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NANOPARTICLES BASED DRUG DELIVERY SYSTEM (A REVIEW)

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ABSTRACT

Recently nano-pharmaceuticals reveal enormous potential in drug delivery as carrier for spatial and temporal delivery of bioactive and diagnostics. Additionally it also provides smart materials for tissue engineering. This discipline is now well- established for drug delivery, diagnostics, prognostic and treatment of diseases through its nanoengineered tools. Nanotechnology explores electrical, optical, and magnetic activity as well as structural behavir at the molecular and submolecular level. It has the potential to revolutionize a series of medical and biotechnology tools and procedures so that they are portable, cheaper, safer, and easier to administer. Nanoparticles are being used for diverse purposes, from medical treatments, using in various branches of industry production such as solar and oxide fuel batteries for energy storage, to wide incorporation into diverse materials of everyday use such as cosmetics or clothes, optical devices, catalytic, bactericidal, electronic, sensor technology, biological labelling and treatment of some cancers.

KEYWORDS: Nano-pharmaceuticals, Nanotechnology, Nanoparticles.

INTRODUCTION

Nanotechnology is the science that deals with matter at the scale of 1 billionth of a meter, and is also the study of manipulating matter at the atomic and molecular scale. A nanoparticle is the most fundamental component in the fabrication of a nanostructure, and is far smaller than the world of everyday objects that are described by Newton ' s laws of motion, but bigger than an atom or a simple molecule that are governed by quantum mechanics. The United States instituted the National Nanotechnology Initiative (NNI) back in 2000, which was soon followed (2001) by a plethora of projects in nanotechnology in nearly most of the U.S. Departments and Agencies.[1] About 20 Research Centers were subsequently funded by theNationa1 Science Foundation (NSF), an agency responsible solely to the President of the United States and whose mandate is to fund the best of fundamental science and technology projects. NSF was the lead U.S. agency to carry forward the NNI. The word "nanotechnology" soon caught the attention of various media (TV networks, the internet, etc.) and the imagination and fascination of the community at large. In general, the size of a nanoparticle spans the range between 1 and 100 nm. Metallic nanoparticles have different physical and chemical properties from bulk metals (e.g., lower melting points, higher specific surface areas, specific optical properties, mechanical strengths, and specific magnetizations), properties that might prove attractive in various industrial applications. However, how a nanoparticle is viewed and is defined depends very much on the specific application of particular importance, the optical property is one of the fundamental attractions and a characteristic of a nanoparticle. For example, a 20-nm gold nanoparticle has a characteristic wine red color. A silver nanoparticle is yellowish gray. Platinum and palladium nanoparticles are black. Not surprisingly, the optical characteristics of nanoparticles have been used from time immemorial in sculptures and paintings even before the 4th century AD. The most famous example is the Lycurgus cup (fourth century AD). This extraordinary cup is the only complete historic example of a very special type of glass, known as dichroic glass, that changes color when held up to the light. The opaque green cup turns to a glowing translucent red when light is shone through it internally (i.e., light is incident on the cup at 90° to the viewing direction). Analysis of the glass revealed that it contains a very small quantity of tiny (~ 70 nm) metal crystals of Ag and Au in an approximate molar ratio of 14: 1, which give it these unusual optical properties. It is the presence of these nanocrystals that gives the Lycurgus Cup its special color display. The reader can marvel at the cup now in the British Museum.[2] The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is

confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Depending upon to the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carrier of DNA in gene therapy, and their ability to deliver proteins, peptides and genes. The input of today's nanotechnology is that it allows real progress to achieve temporal and spatial site-specific delivery. The market of nanotechnology and drug delivery systems based on this technology will be widely felt by the pharmaceutical industry. In recent years, the number of patents and products in this field is increasing significantly. Several terminologies have been used to describe nanoparticulate drug delivery systems. In most cases, either polymers or lipids are used as carriers for the drug, and the delivery systems have particle size distribution from few nanometers to few hundred nanometers. Nanomedicine is a large subject area and includes nanoparticles that act as biological mimetic (e.g. functionalized carbon nanotubes), "nanomachics" (e.g. those made from interchangeable DNA parts and DNA scaffolds such as octahedron and stick cube), nanofibers and polymeric nanoconstructs as biomaterials (e.g. molecular self-assembly and nano-fibers of peptides and peptideamphiphiles for tissue engineering), shape memory polymers as molecular switches, nanoporous membranes), and nanoscale micro fabrication based devices (e.g. silicon microchips for drug release and micro machined hollow needles and two dimensional needles assay from single crystal silicon), sensors and laboratory diagnostics. Recent developments in nanotechnology have shown that nanoparticles (structures smaller than 100 nm in at least one dimension) have a great potential as drug carriers. Due to their small sizes, the nanostructures exhibit unique physicochemical and biological properties (e.g., an enhanced reactive area as well as an ability to cross cell and tissue barriers) that make them a favorable material for biomedical applications. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties.[2,4]

HISTORY OF NANO PARTICLES

Nanoscience, nanotechnology, nanoparticles have become common words not only in research but also in normal life. The history of nanoparticle usage dates back to the 9th century when the artisans of Mesopotamia used nanoparticles to generate glittering effects to pots. The properties of nanoparticles were proved in 1857 in Faraday's famous paper, "Experimental relations of gold (and other metals) to light". In early 1940's silica nanoparticles were being manufactured in USA for making ultrafine carbon black for rubber reinforcement. In 1960's and 1970 metallic nano powders were developed for magnetic recording tapes. Graqvist and Buhrman (1976) described the production of nanocrystals by gas evaporation techniques. Nanosized particles are used in manufacture of several every day consumer products. Chaudhary et al (2011) reported that Ayurvedic bhasmas are in nanometer dimensions and are considered as nanomedicine free from toxicity in therapeutic doses. Bhasmas produced by biological methods of nanoparticles is prescribed with several medicines in the ayurvedic field. This is one of the most ancient applications of nanomedicine. Bhasmas are produced by two methods viz., Putapaka method and Kupipakwa method. These preparation methods of Bhasmas are in tone with nanotechnology and contemporary era and proved advancement of Rasashastra, a branch of Ayurveda (Prasanta Kumar and Chaudhary 2010).[5]

ADVANTAGE OF NANO PARTICLES

The advantages of using nanoparticles as a drug delivery system include the following:

- Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
- They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
- Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

- The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.[6]
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- They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.[7]
- Nanoparticles can better deliver drugs to tiny areas within the body.
- Engineering on this scale enables researchers to exercise exquisite and previously unthinkable control over the physical attributes of polymers and other biomaterials.
- Nanoparticles overcome the resistance offered by the physiological barriers in the body because efficient delivery of drug to various parts of the body is directly affected by particle size.
- Nanoparticles aid in efficient drug delivery to improve aqueous solubility of poorly soluble drugs that enhance Bioavailability for timed release of drug molecules, and precise drug targeting.
- The surface properties of nanoparticles can be modified for targeted drug delivery for e.g. small molecules, proteins, peptides, and nucleic acids loaded nanoparticles are not recognized by immune system and efficiently targeted to particular tissue types.
- Targeted nano drug carriers reduce drug toxicity and provide more efficient drug distribution. Nanocarriers holds promise to deliver biotech drugs over various anatomic extremities of body such as blood brain barrier.[8]

