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UPDATE ON NOVEL TARGETED DRUG DELIVERY SYSTEMS

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ABSTRACT

Novel methods of drug delivery have revolutionized the field of therapeutics. The technique of increasing the concentration of the medication in an affected/specific area of interest as compared to rest of the body by specialized way of drug delivery is termed as targeted drug delivery. This is beneficial to improvise the efficacy of medication as well as to reduce its individual dose requirement and the side effects. Targeted delivery of drugs, as the name suggests, enables the drug molecule to reach preferably to the desired tissue. Now a days in the pharmaceutical world, the research related to development of targeted drug delivery system is highly preferred and encouraged. A semiconductor nanostructure called quantum dot has made its significance in optics world due to its theoretically high quantum yield. Transdermal devices allow the drugs to be efficiently delivered across the skin barrier. Molecules irrespective of their sizes have successfully been delivered inside Folate Receptor-positive cells and tissue. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics.

KEYWORDS: targeted drug delivery, quantum dot, folate receptor, transdermal.

INTRODUCTION

Development of new drug molecule is cumbersome, expensive and time consuming. Getting a new drug through discovery, clinical testing, development, and regulatory approval is currently estimated to take a heavy toll of well over $ 120 million and a waiting time of over a decade.[1-3] Hence improving safety-efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration, and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, targeted delivery are other very attractive methods and have been pursued vigorously. There are a number of factors stimulating interest in the development of the new devices, concepts, and techniques implemented for the novel drug delivery technology. Conventional drug administration though widely used, have many problems that may be potentially overcome by the above mentioned advancements. Moreover, these advances may appear attractive relative to the costs of new drug development.

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. The increasing number of peptide and protein drugs being investigated demands the development of dosage forms which exhibit site-specific release. It is very difficult for a drug molecule to reach its destination in the complex cellular network of an organism. Thus drug targeting, a novel technique of site-specific drug delivery has been explored, wherein a particular drug is delivered to receptors or organ or any other specific part of the body to which an exclusive delivery of that drug is desired. The drug's therapeutic index, as measured by its pharmacological response and safety, relies in its access to the candidate receptors, whilst minimizing its introduction to the non-target tissues. The desired differential distribution of drug targeting the specific tissue would spare the rest of the body, significantly reducing the overall toxicity while maintaining the therapeutic benefits. This is indeed very attractive as it discovers one of the most potential ways to improve the therapeutic index of drugs.[4,5] The current review deals with various targeted drug delivery approaches that have revolutionized the field of pharmaceutics and therapeutics.

Approaches in Targeted Drug Delivery

1. Gastro-retentive drug delivery system

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or

systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach[6], low density (floating) systems that causes buoyancy in gastric fluid[7, 8, 9], mucoadhesive systems that causes bioadhesion to stomach mucosa[10], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[11, 12], super-porous hydrogel systems[13], magnetic systems[14] etc. (figure 1)

