URL: http://dx.doi.org/10.31703/gdddr.2019(IV-I).05 Vol. IV, No. I (2019) DOI: 10.31703/gdddr.2019(IV-I).05 Pages: 41 – 50

Irsah Maqbool [a] Sobia Noreen [b]

A Review of Novel Techniques for Nanoparticles Preparation

Abstract Various types of material are produced by using nanotechnology techniques at nano scale level. Nanoparticle is wide class of nanotechnology having one dimension and particle size less than 100 nm. Nano particles has wide range of application in the field of biomedical because a large number of nano materials such as nano carriers, nanotubes, nanowires and nanorods have been developed. In this review our main focus is to discuss different methods for the preparation of nanoparticles

Key Words: Nanotechnology, Nanoparticles, Delivery Vehicle, Preparation Techniques

Introduction

Novel drug delivery system has been developed to overcome the limitations conventional drug delivery system e, g, higher dosage, lower effectiveness, adverse effects and toxicity (Bhagwat & Vaidhya, 2013). Novel drug system has some advantages over the conventional drug delivery system. These advantages are states as below

- Lower side effects of various drugs
- Targeted drug delivery to the specific site of action
- Lower systemic dosage release
- Increase bioavailability by improving their efficacy and safety
- Lower dosage frequency result in less chances of medication error (Yang & Pierstorff, 2012)

Commencement of nanotechnology over last two decays has revealed various prospect of research in the field of nanomedicine (Pandey, Dhiman, Srivastava, & Majumder, 2016). NDDS has been established as a new interdisciplinary sciences (Agashe, Sahoo, Lagisetty, & Awasthi, 2011; El-Nour, Eftaiha, Al-Warthan, & Ammar, 2010). Novel drug delivery system is explained by three ways polymer-drug conjugates system (polymer forms conjugates with drugs), Monolithic matrix system (drug is non - covalently dissolved or dispersed with in the polymer), Reservoir based system (drug is non-covalently enclosed with in the polymer coating). However the introduction of nanotechnology in naoparticulate formulation contributes a major role in the development of TDDS for higher skin permeation and higher concentration of drug at targeted site (In & Nieva, 2015; Z. Liu et al., 2014). The delivery of poorly water soluble drugs to several parts of the body by means of by passing the liver, in order to avoid the first pass metabolism(protection of drug from gastrointestinal tract degradation) and to increase oral bioavailability is also possible through nanotechnology (Emeje, Obidike, Akpabio, & Ofoefule, 2012; Muhamad12, Selvakumaran, & Lazim, 2014).

Various types of material are produced by using nanotechnology techniques at nano scale level. Nanoparticle is wide class of nanotechnology having one dimension and particle size less than 100 nm (Laurent et al., 2008). Nano particles has wide range of application in the field of biomedical because a large number of nano materials such as nano carriers, nanotubes, nanowires and nanorods have been developed (Stevanovic & Uskokovic, 2009). Nanoparticles are composed of three part a) surface layer b) shell layer c) core. Nanoparticles are classified into various categories on the basis of morphology,

[a]Department of Pharmaceutics, Faculty of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Punjab, Pakistan.

[b]Ph.D. Scholar, Department of Pharmaceutics, Faculty of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Punjab, Pakistan. Email: sobianoreen07@gmail.com

physical and chemical properties and size. On the basis of physical and chemical properties nanoparticles are classified as a) Carbon base NPs b) metal NPs c) ceramic NPs d) semiconductor NPs e) polymeric NPs f) lipid based NPs (Khan, Saeed, & Khan, 2017). Nano particles have ability to encapsulate and protect the drug from degradation or deactivation prior to reach the target site Nano particle improves circulation time of drug, bioavailability and controlled drug delivery. These entire objectives made the nanoparticles an ideal drug delivery system (Anselmo & Mitragotri, 2014). For the treatment of dermalogical diseases, the drug must accumulate in the skin to produce the local effect. Active and passive delivery of drug produces skin irritation, damage or disruption of skin surface. So, to overcome these problems and for topical delivery nanoparticles are developed (Jain, Mittal, & K Jain, 2011). Most of the nanoparticles retained on the upper layer of the skin and are not able to penetrate into the skin. Polymers used strongly effect the structure, properties and application of nanoparticles. To enhance the contact time of drug with skin and to increase the skin penetration nanoparticles are incorporated into the gel matrix system. Hydrophilic polymers are used in forming gel such as Carbopol and hydroxypropyl methyl cellulose etc. (Khan et al., 2017).

