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An Imperative Note on Novel Drug Delivery Systems

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Abstract

A new era of science and technology has evolved in pharmaceutical research focussed at development of different novel drug delivery systems. The evolution of an existing drug from its traditional form to a novel delivery system may considerably improve its performance in aspects of efficacy, safety and patient compliance. So the method of administrating a drug can also have significant effect in its efficacy. In recent years the considerable advances in drug delivery systems have enabled more effective routes of administration. This review highlights the different novel drug delivery system, drug carriers and their potential to resolve the current challenges faced by biotechnology and pharmaceutical Industries.

Keywords: Nanoparticles; Carriers; Drug delivery; Hydrogels

Introduction

Most of the pharmaceutical companies for their industrial existence have primarily consisted of fast reacting and simple chemical compounds that are taken in different forms such as solid pills, injections, paste, ointments etc., [1] but during the past three decades a new era of science and technology has evolved in pharmaceutical research focussed at development of different novel drug delivery systems [2,3]. The process of delivering a pharmaceutical compound to achieve a significant therapeutic effect in an efficient manner can be defined as novel drug delivery system [4]. The evolution of an existing drug from its traditional form to a novel delivery system may considerably improve its performance in aspects of efficacy, safety and patient compliance [5].

Drug characteristics differ dramatically depending upon its size, chemical composition, hydrophilicity and potency to identify the molecules, even though they are aimed to treat the same symptoms. The result of drug activity is nothing but the molecular interactions in certain cells [1,6-8]. Some drugs possess an accomplished concentration range within where the maximum benefit is derived and the concentration levels above or below this range can lead to toxic effect or no therapeutic effect produced at all [4,9-11]. So the method of administrating a drug can also have significant effect in its efficacy. Therefore it is very necessary for the drug to *deliver at the right place, at the right concentration for the right period of time* [1,12]. These aspects suggested a growing need for multidisciplinary approaches to deliver the drugs to their target tissues. The new strategies like controlling the pharmacokinetics, immunogenicity, bio recognition, pharmacodynamics, non-specific activity and efficacy of drugs were generated which were based on the interdisciplinary approaches like integration of pharmaceutics, polymer science, molecular biology and bio conjugate chemistry. In order to increase the therapeutic effects of drugs, simultaneously to minimize their side effects different drug delivery systems were designed [4,13-15].

Novel Drug Delivery Systems

In the 21st century a scenario raised where the pharmaceutical companies caught between the reducing prices of existing drugs and increasing cost for successful drug discovery and its development. The average cost and time for a new drug discovery and its development are much higher (approximately \$500 million and 10–12 years) than compared to development of novel drug delivery systems (NDDS) (\$20–50 million and 3–4 years). Due to patent expiry with subsequent entry of generic competition and limited formularies the entire pharmaceutical companies approximately (350 drug delivery companies and 1000 medical device companies) concentrated on developing and designing new drug delivery systems [5,16-17]. The significant improvements in clinical efficacy, patient compliance, extension of product life through control release formulations as well as economic considerations such as reduced frequency and cost of the administering the drug are driving the demand for high performance, versatility and controlled-release systems [18-19]. This made the novel drug delivery systems as one of the fastest growing segment in the pharmaceutical companies [20]. The global market for advanced drug delivery systems was more than \$75 billion in 2005 and mounted to\$139 billion in 2009.It was estimated to increase \$196.4 billion for a compound annual growth rate (CAGR) of 7.2% in the 5-year period. Targeted drug delivery which reached \$50.9 billion in 2009 and is expected to \$80.2 billion in 2014 for a CAGR of 9.5%., whereas sustained release products reached \$36.1 billion in 2009 and expected to \$45.8 billion in 2014 for a CAGR of 4.9%. There is a rapid development within this market preferably in the area of alternatives to injected macromolecules, peptide drugs, genetically engineered proteins and other biological therapeutics [21,22].