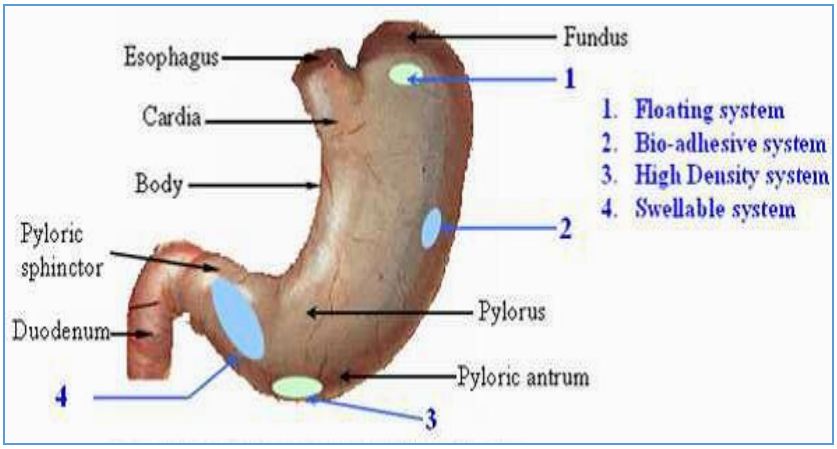

Figure 1. Various gastroretentive drug delivery approaches

Potential drug candidates for gastroretentive drug delivery systems

1) Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
2) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L DOPA, para-amino-benzoic acid (PABA), furosemide, riboflavin etc.
3) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4) Drugs that disturb normal colonic microbes e.g.antibiotics against Helicobacter pylori.
5) Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

Drugs those are unsuitable for Gastroretentive drug delivery Systems

1) Drugs that have very limited acid solubility e.g. phenytoin etc.
2) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3) Drugs intended for selective release in the colon e.g. 5-ASA

One of the most promising areas of research for gastroretentive drug delivery system, is eradication of Helicobacter pylori, which is now believed to be causative bacterium of chronic gastritis and peptic ulcers. Although, this microorganism is highly sensitive to many antibiotics, its complete eradication requires high concentration of antibiotics be maintained within gastric mucosa for prolonged time period.

Floating drug delivery system

Floating drug delivery system is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability.[15] This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine.[16] This have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system (figure 2). After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration.

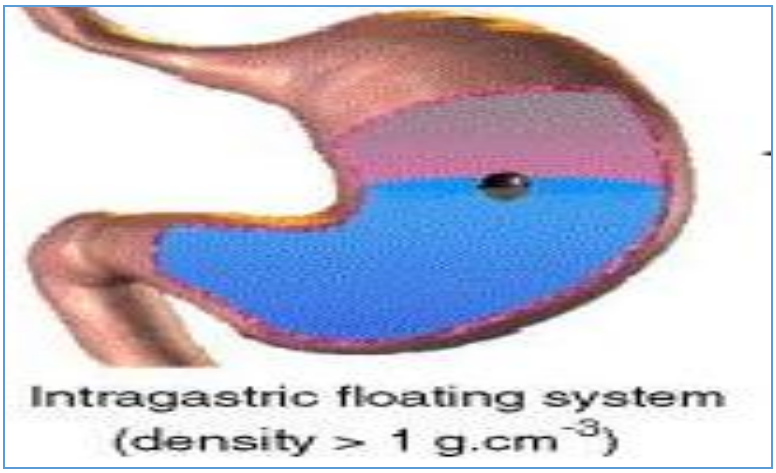

Figure 2. Floating drug delivery system in the stomach with its bulk density lesser than gastric fluids

The major requirements for floating drug delivery system are[17]

• It should release contents slowly to serve as a reservoir.

• It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).

• It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers)[18] or by the incorporation of low density materials (e.g. fatty materials or oils, or foam

powder).[7, 19, 20] These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler.[21] The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping.[16] Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery systems.

2. Quantum dots: Quantum dots are particularly significant for their optical applications due to theoretically high quantum yield.[4] It is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes, or excitons (bound pairs of conduction band electrons and valence band holes) in all three spatial directions (figure 3). The confinement can be due to the presence of an interface between different semiconductor materials (e.g. in core-shell nanocrystal systems), electrostatic potentials (generated by external electrodes, doping, strain, impurities), the presence of the semiconductor surface (e.g. semiconductor nanocrystal), or a combination of the above.