Nano Particles Based Drug Delivery System

Nano particle is a broader term that covers a large number of different drug delivery systems that have distinct composition. Apart from the fact that all micro particles can also be made in nano range like nano-micelles, nano-niosomes, nano-liposomes, the researchers discovered a number of nano particles like nanorods, nanospheres, nanocapsules and nano tubes as shown in **Fig 1**.

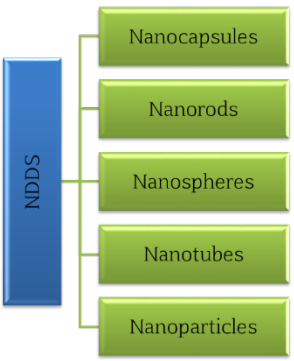

Figure 1: Various Novel Drug Delivery Systems

Nano Spheres

These are the particles of nano range spherical in shape. Nanotechnology refers nano spheres as solid balls of nano range made up of different materials. These are made up of carbohydrates, lipids or proteins. Due to the therapeutic application, metallic nano spheres are also getting importance (Ouyang, Shi, Fu, & Wu, 2013). During synthesis drug may be mixed to form matrix with supporting material or drugs may be loaded on the nano spheres after their formation. When drugs are loaded on the nano spheres, different drugs show different loading pattern. Some drugs move out to form shell, other tend to form core while some drugs dispersed homogenously in the matrix. Drugs forming shell fails to provide sustained release system while drugs forming core show excessively delayed release. Thus loading pattern of candidate drug determines the successful formulation of nano spheres. Nano spheres are easy to prepare because very simple physical and chemical methods are involved in their preparation. Mechanisms involved in their preparation are oxidation, polymerization, reduction, solvent evaporation and precipitation. All these methods of preparation are simple, easy to perform and economical. Some of these reactions require only a single vessel to carry out the reaction. Wide range and variety of solvents and reagents helps to optimize the required characteristics of the drug delivery system (Ouyang et al., 2013).

Nanocapsules

Nano capsules describes a system in which drug is enclosed in a shell of other material to form core.

Different type of nano capsules can be prepared with different composition of the core i.e. liquid, solid or aqueous core. Nano capsules are different from surface functionalized nano spheres in that nano capsules have distinct core and shell system while nano spheres have a layer of molecules of functional ligand. Production of nano capsules involves two step i.e. formation of core followed by the formation of shell thus their production is complex as compared to the formation of nano spheres (Lu, Bei, & Wang, 1999).

Nanorods

Nanorods are the rod shape molecules of nano size range with high length to diameter ratio. Other names of nanorods are nano needles, nanotowers, nano wires and nanofibres. This naming trend depends on the physical and chemical characteristics of the molecule. But nano rods have limited application in the field of medicine because of their needle like shape (Kozek, Kozek, Wu, Mishra, & Tracy, 2013).

Nanotubes

Nanotubes are hollow tube like structures made up of polymers or any other related material. Carbon nanotubes made up of carbon found their application in pharmaceutics for therapeutic and diagnostic purposes. In bio imaging modified carbon nanotubes provides promising results but their clinical acceptance is low because their length may reach in micrometer range which hinders their entrance in the cell ((P. Liu, 2013).

Merits of Nanoparticle drug Delivery

Nanoparticle drug delivery system shows number of advantages over other drug delivery systems. Some of them are discussed here:

1. The most prominent feature of nanoparticle drug delivery system is their potential of site targeting. Research has been done on nanoparticles for targeting different pathological sites. Two types of targeting can be done either active or passive. Active targeting is done by attaching some functional ligand to the surface of the nanoparticle while passive targeting can be done by enhanced penetration and retention effect because of leaky structure. Ligands used for active targeting may include overexpressed receptors or monoclonal antibodies (Allen, 2002; Marelli, Rechenmacher, Sobahi, Mas-Moruno, & Kessler, 2013). Site specific targeting provides benefit of optimum drug delivery to the affected cells while preventing healthy normal cells for toxic effects of chemotherapeutic agents. This helps to improve the toxic effect profile of encapsulated drugs.
2. Some drugs have poor solubility in aqueous medium so nanoparticles are made to improve the solubility of such type of drugs. Solubility of drugs can be enhanced by two ways either by incorporating the drug in the nanoparticle having a layer of hydrophilic material or by directly encapsulating the drug in the hydrophilic polymer. Chitosan and polyethylene glycol (PEG) are two most widely used hydrophilic polymers to enhance the solubility of such drugs (Geçer, Yıldız, Çalımlı, & Turan, 2010). Due to enhanced surface area, improved wettability and reduced path length, amorphous nanoparticles have been investigated to enhance the solubility of incorporated drugs with poor solubility (P. Liu, 2013).
3. Nanoparticles have been successfully designed for the sustained delivery of the encapsulated drugs. The sustained effect with nanoparticles can be obtained by homogenously dispersing the drug in the nanoparticle matrix. This sustained release system depends on the slow diffusion due to polymer swelling, degradation of nano carriers and slow release of homogenously dispersed drug dependent on the diffusion path length (Attama, Reichl, & Müller-Goymann, 2009).
4. Nanoparticles shows enhanced therapeutic effects and reduced side effects of the number of drugs (Wang, Wei, Zhang, Zhang, & Liang, 2010). Nanoparticles show enhanced penetration due to their small size, loading of multiple drugs at a time. All these unique properties help them to combat with the multidrug resistance phenomena against infectious microorganism and even against cancer (Gao, Chen, Zhang, Chen, & Li, 2011).
5. Due their nano range size and surface modification with different type of ligands, nanoparticles show enhanced penetration in the cells. They also show targeted drug delivery to the tumor cells due to their leaky structure. Leaky vasculature of tumor cells is due to rapid proliferation of cells and increased nutrition and blood supply to them. Thus it provides better penetration of