Site Directed Drug Carrying Vehicles / Drug Carriers

In recent years the considerable advances in drug delivery systems have enabled more effective routes of administration. To deliver the drugs to their specific target tissues, drug carriers (the substances which play crucial role in significant delivery and effectiveness of drugs) are used [23]. A wide range of organic systems like liposomes, micelles, vesicles, dendritic polymers, nanoparticles, liquid crystals, microspheres, Implants etc., are used which have significant advantages and few limitations [4,20,24-26] (Figure 1).
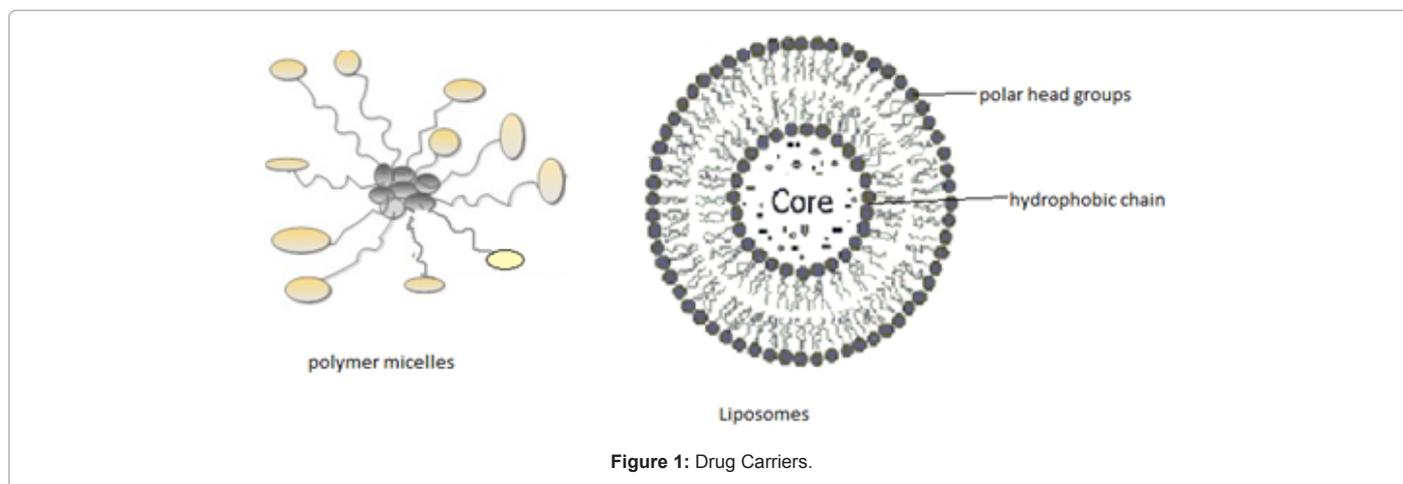
Figure 1: Drug Carriers.

Liposomes: Liposomes are colloidal, biodegradable and spherical vesicles whose size varies from low micrometres range to tens of micrometres. They consist of a bilayer membrane entrapping an aqueous core. The membranes of liposomes are usually derived from phospholipids with mixed lipid chains and head groups or pure synthetic lipids with defined acyl chains and head groups. The drugs can be either entrapped at bilayer interface, in aqueous volume or in phospholipids bilayer [27]. Liposomes which are formed from phospholipids are mostly used to modify the pharmacokinetic profile of drugs, enzymes etc. This particular drug carrier is very advantageous in enhancing the therapeutic effect of anti-cancer agents through increasing drug concentration levels in tumour cells and decreasing the exposure to normal cells [28-29]. Liposomes play an important role in solubility enhancement, bioavailability, targeting sites and prolonged release of drug [30,31].

Microspheres: There are various drug delivery systems to deliver a drug to target site in a sustained controlled release fashion. One of the methods is using microspheres as drug carriers. These are produced from solid polymer matrices for intravenous and intra-arterial targeted drug delivery systems. Microspheres are spherical in shape and size varies from 1-300μm. There are different kinds of polymers which are used for fabrication of microspheres are albumin, starch, gelatin, dextran, polypropylene etc. The administration of drug mediated by these microspheres is controlled by degradation and dissolution of matrix. The drug delivery is also affected by polymer concentration and type, size of matrix. There are various types of methods to produce these micro particulate systems such as evaporation technique, cross linking and high pressure homogenization technique. The specific advantages of these micro particulate systems are they can be injected or ingested and also they produce sustained release action and site specific delivery [21,32,33].

Nano-particles: Nanoparticles are sub-micron sized particles having size of 10 to 200 nm are in the solid state either in amorphous or crystalline form [34-37]. The nanoparticles are widely used as carriers due to their stability and long term storage. They can encapsulate or adsorb the drug and help in protecting it from chemical and enzymatic degradation [38-42]. Nanoparticles include nanocapsules and nanospheres. The nanocapsules are vesicular systems in which drug is restrained or enclosed in a cavity surrounded by polymeric membrane, where as the drug is uniformly spread in the nanosphere matrix systems. The nanoparticles are very efficient in delivering both hydrophilic and hydrophobic drugs [43-48]. In the recent years the biodegradable polymeric nanoparticles have gained a significant attention as potential drug carrier in the applications of targeted drug delivery system, controlled release of drugs and as an efficient carrier of DNA in gene therapy and also capable to administrate proteins, peptides and genes through pre-oral route [4,30,49-56].

