REVIEW

Nanopreparations for better drug delivery

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Abstract: Nanomedicines are a recent development to face medical and pharmaceutical challenges because nanoparticles have unique properties. They are very small in size and are easy to handle. One more advantage is that they are not harmful for the human body. Poorly soluble drugs have serious problems with their delivery and dosage forms. Formulation strategies by means of nanocarrier systems, such as polymeric micelles, can resolve the trouble. Micelles from PEG-diacyllipids, e.g. PEG-PE, are of special attention. On the other hand, the layer-by-layer (LbL) technique can be useful to set up stable nanocolloids of low solubility. In some cases, the use of nanopreparations is the only way to fulfill medical requirements. Thus, for the blood group CT imaging, one has to prepare long-circulating contrast-loaded nanoparticles. In other cases, poor stability of potential drugs creates a problem, such as with siRNA, and the use of nanocarriers may present a solution e.g. Polymeric micelles having a hydrophobic derivative of siRNA. We will discuss the preparation, properties, and anti-cancer activity of drug-loaded PEG-PE micelles and LbL nanoparticles and other "approaches" for making "undeliverable" substances deliverable. Injectable, implantable, topical delivery of active compounds, oral drug delivery system and many other methods have been improved by nanotechnology.

Keywords: Nanomedicine, Archaeosomes, Matrine, Aptamer.

INTRODUCTION

With the advancement in field of medicine, new drugs are being investigated (Javed *et al*., 2011; Masood *et al*., 2011; Qadir & Sajjad, 2017). But the diseases are still a problem either due to poor diagnosis (Qadir *et al*., 2010; Nisar *et al*., 2011), resistance (Janbaz *et al*., 2012; Ameen *et al*., 2012) or failure in drug delivery. Drug delivery to the target site is major issue in these days for pharmaceutical sciences. Different approaches have been tried to target the active site (Qadir and Malik, 2010; Qadir and Malik, 2011; Qadir, 2011). Advances in the management of different diseases are being tried especially for cancer (Qadir, 2017; Qadir *et al*., 2017; Qadir & Cheema, 2017; Qadir & Faheem, 2017; Qadir & Rizvi, 2017), AIDS (Qadir & Zafar, 2017; Qadir & Abid, 2017), diabetes (Qadir & Ahmed, 2017), and neurological disorders (Qadir & Anwar, 2017). Nanomaterials have received considerable attention because of their potential for application in a wide spectrum of areas that include biology and medicine (Ehsan *et al*., 2012; Naz *et al*., 2012). One of the important parts in developing different types of products is its method of administration and its *in vivo* imaging (Hobson, 2009). Different types of nanomedicines are functioning as nanodevices that work within the body (Brigger *et al*., 2002). Furthermore, the nanoparticles may occur as nanospheres (dispersion of drug thoroughly in particles to form a matrix) and nanocapsular form (in which the drug is curbed in hydrous or anhydrous hollow space bounded by a polymeric covering). Nanomedicines are of great importance because they can solve medical and pharmaceutical problems (Smith *et al*., 2006). The supramolecular chemistry prime factor is Self-assembly processes (Mansour *et al*., 2010). Reduction in side effects and elevated therapeutic effects are one of its most important achievements (Mitchell, 2003). Nanomedicines also offer advantages of **c**ontrolled release drug delivery (available for many routes of administration) over immediate release delivery (Youns *et al*., 2010).

Emerging nanopharmaceuticals

A huge number of advancements have been made in recent years due to budding interest in nanopharmaceuticals. The disease can be managed fastly by concurrent diagnosing as well as treating. With the help of nanotechnology, we can detect and diagnose problems like hidden metastasis of patients of breast, lungs, colon etc in their initial stage, that would serve as a microbe and brighten the future of nanotechnology (Krzysztof *et al*., 2010). New pharmaceuticals have been prepared by combining a lot of technologies and/or medicines (Timmermans *et al*., 2011).