nanoparticles to the tumor cells rather than normal healthy cells (Greish, 2010).

Problems of Nanoparticles drug Delivery

The above mentioned characteristics of nanoparticles made them ideal candidate for drug delivery but there are some problems with the toxicity and fate of the nanoparticles. These problems occur due the structural components of the nanoparticles i.e. polymers and other materials used. Few of the problems are discussed here:

1. As the nanoparticles are of nano size range so their route of administration is often complex. During oral delivery of nanoparticles, they may be inhaled by breath. Similarly when given topically they may irritate the skin (Morones et al., 2005). Different individuals have different levels of contamination thus different levels of toxicity but there are no proper evidences so conclusion is not yet made (Kreyling, Semmler, & Möller, 2004).
2. Due to the involvement of large number of variables like particle size and complex vasculature of nanoparticles, bio-distribution is not clear (Poland et al., 2008). Surface modification is done for the special application of nanoparticles but sometimes it may induce toxicity. Thus extensive work has to be done on fate and toxicity and biocompatibility data of nanoparticles for their approval.
3. High cost is required for manufacturing nanoparticles because highly advance equipment is required for their formulation and quality control testing. Many processes require removal of toxic solvents and reagents which exhibits high cost. All these factors limit the nanoparticle manufacturing and application to very sophisticated areas of research (Xu, Roy, Cassaro, & Ramsden, 2009).
4. Nel et al., 2006 reviewed that apart from the general toxicities of nanoparticles, some nanoparticles have ability to aggregate to form clumps while some nanoparticles produces reactive oxygen species which may lead to cancer (Nel, Xia, Mädler, & Li, 2006).

Preparation Techniques for Polymeric Nanoparticles

For the preparation of nanoparticles lots of variety in techniques and material are involved. The selection of method and materials is dependent on many factors comprising of mandatory size of nanoparticles, desired drug release profile, intrinsic properties of the drug, (aqueous solubility and stability), Toxicity, biodegradability, biocompatibility, charge and permeability features related to surface. For nanoparticles preparation proteins, peptides, polysaccharides, natural and synthetic polymers are chiefly used as materials(Mohanraj & Chen, 2006). Most commonly used techniques are shown in **Fig 2.**