DISADVANTAGES OF NANO PARTICLES

- One of the major disadvantages of nanotechnology at present is that it is very expensive and developing it can cost a lot of money. Moreover it is also difficult to set up and manufacture the technology. Even the labor costs are high and this is why the resultant items or products are quite expensive.
- Nanotechnology has put a lot of people out of jobs in the past few decades. This is yet another major disadvantage associated with this technology. There has been a loss in jobs in the manufacturing and traditional farming industry and this loss is only expected to increase in the coming time.
- Development of nanotechnology can bring about a certain kind of a crash in the markets which is due to the lowering of value of diamonds and oil due to the development of alternate source of energy. Since these sources of energy are more efficient and won't require fossil fuels, it can put many markets to their brink. This also means that since people are now capable of developing products at a molecular level, diamonds may lose their value because they can now be mass produced.
- Due to the development of Nano technology, atomic weapons can now be made more accessible and can also be made more destructive and powerful. This is yet another major disadvantage of nanotechnology.
- Another issue with nanotechnology is that since the particles of nanotechnology are very minute, problems can crop up from the inhalation of these particles.
- Working with nanotechnology can prove to be very risky too. The investment needed to start up a project involving this science can be huge without any guarantee of success and this can lead to huge losses. At the same time, the technology poses risks to health as well.
- It is true that nanotechnology has raised our standard of living but it has also led to an increase in the levels of pollution. The pollution caused due to nanotechnology is known as Nano pollution and this can be very dangerous for living organisms.
- Another major disadvantage of nanotechnology is the possible mass poisoning of material which is processed at a Nano scale. This can leave a negative impact on the health and industry and can happen if the coatings on the products produced by this technology include some of the poisonous micro particles which can penetrate into our brains.[9]

PROPERTIES OF NANO PARTICLES

Particle size

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over microparticles as a drug delivery system.[10] Generally nanoparticles have relatively higher intracellular uptake compared to microparticles and available to a wider range of biological targets due to their small size and relative mobility. Desai et al found that 100 nm nanoparticles had a 2.5 fold greater uptake than 1 µm microparticles, and 6 fold greater uptake than 10 µm microparticles in a Caco-2 cell line.[11] In a subsequent study,[12] the nanoparticles penetrated throughout the submucosal layers in a rat in situ intestinal loop model, while microparticles were predominantly localized in the epithelial lining. It was also reported that nanoparticles can across the blood-brain barrier following the opening of tight junctions by hyper osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumors. Tween 80 coated nanoparticles have been shown to cross the blood-brain barrier. In some cell lines, only submicron nanoparticles

can be taken up efficiently but not the larger size microparticles.[13-14] Drug release is affected by particle size. Smaller particles have larger surface area, therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out.[15] Smaller particles also have greater risk of aggregation of particles during storage and transportation of nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability. Polymer degradation can also be affected by the particle size. For instance, the rate of PLGA polymer degradation was found to increase with increasing particle size in vitro.[16] It was thought that in smaller particles, degradation products of PLGA formed can diffuse out of the particles easily while in large particles, degradation products are more likely remained within the polymer matrix for a longer period to cause autocatalytic degradation of the polymer material. Therefore, it was hypothesized that larger particles will contribute to faster polymer degradation as well as the drug release. However, Panyam et al prepared PLGA particles with different size ranges and found that the polymer degradation rates in vitro were not substantially different for different size particles.[17] Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by Brownian motion and light scattering properties.[18] The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

Surface properties of nanoparticles

When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation.[19] Apart from the size of nanoparticles, their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the in vivo fate of nanoparticles.[20,21] Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. The association of a drug to conventional carriers leads to modification of the drug biodistribution profile, as it is mainly delivered to the mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. Indeed, once in the blood stream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs.[22] Generally, it is IgG, compliment C3 components that are used for recognition of foreign substances, especially foreign macromolecules. Hence, to increase the likelihood of the success in drug targeting by nanoparticles, it is necessary to minimize the opsonization and to prolong the circulation of nanoparticles in vivo. This can be achieved by:

(a) Surface coating of nanoparticles with hydrophilic polymers/surfactants.
(b) Formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, poloxamer, poloxamine and polysorbate 80 (Tween 80). Studies show that PEG conformation at the nanoparticle surface is of utmost importance for the opsonin repelling function of the PEG layer. PEG surfaces in brush-like and intermediate configurations reduced phagocytosis and complement activation whereas PEG surfaces in mushroom-like configuration were potent complement activators and favored phagocytosis.[23]

Zeta potential

The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles.[24] It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. The zeta potential can also be used to determine whether a charged active material is encapsulated within the centre of the nanocapsules or adsorbed onto the surface.[24]

Atomic Force Microscopy

This technique is also known as scanning force microscopy (technique that forms images of surfaces using a prob that scans the specimen), very high resolution type of scanning probe microscopy, with reported resolution on the order of fractions of a nanomerter, more than 100 times better than the optical diffraction limit. The atomic force microscopy is based on a physical scanning of samples at sub-micron level using a probe tip of atomic scale and offers ultra-high resolution in particle size measurement.[25] Depending upon properties, samples are usually scanned in contact or noncontact mode. During contact mode, the topographical map is generated by tapping the probe on to the surface across the sample and probe hovers over the conducting surface in non-contact mode. One of the prime advantages of AFM is its ability to image non-conducting samples without any specific treatment. This feature allows the imaging of delicate biological and polymeric nano and microstructures.[26] Moreover AFM (without any mathematical calculation) provides the most accurate description of size, size distribution and real picture which helps in understanding the effect of various biological conditions.[27]

Surface Hydrophobicity

Techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption of probes, contact angle measurements etc. can be utilized for the determination of surface hydrophobicity. Recent

advancement in research offers several sophisticated analytical tools for surface property analysis of nanoparticles. modern technique such as X-ray photon correlation spectroscopy not only determine surface hydrophobicity but also permits the identification of specific chemical groups on the surface of nanoparticles.[27]

Method of preparation[28-31]

Nanoparticles are aimed to be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection criteria of matrix materials depend on many factors such as:

(a) Size of nanoparticles required.
(b) Inherent properties of the drug, e.g., aqueous solubility and stability.
(c) Surface characteristics such as Charge and Permeability.
(d) Degree of biodegradability, biocompatibility and toxicity.
(e) Drug release profile desired.
(f) Antigenicity of the final product.

Nanoparticles preparation is most frequently by three methods

(1) Dispersion of preformed polymers.
(2) Polymerization of monomers.
(3) Ionic gelation or coacervation of hydrophilic polymers. However, other methods such as supercritical fluid technology and particle replication in non-wetting templates have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of nanoparticles in industry.

Dispersion of preformed polymers

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticle from poly (lactic acid) (PLA); poly (D, L-glycolide), PLG; poly (D, Llactide-coglycolide) (PLGA) and poly (cyanoacrylate) (PCA), this technique can be used in various ways as described further.