Properties of nanoparticulates

Nanoparticulate systems are capable to compose a new generation of drug delivery systems (Bawarski *et al*., 2008). Basically, the nanoparticles act as a vehicle to help drug to reach its destination without damaging body or without itself being damaged, accurately diagnosing the disease and than finally proper elimination from the body (Youns *et al*., 2010). When the size reaches to nanoscale it

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changes its properties. The change in property due to size i.e. confinement of quantum in semiconductors and magnetic materials processes supramagnetism (Gubin *et al*., 2009). It can also undergo sintering, diffusion and is photostable so frequently used in preparations like sun protective lotions and protect from damage caused by sun (Kockler *et al*., 2012).

Biomedical nanoparticles

Nanoparticles are of two major kinds
Inorganic nanoparticles
Organic nanoparticles

The group of organic particles includes carbon nanotubes, Liposomes, dendrimers, emulsions, and different polymers (Arayne and Sultana, 2006). Liposomes and nanovectors are used as drug delivery carrier for human cancers. Dendrimers help in visualizing various pathological processes. Inorganic type show almost similar structure (Yezhelyev *et al*., 2006). Also, carbon like fullerenes or certain medicated creams.

Multifunctional nanoparticles

Nanoparticles are better for each type of targeted drug delivery including hydrophilic, hydrophobic, proteinaceous, vaccines, macromolecules etc.

A broad progress of nanotechnologies has brought new perception of plasma lipoproteins (LP), having more penetratibility into the cells (Torkhovskaia *et al*., 2010).

Quantum dots can be used for biological imaging and cellular studies because of large surface-to-volume ratio that help in fabrication of multifunctional nanoplatform. They are used for biomolecular/cell separation and diagnosis as well.

Lipid/polymer nanoparticles

Cations that are lipid based are useful for tumor therapy (Cavalcanti *et al*., 2005). They are extensively used due to biocompatibility of lipid matrix. They are unique and having safety as well in administration (Battaglia *et al*., 2012).

Nanoparticles of gold

Gold and silica nanoparticles are useful as nanobullets for cancer (Drummond *et al*., 1999; Jain, 2005). They are focused into the nuclei of cancerous cells to inhibit multiplication as well as kill them (Fender and Jessica, 2008). Nanosurgeon use aptamers for the selective deletion of cells (Nair *et al*., 2010).

Virus based nanoparticles

Such particles have extensive use in biotechnology (Pattenden *et al*., 2005; Rae *et al*., 2005; Singh *et al*., 2006 and Singh *et al*., 2006). Viruses act as carriers to administer drug etc. The targeting and drug delivery capabilities of nanoparticles can be enhanced by changing the protein coat (Portney and Ozkan, 2006).

The cold causing adenovirus and relaxin producing gene were entrenched. After injecting, the virus multiplies and kill cancer cells not the normal cells (Kim *et al*., 2006). Biological molecules like deoxyribonucleic acid (DNA) have revealed huge potential in production and construction of nanostructures and devices (Abu-Salah *et al*., 2010).

Nanopreparations

Some Drugs are poorly soluble that have very less stability in the body, exhibit rapid elimination and/or poor accumulation in the required zone, so it is too much difficult to convert into suitable dosage forms.

Thus, for example, poorly soluble substances often represent promising drug candidates, however grave troubles with their delivery in the body and preparation of bioavailable dosage forms of such substances prevent them from becoming real drugs. A range of methods are employed to combat the problem of poor solubility of drugs e.g. anticancer drug (paclitaxel, camptothecin, and photodynamic therapy). Among such systems, polymeric micelles have good pharmacological characteristics. Micelles prepared from PEG-diacyllipids conjugates, such as PEG-PE, are of great attention. On the other hand, a so-called layer-by-layer (LbL) technology can also be useful for such drugs. Similarly, the results with the nanocolloids of poorly soluble drugs prepared using the LbL in combination with sonication will also be discussed (Torchilin *et al*., 2003).

In some cases, the utilization of nanopreparations is the only way to meet an unmet medical need. Thus, to keep contrast agent in the blood during the time sufficient for a useful CT imaging, one has to prepare long-circulating nanoparticles loaded with the contrast, such as heavily iodinated micelles. In other cases, poor stability of a potential drug in the body can pose a serious problem, such as in case of siRNA, and the use of nanocarriers may represent a possible solution. Polymeric micelles containing a hydrophobized derivative of siRNA can serve as a good example (Musacchio *et al*., 2010).

