Review Article

Nanoparticles as carrier for oral drug delivery system

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ABSTRACT

Due to the non-targeted drug delivery systems, various types of side effects are observed, in case of nanoparticle (NP), it acts as boom form the management of various diseases, with negligible side effects with maximum bioavailability of the drugs. However, many biological therapeutics that have poor solubility, poor permeability, or poor stability in the gastrointestinal environment include poor oral bioavailability and are consequently rarely used for oral drug delivery. Oral route is most frequent used method for drug delivery. In this paper, we have tried to cover the various nanocarriers for oral drug delivery system also brief about the challenge in drug delivery system such as dendrimers, liposomes, solid lipid nanocarriers, micelles, and polymeric NPs. These nanocarriers have been tailored as per the need of the disease for obtaining cellular level such as pH and presence of enzymes. The advantages of novel drug delivery carrier system over conventional drugs have been discussed, last discussed about Food and Drug Administration approved medicine as nanocarrier.

Keywords: Oral drug delivery system, novel drug delivery system, control release, sustained release

INTRODUCTION

Oral ingestion is the preferred route for administration of therapeutic agents, providing a convenient method of effectively achieving both local and systemic effects. Routes of drug administration that can be utilized to achieve systemic delivery of a drug include parental, oral, buccal, transdermal, nasal, and pulmonary. Patients are usually accustomed to orally delivered drugs and find the method non-invasive. Today, it is estimated that around 80% of all medications used utilize the oral route, in which tablet, capsule, and granules continue to remain the dosage form of first choice.[1] Oral dosage forms represent the vast majority of the drug delivery market because of the safety, efficacy, economic, and consumer compliance advantages; they possess over alternative routes of delivery. Oral drug delivery is the most common, convenient, and extensively used route of administration as it offers advantages such as painless administration, no assistance, and patient compliance as compared to other routes such as intramuscular, intravenous, and pulmonary.

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However, several compounds are unsuccessful and fail in research and development due to their low absorption and low bioavailability on oral administration.[2] Most of these drugs possess some significant drawbacks such as low bioavailability, short half-life, low permeability, adverse side effects, and first pass metabolism, irregular absorption, and degradation by gastrointestinal enzymes.

CHALLENGES IN ORAL DRUG DELIVERY SYSTEM

Although the oral drug delivery is effective for drugs with high aqueous solubility and epithelial permeability, efficient oral administration of poorly water-soluble drug is a challenge. At present, most of the new chemical entities are lipophilic and consequently have poor aqueous solubility.[3] On the basis of biopharmaceutical classification system (BCS), a number of new therapeutic entities are characterized under BCS Class II (low solubility and high permeability) or BCS Class IV (low solubility and low permeability). Besides, the oral bioavailability of certain drugs is also affected by their poor gastrointestinal permeability. To achieve effective therapeutic action, these drugs have to be given at a high dose. Moreover, chemical land enzymatic barriers presented by the gastrointestinal tract (GIT) also affect

oral administration of drugs. The change in GIT pH and presence of variety of enzymes significantly affects the oral bioavailability of drugs such as antihypertensive, antibiotics, and antihyperlipidemic agents. Furthermore, drugs with high first-pass metabolism such as repaglinide, β-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors also have low oral bioavailability. These drugs also present challenge in formulation development for oral administration.[4]

NOVEL DRUG DELIVERY SYSTEMS (NDDSS)

In the NDDSs, there are various novel carriers which have advantage over conventional dosage forms. Conventional dosage forms show high dose and low availability, instability, first-pass effect, plasma drug level fluctuations, and rapid release of the drug.[5] NDDS is one of the important tools expanding drug markets in pharmaceutical industry. NDDS can minimize problems by enhancing efficacy, safety, patient compliance, and product shelf life.[6] NDDSs are the new system recent advances in the understanding of pharmacokinetic and pharmacodynamic behavior of drug which have offered a more rational approach to the development of optimal drug delivery system. The NDDSs are carriers which maintain the drug concentration in therapeutic range for longer period of time. There are several advantages of NDDSs over conventional drug delivery. There are several advantages of NDDSs over conventional drug delivery.[7]

- Optimum therapeutic drug concentration in the blood or in tissue may be maintained over a prolonged period of time
- Pre-determined release rates of extended period of time may be achieved
- Duration for short half-life drug may be increased
- By targeting the site of action, side effects may be eliminated
- Frequent dosing and wastage of the drug may be reduced or excluded
- Better patient compliance may be ensured.