Solvent evaporation method[32]

Solvent evaporation method is one of the most frequently used methods for the preparation of nanoparticles. This method involves two steps (first is emulsification of the polymer solution into an aqueous phase and second is evaporation of polymer solvent, inducing polymer precipitation as nano spheres). This method is based on the solubility of polymer and hydrophobic drug since both polymer and hydrophobic drug are dissolved in an organic solvent (dichloromethane, chloroform or ethyl acetate) which is also used as the solvent for dissolving the. Mixture obtained from polymer and drug solution is then emulsified in an aqueous solution. This aqueous solution contains surfactant or emulsifying agent to form oil in water (o/w) emulsion. Once the stable emulsion forms, the organic solvent is evaporated either by continuous stirring or by reducing the pressure. Size range of nanoparticles was found to be influenced by the concentrations and type of stabilizer, polymer concentration and homogenizer speed.[33] Ultra sonication or high-speed homogenization may be often employed in order to produce small particle size.[34]

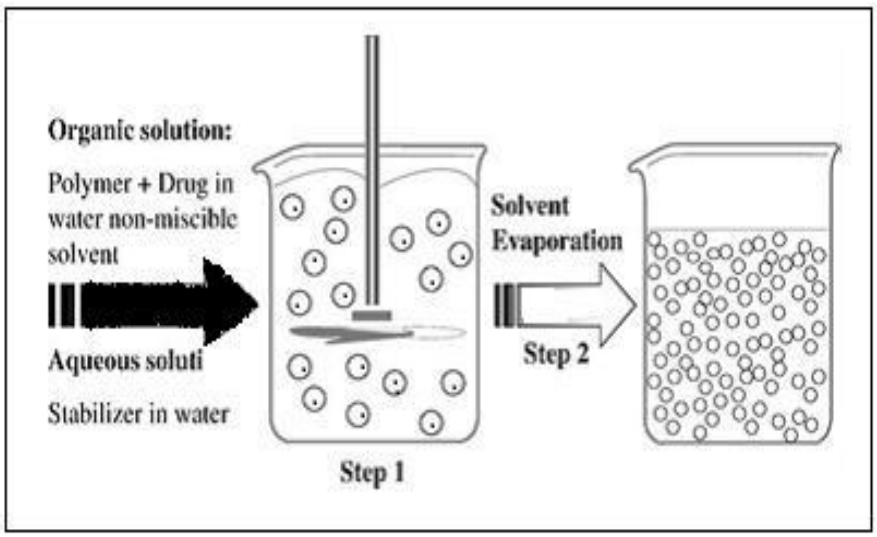

Fig. 1: Representation of Solvent Evaporation Method.

The nano particles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug and lyophilized for storage.[35] Modification of this method is known as solvent evaporation method and high pressure emulsification.[36] This method involves preparation of a emulsion which is then subjected to homogenization under high pressure followed by overall stirring to remove organic solvent.[37] The size can be controlled by adjusting the stirring rate, type and amount of dispersing agent, viscosity of organic and aqueous phases and temperature.[38] However this method can be applied to lipo soluble drugs and

limitation are imposed by the scale up issue. Polymers used in this method are PLGA,[39] PLA,[40] cellulose acetate phthalate,[41] EC,[42] Poly (β –hydroxy butyrate) (PHB),[43] Poly (β-capro lactone)\ (PCL).[44]

Spontaneous emulsification or solvent diffusion method[45]

This is a modified version of solvent evaporation method. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as anoil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase.

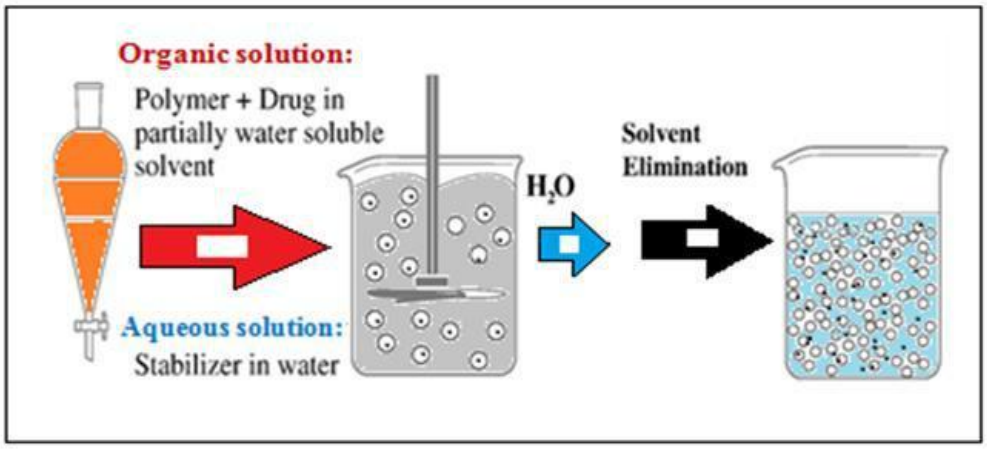

Fig 2: Representation of the emulsification-diffusion technique.

Polymerization method[46]

In this method, monomers are polymerized to form nanoparticle in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption on to the nanoparticles after polymerization completed. The nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutyl cyanoacrylate or poly (alkyl cyanoacrylate) nanoparticles.

Coacervation or ionic gelation method[47]

Recent exploration of biodegradable polymers such as gelatin and sodium alginate has been focused now to yield biodegradable nanoparticles having features like biocompatibility and low toxicity. Methods such as ionic gelation can be used for preparing hydrophilic polymer based nanoparticles. Calvo and co-workers developed method for preparing chitosan based nanoparticles by ionic gelation method.[47] In this method two different aqueous phases are prepared for polymer [chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO)] and the other is for poly anion sodium tri poly phosphate. This method is based on the strong electrostatic interaction between positively charged amino group of chitosan and negative charged tri polyphosphate to form coacervates with a size in the range of nanometer. Existence of strong electrostatic interaction between two aqueous phases leads to the formation of coacervates. In contrast ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

Production of nanoparticles using supercritical fluid technology[48]

Conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods require the use of organic solvents which are hazardous to the environment as well as to physiological systems. Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles because supercritical fluids are environmentally safe. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure.[48] Supercritical CO2 (SC CO2) is the most widely used supercritical fluid because of its mild critical conditions (Tc = 31.1 °C, Pc = 73.8 bars), nontoxicity, non-flammability, and low price. The most common processing techniques involving supercritical fluids are supercritical anti solvent (SAS) and rapid expansion of critical solution (RESS). The process of SAS employs a liquid solvent, eg methanol, which is completely miscible with the supercritical fluid (SC CO2), to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting the formation of nanoparticles. RESS differs from the SAS process in that its solute is

dissolved in a supercritical fluid (such as supercritical methanol) and then the solution is rapidly expanded through a small nozzle into a region lower pressure,[49] Thus the solvent power of supercritical fluids dramatically decreases and the solute eventually precipitates. This technique is clean because the precipitate is basically solvent free. RESS and its modified process have been used for the product of polymeric nanoparticles. Supercritical fluid technology technique, although environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive.[50]

