International Journal of Pharmaceutical and Medicinal Research

Journal homepage: **www.ijpmr.org**

Review Article

Targeted Drug Delivery System: Current and Novel Approach

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ARTICLE INFO:

Article history:
Received: 10 April, 2017
Received in revised form:
23 April, 2017
Accepted: 25 April, 2017
Available online: 30 April, 2017

Keywords:
Targeted drug delivery
Drug carriers
Pharmacokinetic

ABSTRACT

Nowadays, most of the dosage form has a poor pharmacokinetic and biopharmaceutical properties. Hence there is need to develop a suitable drug system that distributed the active drug molecule only to the site of action, without affecting other tissues or organs. Targeted drug delivery is a method of delivering 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 administered. The inherent advantage of this technique leads to administration of required drug with reduced dose and reduced its side effects. Various drug carriers which can be used in this advance delivery system are Lipoproteins, Liposomes, Microspheres. The present review deals with the Targeted drug delivery system its advantages, disadvantages, need of Targeted drug delivery system and research update on Targeted drug delivery system.

1. Introduction

Targeted drug delivery is a kind of smart drug delivery system which is miraculous in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form**[1,2].**

The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologist and engineers, to join forces to optimize this system. 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 the disease**[3].**

Targeted drug delivery system is preferred over conventional drug delivery systems due to three main reasons. The first being pharmaceutical reason. Conventional drugs have low solubility and more drug instability in comparison to targeted drug delivery systems. Conventional drugs also have poor absorption, shorter half-life and require large volume of distribution. These constitute its pharmacokinetic properties. The third reason constitutes the pharmacodynamic properties of drugs. The conventional drugs have low specificity and low therapeutic index as compared to targeted drug delivery system. Due to these reasons targeted drug delivery system is preferred over conventional drug delivery systems**[4].**

1.1 Characteristics of targeted drug delivery systems

- Should be biochemically inert.
- Should be non immunogenic.
- Should be physically and chemically stable in vivo and in vitro conditions.
- Should have therapeutic amount of drug release.
- Should have minimal drug leakage during transit.
- Carriers used should be biodegradable or readily eliminated from the body**[5].**

1.2 Applications of targeted drug delivery system

- Targeted drug delivery can be used to treat many diseases, such as cardiovascular diseases and diabetes. However the most important application of targeted drug delivery is to treat cancerous tumours**[6].**

- 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 the failure of chemotherapy to make a high enough concentration at the infection site. The liposome delivery system allows for better microphage penetration and better builds a concentration at the infection site**[7].**

1.3 Generation of drug delivery

There are five generations of drug delivery system. First generation includes tablets, capsules etc. Second generation includes repeat action, prolonged action etc. Third generation includes osmotically controlled system, swelling controlled system etc. Fourth generation include targeted drug delivery system, modulated drug delivery system. Fifth generation includes gene therapy under various phase of development.