Nanotechnology affecting administration

Injections

Nanotechnology is striving to formulate such dosage forms as can easily be administered and the patient, receives it easily e.g. a new 'nano formulation' of an older drug paliperidone palmitate, schizophrenic drug prepared by reducing particle size to less than two hundred nanometre (Bishara and Taylor, 2008; Bishara, 2010; Wischke and Schwendeman, 2008).

Aerosol

Drug carrying nanoparticulates are used for treatment of local lung cancer (Azarmi *et al*., 2006). Nanosuspension technology is used for water and oil insoluble drugs. This

method increases the bioavailability as well as crystalline state of small particles (Fadi *et al*., 2004).

Implantable delivery

This route is preferred over injections. It minimizes highest plasma levels and decrease the side effects. It has prolonged duration of action, proper acceptance by patient without repated doses. Implantables carry nano- pockets of active ingredient that release a small quantity of drug after the dissolution of silicon. The membrane of such devices is antibiofoul and compatible (Adiga *et al*., 2009). PSivida a current process to engineer tissue and for eye administration (Kassem *et al*., 2007).

Nanoshells are being used for cancer therapy (Tang *et al*., 2010). Experiments are also being performed on temperature-sensitive drug delivery control methods, that discharge their consignment on illumination.

Oral delivery system

Oral delivery system has been improved by nano-engineering. The nano-enhanced drugs increase oral bioavailability and reduce adverse affects. The bioavailability is directly proportional to yield in drug development and significantly may assist in treating untreatable diseases. The systems have been developed that are able to reach the brain for anaesthesia, cancer drugs and many others.

The nanosphere acts as carrier obtained from hydrogels, which puff up when the environment tends more acidic. Its successful applications are in controlled-release tablets and capsules, as a result of release the hydrogel body swells up (Blanchette and Peppas, 2005). Multifunctional lipid nanosystem improve permeability, imaging etc (Ganta *et al*., 2010).

Topical delivery

Topical delivery is not easy because the skin acts as a natural and defending barrier (Desai *et al*., 2010). The topical delivery of active compounds is improved because of small size consequently easily enter human tissues and cells. And the skin is the primary point of contact for a whole host of nanomaterials (Nasir and Friedman, 2010). Novavax is developing Estrasorb and Androsorb. This result in smaller and less invasive patches.

Ophthalmology

The drug prepared by nanoparticles greatly enhances the time of residence and contact time with the affected part