Methods of Nanoparticles Synthesis

Two approaches have been known in the preparation of ultra fine particles from ancient times. The first is the breakdown (top-down) method by which an external force is applied to a solid that leads to its break-up into smaller particles. The second is the build-up (bottom-up) method that produces nanoparticles starting from atoms of gas or liquids based on atomic transformations or molecular condensations. The top-down method is the method of breaking up a solid substance; it can be sub-divided into dry and wet grinding. A characteristic of particles in grain refining processes is that their surface energy increases, which causes the aggregation of particles to increase also. In the dry grinding method the solid substance is ground as a result of a shock, a compression, or by friction, using such popular methods as a jet mill, a hammer mill, a shearing mill, a roller mill, a shock shearing mill, a ball mill, and a tumbling mill. Since condensation of small particles also takes place simultaneously with pulverization, it is difficult to obtain particle sizes of less than 3μ m by grain refining. On the other hand, wet grinding of a solid substrate is carried out using a tumbling ball mill, or a vibratory ball mill, a planetary ball mill, a centrifugal fluid mill, an agitating beads mill, a flow conduit beads mill, an annular gap beads mill, or a wet jet mill. Compared with the dry method, the wet process is suitable for preventing the condensation of the nanoparticles so formed, and thus it is possible to obtain highly dispersed nanoparticles. Other than the above, the chemical method and the mechanical alloying method are also known top-down methods. The bottom-up approach is roughly divided into gaseous phase methods and liquid phase methods. For the former, the chemical vapor deposition method (CVD) involves a chemical reaction, whereas the physical vapor deposition method (PVD) uses cooling of the evaporated material. Although the gaseous phase methods minimize the occurrence of organic impurities in the particles compared to the liquid phase methods, they necessitate the use of complicated vacuum equipment whose disadvantages are the high costs involved and low productivity. The CVD procedure can produce ultra fine particles of less than 1μm by the chemical reaction occurring in the gaseous phase. The manufacture of nanoparticles of 10 to 100 nm is possible by careful control of the reaction. Performing the high temperature chemical reaction in the CVD method requires heat sources such as a chemical flame, a plasma process, a laser, or an electric furnace. In the PVD method, the solid material or liquid material is evaporated and the resulting vapor is then cooled rapidly, yielding the desired nanoparticles. To achieve evaporation of the materials one can use an arc discharge method. The simple thermal decomposition method has been particularly fruitful in the production of metal oxide or other types of particles and has been used extensively as a preferred synthetic method in the industrial world. For many years, liquid phase methods have been the major preparation methods of nanoparticles; they can be sub-divided into liquid/liquid methods, and sedimentation methods. Chemical reduction of metal ions is a typical example of a liquid/ liquid method, whose principal advantage is the facile fabrication of particles of various shapes, such as nano rods, nanowires, nano prisms, nano plates, and hollow nanoparticles. With the chemical reduction method it is possible to fi ne-tune the form (shape) and size of the nanoparticles by changing the reducing agent, the dispersing agent, the reaction time and the temperature. The chemical reduction method carries out chemical reduction of the metal ions to their 0 oxidation states (i.e., $M^{n+} \rightarrow M^{0}$); the process uses non-complicated equipment or instruments, and can yield large quantities of nanoparticles at a low cost in a short time. Of particular interest in this regard is the use of microwave radiation as the heat source that can produce high quality nanoparticles in a short time period. Besides the chemical reduction method which adds a reducing agent (direct reduction method), other reduction methods are known, such as photoreduction using gamma rays, ultrasonic waves, and liquid plasma which can be used to prepare nanoparticles. These methods that do not use a chemical reducing substance have the attractive feature that no extraneous impurities are added to the nanoparticles. Other than these methods, spray drying, spray pyrolysis, solvothermal synthesis, and the supercritical method are also known. The general technique in the sedimentation method is a sol–gel process, which has been used extensively for the fabrication of metal oxide nanoparticles. This procedure transforms a solution of a metal alkoxide into a sol by hydrolysis, followed by poly condensation to a gel. Several books are available that provide details of the sol–gel process [51] The wet process (liquid phase method) guarantees a high dispersivity of nanoparticles compared to the dry method. However, if the resulting nanoparticles are dried, aggregation of the particles soon follows. In this case, re-dispersion can be carried out according to the process used in the solid phase method.

That is, the synthesis of nanoparticles requires the use of a device or processes that fulfills the following conditions:

- Control of particle size, size distribution, shape, crystal structure and composition distribution • Improvement of the purity of nanoparticles (lower impurities).

- Control of aggregation.
- Stabilization of physical properties, structures and reactants.
- Higher reproducibility.
- Higher mass production, scale-up and lower costs.[52]

EVALUATION OF NANO PARTICLES

Evaluation parameter of nanoparticles

Yield of Nanoparticals

Percentage yield[53]

The yield of nanoparticles was determined by comparing the whole weight of nanoparticles formed against the combined weight of the copolymer and drug.

Zeta potential[54]

The Zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (±) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles.

Particle Shape[55]

SEM characterizes the nano suspension before going for evaluation; the nanosuspension is lyophilized to form solid particles. The solid particles are coated with platinum alloy using a sputter coater.

Particle size[56]

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, and toxicity and targeting ability of nanoparticle system. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Currently, the faster and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

Drug Entrapmaent Efficiency[57]

The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 50C. Then the resulting supernatant solution was decanted and dispersed into phosphate buffer saline pH 7.4. Thus the procedure was repeated twice to remove the unentrapped drug molecules completely. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium. Drug Entrapment efficiency (%) = Amount of released from the lysed nanoparticle X 100 Amount of drug initially taken to prepare the Nanoparticles.

Polydispersity index

Polydispersity index of prepared nanoparticles was carried out by using Malvern Zetasizer.[58]

In-vitro release Study

In-vitro drug release studies were performed in USP Type II dissolution apparatus at rotation speed of 50 rpm. The prepared immersed in 900ml of phosphate buffer solution in a vessel, and temperature was maintained at 37±0.20°C. Required quantity 5ml of the medium was withdrawn at specific time periods and the same volume of dissolution medium was replaced in the flask to maintain a constant volume. The withdrawn samples were analyzed using UV spectrophotometer.[59]

Kinetic Study

For estimation of the kinetic and mechanism of drug release, the result of in vitro drug release study of nanoparticles were fitted with various kinetic equation like zero order (cumulative % release vs. time), first order (log % drug remaining vs time), Higuchi‟s model (cumulative % drug release vs. square root of time). r2 and k values were calculated for the linear curve obtained by regression analysis of the above plots.[60]

Stability of Nanoparticles

Stability studies of prepared nanoparticles determined by storing optimized formulation at 4°C ±1°C and 30°C ± 2°C in stability chamber for 90 days. The samples were analyzed after a time period like at 0, 1, 2, and 3 months for their drug content, drug release rate (t50%) as well as any changes in their physical appearance (ICH Q1A (*R*2) 2003).[61]

Applications of Nanoparticles

Tumor targeting using Nanoparticulate delivery system[62]

The rational of using nanoparticles for tumor targeting is based on:

(1) Nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active nanoparticles.

(2) Nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ. An experiment demonstrated in mice treated with doxorubicin incorporated into poly (isohexylcynoacrylate) nanospheres that higher concentration of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin.

Nanoparticles for oral delivery of peptides and proteins[62]

Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal

tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration. The surface area of human mucosa extends to 200 times that of skin 62.

The gastrointestinal tract provides a variety of physiological and morphological barriers against protein or peptide delivery, e.g.