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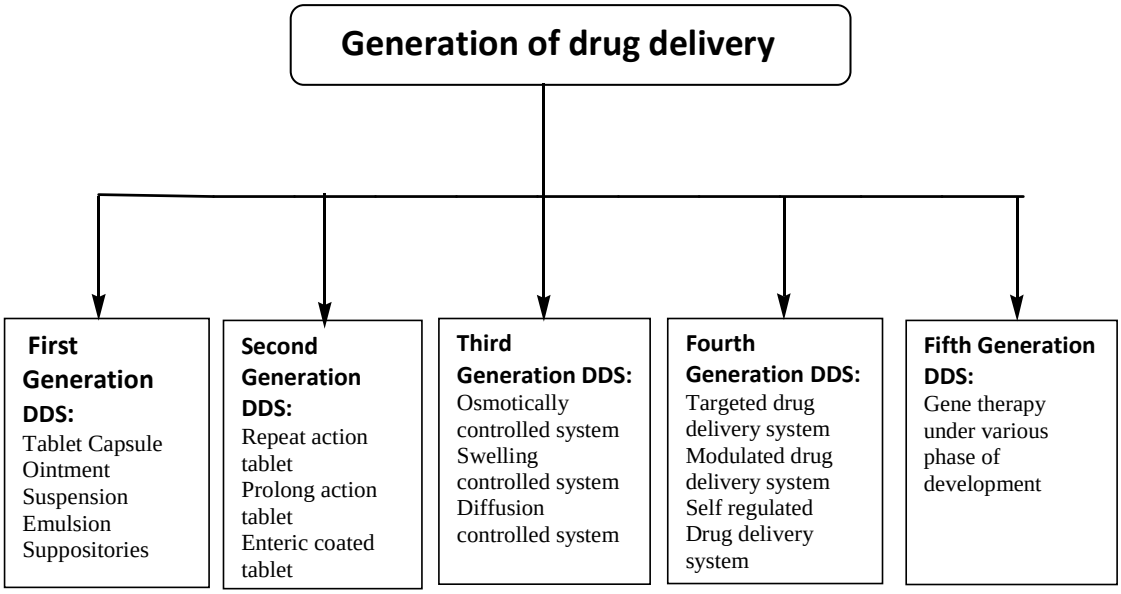

Figure No. 1: Generation of drug delivery system**[8]**

2. Need of targeted drug delivery

Targeted drug delivery system means specific organ or a cell or group of cells, which is chronic or acute condition need treatment. Drug carrier is one of the special molecules required for effective transportation of loaded drug to pre selective site. The drug carrier should be bio degradable or readily eliminated from the body without any problem. The need of this system is to deliver the certain amount of drug to the targeted disesed area within the body. This will help to maintain the required plasma level and tissue drug level in the body therefore avoiding any damage to the healthy tissue via drug.

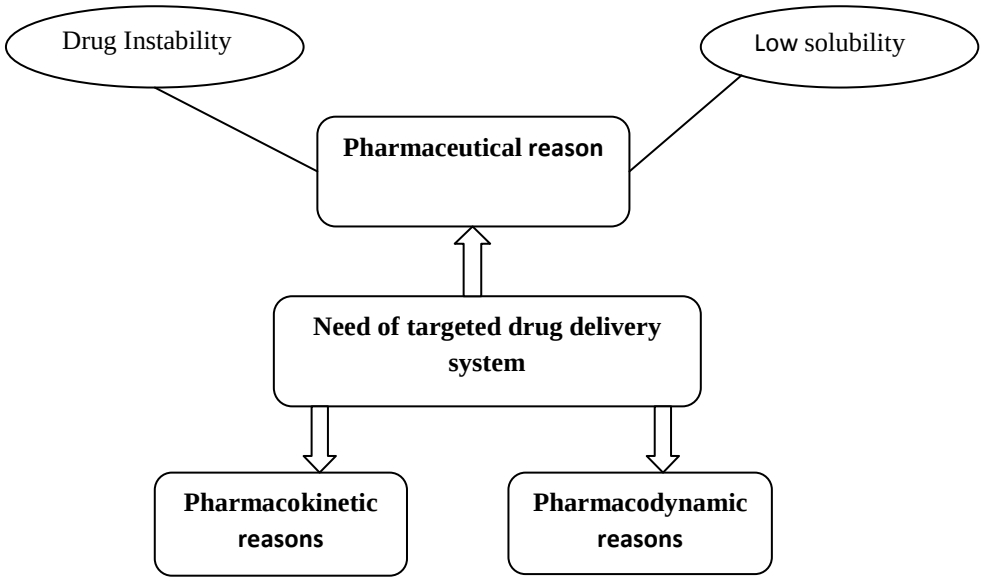

Figure No. 2: Need of targeted drug delivery**[9]**

2.1 Advantages

Target drug delivery system reduces the side effects and toxicity. The Dose of the drug reduces by targeting organ. It avoids the degradation of drug (first pass metabolism). Drug bioavailability increases and fluctuation in concentration decreases. It also has positive effect on permeability of proteins and peptid. These all factors in combination cause in reduction in dosage frequency and hence reduce the cost of expensive drug.