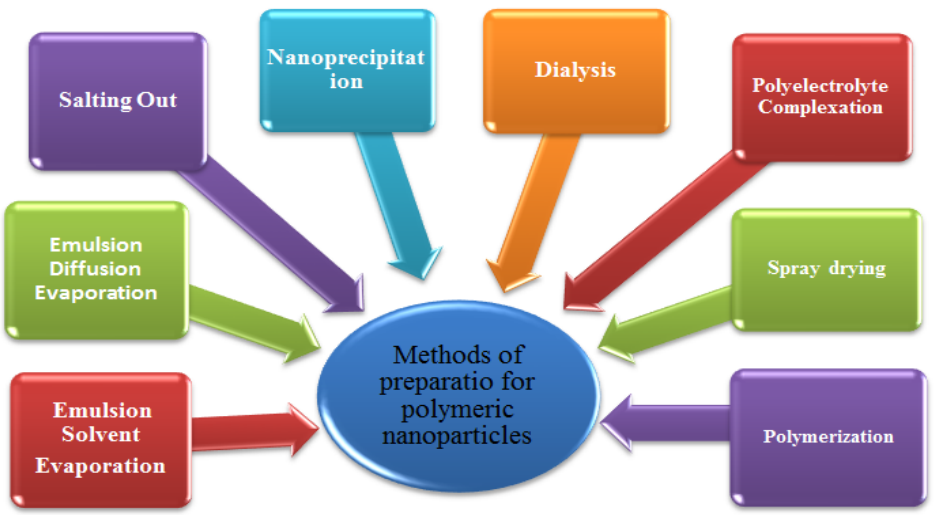

Figure 2: Method of Preparation for Polymeric Nanoparticles

Emulsion Solvent Evaporation Method

Solvent evaporation was the prime method proven to prepare PNPs from a preformed polymer. In the preparation of nanoparticles emulsion solvent evaporation method was uses successfully which consist of making nanoparticles from some biocompatible polymers such as poly (d,l-lactide-coglycolide), (poly-caprolactone) and Eudragit. Emulsion solvent evaporation method includes dissolution of polymer in a volatile organic solvent followed by dispersion of drug in the organic solvent (polymer containing solution) to form dispersion **Fig 3**. After forming of dispersion mixture is added into large volume of aqueous solution, containing a suitable emulsifying agent. Stable emulsion was prepared by evaporating of organic solvent at a suitable temperature and with continuous stirring at reduced pressure(Hans & Lowman, 2002). The technique requires only mild conditions such as ambient temperature and constant stirring which makes it more advantageous over other preparation methods such as spray drying, sonication and homogenization, etc.. Consequently, a stable emulsion can be formed without negotiating the activity of the drugs(Kim, Hwang, Park, & Park, 2002).Emulsion-solvent-evaporation method further divided into two types:

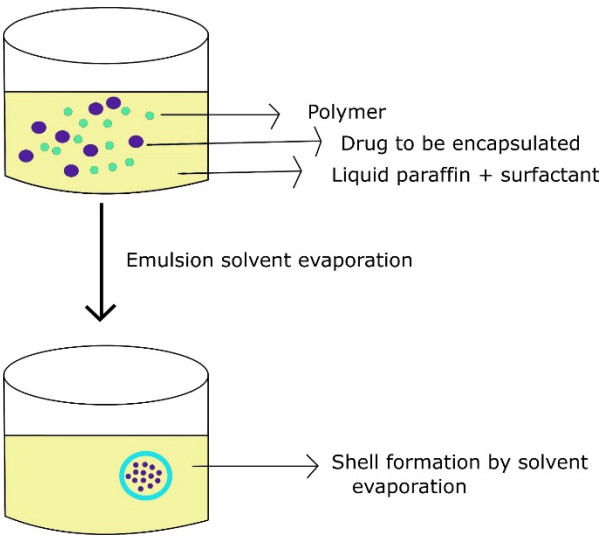

Figure 3: Solvent evaporation method of preparation for nanoparticles

Single Emulsion Solvent Evaporation Method

To formulate nanoparticles from biodegradable polymers such as PLGA single emulsion solvent evaporation method is used. Single emulsion-solvent-evaporation method involves the dissolution of polymer in a volatile organic solvent such as acetone, ethyl acetate, dichloromethane and chloroform followed by dissolution or dispersion of API in the organic solvent (polymer containing solution) to form dispersion. Foremost dispersion is then added in bulk of aqueous solution, having a suitable emulsifying agent such as polyvinyl alcohol (Mu & Feng, 2003) or gelatin to form oil in water emulsion. Serving washing step and avoidance from agglomeration. Makes this method very cost-effective. Particle size of formulation depends on stirring speed, temperature, pressure and dispersing agent. The only drawback of this method is the use of high speed homogenizer for continuous stirring. For hydrophobic drugs this method is used. The production of heterogeneous size distribution is the main problem happened during this method(Kumar, Sulochana, Nirmala, Haridattatreya, & Satchidanandam, 2004).

Double Emulsion Solvent Evaporation Method

For hydrophilic drugs such as proteins, and nucleic acid into PLGA nanoparticles double emulsion solvent evaporation method is used. This method includes firstly, the dissolution of drug in aqueous solution and dissolution of PLGA inorganic phase (acetone, dichloromethane) followed by PLGA solution addition in drug containing aqueous solution

to form W/O emulsion; known as primary emulsion. After that primary emulsion was added in aqueous solution of PVA. At that stage it was emulsified for 1-2 minute underneath stress mixing condition and solvent was evaporated under vacuum. Collection and washing of formed nanoparticles was done by ultracentrifugation and distilled water (Danhier et al., 2012)PLGA nanoparticles which acts as protein carrier are identified to be superior in aspect of stability by this method(Lamprecht et al., 2000). Double emulsion solvent-evaporation technique was also used in making of triptolein loaded nanoparticles(Nicoli et al., 2001).