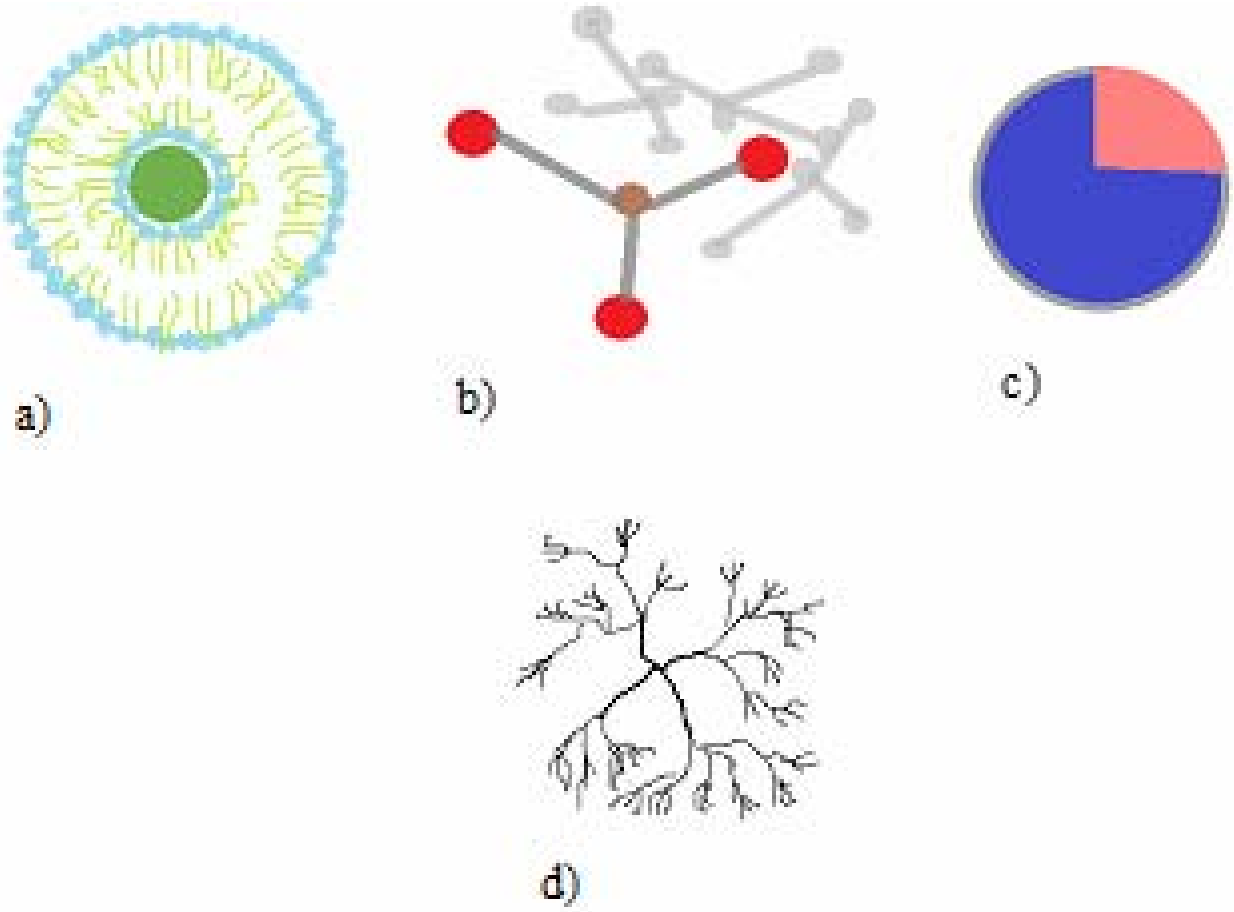

Fig. 1: Emerging Nanopharmaceuticals (a) Liposomes, (b) Polymer Nanoparticles, (c) Magnetic Nanoparticle, (d) Dendrimers

Table 1: FDA approved Nanopharmaceuticals

Liposomals: Liposomal Amphotericin B - Mycotic infection 1990 Liposomal Daunorubicin - Kaposi's Sarcoma 1995 Verteporfin liposome - wet macular degeneration 2000 Collagran MMP inhibiting - wound dressings 2006
Solid Polymeric: Carmustine- Glioblastoma multiform 1996 Abraxane (paclitaxel taxol) mammary cancer 2005
PEGylated: PEG-succinimidyl-L-asparaginase- Lymphoblastic Leukemia 1994 PEG-adenosine-deaminase- Serius immunodeficiency 1990 PEG-interferone-2a (pegasyis) - Hepatitis C 2002
Nanocrystal: Emend nanocrystal - protection from nausea in chemotherapy 2003 Rapamune nanocrystal - prevention from rejection 2000

of eyes e.g. in case of a drug brimonidine that is used to cure glaucoma, corticosteroids to cure autoimmune uveitis. The nanocarriers permit the non-steroidal anti-inflammatory drug e.g. indomethacin to get in touch with interior of the eye (Diebold and Calonge, 2010).

The encrustation of Layered double hydroxide (LDHs) nanovehicle with an anionic polymer improves aqueous solubility of certain drugs. The oral bioavailability of lovastatin is made better by a biodegradable porous starch foam (BPSF) (Wu *et al*., 2010). The solubility of weak aqueous drugs is made possible by lipids emulsion of colloids and solid lipid nanoparticles (Bunjes, 2010).

Nanomedicine as Targeted drugs

Small molecules can be incorporated into nanoparticles to target them at specific site and provide benefits for improved bioavailability, biocompatibility and safety. Immunotargeting is done by engineering antibodies to develop human like antibodies that are helpful in certain research studies of biomarkers, interaction of nanocarrier with receptor and aptamer prove to be efficacious (Debbage, 2009).