Various drug delivery systems have been developed and some of them under development with an aim to minimize drug degradation or loss, to prevent harmful side effects, and to improve drug bioavailability and also to favor and facilitate the accumulation of the drug in the required biological site. There is number of novel carries which have been established and documented to be useful for controlled and targeted drug delivery, as shown in Table 1. Various novel carriers are liposomes, nanosomes, microparticles, nanoemulsions, nanostructured lipid carriers, etc.

ORAL DRUG DELIVERY THROUGH NANOCARRIERS

Before the orally applied drug is able to reach its target, in most instances, it needs to overcome multiple compartments of the human body, which is challenging for a broad spectrum of pharmaceuticals, especially for protein- or peptide-based ones. In general, the first major challenge for the drug after ingestion is surviving the harsh acidic pH value in the stomach. Once the drug passes the stomach and enters the small intestine through the duodenum, it faces the major enzymatic digestion machinery of the human body. Oligosaccharides and maltose are degraded into glucose, fructose, galactose, and mannose through sucrose, maltase, and lactase. Lipids are cleaved into glycerol and fatty acids through the pancreatic triacylglycerol lipase and carboxyl ester lipase. Peptides are digested into amino acids through trypsin, chymotrypsin, carboxypeptidase, dipeptidase, and aminopeptidase. Upon surviving these two major locations of digestion in the human body, the drug needs to be absorbed primarily through enterocytes in the small intestine to reach the blood stream. Up to now, many pharmaceuticals exhibit a fairly low resorption percentage, resulting in a poor bioavailability.[8]

Table 1: List of various marketed formulations based on NDDSs

Drug	Indication	Company name
Doxorubicin	Kaposi's sarcoma	SEQUUs
Daunorubicin	Advanced Kaposi's sarcoma	NeXstar
Amphotericin B	Systemic fungal infection	NeXstar
Amphotericin B	Systemic fungal infection	SEQUUs
Leuprolide acetate	Prostate cancer	Takeda-Abbott
Triptorelin	LHRH agonist	Novartis

NDDSs: Novel drug delivery systems

One of the most promising approaches to overcome obstacles for oral drug delivery is the employment of nanomedicines. Nanomedicines can be defined as either nanoscale (<100 nm) imaging agents or therapeutic agents that lead to a systematic enhancement, protection, controlled release, precise targeting, or less cytotoxicity of a drug. During the past years, the range of different nanomedicines has been considerably expanded. At present, the most clinically relevant nanomedicines are liposomal, protein-based, polymeric/micelle-based, iron oxide, silica, and gold (Au) nanoparticle (NP) formulations.[9]

NP research is currently an area of intense scientific research, due to a wide variety of potential applications in biomedical, optical, and electronic fields. The word "Nano" is a Greek word synonymous to dwarf meaning extremely small. NPs are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. The properties of materials change as their size approaches the nanoscale. Nanomaterials often show unique and considerable change in physical, chemical, and biological properties compared to their macroscale counterparts. In general, metal NPs can be prepared and stabilized by physical and chemical methods; the chemical approach, such as chemical reduction, electrochemical techniques, and photochemical reduction, is most widely used.[10] A number of approaches are available for the synthesis of NPs, such as reduction of metal salt in aqueous phase,[11] microemulsion approach,[12] sol-gel technique,[13] hydrothermal technique,[14] and green approach[15]. Nanomedicine ranges from the medical applications of nanomaterials to nanoelectronic biosensors and even possible future applications of molecular nanotechnology.[16-18]. The commercial applications in the pharmaceutical industry may include advanced drug delivery systems, new therapies, and *in*