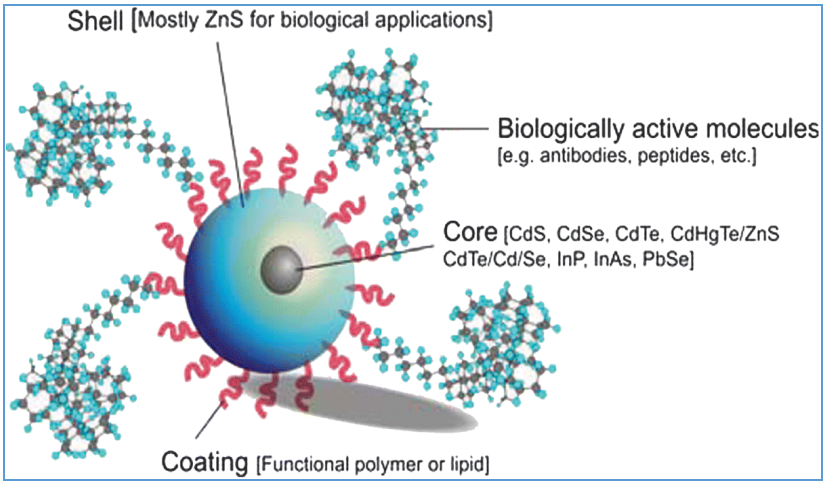

Figure 3. Quantum dot designed as per core-shell nano-crystal system with a functional polymer or lipid coating

Quantum dots can detect early DNA changes. These are tiny crystals which glow when they are stimulated by UV light. Latex beads filled with these crystals can be designed to bind to

the specific DNA sequences. Hence to detect cancer, these latex beads containing quantum dots which bind to the specific sequences of DNA associated with cancerous cells can be employed.[22] The ability to tune the size of quantum dots is advantageous for many applications and it is one of the most promising candidates for use in solid-state quantum computation and diagnosis, drug delivery, catalysis, filtration, tissue engineering and textiles technologies.

3. Transdermal Approach

Transdermal drug delivery system is topical administration of medicaments in the form of patches that deliver drugs at a predetermined and controlled rate either for targeted (cutaneous) or systemic effects. A transdermal drug delivery device, either of an active or a passive design, is a device which allows the pharmaceuticals to be delivered across the skin barrier. In theory, transdermal patches work very simply. A drug is concentrated in a relatively high strength within the patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Due to the patch-blood concentration gradient, the drug will keep diffusing into the blood for over a period of time, maintaining a constant concentration of drug in the plasma.[23] Bioadhesive liposomes bearing levonorgestrel as controlled drug delivery system has been studied,[24] where the vesicles were mostly unilamellar and some were multilamellar, with their drug release of zero order kinetics. Liposomal reservoir system bearing local anesthetic benzocaine suspension formulated into an ointment or a gel base was developed[25] for controlled and localized delivery via topical route. The systems delivered the drug at a controlled rate over 24 hours compared to plain ointment which had a rapidly decreased release rate.

4. Colon specific drug targeting

A novel mode of introducing peptide and protein drug molecules and drugs that are poorly absorbed from the upper gastrointestinal (GI) tract is by delivering the drugs into systemic circulation through colonic absorption.[26] Oral colon-specific drug delivery systems offer obvious advantages over parenteral administration. Colon targeting is naturally of value for the topical treatment of diseases of the colon such as Crohn's disease, ulcerative colitis and colorectal cancer. Sulfasalazine, ipsalazide, and olsalazine have been developed as colon-specific delivery systems for the treatment of inflammatory bowel disease (IBD). [27] Sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina

and arthritis. Colonic drug delivery systems have gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of candidates like proteins, peptides, oligonucleotides and vaccines.[28,29] The vast host intestinal flora and distinct enzymes present in the colon are being increasingly exploited to release drugs in the colon. Although the large intestine is a potential site for absorption of drugs, difficulties are encountered in the effective local delivery of drugs to the colon such as bypassing the stomach and small intestine which have differential pH conditions and long transit time during the passage of drug formulations from mouth to colon. The concept of using pH as a trigger to release a drug in the colon has been devised and is based on the pH conditions that vary continuously down the GI tract.[30] The pH changes is therapeutically exploited to develop formulations similar to enteric coating which consist of employing a polymer with an appropriate pH solubility profile. In the past, the primary approaches to obtain colon-specific delivery such as prodrugs, pH- and time-dependent systems, and microflora-activated systems achieved limited success. Recent developments in pharmaceutical technology include coating drugs with pH-sensitive and bacterial degradable polymers, embedding in bacterial degradable matrices and designing into prodrugs which have renewed hope to effectively target drugs to the colon [figure 4]. Polysaccharide and azo-polymer coating, which is refractory in the stomach and small intestine yet degraded by the colonic bacteria, have been used as carriers for colon-specific targeting.