Nanoparticles deliver siRNA

Melanoma is a type of skin cancer that has a high mortality rate. The c-Myc siRNA in Anisamide nanoparticles are therapeutic mediator for malignancy. This method is used for systemic delivery of siRNA. It partially depresses the c-Mycin cancer. Injections given thrice of c-Myc siRNA prepared in the targeted nanoparticles containing DSAA could weaken cancer growth (Chen *et al*., 2010).

Noninvasive imaging of transplanted cells

Transplantation is one of the important needs. And different non-invasive techniques like magnetic resonance imaging, optical imaging etc can examine bio-distribution. Multi modal imaging is emerging as an important development to provide complimentary and confirmatory information (Modo, 2008).

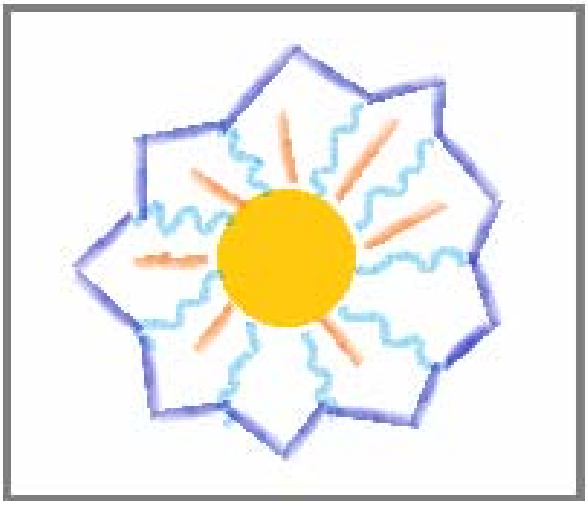

Fig. 2: Nanoparticle as a vehicle for new drug delivery

Bioimaging by Nanoparticles

The agents like dye-doped silica nanoparticulates are advantageous for non-invasive bioimaging (Sharma *et al*., 2006). Conjugated polymer based fluorescent nanoparticles used as an alternative to the conventional fluorescent probes is of great importance in bio imaging (Kai and Bin, 2012).

Nanomedicine for cardiovascular diseases

Perfluorocarbon nanoparticles are helpful for a wide range of cardiovascular diseases (Lanza *et al*., 2006). Nanotechnology dependent local drug delivery have ability to attain inhibition from restenosis while not impeding endothelial.

Nanostructured drug delivery

Different types of nucleic acids, proteins, small-molecule drugs can be delivered by nanostructured drug carriers. Such molecules can be delivered to specific site of the body with more efficacy and less side effects (Hughes, 2005).

Nanoparticles for the delivery of drug to brain

The combination of drug carrying nanoparticles with principle of differential protein adsorption. To deliver drugs to endothelial of the brain, nanoparticulates drug carriers are targeted on Apolipoprotein E, so they cross the blood brain barrier (Müller and Keck, 2004).

Delivery of matrine

The oral bioavailability of matrine is increased by a new drug system named as self-nanoemulsifying drug delivery system (SNEDDSs) that rely on drug-phospholipid

