Abstract

Introduction

Over the last couple of decades, the area of drug delivery has become important for its possible gaining in the pharmaceutical industry. Studies show that drug delivery systems which are developed by nanotechnology offer the opportunity to achieve more efficient drugs and to minimise side effects. The aim of this present article is to overview nanocarrier systems and point to their contributions to drug delivery systems. Pharmaceutical nanocarrier systems offer us plenty of possible solutions for drug delivery difficulties and to overcome important barriers such as ocular, intestinal barriers and the blood–brain barrier.

Conclusion

Novel drug delivery systems can enhance important characteristics of drugs such as bioavailability and drug solubility. Pharmacokinetic and pharmacodynamic properties of drug molecules can be improved by nanotechnology. In spite of all the possible advantages of nanosystems, they have some practical problems to overcome. Nanosystems have the potential to become one of the main human health care products in the future; therefore, the pharmaceutical nanotechnology area needs more studies so that we can completely understand their characteristics.

Introduction

Biodegradable nanoparticles (NPs) have played an important role for developing new drug delivery systems in recent years. Therapeutic effectiveness of the drugs increased while side effects of drugs were minimised by various polymers. According to relevant specialised encyclopaedias, the definition of NPs is 'Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm (1µm). They consist of macromolecular materials in which the active principle (drug or biologically active material) is dissolved, entrapped, encapsulated and/or to which the active principle is adsorbed or attached'.

Nanotechnology can be defined as producing nanoscale materials and devices from nanostructures. Nanotechnology is a developing area in both research and industry. Studies with nanomaterials are on the increase each passing day. At the end of 2014, the global nanotechnology market is expected to reach 26 billion US$. As we can see in Figure 1, the nanotechnology market gradually increases in both pessimistic and optimistic scenarios. The forecast shows significant differences between two scenarios, but the general trend is rising eventually. Total market forecast of nanotechnology can reach nearly 2.5 trillion US$ in 2014. Also, volume of nanotech articles substantially increased in the early 2000s in the EU correspondingly to economic impact of nanotechnology.

Drug delivery with nanosystems can be used to improve pharmacokinetics, obtain proper targeting and reduce toxicity of therapeutic agents. Solubility of hydrophobic materials and drugs can be increased by using nanocarriers which also can enhance the stability of drugs. NPs enable the therapeutic agent targeting and delivering to the brain. Drug carriers which are generated by nanotechnology offer the opportunity to penetrate or overcome some biological barriers such as blood–brain barrier and tight epithelial junctions. Nanotechnology is a multidisciplinary area which can be used for biotechnology, pharmacy, electronics, industrial manufacturing etc., and is promising for technological breakthroughs.

Figure 1: Market forecasts for nanotechnology between 2001 and 2015 in billions of US dollars.
The purpose of this article is to focus and illuminate drug delivery systems which are related to nanotechnology. Nanotechnology has great potential for drug delivery. Poorly soluble drugs can be encapsulated, and therapeutic molecules can be protected by using nanotechnology. Also, it offers the opportunity to modify blood circulation and tissue distribution profiles of drug molecules. Nanotechnology provides the opportunity to generate new formulations by novel drug delivery systems. Conventional drugs can be reformulated to reduce side effects. In addition, nanotechnology gives us a chance to produce and try new formulations with drug candidates which failed to pass the trial phases.

**Discussion**

**Nanotechnology**

The prefix ‘nano’ originates from a Greek word, which means ‘dwarf’. The concept of nanotechnology was first introduced by Richard Feynmann with his lecture titled “There’s plenty of room at the bottom”. In the nanoscale range (1–100 nm), materials’ magnetic, thermal, optical and electrical properties may change. These changes occur due to increased surface area and quantum effect.

Nanotechnology represents a strategic tool for the pharmaceutical industry and provides improved stability and absorption of the drug. Also, it increases therapeutic concentration of the drug at the target site. Drugs, which are water insoluble and unstable in the biological environment, may deliver properly with nanotechnology. Nanostructures can protect drugs from hydrolytic and enzymatic degradation. They also prevent drugs from first-pass metabolism and increase the blood residence time. They can penetrate tissues efficiently due to their reduced size. On the other hand, drugs which are produced at nanoscale may pass biological barriers.