Polymeric micelle formulations: The polymeric micelles consists of good pharmaceutical properties and are easily controllable. They are the excellent drug carriers which contains inner hydrophobic core and outer hydrophilic corona [57-60]. The inner core is capable of solubilizing lipohilic substances and it is stabilized by hydrophilic polymer chains which are towards aqeous environment. The outer corona acts as a interface between inner core and aqueous environment [30,61]

Implants: Implants are the polymeric devices which are used for the sustained drug release or to target high drug concentrations to the surrounding area of target tissue. These are usually applied when chronic therapy is indicated in situations like chemical castration in prostate cancer treatment, in hormones replacement. The Implants are highly viscous liquids or semisolid formulations which are directly placed in the body fluids, injected or fabricated with biodegradable polymers. Duros®, Zoladex® are the Implants used for long term delivery of proteins [4,21,30].

Drug Delivery Technologies/ Administration Routes

The main aim of the drug delivery systems is to liberate the drug sat the right time in a right amount of concentration at a specified targeted site. The purpose of delivering drugs to patients in an efficient manner with fewer side effects encouraged pharmaceutical industries to develop various novel drug delivery technologies with enhanced site specificity, efficacy and profitability [5]. The various drug technologies include:

OCRS

Oral ingestion is a very traditional way of drug delivery system where effectively achieved local and systemic effects. The development of oral controlled release formulations is to be difficult challenge to the industries because of various gastrointestinal environments [62-63]. Among the numerous platform technologies the matrix type drug delivery system was interesting option. One of the new techniques developed in oral drug delivery is to make gastroretentive platforms

for long hours (8-24 hr) delivery of drugs [64]. This technology is beneficial for the drugs which are poorly absorbed in gastro intestinal tract. Oral delver of protein and peptide drugs is the most research activity performed. Emisphere technologies introduced the drug delivery through macromolecules where the carrier molecules are used to deliver the drugs. [5,21]

Pulmonary delivery system

Pulmonary delivery systems are primarily used for treatment of respiratory diseases. Recently this method is also used for administrating the drugs to systemic circulation by utilizing lung's natural capability to transfer molecules in to blood stream. This method is known as non-invasive which is used as alternative to painful injections. This delivery system provides an opportunity for enhanced and innovative delivery system, good bioavailability and greater patient's compliance. The inhale therapeutic systems are effected in various different ways like via metered dose inhaler systems (MDI's), aerosols, solutions (nebulizers) and dry powder inhaler systems (DPI's) [5,21]. In MDI's the drug is present in the form of solutions or suspension of fine particles in a pressurized liquefied propellant and drug is released through an orifice from metering valve. Recently the industries designed a technology to deliver peptides, proteins and large molecules in precise doses. The industries developed dry powder formulations that use glass stabilization technology, this extracts critical amount of water from proteins and helps to achieve glassy state. In this glassy state the proteins are grid locked and give long term storage, stability and sterility. Pulmospheres and pulmosols are also developed by companies through spray drying and supercritical fluid condensation respectively. Pulmospheres are hollow porous particles with high redispersibility, low density less than 0.1 gm/nil helps in 68% pulmonary targeting. The developed novel pulmonary delivery system includes Oralin (Generex), AIR (Alkermes) and AERx (Aradigm) [4,21]

Transdermal and Tropical delivery

The administration of drugs through skin i.e., via transdermal routes in to the systemic circulation at a predetermined rate developed a significant interest during the last two decades [65]. Human skin is wonderful selective and highly effective barrier to chemical permeation. Specifically stratum corneum plays a major role in diffusion of small water soluble non-electrolytes in to the systemic circulation without any barrier hindrance. The drug flux is also maximized through other potential pathways like hair follicular route with sebaceous glands and via sweat ducts. The amount of active ingredient required for transdermal delivery system is considerably less when compared to oral systems. To increase the transdermal permeability of drugs the prodrugs or penetration enhancers are used, for these different electrically assisted techniques like ultrasound, electroporation, magnetophoresis, iontophoresis, and photomechanical waves are used [66]. The stratum corneum can also be modified by following some chemical enhancers, hydration procedures and removing the tissue by using micro needles [67]. There are also some needle-free injection devices which are operated by compressed gas a system that drives liquid or powder at very high speed and makes it to penetrate through skin for intra dermal, subcutaneous or intramuscular administration. Intraject, Biojector and Medijector systems are used for administration of liquids while solids are administrated through PowderJect's technology. In this technology the dry powder formulations of small solid particles are forced in to the target tissue layers. The drug particles are accelerated with supersonic speed within a helium gas jet inside the device. Due to microscopic size of drug particles, they enter into

the cells without damaging the cell membranes. PowderJect is working on genetic vaccines in collaboration with GlaxoWellcome, and their hepatitis B prophylactic DNA vaccine has successfully completed clinical trials. This delivery system enhances bio availability with fewer side effects and is an easy application [5,21,68].