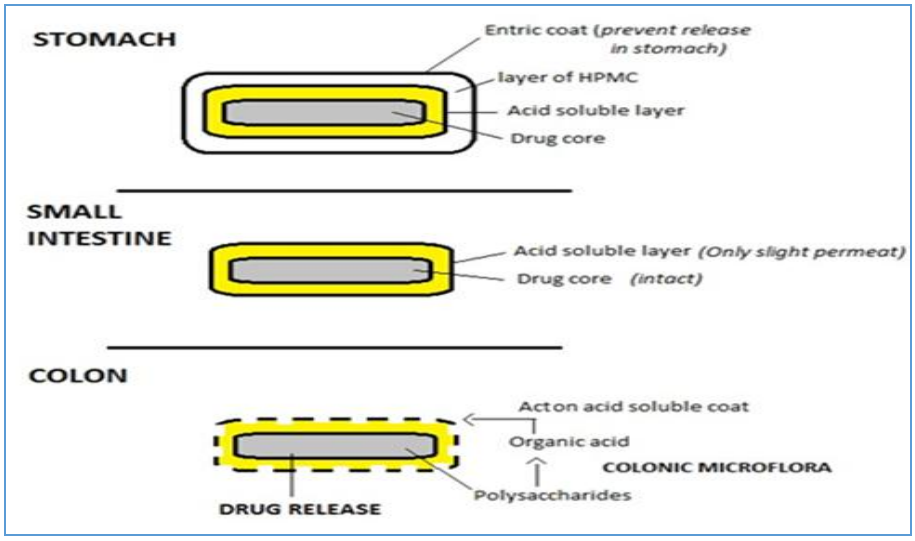

Figure 4. Colon specific drug delivery system consisting of an innermost drug core protected by outer pH-sensitive layer followed by biodegradable polymeric layer (HPMC – Hydroxy-propyl-methyl cellulose) and polysaccharide coating to ensure a site-specific drug release

Finally, the availability of optimal preclinical and clinical techniques accelerated the development and evaluation of colon-specific drug delivery systems for clinical use. Continuous efforts have been focused on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accommodate different therapeutic needs.[31] Four out all of the systems developed most recently for colon-specific delivery namely Pressure-controlled Colon Delivery Capsules (PCDCs), CODES, colonic drug delivery system based on pectin and galactomannan coating, and Azo hydrogels, are unique in terms of achieving *in vivo* site specificity, design rationale, and feasibility of the manufacturing process.

5. Brain targeted drug delivery system

The delivery of drugs to central nervous system (CNS) is a challenge in the treatment of neurological disorders. Though drugs can be administered directly into the CNS or administered systematically (e.g. by intravenous injection) for targeted action in the CNS, the major challenge to central drug delivery is the blood-brain barrier (BBB) which limits the access of drugs to the brain substance.