(a) Proteolytic enzymes in the gut lumen like pepsin, trypsin and chymotrypsin;
(b) Proteolytic enzymes at the brush border membrane (endopeptidases);
(c) Bacterial gut flora;
(d) Mucus layer and epithelial cell lining itself.

The histological architecture of the mucosa is designed to efficiently prevent uptake of particulate matter from the environment. One important strategy to overcome the gastrointestinal barrier is to deliver the drug in a colloidal carrier system, such as nanoparticles, which is capable of enhancing the interaction mechanisms of the drug delivery system and the epithelia cells in the GI tract.

Nanoparticles for Gene delivery[63]

Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral and cell mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system.

Targeting of nanoparticles to epithelial cells in the GI tract using ligands

Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be classified into those utilizing specific binding to ligands or receptors and those based on nonspecific adsorptive mechanism. The surface of enterocytes and M cells display cell-specific carbohydrates, which may serve as binding sites to colloidal drug carriers containing appropriate ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure by specific receptor-mediated mechanism. Different lectins, such as bean lectin and tomato lectin, have been studied to enhance oral peptide adsorption. Vitamin B-12 absorption from the gut under physiological conditions occurs via receptor-mediated endocytosis. The ability to increase oral bioavailability of various peptides (e.g., granulocyte colony stimulating factor, erythropoietin) and particles by covalent coupling to vitamin B-12 has been studied. For this intrinsic process, mucoprotein is required, which is prepared by the mucus membrane in the stomach and binds specifically to cobalamin. The mucoprotein completely reaches the ileum where resorption is mediated by specific receptors.

Nanotechnology in Medicine Application
Anti-Microbial Techniques[64]

One of the earliest nanomedicine applications was the use of nanocrystalline silver, which is as an antimicrobial agent for the treatment of wounds; A nanoparticle cream has been shown to fight staph infections. The nanoparticles contain nitric oxide gas, which is known to kill bacteria. Studies on mice have shown that using the nanoparticle cream to release nitric oxide gas at the site of staph abscesses significantly reduced the infection. Burn dressing that is coated with nanocapsules containing antibiotics. If a infection starts the harmful bacteria in the wound causes the nanocapsules to break open, releasing the antibotics. This allows much quicker treatment of an infection and reduces the number of times a dressing has to be changed. A welcome idea in the early study stages is the elimination of bacterial infections in a patient within minutes, instead of delivering treatment with antibiotics over a period of weeks.

Absorption enhancement using non-specific interactions

In general, the gastrointestinal absorption of macromolecules and particulate materials involves either paracellular route or endocytotic pathway. The paracellular route of absorption of nanoparticle sutilises less than 1% of mucosal surface area. Using polymers such as chitosan, starch or poly (acrylate) can increase the paracellular permeability of macromolecules. Endocytotic pathway for absorption of nanoparticles is either by receptor-mediated endocytosis, that is, active targeting, or adsorptive endocytosis which does not need any ligands. This process is initiated by an unspecific physical adsorption of material to the cell surface by electrostatic forces such as hydrogen bonding or hydrophobic interactions. Adsorptive endocytosis depends primarily on the size and surface properties of the material. If the surface charge of the Nano particles is positive or uncharged, it will provide an affinity to adsorptive enterocytes though hydrophobic, whereas if it is negatively charged and hydrophilic, it shows greater affinity to adsorptive enterocytes and M cells. This shows that a combination of size, surface charge and hydrophilicity play a major role in affinity. This is demonstrated with poly (styrene) nanoparticles and when it is carboxylated.

Nanotechnology in Medicine Application
Cell Repair[65]

Nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes. Read about design analysis for one such cell repair nanorobot in this article:

The Ideal Gene Delivery Vector
Chromallocytes, Cell Repair Nanorobots for Chromosome Repair Therapy.

Nanoparticles for drug delivery into the brain[66]
The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. Relatively impermeable endothelial cells characterize the BBB with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water-soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid soluble molecules by the function of enzymes or efflux pumps. Consequently, the BBB only permits selective transport of molecules that are essential for brain function. Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with specific receptor mediated transport systems in the BBB. For example polysorbate 80/LDL, transferrin receptor binding antibody (such as OX26), lactoferrin, cell penetrating peptides and melanotransferrin have been shown capable of delivery of a self non transportable drug into the brain via the chimeric construct that can undergo receptor-mediated transcytosis. It has been reported poly (butylcyanoacrylate) nanoparticles was able to deliver hexapeptidedalargin, doxorubicin and other agents into the brain which is significant because of the great difficulty for drugs to cross the BBB. Despite some reported success with polysorbate 80 coated NPs, this system does have many shortcomings including desorption of polysorbate coating, rapid NP degradation and toxicity caused by presence of high concentration of polysorbate 80. OX26MAbs (anti-transferrin receptor MAbs), the most studied BBB targeting antibody, have been used to enhance the BBB penetration of lipsosomes. However, recently, Jiet al. demonstrated that brain uptake of lactoferrin, an iron binding glycoprotein belonging to the transferrin (Tf) family, is twice that of OX26 and transferrrinin vivo. It is possible soon we will see these BBB specific molecules used for targeting nanoparticles to the brain.

Recent Advances of Nano particles
Many types of nanoparticles drug delivery systems are in various stages of investigation. These particles have been fabricated from various materials with unique architectures to serve as a possible drug vehicle to treat a particular disease. The real thrust of the current therapy for the puzzling diseases are in the direction of developing new powerful drugs. The next generation of drugs will involve more complex biological or chemical entities and gene therapy. The solubility, in vivo stability, intestinal absorption, route of administration and targeting, effectiveness, and/or the side effects of these new drugs are among the challenges that push researchers toward exploring a new drug delivery strategy. A major idea behind the development of solid lipid nanoparticles was the hypothesis that a solid lipid nanoparticulate carrier would offer the potential for sustained or controlled drug release by immobilisation of the drug within a solid matrix. The physical and chemical stability of such particles might also be increased due to the presence of a solid particle core. Such a carrier system would thus combine the advantages of fluid-like lipid-based colloidal particles (good biocompatibility of ingredients and ease of production) with those of polymeric nanoparticles (solid matrix). Solid lipid nanoparticles can be based on a broad range of solid lipids with quite different degrees of polarity, ranging from the rather non-polar triglycerides and waxes through glyceride mixtures to fatty acids and emulsifying wax. Their preparation requires the use of surfactants as stabilisers, which include natural substances such as phospholipids and bile salts but also many other kinds of surface active agents, e.g non-ionic surfactants such as poloxamers, polysorbates, etc.[67] The composition of the dispersions has to be adapted to the intended way of administration (e.g. only a very limited number of excipients can be used in parenteral formulations) but also depends on the preparation method. Although nanotechnology in drug delivery has been successful, as evidenced by some nano drug products in the market, not all approaches have met with the same success. New nanomaterials being developed come with challenges which have to be surmounted. For solid lipid nanoparticles, the situation is much more complex since the solid state of the particle core causes several additional phenomena. The lipids used for the preparation of solid lipid nanoparticles are crystalline substances, which mean that the particles will also crystallize on solidification. Thus, they will show all the features of crystalline materials. This includes a solid–liquid transition at a certain temperature and the occurrence of various crystalline modifications if polymorphic raw materials are used which is often the case for lipids (e.g. triglycerides). Chemical composition characterized by their particle size distribution and their surface properties are important for stability against coalescence. Problems with the stability of the dispersions have also been related to alterations caused by polymorphism and increase in crystallinity. Both the crystallization behaviour and the kinetics of polymorphic transitions can bemodified by the type of emulsifier used for the stabilisation of the nanoparticles. However some of the challenges encountered have been and are still being tackled by modification of the physicochemical characteristics of the nanomaterials to improve on properties such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site-specific targeting.[68] Another challenge of research and development (R&D) of nanomaterials for drug delivery is large scale production. The development and quality control of solid lipid nanoparticle dispersions thus require the investigation of more parameters than emulsions. Apart from the common techniques, such as particle size characterization, the particle shape and, in particular, the solid state properties (in particular the crystalline status and melting behaviour) need to be