**Advantages of nanocarriers**

Polymeric NPs which are made from natural and synthetic polymers were generated to achieve controlled drug release and targeting. Hydrophobic and biodegradable polymeric NPs can act as a local drug depot by providing encapsulated continuous drug release at the target site which are related by the surface make-up of the carrier system. These systems offer the opportunity to improve bioavailability, sustain the release of drugs, provide targeted delivery and solubilise drugs for systemic delivery. They also offer the opportunity to decrease the toxicity of existing drugs and overcome multidrug resistance of cancer cells.

Drug solubility can be increased by nanocarrier systems. A study with water-insoluble drug simvastatin showed that simvastatin-loaded HMC (highly ordered mesoporous carbon) samples, which were synthesised by the nanocasting technique, provided a much faster dissolution rate. Simvastatin-loaded SHMC (spherical HMC nanomatrix) provided significantly shorter $t_{\text{max}}$ and higher $C_{\text{max}}$ and larger AUC$\text{0–24h}$ when compared with Zocor, which is the marketed conventional tablet.

Nanotechnology can be used to improve oral absorption. The efficacy of highly lipophilic drugs is much lower than the desirable level, and to enhance their pharmacological effects, their key issues must be solved such as their poor solubility and reduced systemic exposure. Probufol is one of these lipophilic drugs. Zhang reported that the blood concentration of probucol was considerably enhanced with the nanodelivery system loaded with probucol than free probucol suspension. Also, cellular uptake of probucol in Caco-2 cell monolayers increased when the nanodelivery system was administered.

Nanosystems can be used for reducing toxicity. There are some anticancer drugs which contain platinum, but there are some disadvantages of platinum such as nephrotoxicity and neurotoxicity. Also, they caused developing drug resistance limiting their uses. But nanocarrier-based delivery of platinum complexes offer the opportunity to reduce non-target toxicity. Also, in some cases nanocarriers prevent to develop drug resistance against platinum. Additionally, these drug delivery systems can be used for multidrug resistant cancer treatment. Paclitaxel loaded NPs were eight times more efficient than Taxol plus XR9576.

**Effecting parameters of nanoparticlar drug delivery**

**Particle size**

The most important characteristics of NPs are particle size and size distribution due to their direct impact on in vivo distribution, biological fate, toxicity and targeting ability as well as drug loading, drug release and stability of NPs. Because of their small size and mobility, NPs perform higher cell uptake than microparticles providing the opportunity to use wider range such as cellular and intracellular targets. Smaller particles provide faster drug release due to their larger surface area to volume ratio. However, more drugs can be encapsulated per particle in larger particles, and they also provide slower release. Due to difference between small and large particles, drug-release rate can be controlled with adjusting particle size. Different particle size distribution of various nanoparticulate drug delivery systems was shown in Figure 2. Adequate size must be designed to determine the particle faith.

**Surface properties of nanoparticles**

**In vivo fate of NPs** can be determined by their hydrophobicity. The mononuclear phagocyte system (MPS) opsonises and clears NPs from the blood stream. Minimising the opsonisation and prolonging the circulation of NPs enables success in drug delivery.
targeting. Hence, coating NPs with hydrophilic polymers/surfactants or formulating NPs with biodegradable copolymers with hydrophilic characteristics such as polyethylene glycol (PEG) can be useful and necessity for successful drug delivery (Figure 3)\(^{13,19}\). Conforming the nanoparticle surface with PEG is one of the most effective ways for repelling the opsonisation. Phagocytosis and complement activation can be reduced by brush-like PEG surfaces\(^{19}\).

**Drug loading and drug release**

High drug loading capacity is the necessity for a successful nanodelivery system. There were two methods reported for drug loading which were the incorporation method and the adsorption/absorption method. Drugs should be incorporated during formulation of the nanoparticle for the incorporation method. For the adsorption/absorption method, the nanocarriers must be incubated in the concentrated drug solution\(^ {13}\).

Solid-state solubility of drugs in the matrix or polymer which is affected by polymer composition, the molecular weight, drug-polymer interactions and functional group presence majorly determines drug loading and efficiency. The way to achieve efficient loading is related to properties of the drug molecule. However, ionic interaction between drug molecules and matrix materials is the efficient way to enhance the drug loading for small molecules\(^ {19}\). Additionally, subsequent biodegradation and drug release from NPs are important factors. Desorption of the drugs which are bound or adsorbed to the surface, drug diffusion from the nanoparticle matrix or the polymer wall of the nanocapsules, matrix erosion of nanoparticle, combination of diffusion and erosion processes determine the release rate of the drug\(^ {1}\).