vivo imaging. Neuroelectronic interfaces and other nanoelectronics based sensors are another active goal of research. Two forms of nanomedicine that has already been tested in mice are using Au nanoshells to help diagnose and treat cancer and using liposomes as vaccine adjuvants and as vehicles for drug transport.[19] Similarly, drug detoxification is also another application for nanomedicine which has shown promising results in rats.[20] A benefit of using nanoscale materials for medical technologies is that smaller devices are less invasive and can possibly be implanted inside the body. These devices are faster and more sensitive than typical drug delivery. Drug delivery systems, lipid- or polymer-based NPs can be designed to improve the pharmacological and therapeutic properties of drugs.[21]

CLASSIFICATION OF NPS AS CARRIER

Dendrimers

These are nanosized particles with a core and a series of symmetrically shaped branches formed around the core. The branched structure offers many conjugation sites for drugs or targeting molecules. The large cavity of dendrimers allows incorporation and the controlled release of drugs. By altering the properties of this cavity, a significant advantage can be established for encapsulation of both hydrophilic and hydrophobic drugs.[22] Dendrimers consist of three main sections: A core, several interior layers composed of repeating units, and external functional groups. The branched interior layers are called "generations" and represent the repeating monomer unit of these macromolecules.[23]

Liposomes

Liposomes were first developed as small vesicles composed of one or more phospholipid layers, which have hydrophilic and hydrophobic functionality. Liposomes can be formed of single or multiple bilayers by changing the method of preparation. Based on the range of size, these single monolayers are labeled as small unilamellar vesicles or large unilamellar vesicles. They are labeled as multilamellar vesicles if more than 1 bilayer is present.[24] Liposomes have been studied to enhance drug solubility, improve the pharmacokinetic properties, decrease the toxic side effects, and improve the *in vitro* and *in vivo* anticancer activity.[25] Liposomal carriers have some drawbacks, including limited encapsulation of drugs and fast burst release from the matrix. However, solid lipid NPs (SLNs) provide an effective alternative due to their stability. Other vesicular structures include transferosomes, ethosomes, niosomes, and marinosomes which are used mainly for transdermal delivery.[26]

Solid lipid nanocarriers

SLNs, nanostructured lipid carriers, and lipid drug conjugates are novel types of carrier systems based on a solid lipid matrix for overcoming the limitations of liposomes.[27] The key characteristics of these carriers include a good physical stability, protection of incorporated drugs from degradation, controlled drug release, and good tolerability. SLNs can be prepared with three principles: A homogenous matrix, a drug-enriched shell, or a drug-enriched core. These are used to load and unload SLNs for the delivery of drugs. In addition, the preparation technique and the amount of surfactant used during preparation affect the release profile of the drug.[28]

Micelles

Micelles are perfect biocompatible NPs, mainly used as a carrier for water-insoluble drugs. For the preparation of micelles, generally, amphiphilic block copolymers are used.[29] Polymeric micelles are capable of reaching parts of the body that is not possible to reach using liposomes as carrier systems. Due to increased vascular permeability, the accumulation of drugs in tumor tissues was found to be greater than for other drug delivery systems.[30]

Polymeric NPs

Polymeric NPs are colloidal materials with a size range of 10–1000 nm in different structures. They can be produced using biologically compatible synthetic polymers or natural polymers. Polymeric NPs are biodegradable and biocompatible in nature. Polymeric NPs may have a core–shell structure, which can be modified by altering the hydrophobic and hydrophilic block composition of the polymer chains.[31]