carefully monitored. There is always a need to scale up laboratory or pilot technologies for eventual commercialization.[68] A number of nano drug delivery technologies may not be scalable due to the method and process of production and high cost of materials employed. The challenges of scaling up include low concentration of nanomaterials, agglomeration and the chemistry process it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale. Maintaining the size and composition of nanomaterials at large scale is also a challenge. Despite the number of patents for nano drug delivery technologies, commercialization is still at its early stage. This is partially due to the fact that most of the research studies in nano drug delivery are carried out by researchers in academia. Therefore, for these technologies to get to the market there has to be increased partnership with the pharmaceutical companies. Unfortunately, a number of the major pharmaceutical industries are yet to consider nanotechnology as one of their priorities due to lack of regulatory guidelines and challenges of scaling up. However, it is envisaged that with the expiration of more patents and market loss, more pharmaceutical industries will take up the production of nano drug products in order to compete favourably. Advances in nano drug delivery technology also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products.[68] The United States Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) have taken the initiative to identify some possible scientific and regulatory challenges. Furthermore, the International Organization for Standardization has set up a technical committee (TC 229) for the field of nanotechnologies to develop standards pertaining to terminology and nomenclature, measurement and characterization; and health, safety and environment amongst other standards. These standards are still under development.[68] With increased R&D work on nano drug delivery, emerge concerns about the safety of the nanotechnologies in humans. Some of the nanomaterials are biodegradable while some are not, furthermore, the side effects of the byproducts present a huge concern. Materials which may be safe at macro scale may not be at nanoscale since there may be change in physicochemical characteristics at nanoscale. These nanomaterials may not clear completely from the body and their accumulation may have several possible effects. Safety and possible impact nanomaterials should not be considered for the patient population alone but also for the entire manufacturing and disposal processes.[68] Conventional safety measures in a pharmaceutical factory may not be appropriate for the development and fabrication of nanomaterials. Also extra measures are to be taken to protect the environment from increased envisaged negative impacts of nanomaterials. Although reduced cost to the patients is envisaged to be one of the advantages of nanotechnology since fewer materials are expected to go into production as compared to bulk production; it is doubtful if this will be so, as successful commercialization will be expensive. There is also the general public reluctance to embrace nanotechnology based on the unavailability of documented safety guidelines.[68] Although solid lipid nanoparticles have now reached a more mature stage of development, latter mostly refer to an improved administration of poorly water-soluble drugs. Solid lipid nanoparticles should be highly interesting carrier candidates for drug substances that localize at the particle surface since their often platelet-like shape offers much space for the association with such drugs. On the other hand, they usually display an even more complex physicochemical behaviour than lipid emulsions. Such aspects need to be carefully balanced in order to choose an optimal carrier system for a given delivery task. Another challenge for researchers exploring a new drug delivery strategy is in vivo biodistribution of solid lipid nanoparticles, will mainly depend on the route of administration and interactions of SLN with biological surroundings which, in general, include two types of processes: distribution processes (adsorption of biological materials on the particle surface and desorption of SLN components into the biological surrounding) and enzymatic processes (lipid degradation by lipases and esterases). Physiological or physiologically related lipids or waxes generally constitute the SLNs. Therefore, the in vivo fate of the carrier, to a large extent, occurs through the pathways of transportation and metabolism present in the body. Lipases, the enzymes present in various organs and tissues of the body, are most responsible for SLN degradation. Lipases split the ester linkage and form partial glycerides or glycerol and free fatty acids. Activation by an oil/water interface, which opens the catalytic centre, is a prerequisite for lipases to act. Solid lipid nanoparticles show different degradation rates, in vitro, by the lipolytic enzyme pancreatin lipase as a function of their composition (lipid matrix, stabilizing surfactant.

Peroral administration

Aqueous dispersions or SLN-loaded traditional dosage forms (tablets, capsules, pellets or powders in sachets) may serve as peroral administration forms of SLN. Pandey et al. formulated and evaluated the chemotherapeutic potential of solid lipid nanoparticles incorporating antitubercular drugs following oral administration to mice and suggested that oral SLN based antitubercular drug therapy forms a sound basis for reducing dosing frequency and improving patient compliance for better management of tuberculosis.[69] Zhang et al. administered orally insulin-loaded SLN and WGA-modified SLN to rats and demonstrated that both of these formulations promoted the intestinal absorption of insulin after oral administration.[70]

Parenteral administration

Parenteral drug delivery took a major leap after successful development of the submicronic parenteral fat emulsion in the 1960s. Quick commercialization of submicron emulsion based products, such as Diazemuls (diazepam) and Diprivan (propofol), indicated the interest of pharmaceutical industries in colloidal carriers. Wissing et al. reviewed, in detail, the bioactivity of SLN after parenteral administration, i.e. tolerability, toxicology, cellular uptake, albumin adsorption, pharmacokinetics, tissue distribution and drug targeting.[71] Reddy et al. studied the influence of the route of administration on tumor uptake and biodistribution of etoposide loaded solid lipid nanoparticles in mice bearing Dalton's lymphoma after subcutaneous, intravenous and intraperitoneal injections. It was observed that subcutaneous injection reduced the biodistribution of SLN to all the tissues studied, whereas intravenous injection resulted in lower levels of etoposide-loaded SLN in RES rich organs compared to free etoposide. SLN experienced significantly higher brain distribution after intraperitoneal injection, indicating its potential application in targeting etoposide to brain tumors.[72]

Transdermal administration

Since the epidermal lipids are found in high amounts in the penetration barrier, lipid carriers (liposomes, SLN, NLC etc.) attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneum and the carrier appear promising. Incorporation of SLN dispersion in an ointment or gel, by reduction of the lipid content of the SLN dispersion, is necessary to achieve a formulation that can be easily administered to the skin.