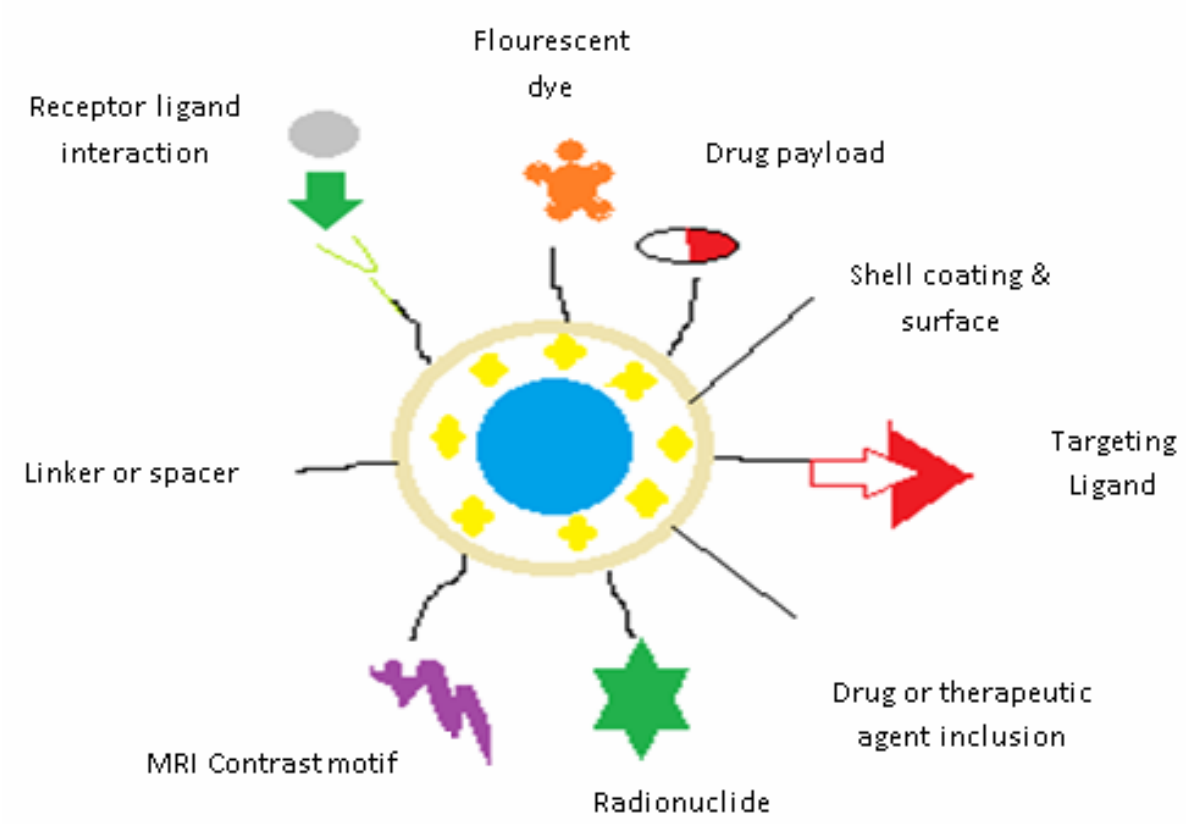

Fig. 3: Multifunctional nanoparticles

complex technique. By using solvent evaporation, morin-phospholipid complex (MPC) was formulated to enhance lipophilicity and bioavailability (Ruan *et al*., 2010).

Gelatin nanocarriers

Rifampicin loaded gelatin nanoparticulate has ability to increase targeting of drug by reduction in frequency of dose and adverse effects in tuberculosis (Saraogi *et al*., 2010). The nanoparticles of gelatin are loaded with the poly(ل-caprolactone) nanofibrous semi-synthetic scaffolds to engineer bone tissues (Binulal *et al*., 2012).

Enhanced liver targeting

To improve liver targeting, encapsulated N1-stearyl-5-Fu is used (Yu *et al*., 2003). 5-Flourouracil is acylated with steryl chloride to gain N1-stearyl-5-Fu and encapsulated into solid lipid nanoparticles (Yu *et al*., 2003).

Amphotericin B nano-sphere (LNS)

The lipid nano spheres are less prone to liver so the high concentration is available in the plasma. Thus, the combination of amphotericin B with Lipid nano-sphere helps in low dose administration (Fukui *et al*., 2003).

Cucurbitacin BE polylactic acid nano-particles

The peri-cancer submucosal injection of cucurbitacin BE polylactic acid nano-particles can pass peri-oral cancer lymphatic capillaries and reach the targeted cervical lymph nodes. Cucurbitacin BE poly-lactic acid nano-particles (CuBE-PLA-NP) was geared up with the technique of emulsion solvent evaporation, and then CuBE-PLA-NP lyophilization injection was primed by using 10% manninositose as the supporting agent (Yang *et al*., 2001).

Nano-encapsulation of azole

The antifungal drugs are incorporated into nanoparticles to increase oral bioavailability like clotrimazole and econazole. The drug can be loaded in synthetic (PLG) as well as natural polymer (alginate stabilized with chitosa) and this alginate is better than the PLG formulations (Pandey *et al*., 2005).

Aptamers for nanodelivery

Aptamers are one of the class of synthetic molecules that are very small, highly specific and resemble a lot to antibodies. They are being used to treat complicated diseases of eye, inflammation and cancer (Kanwar *et al*., 2010).