Inorganic NPs

Inorganic nanomaterials are evolving systems for drug delivery[32] "Inorganic NPs" can be described as particles of metal oxide or metallic composition possessing at least one length scale in the nanometer range. These remarkable systems show unique and individual chemical, physical, and biological properties due to their smaller size and different shapes.[33] The application of inorganic NPs in drug delivery is generally the use of these systems for both therapeutic and diagnostic purposes. Au, silver (Ag), iron oxide, or mesoporous silica NPs and quantum dots are the commonly used inorganic NPs for this purpose. PEGylation of inorganic NPs enhances biocompatibility and biological half-life.[34]

Metal NPs

Metal NPs, such as Au, Ag, PD, Ni, Cu, and Fe, in colloidal form have been used for a number of purposes in human life. Iron oxide, Au, Ag, gadolinium, and nickel NPs have been developed to investigate the effect of these NPs for targeted cellular delivery.[35] Magnetic NPs have been gaining great interest in recent years because of their novel magnetic characteristics and ability to function at the cellular and molecular level of biological interactions. These unique properties make them ideal carriers for contrast agents for magnetic resonance imaging and drug delivery.[36] Iron (II) oxide NPs are metallic NPs with some superparamagnetic properties. They can be used for targeted drug delivery using an external magnetic field. These NPs can also enhance the permeability of NPs by the application of external magnetic fields.[37]

Ceramic NPs

These are generally used in dental and orthopedic applications for strengthening hard tissue implants. Ceramic NPs protect

the drugs and encapsulated molecules from degradation by external pH and temperature. Ceramic NPs, such as silica and alumina, have a great potential in drug delivery because of their biocompatibility, especially for the encapsulation of peptides and other biomolecules.[38]

Silica NPs

Silica NPs are the most important type for drug delivery because of their biocompatibility.[39] There are three main types of silica NPs: Solid, non-porous, and mesoporous. Due to their chemical and physical stability, well-defined hydrophilic surface, and ability to protect drugs from an active immune response, silica NPs have become an important system used for biological imaging and the delivery of drugs and genetic. Silica NPs have a superior biocompatibility. It has been mentioned that silica NPs are not toxic up to 100 mg ml concentration if the size of the particles is 100 nm.[40]

Carbon-based NPs

These nanomaterials are amorphous structures composed of sp2 hybridized carbon without crystalline components. The size of carbon nanomaterials may vary from 5 to 50 nm. This range is very close to proteins in cells and tissues, and this similarity helps the uptake of carbon-based NPs by cells. Furthermore, the surface of carbon-based nanomaterials can be modified by nucleic acids, peptides, and proteins.[41] Carbon-based NPs are further classified into:

Fullerenes

Fullerenes containing 60 carbon atoms with C5–C5 single bonds forming pentagons and C5–C6 double bonds forming hexagons. By hydrophilic chains or groups, fullerenes can carry drugs or genes. After derivatization, fullerenes can be targeted to mitochondria.[42]

Graphene

Graphene is a sheet of two-dimensional nanomaterial consisting of a single layer of sp2 hybridized carbon atoms, which has gained attention in the medical field due to its exceptional electrical, mechanical, and thermal properties.[43]

Carbon nanotubes

Carbon nanotubes were primarily discovered in cathode deposits following arc evaporation of graphite and isolated after pyrolysis of hydrocarbons, such as ethylene or acetylene over NPs of iron, cobalt, or other dispersed metals. Structurally, carbon nanotubes can be explained simply as rolled-up sheets of graphite. The formation of carbon nanotubes can be classified into two main types: Single-walled carbon nanotubes and multi-walled carbon nanotubes.[44]

Diamonds

Nanodiamonds are diamond-shaped particles with a particle size of less than 100 nm. Nanodiamonds can be either covalently or non-covalently modified to enhance the biocompatibility.[45]