**Nanosystems for drug delivery**

**Inorganic NPs**

Inorganic NPs are metal oxide particles or the particles which possess at least one metallic composition at nanoscale. They have novel chemical, physical and biological properties due to their reduced particle size\(^ {10}\).

Inorganic NPs can be used for drug delivery. Cheng et al. have shown that porous hollow NPs of Fe\(_3\)O\(_4\) can be used for targeted drug delivery and controlled release of cisplatin. Herceptin-bound porous hollow NPs

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**Figure 2:** Different particle size distribution of various nanoparticulate drug delivery systems. Nanoparticle clearance and biocompatibility are dependent on various factors including physical characteristics especially particle size. Deliberate selection of particle size is mandatory to determine the *in vivo* behaviour.

**Figure 3:** Schematic view of opsonisation and phagocytosis of nanoparticles. Without surface modification, nanoparticles marked by opsonin proteins and recognised by phagocytes. Therefore, surface modification is essential. Coating nanoparticles surface with hydrophilic moieties such as PEG helps nanosystem escaping from RES.
Mesoporous silica systems
Mesoporous materials’ well-known surface properties and stable structures make them desirable option for encapsulating pharmaceutical drugs. Their major characteristics are the surface area and pore size. They have some main advantages such as tunable particle size (50–300 nm), stability against physical stress like heat and pH, uniform pore size distribution, ability to load great amounts of drug molecules because of their high surface area and large pore volume and internally and externally divisible surface which allows selective functionalisation.

Polymeric NPs
Nanospheres
Polymeric nanospheres are matrix-type solid colloidal particles. Drugs can be dissolved, entrapped, encapsulated, chemically bound or absorbed by the polymer matrix. Their particle size is generally between 100 and 200 nm. These particles are very sensitive to opsonisation because of their hydrophobic surface characteristics. Therefore, the nanocarrier surface needs modification to prolong the circulation in the blood stream Which makes nanospheres invisible to the reticuloendothelial system (RES). Studies have shown nanospheres can be designed to obtain mucoadhesive property. These systems offer the opportunity to enhance peptide delivery by mucus membranes when orally administrated for instance.

Polymeric micelles
Polymeric micelles have unique amphiphilic properties with a core-shell structure. The diameters of micelles are between 10 and 100 nm. The inner core of micelles demonstrates hydrophobic properties which offer the opportunity to dissolve lipophilic drugs. The corona of micelles show hydrophilic properties which allow them to escape from RES. Polymeric micelles enhance solubility and permeability of drugs which increase bioavailability. They minimise the toxicity and side effects as well as providing controlled release for the incorporated drugs. Their surface can be modified by decorating targeting moiety which enables targeting to specific sites, and this improves efficacy of drugs in the target site. Solubilisation of drugs with polymeric micelles was higher than regular micelles because of their larger core. Micelles can be produced by amphiphilic copolymers. These amphiphilic copolymers show tendency to self-assemble due to large solubility difference in optimal solvent media. These systems were appropriate for the delivery of hydrophobic drugs. There are many types of micelles with different behaviour characteristics in particular media, such as: stimuli, temperature, reductive environment or pH responsive micelles.

Liposomes
Liposomes are spherical shaped artificial vesicles which are produced by natural non-toxic phospholipids and cholesterol. Liposome properties may be changed by their lipid composition, size, surface charge and preparation method. They can be used for reducing systemic toxicity and preventing early degradation of the encapsulated drugs. Their blood circulation time can be enhanced by attaching PEG units to the bilayer. Also they can be targeted to special sites by conjugating with antibodies or ligands. Lipid composition, size and electric charge of liposomes are easily modificable. They can be easily targeted by surface polymers, carbohydrates and antibodies. Their level of antigenicity is low and they hardly cause toxic effects. Liposomes were made of biodegradable materials which can be metabolised in vivo. In addition, they can encapsulate solutes which have different properties.

Dendrimers
The dendrimer term, named from their structural shape, was firstly proposed by Donald Tomalia and his co-workers in the early 1980s.

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Dendrimers are monodisperse symmetric macromolecules with highly branched structures around an inner core. Their structures are comprised of three components: a focal core, several layered building blocks which are formed by repeating units and functional groups on the periphery. The terminal groups of dendrimers mostly control the dendrimer interactions with the molecular environment. The interior of a dendrimer can show hydrophilic characteristics while the exterior surface of a dendrimer is hydrophobic or vice versa by modifying their termini. Their properties such as nanometre size range, ease of preparation and functionalisation, also their multiple copies of surface groups displaying ability, make them an attractive system for drug delivery.