Emulsion diffusion Evaporation Method

Single emulsion diffusion evaporation method includes the dissolution of drug and the polymer in organic solvent at room temperature followed by organic phase addition in drop wise fashion into aqueous phase containing an emulsifier/stabilizer. Evaporation of organic solvent was done by high speed homogenizer at high stirring which ended in formation of O/W emulsion that causes formation of nanoparticles. Then washing of nanoparticles occurs to remove excess surfactant (Jain, Mittal, K Jain, R Mahajan, & Singh, 2010)..Avoidance to accumulation of nanoparticles and proliferation in shelf life is done by PVA in this method. Cyclosporine loaded PLGA nanoparticles were also prepared by this method which enhance the topical delivery(Jain et al., 2011). Uniform size distribution makes this method superior then the single emulsion solvent evaporation method.

Salting Out

To overcome hazardous to the environment and likewise physiological systems of previously described methods of using organic solvent can be overcome by an altered form of emulsion solvent diffusion method which involves a salting-out process. In this there is avoidance of surfactants and chlorinated solvents happens. In salting out method separation of aqueous phase from water miscible solvent i.e., acetone occurs by adding salting-out agent with stabilizer. As strong salting-out effect agents, salt or sucrose are chosen in the aqueous phase which do not pay any high-shear forces. As appropriate electrolytes magnesium chloride, calcium chloride and magnesium acetate are commonly used(Ganachaud & Katz, 2005).Addition of additional amount of water in the emulsion becomes the cause of precipitation of the polymer leads to reverse salting out effect. In reality, dilution can cause reduction of salt or sucrose concentration in the continuous phase of the emulsion and brings the movement of the solvent from the emulsion droplets(Galindo-Rodriguez, Allemann, Fessi, & Doelker, 2004). For topical drug delivery sometime, interfacial polymerization and emulsion polymerization and dialysis methods are used(Ochekpe, Olorunfemi, & Ngwuluka, 2009).

Nanoprecipitation

The nanoprecipitation method was established for the formulation of PNP. Another name of this method is solvent displacement method. this method includes the addition of polymer in water-miscible organic solvent followed by addition in aqueous phase in the existence of surfactant. Basic components of this method have polymer (natural, synthetic or semi synthetic), the polymer solvent and Organic solvent (i.e., ethanol, hexane, methylene chloride, acetone or di oxane). Due to miscibility and easy removal by evaporation acetone is the most commonly used polymer solvent in nanoprecipitation method(Dalpiaz, Vighi, Pavan, & Leo, 2009).Due to instant diffusion from oily phase and polymer is precipitated that primes to the formation of small droplets of organic solvent becomes cause of increase in surface area(Mishra, Patel, & Tiwari, 2010). Lipophilic drugs are more prone to this method than the hydrophilic drugs. Nanoprecipitation has fast, simple and reproducible properties that make this method similar to other methods which is generally used like Nano spheres and nanocapsules(Rangari & Ravikumar, 2015). PLGA loaded nanoparticles with Nelfinavir by using nanoprecipitation method was also published(Venkatesh et al., 2015).

Dialysis (analogous to Nano precipitation)

Dialysis is a flippant method i.e. parallel to nanoprecipitation engaged in the formulation of tiny, finely distributed PNP. This method includes dissolution of polymer in an organic solvent followed by positioning of it inside a dialysis tube with an suitable molecular weight cutoff. Dialysis is completed further by a non-solvent miscibility with the former miscible. The flow of the solvent along the membrane is followed by the full buildup of polymer attributed to decline in solubility primes to development of homogeneous suspensions of nanoparticles(Kostag, Köhler, Liebert, & Heinze, 2010).

Polyelectrolyte complexation (PEC)

The ionic interactions of two oppositely charged

polymers leads to development of complex in polyelectrolyte complexation (PEC) method. A network is made when two oppositely charged polyelectrolytes impasse each other in an aqueous solution and cross-linked ionically. It has been reported that interaction between the amino groups of cationic chitosan with an anionic polymer through ionic binding that has carboxylic groups, like alginate causes the formation of polyelectrolyte complex(Douglas & Tabrizian, 2005).The first step in preparation of nanoparticles through polyelectrolyte complexation involves the dissolution of chitosan in acetic acid solution and sodium alginate in purified water to get stock solutions followed by dissolution of drug into required solvent and further added into sodium alginate solution. The spontaneous production of nanoparticles take place by incorporation, under sufficient magnetic stirring at room temperature, of the sodium alginate containing drug solutions into CS solution. At the end, freshly made nanoparticles were then concerted by centrifugation and collected after freeze drying(Rodrigues, da Costa, & Grenha, 2012).