Strategies for drug delivery to the brain

Several drugs do not have adequate physiochemical characteristics such as high lipid solubility, low molecular size and positive charge which are essential to succeed in traversing BBB.[21] Advances in understanding the cell biology of the BBB have opened new avenues and possibilities for improved drug delivery to 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.

a. Disruption of the BBB

Various pharmacological agents have been used to open the BBB and direct invasive methods which can introduce therapeutic agents into the brain substance. One such approach was to break down the barrier momentarily by injecting mannitol solution into arteries in the neck. The resultant high osmolarity in brain capillaries takes up water out of the endothelial cells, shrinking them and opening tight junctions. The effect lasts for 20-30 minute, during which the drugs diffuse freely, that would not normally cross BBB. This method permits delivery of chemotherapeutic agents in patients with cerebral lymphoma, malignant glioma and disseminated CNS germ cell tumors. Physiological stress, transient increase in

intracranial tension, and undesirable delivery of anticancer agents to normal brain tissues are the side-effects of this approach in humans.[32]

b. Intra-ventricular/ Intra-thecal drug delivery

Other strategies for drug delivery to the brain involve bypassing the BBB like drug injections made directly into the subarachnoid space via intrathecal injections e.g. liposomal injection of amphotericin for systemic candidiasis and cryptococcosis is a very feasible strategy. Also using a plastic reservoir which is implanted subcutaneously in the scalp and connected to the ventricles within the brain by an outlet catheter is suitable for those ventricles lying in close proximity to scalp.[33]

c. Nanoparticulate systems for brain delivery of drugs

It is important to consider not only the net delivery of the agent to the CNS, but also its ability to access the relevant target site within the CNS. One of the possibilities to deliver drugs to the relevant site within the brain is by employment of nanoparticles. The main goals of nanotechnology are to improve drug stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers.[34] Nowadays nanotechnology is proved to be more efficient for enhancing site-specific drug delivery to brain. Nanoparticles are polymeric particles made of natural or artificial polymers ranging in size between about 10 and 1000 nm (1 mm). Drugs may be bound inform of a solid solution or dispersion or be adsorbed to the surface or chemically attached. Poly (butylcyanoacrylate) nanoparticles represent the only nanoparticles that were so far successfully used for the in vivo delivery of drugs to the brain. The first drug that was de-livered to the brain using nanoparticles was the hexapeptidedalargin (Tyr-D-Ala- Gly- Phe-Leu-Arg), a Leu-enkephalin analogue with opioid activity.[34] Nanoparticles and nanoformulations have already been applied as drug delivery systems with great success; and nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumors therapy, gene therapy, and AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, and vaccines and as vesicles to pass the blood-brain barrier.

6. Intra-nasal drug delivery

As nasally delivered drugs first reach the respiratory epithelium, compounds get absorbed into the systemic circulation by trans cellular and para cellular passive modes, carrier-mediated transport, and transcytosis. Whereas a nasal drug formulation delivered deep and

high enough into the nasal cavity, the olfactory mucosa may be accessed and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur.[33]

7. Lung-specific drug delivery

Inhalation therapy enables the direct application of a drug within the lungs. Pulmonary drug delivery offers several advantages in the treatment of respiratory diseases over other routes of administration. The intravenous application of short acting (SA) vasodilators has been the therapy of choice for patients with PAH over the past decade. Locally deposited drug-facilitated targeted treatment of pulmonary arterial hypertension (PAH) developed lately has enabled to overcome the earlier need for high dose exposures by other routes of administration for this condition. The relative severity of side effects with SA-vasodilators led to the development of new prostacyclin analogues and alternative routes of administration. One such analogue, iloprost (Ventavis®), is a FDA approved therapeutic agent for treatment of PAH. Inhalation of this compound is an attractive concept for minimizing the side effects owing to its pulmonary selectivity. Unfortunately, the short half-life of iloprost requires frequent inhalation maneuvers, ranging up to 9 times a day. Therefore, an aerosolizable controlled release formulation would improve a patient's convenience and compliance.[36] Controlled drug delivery systems have become increasingly attractive options for inhalation therapies. A large number of carrier systems have been developed and investigated as potential controlled drug delivery formulations to the lung, including drug loaded lipid and polymer based particles. The use of colloidal carrier systems for pulmonary drug delivery is an emerging field of interest in nanomedicine. Upon introduction of the metered dose inhaler (MDI), medical treatment of lung diseases changed significantly. Since that time, MDIs have become the most effective means of controlling symptoms of lung diseases such as asthma and chronic obstructive pulmonary disorder (COPD). They are well accepted and highly utilized by patients across the globe today. As a way forward, the effectiveness, ease of use, relatively low cost of aerosol preparations in combination with modifications in delivery technology and formulation sciences, will likely increase the spectrum of treatable diseases. Liposomes are believed to alleviate the major problem encountered with conventional aerosol delivery (i.e. rapid absorption of most drugs from the lung, demanding frequent dosing, e.g. of bronchodilators and corticosteroids) due to their ability to: (i) serve as a solubilization matrix for poorly soluble agents; (ii) act as a pulmonary sustained release reservoir; and (iii) facilitate intracellular delivery.

