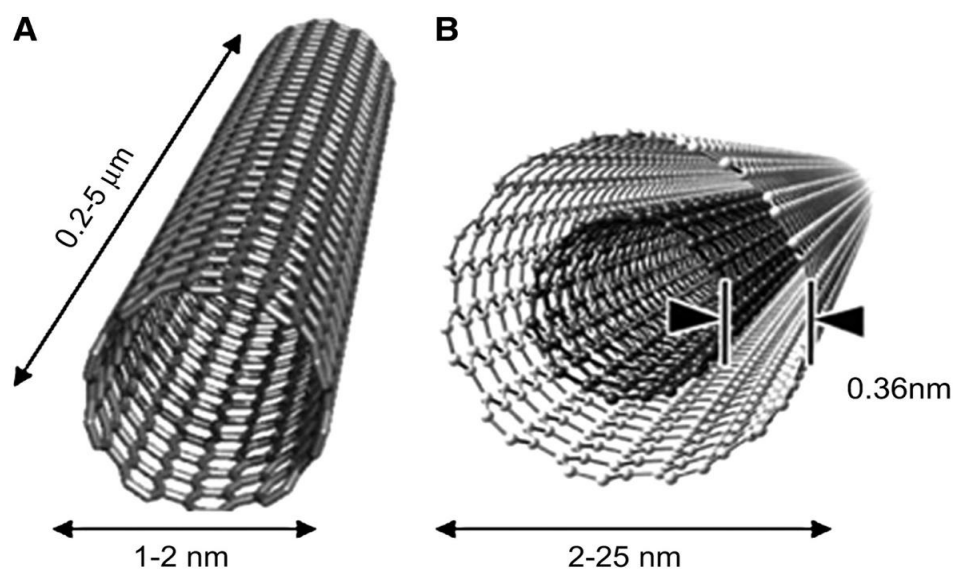


Fig. 2: Structure of Nanotubes

- 2) **Nano shells -** It has potential for targeting cancerous drug. Nano shells are hollow silica spheres covered with gold.

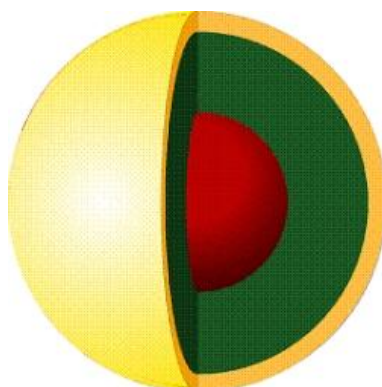


Fig. 3: Structure of Nanoshells

- 3) **Dendrimers** – these have branching shape which gives them vast amounts of surface area to which therapeutic agents or other biologically active molecules can be attached. Dendrimers are new class of macromolecules which have a symmetric core and form the 3 – D spherical structure. Useful in gene transfection and medical imaging.

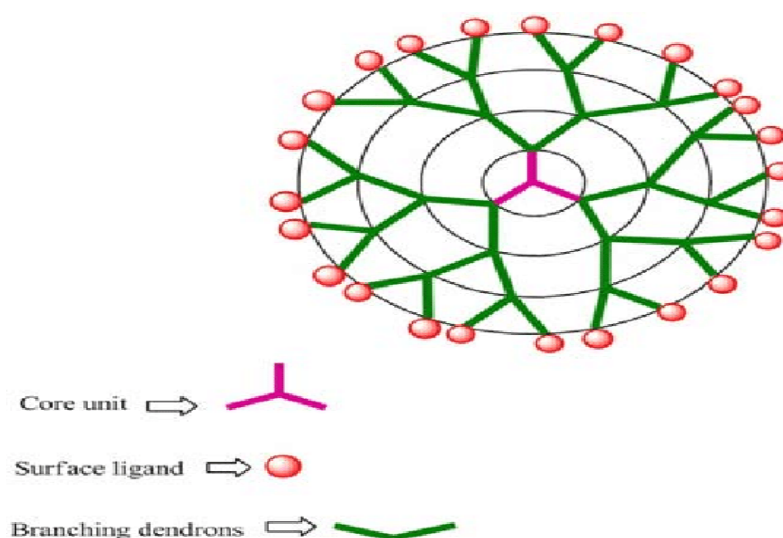


Fig. 4: Structure of Dendrimers

Recent Research Work on Targeted Drug Delivery System:

1) **Diltiazem HCL** –

Other Ingredients – Polysaccharide, inulin and shellac

Method Employed – Tablet Compression and Coating

Effect - Studies revealed that the tablet coated with inulin and shellac have limited the drug release in stomach and small intestine. And released maximum amount of drug in colonic environment.

2) **Meloxicam** –

Other Ingredient – Ethyl cellulose

Method Employed – Tablet compression and coating.

Effect – Retarded the drug release up to 12 hrs. and shows max. Of 98.69% drug release.

3) **Doxorubicin hydrochloride** –

Other Ingredient - Chitosan

Method employed- HPLC

Effect – In-vitro release of doxorubicin is of zero order kinetic. This shows that release is independent of the concentration of drug loaded in the Nano spheres.

4) Paracetamol –

Other Ingredient – Dextrin, Polysaccharide

Method Employed – Wet granulation

Effect – Tablet containing dextrin as a carrier and ethyl cellulose as a binder found to be suitable for targeting Paracetamol for local action in the colon Matrix tablets containing dextrin released 95-98% Paracetamol.

5) Variable –

Other Ingredient – HPMC and Ethyl cellulose

Method Employed – Tablet compression and enteric coating

Effects – Combination of two polymers in optimized concentrations can be used to increase the delayed action of drug release to deliver the drug in delayed manner.

CONCLUSION:

Delivery of drug molecule to reach its specific site is itself a difficult task. Finally, a targeted drug delivery is coming towards as an advanced technique used in the treatment of lethal disease. Targeted delivery of drugs, as the name suggested, is to assist the drug molecule to reach preferably to the desired site. The advantage of this technique has been the reduction in dose and side effects of the drug. Overall it may be concluded from different studies, the science of site specific or targeted delivery of these drugs become wiser. Manifestation of these strategies in clinical now seems possible in near future.

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