2.2 Disadvantages

With the targeted drug delivery it becomes difficult to target the tumor cells. Advanced techniques and skilled persons are required. Sometimes it may causes toxicity and it is very difficult to maintain stability of dosage forms**[10].**

3. Types of targeted drug delivery

Targeted drug delivery may be of following types as discussed below.

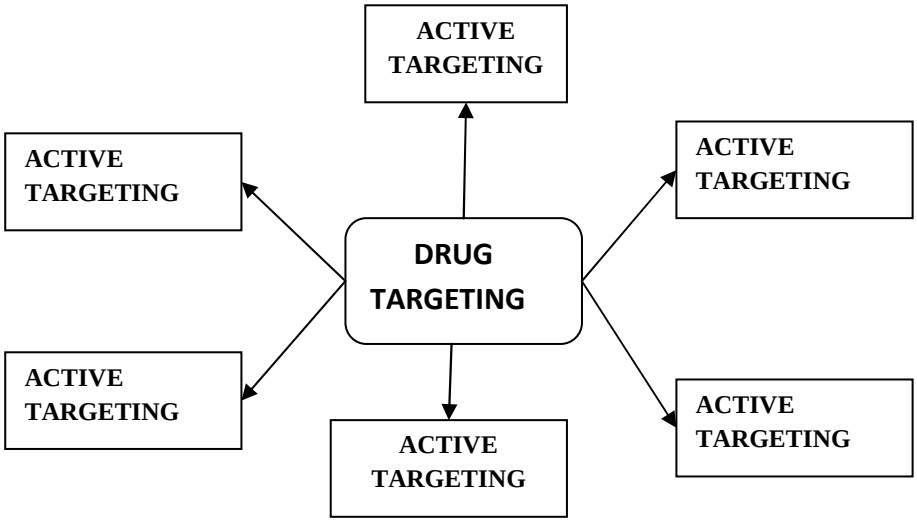

Figure No. 3: Types of targeted drug delivery[9]

3.1 Active targeting

Active targeting means a specific ligand– receptor type interaction for intracellular localization which occurs only after bloodcirculation and extravasations.This active targeting approach can be further classified into three different levels of targeting which are 1) First order targeting refers to restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ or tissue e.g. compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles and eyes, joints. 2) Second order targeting refers to selective delivery of drugs to specific cell types such as tumour cells and not to the normal cells e.g. selective drug delivery to kupffer cells in the liver. 3) Third order targeting refers to drug delivery specifically to the intracellular site of targeted cells e.g. receptor based ligand mediated entry of a drug complex into a cell by endocytosis**[11].**

3.2 Passive targeting

Drug delivery systems which are targeted to systemic circulation are characterized as Passive delivery systems. In this technique drug targeting occurs because of the body's natural response to physicochemical characteristics of the drug or drug carrier system. The ability of some colloid to be taken up by the Reticulo Endothelial Systems (RES) especially in liver and spleen made them ideal substrate for passive hepatic targeting of drugs**[12].**

3.3 Inverse targeting

This approach leads to saturation of RES and suppression of defense mechanism. This type of targeting is a effective approach to target drug(s) to non-RES organs.

3.4 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**[9].**

3.5 Double targeting

When temporal and spatial methodologies are combined to target a carrier system, then targeting may be called double targeting. Spatial placement relates to targeting drugs to specific organs tissues, cells or even subcellular compartment .whereas temporal delivery refers to controlling the rate of drug delivery to target site.