8. Cancer therapy related targeted drug delivery strategies

a. Drug-conjugates based targeting

Folate targeting is one of the drug-conjugates based genetically engineered novel technology for drug delivery.[4,5] It involves the attachment of the vitamin, folate (folic acid), to a molecule/drug to form a "folate conjugate". Folic acid displays high affinity for the folate receptor (FR) protein, a glycosylphosphatidylinositol-protein that captures its ligands from the extracellular milieu and transports them inside the cell via a non-destructive, recycling endosomal pathway. Based on inherent high affinity of folate for the folate receptor (FR) protein, a recognized tumor antigen/biomarker which is commonly expressed on the surface of many human cancers such as non-mucinous ovarian cancer, uterine adenocarcinoma, pediatric ependymal brain tumors, mesothelioma, and breast, colon, renal and lung tumors, the folate-drug conjugates bind tightly to the FR protein and undergo endocytosis-mediated intra-cellular uptake. Diagnostic and therapeutic modalities which exploit the FR protein's functions are being developed for cancer therapy. Molecules as diverse as small radiodiagnostic imaging agents to large genetic plasmids have successfully been delivered inside FR-positive cells.

b. Liposomal and ligand based drug targeting in infections and cancer therapy

Liposomes are vesicular concentric structures, range in size from a nanometer to several micrometers, containing a phospholipid bilayer and are biocompatible, biodegradable and non-immunogenic. One end of each molecule is water soluble, while the opposite end is water insoluble. Water-soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into the phospholipid layer. In some cases liposomes attach to cellular membranes and appear to fuse with them, releasing their or drugs into the cell. In the case of phagocytic cells, the liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes, and the medication is released. They were first produced in England in 1961 by Alec D. Bangham. Since then, 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 & strong side effect of various drugs can be overcome by employing the concept of liposomes especially in various diseases like infections, cancer etc. Liposomes are used for delivery of drugs, vaccines, and genes for a variety of disorders.[37] Liposomal delivery systems are still largely experimental; the precise mechanisms of their action in the body are under study, as are ways in which to

target them to specific diseased tissues.[23] Liposomal amphotericin preparation and investigated it in patients with systemic fungal infections and leishmaniasis. It was found to be safe producing significantly less adverse effects compared to plain amphotericin in patients with systemic fungal infection, did not produce nephrotoxicity and could be given to patients with renal damage. Immunoliposomes, in which mAb fragments are conjugated to liposomes, represent a strategy for molecularly targeted drug delivery.[37] The immunoliposomal approach offers a number of theoretical advantages as compared with other antibody-based strategies. Anti-HER2 immunoliposomes have been developed with either Fab' or scFv fragments linked to long-circulating liposomes [figure 5]. Anti-HER2 immunoliposomes loaded with doxorubicin displayed potent and selective anticancer activity against HER2-overexpressing tumors, including significantly superior efficacy versus all other treatments tested (free doxorubicin, liposomal doxorubicin, free mAb [trastuzumab], and combinations of transtuzumab plus doxorubicin or liposomal doxorubicin).[31] Anti-HER2 immunoliposomes are currently undergoing scale up for clinical studies.[38] Anti-HER2 immunoliposome delivery of doxorubicin may circumvent the prohibitive cardiotoxicity associated with combined trastuzumab plus doxorubicin treatment.