Because of their non-polar cavities, they can encapsulate hydrophobic drug molecules. In addition, they have many positively and negatively charged functional groups on their surface which offers the opportunity to easily attach to oppositely charged drug molecules. There were two methods using dendrimers for drug delivery: drug encapsulation and drug conjugation. In the encapsulation method, drug molecules were entrapped into dendrimers. In the conjugation method, drug molecules would be covalently attached onto the surface of the dendrimer.

Carbon nanotubes (CNTs) are attractive systems because of their excellent mechanical, electrical and surface properties. Surface properties, size and shapes of CNTs are several factors which affect interactions with cells. They need to be functionalised due their insolubility in most types of solvents and their cytotoxic properties. CNTs’ solubility and biocompatibility can be increased by functionalisation. Their needle-like shape offers the opportunity to facilitate transmembrane penetration.

The nanotube diameter, degree of chirality and being single walled or multiwalled are some of the factors that affect the properties of the nanotubes. They provide several approaches for drug delivery. Drugs may be incorporated into the CNTs’ core or can be bound covalently to the CNTs.

Nanocrystals
Nanocrystals are molecule aggregates which comprise the crystalline drug. They are especially used for poorly soluble drug molecules. They can be formulated as suspensions by dispersing drug molecules in a liquid medium which are called nanosuspensions and also dry dosage forms such as tablets and capsules. They have several advantages for drug delivery. They can provide enhanced bioavailability by improving solubility and bioadhesion to the intestinal wall. Also they can reduce fasted/fat absorption variation of the drug molecules.

Hydrogels
Hydrogels can be defined as three-dimensional hydrophilic structure networks which are formed chemically or physically. They have some properties which must be optimised such as safety, biodegradability, drug-loading capacity and drug-release kinetics. Drug molecules can be loaded by their porous structure which can be controlled by the density of crosslinks. The drug-release rate is determined by the diffusion coefficient of the drug molecule. Hydrogels can be programmed to alter their structure by environmental changes such as pH and temperature which are called smart hydrogels. Hence, they can be used for developing stimulus-responsive drug delivery systems. They also give us a chance to develop mimetic systems.

Conclusion
Nanotechnology is a very promising and open-ended area for drug delivery. It has great potential to innovate drug delivery systems and offers new opportunities to design variable and game-changing systems which can be adapted for drugs. The area of nanotechnology is still evolving and continuing to grow. Also, it provides a wide variety of nanomaterials which can be used to produce effective drug delivery systems with desirable properties.

There are numerous types of drug delivery systems associated with nanotechnology which gives us a chance to select the system which has desirable properties for our purpose from among these various systems. However, there are some drawbacks in using nanosystems. Stability of nanocarriers is difficult because of their large surface area. Additionally, the characteristics of nanocarrier systems must be fully understood to achieve optimum in vivo efficiency. On the other hand, some of these nanomaterials’ toxicology has not been fully revealed, preclinical and clinical studies are required to reveal and understand toxicity of these materials. Long-term toxicity and stability must be studied before using them in human health care. Behaviours of nanoparticles should be investigated in the human body. They may trigger blood coagulation pathways and may cross the physiological barriers such as blood-brain barrier unintentionally. Also, the toxicity parameters of bulk material can be changed by using them in a nanoformulation. Therefore, toxicity parameters must be examined before they generate formulation for all ingredients which are used in nanoscale.

In spite of their drawbacks, the advantages of nanosystems are uncontestable. Nanotechnology is extremely important for future medicine. Nanotechnology-mediated drug delivery systems offer many solutions for potential therapeutic agents which cannot be used properly due to their characteristics such as low solubility and low bioavailability.
Figure 4: Schematic view of different types of nanoparticulate drug delivery systems. Mainly, there are two subtypes of nanoparticles: polymeric and inorganic NPs. Polymeric NPs consist of numerous different types like dendrimers, nanospheres, nanocapsules, carbon nanotubes, liposomes and hydrogels. On the other hand, there are some inorganic NPs such as metallic and silica NPs.

Therefore, there is much to be done with nanosystems use them more efficiently and safely for human health care.

References
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