3.6 Combination targeting

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

4. Drug delivery vehicles

Drug delivery vehicles are at the most important entity required for successful transportation of the loaded drug at the specific site**[13,14].**

4.1 Characteristics of an ideal drug vehicle

An ideal drug vehicle should be able to cross blood brain barriers. It must be recognized by the target cells specifically and selectively The drug vehicle used should be non-toxic, nonimmunogenic and biodegradable. After recognition, the carrier system should release the drug moiety inside the target organs, tissues or cells**[10,15,16].**

- Liposomes
- Monoclonal antibodies and fragments
- Modified (plasma) proteins
- Quantum dots
- Microspheres and Nanoparticles
- Lipoproteins

4.1.1 Liposomes

Delivery of larger fraction of drug to the desired (diseased) site, by reducing the drug's exposure To normal tissues can be achieved by site specific targeting. 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[20]. On systemic administration, long circulating immunoliposomes Are able to recognize and bind to target cells with greater specificity[18,19]. In patients with Recurrent osteosarcoma, there was an enhanced tumoricidal activity of monocytes, when muramyl Peptide derivatives were formulated as liposomes and administered systemically[20].

4.1.2 Monoclonal antibodies and fragments

The use of monoclonal antibodies (mAbs) as therapeutic agent is gaining importance is the treatment of various conditions such as cancer, cardiovascular diseases and viral infections. In concert with their clinical acceptance,mAbs have become commercially viable drug[21]. In addition, mAbs that target tumors have been conjugated to radioisotopes, chemotherapeutic agent , bacterial toxins, cytokines and enzymes in order to potentiate their cytotoxic effects[22]. Recently human mAbs are developed as antitumor agent[23]. Adalimumab (HUMIRA) is the first human mAb approved for human use.

4.1.3 Modified plasma proteins

Modified plasma proteins can be intelligent drug vehicle for drug transportation due to their solubility and having relatively small molecular weight. 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. In the case of liver cell targeting, extensive modification of protein backbones such as albumin have been carried out effective delivery of the drug[24].

4.1.4 Quantum dots

Optical characterization of quantum dots is usually done by UV-VIS and photoluminescence spectroscopy, which offer fast, non destructive and contactless option. 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. Besides these techniques, field flow fractionation was also successfully employed an excellent complement to characterization of water soluble quantum dots by the conventional tools[25].

4.1.4.1 Action of quantum dots

After administration of colloidal solution of quantum dots by S.C. or I. V. injection, they identify and bound to target. Once bound to target, each quantum dot particle emits light and depending on their size, they can fluorescence in a variety of colours which can be identified or detected by different techniques[26].

4.1.5 Microspheres and nanotechnology

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 200μm. This is the important approach in delivering therapeutic substance to the target site in sustained and controlled release fashion[27].

4.1.5.1 Advantages of microspheres[28]

They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue. They provide protection for unstable drug before and after administration, prior to their availability at the site of action. They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug. They enable controlled release of drug. Examples: Narcotic, Antagonist, Steroid hormones.

4.1.6 Lipoproteins

Lipid particles such as LDL and HDL containing a lipid and an apoprotein moiety is termed as natural targeted liposomes and its core can be used to incorporate lipophillic drugs and it does not require covalent bonding with the drug. Modification at the level of glycolipid incorporation can be used to introduce new targeting moieties. 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[29].

5. Recent updates on targeted drug delivery

Venkateswara reddy and Muneer sayed *et al.* had worked on Formulation and Evaluation of Colon Targeted Oral Drug Delivery system for Meloxicam. According to the research work sustained released matrix formulation of Meloxican targeted to colon by using various polymers developed. For colon targeted, Tablets were prepared in two steps. Initially core tablet were prepared and then the tablet were coated by using different PH dependent polymers. Among all the formulation F3 formulation was found to be optimized as it retarded the drug release up to 12 hrs and showed maximum of 98.69% drug release. From the investigation it was observed that formulation F3 was found to be best among the prepared formulations which may be used for prolong drug release in colon for, thereby improving patient compliance and bioavailability[30].