List of FDA approved nanomedicine

Name	Material description	NP advantage	Indications	Year approved
Polymer NPs – synthetic polymer particles combined with drugs or biologics				
Adagen®/pegademase bovine (Sigma-Tau Pharmaceuticals)	PEGylated adenosine deaminase enzyme	Improve circulation time and decreased immunogenicity	Severe combined immunodeficiency disease (SCID)	1990
Copaxone®/Glatopa (Teva)	Random copolymer of L-glutamate, L-alanine, L-lysine, and L-tyrosine	Large amino acid-based polymer with controlled molecular weight and clearance characteristics	Multiple sclerosis (MS)	1996
Eligard®(Tolmar)	Leuprolide acetate and polymer (PLGH (poly (DL-Lactide-co-glycolide))	Controlled delivery of payload with longer circulation time	Prostate cancer	2002
Macugen®/Pegaptanib (Bausch & Lomb)	PEGylated anti-VEGF aptamer (vascular endothelial growth factor)	Improved stability of aptamer as a result of PEGylation	Macular degeneration, neovascular age-related	2004
Mircera®/Methoxy polyethylene glycol-epoetin beta (Hoffman-La Roche)	Chemically synthesized ESA (erythropoiesis-stimulating agent)	Improved stability of aptamer as a result of PEGylation	Anemia associated with chronic kidney disease	2007
Neulasta®/pegfilgrastim (Amgen)	PEGylated GCSF protein	Improved stability of protein through PEGylation	Neutropenia, chemotherapy induced	2002
Pegasys® (Genentech)	PEGylated IFN alpha-2a protein	Improved stability of protein through PEGylation	Hepatitis B; hepatitis C	2002
PegIntron® (Merck)	PEGylated IFN alpha-2b protein	Improved stability of protein through PEGylation	Hepatitis C	2001
Renagel®(sevelamer hydrochloride)/Renagel® (sevelamer carbonate) (Sanofi)	Poly(allylamine hydrochloride)	Increase circulation and therapeutic delivery	Chronic kidney disease	2000
Somavert®/pegvisomant (Pfizer)	PEGylated HGH receptor antagonist	Improved stability of protein through PEGylation	Acromegaly	2003
Oncaspar®/pegaspargase (Enzon Pharmaceuticals)	Polymer-protein conjugate (PEGylated L-asparaginase)	Improved stability of protein through PEGylation	Acute lymphoblastic leukemia	1994
Krystexxa®/pegloticase (Horizon)	Polymer-protein conjugate (PEGylated porcine-like uricase)	Improved stability of protein through PEGylation; introduction of unique mammalian protein	Chronic gout	2010
Plegridy®(Biogen)	Polymer-protein conjugate (PEGylated IFNbeta-1a)	Improved stability of protein through PEGylation	Multiple sclerosis	2014