Hydrogels as drug delivery systems

Hydrogels are three dimensional hydrophilic polymer networks which can absorb huge amounts of water and other biological fluids. The networks consist of homopolymers or copolymers and they are insoluble because of physical crosslinks like crystallites or entanglements and chemical cross links such as junctions and tie points. Hydrogels possess thermodynamic compatibility with water due to which they swell in aqueous media. They acts as carriers in swellable or swelling-controlled release devices or regulates drug release in controlled release systems. Hydrogels are a stimuli-sensitive and enviro-intelligent system that controls the drug release according to the temperature, pH, electrical field, ionic strength and specific analyte concentrations. Hydrogels as delivery systems can be promising when they combined with the molecular imprinting technology [10,30].

The molecular imprinting technique contains huge potential of producing satisfactory drug dosage forms. It involves a pre-polymerization complex formation between template and functional monomers or oligomers by covalent or non-covalent chemistry. Once the complex formed polymerization occurs with the help of cross linking monomers and appropriate solvent which controls the overall morphology and structure. When the template is removed the result produced is hetero polymer matrix with specific recognition elements for template molecule. The MIP-based drug delivery systems possess a i) rate programmed drug deliver where the drug diffusion from the system follows a specific rate profile. ii) feedback-regulated drug delivery where the concentration of a triggering agent regulated the drug release. Iii) activation- modulated drug delivery where the drug release is controlled by physical, chemical or biochemical processes. It can be foreseen that in the next coming years a considerable change evolves in this drug delivery system [4].

Colon specific delivery

Colon directed delivery is highly suitable for treatment of various bowel diseases like ulcerativecolitis, Crohn's disease, amebiosis, and colonic cancer. I n the past few years' considerable interest on colon targeting drugs because of their reduced proteolytic activity in the colon which is very much advantageous for the drugs like peptides and proteins, that are enzymatically degraded in the small intestine [69]. There are many colon specific dosage forms were developed in past few years including hydrogel matrix, pro drugs and coated dosage forms. These coated dosage forms are mainly based on the two factors, pH-controlled release coatings and time controlled release coatings. The pH- controlled release coatings are generally insoluble at pH of the stomach and dissolves in lumen of the small intestine. The thickness of drug coating is increased and a pH-time controlled release system of polymer dissolution helps in achieving the drug release in colon. In time-controlled release coating the lag time depends upon the thickness of drug coating there by the drug release can be achieved by changes in osmotic pressure or disrupting the drug coating by swelling the core [5,10,70].

Taste masking

Oral drugs often reveal a bitter and unpleasant taste. In order to

improve the flavour in these drugs various methods for taste masking has developed. They are like particle coating, compounding the drugs with cyclodextrins or resins, use of microcapsules, etc [71-73]. In chewable tablets a mild drug complex is spread on a gum base where the drug is released from the dosage form by physical disruption through chewing and chemical disruption from interaction between the drug material and oral cavity. Drug coating technique acts as a physical barrier between the drug and the taste receptors present in mouth. [5]

Vaginal or rectal drug delivery

The vagina has been detected as a highly suitable site for local and systemic drug delivery. This route has many advantages like reduction in hepatic and gastro intestinal side effects, avoid of gut metabolism and local targeting of drugs to reproductive organs. The formulations and vaginal administered agents are mainly developed for dual prophylaxis that is for both contraception and protection against infections, AIDS and other sexually transmitted diseases [5]

Future Directions and Conclusions

As discussed in this article there are numerous drug delivery technologies such as oral, pulmonary, Transdermal, colon, vaginal, etc to deliver the drugs in an efficient manner. Recently biotechnological companies producing many more protein and peptide based drugs by sequencing the human genome. It is estimated in next 10 to 20 years more than half of the drugs are replaced by protein based drugs especially 80%of them are antibodies. The drugs like proteins, peptides, carbohydrates, oligo-nucleotides and nucleic acids in the form of DNA usually cannot be delivered through conventional routes because of their large molecular size, rapid degrading ability, and limited ability to cross cell membranes [4,5]. For such drugs injections may be only route, which presents the industries a new challenge for developing new drug administration routes. Gene therapy is also one of the exciting sector in biotech companies going to be involved in drug delivery technologies. This therapy includes genetically engineered proteins. So far the industries have come in a long way and wish to continue the growth at impressive rate in drug delivery systems. Tomorrow's drugs definitely will be more challenging in terms of the development of delivery systems, and pharmaceutical scientists will have to be ready for a difficult task ahead [10,30]

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