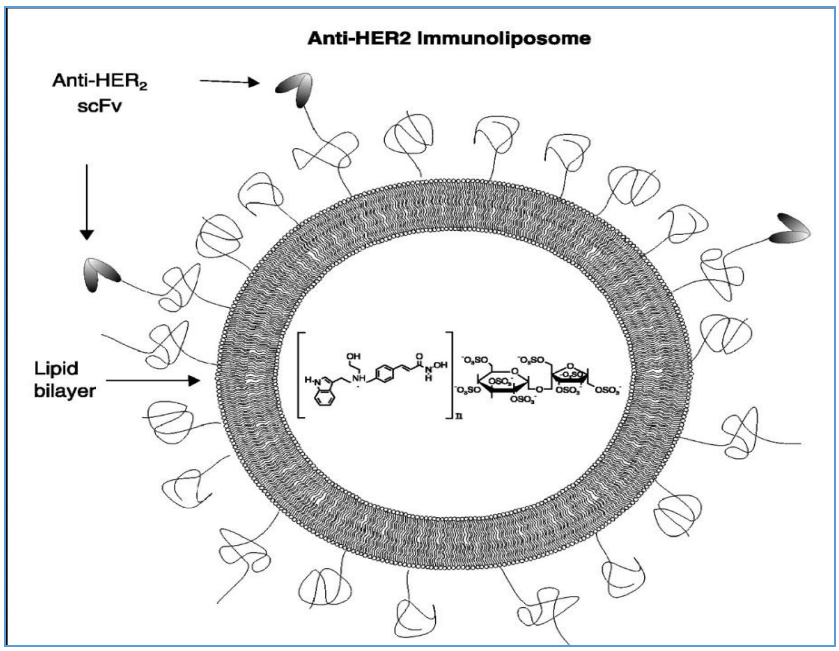

Figure 5. Drug loaded liposome linked to anti-HER2 scFv fragments

Immunoliposomes exploit the exponentially greater capacity of drug-loaded liposomes (up to 104 drugs per liposome). They also appear to be non-immunogenic and capable of long circulation even with repeated administration. [38,39]

Antibody-based targeting is also being developed in conjunction with polymer systems. Similarly, ligand-based targeting using hormones, vitamins (e.g., folate), growth factors, peptides or other specific ligands is being pursued in conjunction with both liposomes and polymers.

c. Nano technology

Nanoparticles provide massive advantages regarding drug targeting, delivery and release, and with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. The nanotechnology includes: Coated nanoparticles, Pegylated nanoparticles, Solid Lipid nanoparticles (SLN) and Nanogels. This technology has been devised for detection and treatment of HPV, HIV/AIDS, fungal infections, diabetes, early stages of cancer as well their metastases.[22] The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.[40,41]

CONCLUSION

Targeted drug delivery systems are being designed and developed enthusiastically in many laboratories in India. These are investigated *in vitro* for the drug release pattern and in some cases *in vivo* in animals for pharmacokinetics but less frequently for pharmacodynamics and efficacy. Based on the literature surveyed, it is evident that the above discussed novel targeted drug delivery systems offer significant advantages over conventional drug delivery systems. The inherent advantage of this technique has been the reduction in dose & side effect of the drug. After going through vast number of studies in major databases, it may be concluded that overall the science of site-specific or targeted delivery of drugs has become progressive; though there is a paucity of data on clinical studies and utility of targeted drug delivery systems in patients. Hence experience of the manifestations of these drug delivery strategies in clinical setting would be possible in real time in near future, provided that the clinical pharmacologists are actively involved in investigating the PK/PD properties, safety and efficacy of these drug targeting systems in clinical trials.

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