List of FDA approved nanomedicine				
Name	**Material description**	**NP advantage**	**Indications**	**Year approved**
ADYNOVATE (Baxalta)	Polymer-protein conjugate (PEGylated factor VIII)	Improved stability of protein through PEGylation	Hemophilia	2015
Liposome formulations combined with drugs or biologics				
DaunoXome®(Galen)	Liposomal daunorubicin	Increased delivery to tumor site; lower systemic toxicity arising from side effects	Kaposi's sarcoma	1996
DepoCyt©(Sigma-Tau)	Liposomal cytarabine	Increased delivery to tumor site; lower systemic toxicity arising from side effects	Lymphomatous meningitis	1996
Marqibo®(Onco TCS)	Liposomal vincristine	Increased delivery to tumor site; lower systemic toxicity arising from side effects	Acute lymphoblastic leukemia	2012
Onivyde®(Merrimack)	Liposomal irinotecan	Increased delivery to tumor site; lower systemic toxicity arising from side effects	Pancreatic cancer	2015
AmBisome®(Gilead Sciences)	Liposomal amphotericin B	Reduced nephrotoxicity	Fungal/protozoal infections	1997
DepoDur®(Pacira Pharmaceuticals)	Liposomal morphine sulfate	Extended release	Analgesia (post-operative)	2004
Abelcet®(Sigma-Tau)	Liposomal amphotericin B lipid complex	Reduced toxicity	Fungal infections	1995
Curosurf®/Poractant alpha (Chiesi Farmaceutici)	Liposome-proteins SP-B and SP-C	Increased delivery for smaller volume; reduced toxicity	Pulmonary surfactant for respiratory distress syndrome	1999
Micellar NPs combined with drugs or biologics				
Estrasorb™ (Novavax)	Micellar Estradiol	Controlled delivery of therapeutic	Menopausal therapy	2003
Protein NPs combined with drugs or biologics				
Ontak®(Eisai Inc)	Engineered Protein combining IL-2 and diphtheria toxin	Targeted T-cell specificity; lysosomal escape	Cutaneous T-cell lymphoma	1999
Nanocrystals				
Emend®(Merck)	Aprepitant	Surface area allows faster absorption and increases bioavailability	Antiemetic	2003
Tricor®(Lupin Atlantis)	Fenofibrate	Increases bioavailability simplifies administration	Hyperlipidemic	2004
Rapamune®(Wyeth Pharmaceuticals)	Sirolimus	Increased bioavailability	Immunosuppressant	2000
MegaceES®(Par Pharmaceuticals)	Megestrol acetate	Reduced dosing	Anti-anorexic	2001
Focalin XR®(Novartis)	Dexmethylphenidate HCl	Increased drug loading and bioavailability	Psychostimulant	2005
Ritalin LA®(Novartis)	Methylphenidate HCl	Increased drug loading and bioavailability	Psychostimulant	2002
Zanaflex®(Acorda)	Tizanidine HCl	Increased drug loading and bioavailability	Muscle relaxant	2002
Vitoss®(Stryker)	Calcium phosphate	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2003
Ostim®(Heraseus Kulzer)	Hydroxyapatite	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2004
OsSatura®(IsoTis Orthobiologics)	Hydroxyapatite	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2003
NanOss®(Rti Surgical)	Hydroxyapatite	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2005
EquivaBone®(Zimmer Biomet)	Hydroxyapatite	Mimics bone structure	Bone substitute	2009
Invega®Sustenna®(Janssen Pharms)	Paliperidone palmitate	Allows slow release of injectable low solubility drug	Schizophrenia schizoaffective disorder	2009 2014
Ryanodex®(Eagle Pharmaceuticals)	Dantrolene sodium	Faster administration at higher doses	Malignant hypothermia	2010
Inorganic and metallic NPs				
Nanotherm®(MagForce)	Iron oxide	Allows cell uptake and introduces superparamagnetism	Glioblastoma	2010
Feraheme™/ferumoxytol (AMAG pharmaceuticals)	Ferumoxytol SPION with polyglucose sorbitol carboxymethyl ether	Magnetite suspension allows for prolonged steady release, decreasing number of doses	Deficiency anemia iron deficiency in chronic kidney disease (CKD)	2009
Venofer®(Luitpold Pharmaceuticals)	Iron sucrose	Allows increased dose	Iron deficiency in chronic kidney disease (CKD)	2000
Ferrlecit®(Sanofi Avertis)	Sodium ferric gluconate	Allows increased dose	Iron deficiency in chronic kidney disease (CKD)	1999
INFeD®(Sanofi Avertis)	Iron dextran (low MW)	Allows increased dose	Iron deficiency in chronic kidney disease (CKD)	1957
DexIron®/Dexferrum®(Sanofi Avertis)	Iron dextran (high MW)	Allows increased dose	Iron deficiency in chronic kidney disease (CKD)	1957
Feridex®/Endorem®(AMAG Pharmaceuticals)	SPION coated with dextran	Super paramagnetic character	Imaging agent	1996 (2008)
GastroMARK™; Lumirem®(AMAG Pharmaceuticals)	SPION coated with dextran	Super paramagnetic character	Imaging agent	2001 (2009)

FDA: Food and Drug Administration, NPs: Nanoparticles

CONCLUSION

As per the previous published reports, it is confirmed that NP has more potential for the management of diseases as compare to conventional drugs, nanocarriers system provides additional benefits such as control and sustained release of drug at specific site, leads to maximum availability of drugs as well as reduction in side effects.

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