Spray drying method

Spray drying is an easy, orthodox and cost effective means that occurs by atomizing/spraying suspensions into droplets engaged by a drying process, later in solid particles. Sols or colloidal particles are classically used as a pioneer in spray drying method. Spherical particles of uniform geometry are produced by this technique(Iskandar, Gradon, & Okuyama, 2003).Double emulsion solvent evaporation and spray drying techniques combined in which w/o/w emulsion was spray dried in a stream of heated air at the temperature 95-110°C and pressure 5-8 bars(Booysen et al., 2013).

Polymerization

Earlier enlightened methods include the production of PNPs from already made polymers and does not having polymerization steps. Monomer's polymerization can also be used to prepare nanoparticles. It stimulated the researchers to study polymerization reactions dynamically. The complete process for the making of PNPs by the polymerization of monomers is deliberated here. In the production of PNPs by polymerization the monomers are mechanically dispersed in aqueous acidic medium in the index of surfactant without irradiation or an initiator followed by addition of surface-active agent (polymerization medium) monomer in aqueous medium under forceful mechanical stirring to polymerize monomer at ambient temperature. Either the drug is added in the polymerization medium afore the addition of the monomer or at the termination of the polymerization reaction. Refining of NP suspension is done through ultracentrifugation or by suspending the particles in an isotonic surfactant-free medium (Soppimath, Aminabhavi, Kulkarni, & Rudzinski, 2001).

Conclusion

Nanoparticles reveals interesting properties owing to their remarkable chemical and physical characteristics and are appropriate for various pharmaceutical fields. For the preparation of nanoparticles of different sizes and shapes different methods have been developed including emulsion solvent evaporation, ionic gelation, nanoprecipataion, polymerization and spray drying. Novel approaches for nanoparticles preparation can be exploited for various drug delivery systems to achieve better therapeutic applications.

References

Agashe, H., Sahoo, K., Lagisetty, P., & Awasthi, V. (2011). Cyclodextrin-mediated entrapment of curcuminoid 4-[3, 5-bis (2-chlorobenzylidene-4-oxo-piperidine-1-yl)-4-oxo-2-butenoic acid] or CLEFMA in liposomes for treatment of xenograft lung tumor in rats. Colloids and Surfaces B: *Biointerfaces, 84*(2), 329-337.

Allen, T. M. (2002). Ligand-targeted therapeutics in anticancer therapy. *Nature Reviews Cancer, 2*(10), 750.

Anselmo, A. C., & Mitragotri, S. (2014). Cell-mediated delivery of nanoparticles: taking advantage of circulatory cells to target nanoparticles. *Journal of controlled release, 190*, 531-541.

Attama, A., Reichl, S., &Müller-Goymann, C. (2009). Sustained release and permeation of timolol from surface-modified solid lipid nanoparticles through bioengineered human cornea. *Current eye research, 34*(8), 698-705.

Bhagwat, R., & Vaidhya, I. (2013). Novel drug delivery systems: An overview. *International Journal of Pharmaceutical Sciences and Research, 4*(3), 970.

Booysen, L., Kalombo, L., Brooks, E., Hansen, R., Gilliland, J., Gruppo, V., . . . Kotze, A. (2013). In vivo/in vitro pharmacokinetic and pharmacodynamic study of spray-dried poly-(dl-lactic-co-glycolic) acid nanoparticles encapsulating rifampicin and isoniazid. *International journal of pharmaceutics, 444*(1-2), 10-17.

Dalpiaz, A., Vighi, E., Pavan, B., & Leo, E. (2009). Fabrication via a nonaqueous nanoprecipitation method, characterization and in vitro biological behavior of N6-cyclopentyladenosine-loaded nanoparticles. *Journal of pharmaceutical sciences, 98*(11), 4272-4284.

Danhier, F., Ansorena, E., Silva, J. M., Coco, R., Le Breton, A., & Préat, V. (2012). PLGA-based nanoparticles: an overview of biomedical applications. *Journal of controlled release, 161*(2), 505-522.

Douglas, K. L., & Tabrizian, M. (2005). Effect of experimental parameters on the formation of alginate–chitosan nanoparticles and evaluation of their potential application as DNA carrier. *Journal of Biomaterials Science, Polymer Edition, 16*(1), 43-56.

El-Nour, K. M. A., Eftaiha, A. a., Al-Warthan, A., & Ammar, R. A. (2010). Synthesis and applications of silver nanoparticles. *Arabian journal of chemistry, 3*(3), 135-140.

Emeje, M. O., Obidike, I. C., Akpabio, E. I., & Ofoefule, S. I. (2012). Nanotechnology in drug delivery. *Recent advances in novel drug carrier systems*, 69-106.