Pulmonary administration

Growing attention has been given to the potential of pulmonary route as an alternative to the non invasive local and systemic delivery of therapeutic agents using lipid particles, since it provides a large absorptive mucosal area. The lung offers a large surface area for drug absorption and the alveolar epithelium allows rapid drug absorption. The superior physicochemical characteristics of SLNs make them more suitable as an appropriate delivery system due to correlation between the diameter within the nanometric range, biocompatible composition and deep-lung deposition ability. Prolonged drug serum concentration and lung retention are both achievable by means of the particulate colloidal drug carrier system including SLNs.[73]

Ocular administration

Eyes are among the most readily accessible organs in terms of their location in the body, yet drug delivery to eye tissues is particularly problematic. Delivery of drugs via nanotechnology-based products fulfils three main objectives, enhanced drug permeation, controlled drug release and higher targeting potential. Attama et al. prepared sodium diclofenac loaded lipid nanoparticles combining the homolipid from goat (goat fat) and a phospholipids', with high encapsulation efficiency applying hot high-pressure homogenization technique. Administration of this formulation to bioengineered human cornea demonstrated sustained release of the analgesic drug. Furthermore, permeation of sodium diclofenac through the corneal construct was improved by surface tailoring of nanoparticles with phospholipids, which showed better performance for ocular administration.[74]

Targeted delivery

One of the most challenging aspects in pharmaceutical research is targeted delivery of drug molecules to a specific organ, tissue or specific cellular sites. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles, a new frontier was opened for improving drug delivery.[75,76] However, despite these challenges, nano drug delivery is a development that cannot be ignored and so the challenges will be tackled with time.

Cosmetics

Sln as topical vehicles for sunscreens, anti-acne and anti-ageing actives Lipid nanoparticles proved to have a synergistic effect of the UV scattering when used as vehicles for molecular sunscreens. Advantages taken from these observations are the possibility to reduce the concentration of the molecular sunscreen, consequently its potential side effects, as well as the costs of formulation of expensive sunscreens. In addition, lipid nanoparticles can be explored to formulate sunscreen products with lower and medium sun protection factor. The loading capacity of lipid nanoparticles depends mainly on the miscibility of the active in the lipid selected for their production. It can range from about 4% (e.g. ferulic acid), 25% (e.g. tocopherol), or even up to 50% and more, in case of well lipid miscible lipophilic actives.[77-78] Sln as topical vehicles for perfumes, fragrances and repellents prolonged release of perfumes has the advantage of creating a once-a-day application with prolonged effect over several hours. This was demonstrated to be possible with the use of lipid nanoparticles in comparison with typical o/w emulsions. The release can be slowed down by incorporating perfumes/fragrances in a SLN instead of an oil droplet. In the first 3h, similar release patterns were observed between lipid nanoparticles and oil droplets because of the release of perfume from the outer layers of the particles. During the remaining 10 h, the release from SLN was prolonged. After 6 hr 100% of perfume was released from the emulsion, but only 75% was released from SLN. This property can also be advantageous for the delivery of insect repellents to be applied onto the skin. SLN have also been employed for dermal application of cosmeceuticals like molecular sunscreens and as carriers for UV blockers. Cosmetic benefits of lipid nanoparticles include enhancement of the chemical stability of actives, film formation on skin, controlled occlusion, skin hydration, drug targeting, enhanced skin

bioavailability and physical stability of lipid nanoparticles as topical formulations. An in vivo study showed increased skin hydration, by 31%, after 4 weeks after addition of 4% SLN to a conventional cream formulation.[77-78]

Topical delivery

The biggest progress in the field of nanotechnology has allowed the scientists to develop the carriers of drug to improve the penetration of skin and also in targeting to specific skin layers such as podophyllotoxin, tretinoin, isotretinoin, flurbiprofen, psoralen, vitamin A. Lipid-based nano-formulation fulfils three main objectives: controlled drug release, enhanced drug permeation and site specific drug delivery. Similar to liposomes they are composed of well tolerated excipients and due to their small particle size they possess adhesive properties leading to film formation on the skin. Moreover they ensure increased penetration of drug into the epidermis by close contact with the stratum corneum. However the drug free nanoparticles can be used to improve occlusive properties. Dermal penetration barriers contain a high concentration of epidermal lipids and lipid based carriers appear to be promising by attaching themselves to the skin surface, allowing lipid exchange between the outermost layers of stratum corneum. Schafer Korting et al. 2002 has investigated that well tolerated lipid nanoparticles are suitable for glucocorticoids targeting to viable epidermis however long term glucocorticoids treatment can cause skin atrophy so prednicarbonate (PC-0.25%) was incorporated in lipid nanoparticles and it was found that PC is much more efficiently incorporated in lipid nanoparticles (>90%) as compared to prednisolone (50-56%), when identical procedure for production was employed. The targeting effect of prednicarbonate was seen after incubating time of 6h. This accelerated drug release was shown due to water evaporation from the skin surface, as a result there was polymorphic transition of lipid structures of lipid nanoparticles. For designing dermal delivery system, it is important to understand principles of drug incorporation into carrier and their permeation through the skin. There are methods which can quantify the drug at the target site. They are fluorescence spectroscopy employing dyes as model agents and paraelectric spectroscopy. A research carried out by fluorescence spectroscopy to check upon the distribution of lipophilic model dye within the skin strata and appendages after application of lipid nanoparticles system revealed that the drug penetration in SLNs increased about four folds as compared from the uptake followed by the cream.[79-80]

Nasal delivery

Nasal administration was a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers. In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups. In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers. The role of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecule. This concept can be useful for solid lipid nanoparticles.[81]

Brain delivery

Nanosystems employed for the development of drug delivery systems intended for CNS targeting. SLNs can improve the ability of the drug to penetrate through the blood-brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders. The most formidable obstacles that often impede drug delivery to the brain are characterized by the presence of relatively impermeable endothelial cells with tight junctions, enzymatic activity and the presence of active efflux transporter mechanisms like P-glycoprotein efflux. However, the bioacceptable and biocompatible nature of SLNs makes them less toxic compared to polymeric nanoparticles and they are taken up by the brain because of their lipidic nature. SLNs below 200 nm have increased blood circulation and hence an increase in the time during which the drug remains in contact with BBB and is taken up by the brain. In vivo well tolerable solid lipid nanoparticles (SLNs) using different types of polysorbate as stabilizers were produced. The influence of the different surfactants on in vitro adsorption of human plasma proteins was investigated using two-dimensional polyacrylamide gel electrophoresis (2-DE). One approach of drug targeting is the incorporation of the substance into colloidal carriers such as polymeric nanoparticles, or solid lipid nanoparticles (SLNs) which have been used for intravenous injection. The next challenge is to direct the colloidal drug carriers to the desired site of action e.g. tumor tissue or brain. After intravenous injection, particles immediately interact with plasma proteins. The adsorbed plasma protein patterns are regarded as the determining factor for the in vivo fate of the carriers. The blood– brain barrier (BBB) represents a strict barrier for water-soluble, charged and high molecular weight drugs [82-83] Mistry et al. suggested that the existence of a direct nose-to-brain delivery route for nanoparticles administered to the nasal cavity and transported via the olfactory epithelium and/or the trigeminal nerves directly to the CNS is relevant in the field of drug delivery as well as new developments in nanotechnology.[84]