Nanodelivery for nevirapine

Nevirapine-loaded liposomal formulations are prepared for anti-retroviral drugs administration with less adverse effects (Ramana *et al*., 2010). The NDDS helps to deliver nontoxic, highly compatible targeted delivery for viral infections as well as prevent first pass metabolism (Sharma *et al*., 2012).

Archaeosomes for drug delivery

Archaeosomes are of great importance in the delivery of drug, as a vector for antigen and in treating and preventing infections. Archaeosomes are composed of synthetic PEGylated archaeal lipid. Archaeosomes compose a new family of liposomes that may be stable, acidic or basic, safe and useful for drug as well as gene delivery. Archeosomal vaccinations work against allergies, tumors and infections (Benvegnu *et al*., 2009).

Nanocapsule delivery system

The tacrolimus are designed by double coated nanoparticulate that are helpful against P-glycoprotein pump and CYP3A barriers without any effect on physiological processes. They simply release the drug rather than dissolving and protect from an intestinsl fluids (Nassar *et al*., 2008).

Nanotechnology in prostate cancer cells

Curcumin is encapsulated in liposomes that is covered by prostate membrane specific antigen specific antibodies for prostate cancer therapy. Such liposomes are prepared by sonication and Un-entrapped curcumin was uninvolved by size segregation chromatography. This improves the targeting and efficacy of curcumin based delivery of the drug (Thangapazham *et al*., 2008).

Inhalable nanoparticles

The lung cancer is treated by inhalable effervescent doxorubicin NPs. It is a non-invasive, efficacious and safe technique that might be helpful in present future and bring revolution in lung cancer patients (Roa *et al*., 2010).

Drug delivery by gold nanoparticles

Gold nanoparticles are very useful for drug delivery due to their unique properties like a very small size of the particles along with their physical and chemical characteristics. Their surfaces can also be tuned for specificity and controlled drug release (Han *et al*., 2007).

Nanoplatforms for brain cancer

The treatment of brain cancer is a challenge because of blood brain barrier and non-specificity of the drug moiety. A single nanoplatform can be made multi functional for identification and treatment of brain cancers that is highly specific in its action (Koo *et al*., 2006).

Indirect delivery to brain

One of the advancement of nanotechnology for administration of drug to nasal cavity and olfactory epithelium delivery by trigeminal nerves directly to CNS. It greatly enhances the availability of drug to the brain as compared to any other form. It is also beneficial on not having any toxicity related problems (Mistry *et al*., 2009).

Ocular drug delivery

Nanoparticles in the form of eye drops can easily be instilled in low dose and lessened side effects (Vandervoort and Ludwig, 2007). Solid lipid nanoparticles have been synthesized from physiological lipids and act as a carrier of drug since 1990's to enhance penetration as well as bioavailability of drug (Seyfoddin *et al*., 2010).

Poly(vinyl benzoate) nanoparticles for molecular delivery

The poly(vinyl benzoate) nanoparticles act as a carrier for small lipophilic molecules. They are highly stable in blood and phosphate buffer and slowly decompose by esterases. The lipophilic compounds can be incorporated into such nanoparticles but not hydrophilic. So, they are widely used in imaging and pharmaceutical agents using lipophilic compounds as a loader of nanopreparations (Labruere *et al*., 2010).

Capped nanoparticles

The reduction of hexachloroplatinic acid using sodium borohydride and capping agent is helpful in the preparation of platinum nanoparticles that are soluble. PVP-capped nanoparticles have greater feasibility for breast cancer cells. So, by adding capping agents the advance drug candidates can be developed (Teow and Valiyaveettil, 2010).

Anti-tumour action of Ganoderma lucidum polysaccharide nanoparticles

Ganoderma lucidum is an edible mushroom consisting of immunomodulatory and anti-tumor activity as well. GLP loaded in novel chitosan nanoparticles manufactured by using the ion-revulsion method, enhance the effect in cancer treatment and also help in promotion of spleen cells growth so it can be used as a complementary tool to treat cancer (Ni *et al*., 2011).

CONCLUSION

Nanopreparations are a unique source for better drug delivery. The drugs that were either impossible or difficult to administered, can be administered by using nanopreparations. They are now extensively being used for targeted drug delivery and multiple desired effects can be achieved.

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