Galindo-Rodriguez, S., Allemann, E., Fessi, H., & Doelker, E. (2004). Physicochemical parameters associated with nanoparticle formation in the salting-out, emulsification-diffusion, and nanoprecipitation methods. *Pharmaceutical research, 21*(8), 1428-1439.

Ganachaud, F., & Katz, J. L. (2005). Nanoparticles and nanocapsules created using the Ouzo effect: spontaneous emulsification as an alternative to ultrasonic and high-shear devices. *ChemPhysChem, 6*(2), 209-216.

Gao, Y., Chen, L., Zhang, Z., Chen, Y., & Li, Y. (2011). Reversal of multidrug resistance by reduction-sensitive linear cationic click polymer/iMDR1-pDNA complex nanoparticles. *Biomaterials, 32*(6), 1738-1747.

Geçer, A., Yıldız, N., Çalımlı, A., & Turan, B. (2010). Trimethyl chitosan nanoparticles enhances dissolution of the poorly water soluble drug Candesartan-Cilexetil. *Macromolecular research, 18*(10), 986-991.

Greish, K. (2010). Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting Cancer Nanotechnology (pp. 25-37): *Springer*.

Hans, M. L., &Lowman, A. M. (2002). Biodegradable nanoparticles for drug delivery and targeting. *Current Opinion in Solid State and Materials Science, 6*(4), 319-327.

In, G. K., &Nieva, J. (2015). Emerging chemotherapy agents in lung cancer: nanoparticles therapeutics for non-small cell lung cancer. *Translational Cancer Research, 4*(4), 340-355.

Iskandar, F., Gradon, L., & Okuyama, K. (2003). Control of the morphology of nanostructured particles prepared by the spray drying of a nanoparticle sol. *Journal of Colloid and Interface Science, 265*(2), 296-303.

Jain, S., Mittal, A., & K Jain, A. (2011). Enhanced topical delivery of cyclosporin-A using PLGA nanoparticles as carrier. *Current nanoscience, 7*(4), 524-530.

Jain, S., Mittal, A., K Jain, A., R Mahajan, R., & Singh, D. (2010). Cyclosporin A loaded PLGA nanoparticle: preparation, optimization, in-vitro characterization and stability studies. *Current Nanoscience, 6*(4), 422-431.

Khan, I., Saeed, K., & Khan, I. (2017). Nanoparticles: Properties, applications and toxicities. *Arabian journal of chemistry*.

Kim, B., Hwang, S., Park, J., & Park, H. J. (2002). Preparation and characterization of drug-loaded polymethacrylate microspheres by an emulsion solvent evaporation method. *Journal of microencapsulation, 19*(6), 811-822.

Kostag, M., Köhler, S., Liebert, T., & Heinze, T. (2010). Pure cellulose nanoparticles from trimethylsilyl cellulose. *Paper presented at the Macromolecular symposia*.

Kozek, K. A., Kozek, K. M., Wu, W.-C., Mishra, S. R., & Tracy, J. B. (2013). Large-scale synthesis of gold nanorods through continuous secondary growth. Chemistry of Materials, 25(22), 4537-4544.

Kreyling, W. G., Semmler, M., & Möller, W. (2004). Dosimetry and toxicology of ultrafine particles. *Journal of Aerosol Medicine, 17*(2), 140-152.

Kumar, P., Sulochana, P., Nirmala, G., Haridattatreya, M., & Satchidanandam, V. (2004). Conserved amino acids 193–324 of non-structural protein 3 are a dominant source of peptide determinants for CD4+ and CD8+ T cells in a healthy Japanese encephalitis virus-endemic cohort. *Journal of General Virology, 85*(5), 1131-1143.

Lamprecht, B., Schider, G., Lechner, R., Ditlbacher, H., Krenn, J. R., Leitner, A., & Aussenegg, F. R. (2000). Metal nanoparticle gratings: influence of dipolar particle interaction on the plasmon resonance. *Physical review letters, 84*(20), 4721.

Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L., & Muller, R. N. (2008). Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical reviews, 108*(6), 2064-2110.

Liu, P. (2013). Modification strategies for carbon nanotubes as a drug delivery system. Industrial & Engineering *Chemistry Research, 52*(38), 13517-13527.

Liu, Z., Wu, Y., Guo, Z., Liu, Y., Shen, Y., Zhou, P., & Lu, X. (2014). Effects of internalized gold nanoparticles with respect to cytotoxicity and invasion activity in lung cancer cells. *PLoS One, 9*(6), e99175.

Lu, Z., Bei, J., & Wang, S. (1999). A method for the preparation of polymeric nanocapsules without stabilizer. *Journal of Controlled Release, 61*(1-2), 107-112.