Chemotherapy

Cancer is characterized by the formation of abnormal tissues known as neoplasm. Developed basically due to change in the way cells proliferate and differentiate. Currently, cancer fighting drugs are toxic to both tumor and normal cells, thus the efficacy of chemotherapy is

always limited by the side effects of the drug. Some nanoscale devices can be targets to the cancer cells. This increases the selectivity of the drugs toward the cancer cells and will reduce the toxicity for normal tissue. The effectiveness of cancer therapy in various solid tumors depends upon adequate delivery of therapeutic agent to tumor cells. Inadequate delivery of drugs to tumor cells leads to regrowth of tumor cells and even result in development of resistant cells. Several drug delivery systems were introduced namely liposomes, microparticles, supramolecular bio-vectors, polymeric conjugates and nano-particulates to facilitate effective chemotherapy with the anti-cancer agents. The introduction of doxorubicin long circulating liposome in the market for cancer therapy has brought a renewed interest in the field of targeted drug delivery to cancer. Due to drawback of these carrier systems such as physical instability, difficulties in scale up, lack of specific tumor targeting and cytotoxicity of the polymers, research groups have focused on nanoparticles prepared using lipid matrices. There are many reports describing potentials of lipid nanoparticles for parenteral delivery particularly for the treatment of cancer. In another research tamoxifen citrate and tamoxifen citrate loaded nanoparticles were administered by intravenous injection in rats and the pharmacokinetic parameters were determined. The t1/2 and mean residence time of TC-loaded SLNs in plasma was about 3.5-folds ($p < 0.001$) and 3-fold ($p < 0.001$) higher, respectively than free tamoxifen, this indicates the potential of TC-loaded SLNs as a long circulating system in blood. Thus the above mentioned solid lipid nanoparticles can be a beneficial system to deliver tamoxifen to cancer tissues through enhanced permeability and retention (EPR) effect. The biodistribution of colloidal carriers and delivery of incorporated drugs to the target sites after intravenous administration are mainly determined by their physicochemical properties such as size, surface charge and surface hydrophobicity through their recognition or non recognition by the body's reticulo-endothelial system. The rapid removal of colloidal particles by the macrophages of the RES is a major obstacle to targeting tissues elsewhere in the body, such as bone marrow and solid tumors. Several reports appeared on incorporation of polyethylene glycol (PEG) moieties for prolonged blood circulation and charged lipids to modify the biodistribution of lipid nanoparticles. The SLNs were loaded with an anticancer agent; tamoxifen citrate (TC). The TC-loaded TSSLN (tristearin SLN) showed lower entrapment efficiency (78.78%) compared to the TPSLN (tripalmitin SLN) and glycerol behenate SLN (GBSLN) (98.64%). Long circulation half-life of the intravenously administered TC-loaded TSSLN compared to the plain TC solution indicates their possible potential use in the drug delivery to cancer tissues by enhanced permeability and retention (EPR) effect. Colloidal drug delivery systems without specific modification usually show a strong tendency to accumulate rapidly in the phagocytic cells of the reticuloendothelial system (RES). Similar phenomenon was found in Camptothecin SLNs. Compared with the commercial emulsion, SLNs showed a higher uptake by RES tissues such as liver and spleen. Therefore, the SLNs containing β- elemene might be an attractive candidate for the treatment of liver cancer. Different kinds of drugs have been incorporated in SLNs, including lipophilic and hydrophilic drugs, small molecular and large molecular biological drugs, but SLNs containing volatile oil has seldom been reported. Being incorporated in the solid matrix of the SLNs, β-elemene might be well protected and providing targeted release different from that of commercial emulsion. Pacilataxel commonly known as yew tree, has antineoplastic activity particularly for ovarian carcinoma, breast cancer, colon, head and neck cancer etc. It is a hydrophobic molecule, which was earlier stabilized in 50:50 mixture of polyethoxylated castor oil (Cremophor EL), however cremophor is associated with number of side effects such as hypersensitivity, nephrotoxicity and neurotoxicity etc. The incorporation of pacilataxel in solid lipid nanoparticles gave promising results by eliminating the need for Cremophor EL and also improved drug's efficacy. This application extends the function of solid lipid nanoparticles as reservoir systems and penetrates into accessible sites, such as tumor and other than mononuclear system. The slow release of pacilataxel from solid lipid nanoparticles suggests that the pacilataxel might be incorporated into lipid matrix of nanoparticles. In 1999, the complete patent rights for production of SLNs by high pressure homogenization have been acquired by Skye Pharma AG (Muttenz, Switzerland), a drug delivery company specialized in oral delivery, but also having the potential for parenteral production.[85] Protein and peptide delivery Increasing attention has been paid to the pulmonary route for systemic delivery of peptide and protein drugs, such as insulin. The SLN production is based on solidified emulsion (dispersed phase) technologies. Therefore, due to their hydrophilic nature most of proteins are expected to be poorly microencapsulated into the hydrophobic matrix of SLN, tending to partition in the water phase during the preparation process, which is further enhanced by the use of surfactants as emulsion stabilizers. Therapeutically relevant peptides (e.g. calcitonin, cyclosporine A, somatostatin), protein antigens (e.g.hepatitis B and malaria antigens) and model protein drugs (e.g. bovine serum albumin and lysozyme) have been investigated for drug release kinetics, protein stability and in vivo performance.[86]

Future perspectives

The future vision of lipid nanoparticles – SLNs as drug delivery systems is to develop a self-actuated therapy with good perspectives to be marketed very successfully. The reason for this is that they were developed considering industrial needs, e.g. scale up, qualification and validation, simple technology, low cost, regulatory excipients status (e.g. GRAS), tolerability etc. Research must continue to develop a therapy through localized medical implants. Yih et al. (2002, 2005) had developed

bio-micro electro mechanical (BioMEMS) micropumps for controlled localized drug delivery systems such as hydrogel nanoparticles. These systems when implanted will be able to determine the necessary dose via sensory systems. The implants are normally designed to operate for a long period of time, possibly months. The stability and usefulness of nanoparticles delivery systems might be influenced by time. Thus, further studies are essential to evaluate their efficacy over time when encapsulated and stored. The smart NLC as the new generation offer much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules and injectables. In addition, research must continue in such a direction to provide improved efficacy, drug loading, targeting and lowering of the drug dose, thereby overcoming the toxicity challenges of this carrier system. Structure and dynamics of SLNs on the molecular level, both in vitro and in vivo, stability, targeting, toxicity and aspects related to interactions of SLNs with their biological surrounding pose a challenge that should be explored in the near future by various research groups around the globe. Implantable devices or nanochips promise improved therapeutics in various disease management and may be potentially applied as antitumor therapy, gene therapy, or vaccines. Nanochips be used to assist in repairing damaged tissue, detecting mutated genes, or detecting high hormone levels indicative of certain malignancies. It is capable of triggering immediate responses to inflamed, ischemic, or neoplastic tissues and simultaneously provide therapy. Surprisingly, a silicon based nano-channel has already been developed to deliver antitumor agents locally with zero order kinetic.[87,88]

CONCLUSION

A number of nanoparticles-related research projects are actively being conducted in several countries. To establish a good correlation between nanoparticles and particle based nanostructures or devices, it is necessary to secure human resources with a systematical organization, e.g. a national project. A real therapeutic breakthrough can be achieved solely by carrying out painstaking studies in the field of nano-therapy. Using nanosystems in therapies of diseases may contribute to achieving an effective cancer treatment. The key applications of nanoparticles in medicine are diagnosis and target therapy; however, their wider use is still the future. Nanoparticle have relatively higher intracellular uptake compared to microparticles and available to a wide range of biological targets due to their small size and relative mobility. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering is still required. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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