Priyanka S chaudhari, K S salunkhe *et al.* had worked on Formulation and Development of Colon specific drug delivery using Dextrin. The objective of the present study is to develop colon targeted drug delivery system by using polysaccharide as a carrier. Matrix tablets containing various different excipients and polysaccharide were prepared by wet granulation technique using different binder systems. According to the results the matrix 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 in simulated colonic fluid with 4% human fecal matter solution**[31].**

Faizan sayeed, Abdul sayeed *et al.* had worked on Targeted drug delivery of colon by using pH and time dependent technology. The polymers used to in the time dependent part of the delivery were HPMC and Ethyl cellulose with different ratios as the time with ethyl cellulose increases due to its insoluble nature and this is reduced by soluble nature of HPMC which would give the coating layer some lipophilicity with which the released would be initiated for the drug release. As a result of this study it may be concluded that the colon targeted drug delivery tablets using a 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**[32].**

Sheela Modani and Meena kharwade *et al.* had worked on Quantum dot: A novelty of medical field with multiple applications. According to them Quantum dots add to the expansion of new diagnostic and delivery systems. As they are well defined in size, shape, provide sole optical properties for highly sensitive detection and can be customized with various targeting principles. It has created powerfull impact in various field s of disease diagnosis, intracellular tagging as photo sensitizer for treatment of cancer,biotechnology and bioassay. Current advancement in the surface chemistry of quantum dots expanded their use in biological applications. Reduced their cytotoxicity and rendered quantum quantum dots a powerfull device for the research of distinct cellular processes like uptake, receptor trafficking and intracellular delivery**[33].**

Sokkalingam Arumugam and Selvadurai Muralidharan *et al.* had work on Formulation and evaluation of Chitosan Nanospheres containing Doxorubicin hydrochloride. According to them Nanoparticles showed increased cytotoxicity compared to DOX alone. These results suggest that DOX was unable to penetrate into cells and did not effectively inhibit cell proliferation. In contrast nanoparticles can penetrate into cells and can effectively inhibit proliferation. The objective of this research is to reduced side effects. HPLC device was used to quatitatively analyze the amount of Doxorubicin loaded in Nanospheres. The result had showed concentration of anticancer drug loaded in Nanospheres is directly proportional to the drug payload capacity until saturation point. The in vitro release of DOX is zero order kinetic. This shows that the release is independent of the concentration of drug loaded in nanospheres**[34].**

V Ravi, M. Pramod Kumar *et al.* had work on Novel colon Targeted Drug Delivery System Using Natural Polymers. A novel colon targeted tablet formulation was developed using pectin as carrier and Diltiazen HCL and Indomethacin as model drugs. The tablets were coated with inulin followed by shellac and were evaluated for average weight, hardness and coat thickness. In vitro released studies for prepared tablets were carried out for 2hrs in PH 1.2 HCL buffer, 3hrs in PH 7.4 phosphate buffer and 6hrs in simulated colonic fluid. The drug released was monitored using UV spectroscopy. In vitro studies revealed that the tablets coated with inulin and shellac have limited the drug released in stomach and small intestine and released maximum amount of drug in colonic environment**[35].**

Table No. 1: Current Research Work on Targeted Drug Delivery System

S.No	Active ingredient	Other ingredient	Method employed	Effect	Reference
1.	Meloxicam	Ethyl cellulose	Tablet Compression and coating	Retarded the drug release upto 12hrs and shows max. of 98.69% drug release	**[34]**
2.	Paracetamol	Dextrin, Polysaccharide	Wet granulation	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.	**[35]**
3.	Variable	HPMC and Ethyl cellulose	Tablet compression and enteric coating	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.	**[36]**
4.	Doxorubicin hydrochloride	Chitosan	HPLC	*In-vitro* release of doxorubicin is of zero order kinetic. This shows that release is independent of the concentration of drug loaded in the nanospheres	**[38]**
5.	Diltiazen HCL and indomethacin	Polysaccharide, inulin and shellac	Tablet compression and coating	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 in colonic environment.	**[39]**

6. 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 diseases. 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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Source of support: Nil, Conflict of interest: None Declared