Marelli, U. K., Rechenmacher, F., Sobahi, T. R. A., Mas-Moruno, C., & Kessler, H. (2013). Tumor targeting via integrin ligands. *Frontiers in oncology*, 3, 222.

Mishra, B., Patel, B. B., & Tiwari, S. (2010). Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery. Nanomedicine: *Nanotechnology, biology and medicine, 6*(1), 9-24.

Mohanraj, V., & Chen, Y. (2006). Nanoparticles-a review. *Tropical journal of pharmaceutical research, 5*(1), 561-573.

Morones, J. R., Elechiguerra, J. L., Camacho, A., Holt, K., Kouri, J. B., Ramírez, J. T., & Yacaman, M. J. (2005). The bactericidal effect of silver nanoparticles. *Nanotechnology, 16*(10), 2346.

Mu, L., & Feng, S. (2003). A novel controlled release formulation for the anticancer drug paclitaxel (Taxol®): PLGA nanoparticles containing vitamin E TPGS. *Journal of controlled release, 86*(1), 33-48.

Muhamad12, I. I., Selvakumaran, S., & Lazim, N. A. M. (2014). Designing polymeric nanoparticles for targeted drug delivery system. *Nanomed*, 287, 287.

Nel, A., Xia, T., Mädler, L., & Li, N. (2006). Toxic potential of materials at the nanolevel. *science, 311*(5761), 622-627.

Nicoli, S., Santi, P., Couvreur, P., Couarraze, G., Colombo, P., & Fattal, E. (2001). Design of triptorelin loaded nanospheres for transdermal iontophoretic administration. *International journal of pharmaceutics, 214*(1-2), 31-35.

Ochekpe, N. A., Olorunfemi, P. O., & Ngwuluka, N. C. (2009). Nanotechnology and drug delivery part 2: nanostructures for drug delivery. *Tropical journal of pharmaceutical research, 8*(3).

Ouyang, Y., Shi, H., Fu, R., & Wu, D. (2013). Highly monodisperse microporous polymeric and carbonaceous nanospheres with multifunctional properties. *Scientific reports, 3*, 1430.

Pandey, N., Dhiman, S., Srivastava, T., & Majumder, S. (2016). Transition metal oxide nanoparticles are effective in inhibiting lung cancer cell survival in the hypoxic tumor microenvironment. *Chemico-biological interactions, 254*, 221-230.

Poland, C. A., Duffin, R., Kinloch, I., Maynard, A., Wallace, W. A., Seaton, A., . . . Donaldson, K. (2008). Carbon nanotubes introduced into the

abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nature nanotechnology, 3*(7), 423.

Rangari, A. T., & Ravikumar, P. (2015). Polymeric nanoparticles based topical drug delivery: an overview. *Asian Journal of Biomedical and Pharmaceutical Sciences, 5*(47), 5.

Rodrigues, S., da Costa, A. M. R., & Grenha, A. (2012). Chitosan/carrageenan nanoparticles: Effect of cross-linking with tripolyphosphate and charge ratios. *Carbohydrate polymers, 89*(1), 282-289.

Soppimath, K. S., Aminabhavi, T. M., Kulkarni, A. R., & Rudzinski, W. E. (2001). Biodegradable polymeric nanoparticles as drug delivery devices. *Journal of controlled release, 70*(1-2), 1-20.

Stevanovic, M., & Uskokovic, D. (2009). Poly (lactide-co-glycolide)-based micro and nanoparticles for the controlled drug delivery of vitamins. *Current nanoscience, 5*(1), 1-14.

Venkatesh, D. N., Baskaran, M., Karri, V. V. S. R., Mannemala, S. S., Radhakrishna, K., & Goti, S. (2015). Fabrication and in vivo evaluation of Nelfinavir loaded PLGA nanoparticles for enhancing oral bioavailability and therapeutic effect. *Saudi Pharmaceutical Journal, 23*(6), 667-674.

Wang, Y., Wei, X., Zhang, C., Zhang, F., & Liang, W. (2010). Nanoparticle delivery strategies to target doxorubicin to tumor cells and reduce side effects. *Therapeutic delivery, 1*(2), 273-287.

Xu, Y., Roy, R., Cassaro, G., & Ramsden, J. (2009). Development of a cost estimating framework for nanotechnology based products Global Perspective for Competitive Enterprise, Economy and Ecology (pp. 193-201): *Springer*.

Yang, W.-W., & Pierstorff, E. (2012). Reservoir-based polymer drug delivery systems. *Journal of laboratory automation, 17*(1), 50-58.