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A Review on Nanoparticulate Drug Delivery System

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Sujit A Desai*[1], Shweta Patil[2], Neha Patil[2], Aishwarya Patil[2], Nilesh B Chougule[1], Sandip B Patil[3]

1. *Annasaheb Dange College of D Pharmacy, Ashta, Sangli*
2. *Bharati Vidyapeeth College of Pharmacy, Kolhapur*
3. *Adarsh College of Pharmacy, Vita, Sangli.*

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ABSTRACT

Nanoparticles are particulate dispersions or solid particles with a size in the range of 10-1000nm. 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. 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. Recently several techniques are available for scope and development of nanoparticle drug delivery system. The present study includes properties of nanoparticles, sources, preparation method, evaluation, clinical importance, application, and future scope of nanoparticles Present review reveals the methods of preparation, characterization, and application of several nanoparticulate drug delivery systems.

INTRODUCTION:

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. 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. In recent years, biodegradable polymeric nanoparticles, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as polyethylene 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 carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes. 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 the 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 a 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[1-4].

What is a drug delivery system?

The term drug delivery refers to a system that can transport and deliver a drug precisely and safely to its site of action. The field of drug delivery is developing rapidly; research is being conducted to study nearly every part of the body as a potential route for administrating both classical and novel medicines[1].

Advantages of using nanoparticles as a drug delivery system:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

2. 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 an increase in drug therapeutic efficacy and reduction in side effects.

3. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction.

4. Site-specific targeting can be achieved by attaching targeting ligands to the surface of particles or use of magnetic guidance.

5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

6. Avoidance of coalescence leads to enhanced physical stability.

7. Reduced mobility of incorporated drug molecules leads to a reduction of drug leakage.

8. Static interface solid/liquid facilitates surface modification[6-7].

- **Disadvantages:**

1. Potential toxicity:

While the small size of the nanoparticle is what makes them so useful in medicine, it is also the factor that might make them potentially dangerous to human health. The exact distribution of the nanoparticles in the body depends on the coating, biodegradable substances are normally decomposed and their waste product excreted by kidneys and intestine.

2. Environmental concerns:

Depending on the excretion and disposal of nanomedicines these nanoparticles can be released into the water or air. Artificially manufacture nanoparticles will be new to the environment in type and quantity and would constitute a new class of nonbiodegradable pollutants.

3. There is no convenient method by which exposure to the nanoparticle in the workplace can be measured or assessed there is a need and for more research into the development of new

improved methods, combinations and strategies to improved assessment of exposure to nanoparticle and nanoparticle aerosol.

4. Insufficient information concerning nanoparticle exposure is available much more information is needed regarding the exposure of workers involved in the production of all the various type nanoparticle via all of the production processes[8,9]

Theory: [10-12, 15]

➢ **Ideal Properties of Polymeric Based Nanoparticles:**[13]

- Natural or synthetic polymer
- Inexpensive
- Nontoxic
- Biodegradable
- Nonthrombogenic
- Nonimmunogenic
- Particle diameter <100nm
- No platelet aggregation
- Noninflammatory
- Prolonged circulation time

➢ **Materials Used In the Preparation of Nanoparticles:**[7,14]

1. Poly(ethylene oxide)-poly(L-lactic acid)/poly(benzyl-L-aspartate*):*

Polymeric micelles often self-assemble when block copolymers are used for their preparation. Micelles, based on the biocompatible copolymers of poly (ethylene oxide) PEO with poly(L-Lactic acid) PLA or with poly(β-benzyl-L-aspartate) PBLA, have been described in the literature. Aldehyde groups on the surface of the PEO-PLA micelles may react with the lysine residues of cell's proteins. They may also be used for attachment of the amino-

containing ligands. The hydroxyl groups on the surface of the PEO-PBLA micelles can be further derivatized and conjugated with molecules capable to pilot the modified micelles to specific sites of the living organism. Such nanospheres have been tested as vehicles for delivery of anti-inflammatory and anti-tumor drugs.

2. Poly(lactide-co-glycolide)-[(propylene oxide)-poly(ethylene oxide)]:

Nanoparticles (80-150 nm) of the biocompatible and biodegradable polyester copolymer PLG [Poly(lactide-*co*-glycolide)] Figure 1 have been reported by the nanoprecipitation method (they have been precipitated with acetone from their oily colloidal nanodispersion in water). Thus formed particles of PLG were coated with 5-10 nm thick layer of the poly (propylene oxide) - poly (ethylene oxide) (PPO-PEO) block copolymer or with tetrafunctional (PEO-PPO) $_2$ -N-CH_2-CH_2-N-(PPO-PEO) $_2$. Such coats are bound to the core of the nanosphere by the hydrophobic interactions of the PPO chains, while PEO chains protrude into the surrounding medium and form a steric barrier, which hinders the adsorption of certain plasma proteins onto the surface of such particles. On the other hand, the PEO coat enhances adsorption of certain other plasma compounds. In consequence, the PEO-coated nanospheres are not recognized by macrophages as foreign bodies and are not attacked by them.

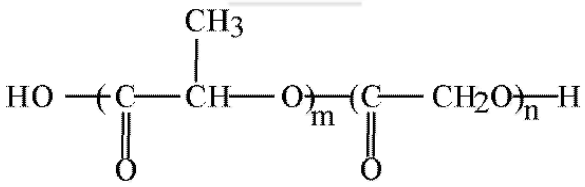

Figure 1: Poly (lactide-co-glycolide) PLG

3. Polyphosphazene derivatives:

Allock and coworkers developed derivatives of the phosphazene polymers suitable for biomedical applications. Long-circulating in the blood, 100-120 nm in diameter, PEO-coated nanoparticles of the poly (organophospazenes) containing the amino acid, have been prepared. PEO-polyphosphazene copolymer or poloxamine 908 (a tetrafunctional PEO copolymer) has been deposited on their surface.

4. Poly (ethylene glycol) coated nanospheres*:*

Poly (ethylene glycol) PEG-coated nanospheres from PLA, PLG, or other biodegradable polymers viz., poly (ε-caprolactone) (PCL), may be used for the intravenous drug delivery. PEG and PEO denote essentially identical polymers. The only difference between the respective notations is that methoxy groups in PEO may replace the terminal hydroxyls of PEG. It has been pointed out that PEG coating of nanospheres provides protection against interaction with the blood components, which induce removal of the foreign particles from the blood. It prolongs, therefore, their circulation in the bloodstream. In consequence, thus coated nanospheres may function as circulation depots of the administered drugs. Slowly releasing drugs into plasma and thus altering their concentration profiles can achieve obvious therapeutical benefits. About 200 nm in diameter PEG-coated nanospheres, in which PEG is chemically bound to the core has been prepared, in the presence of monomethoxy PEG, by ring-opening polymerization (with stannous octoate as a catalyst) of such monomers as ε-caprolactone, lactide, and/or glycolide. Ring-opening polymerization of these monomers in the presence of such multifunctional hydroxy acids as citric or tartaric, to which several molecules of the monomethoxy monoamine of PEG (MPEG-NH_2) have been attached, yields multiblock $(PEG)_n$-$(X)_m$ copolymers. PEG-PLA copolymer in which NH_2 terminated methoxy PEG molecules has been attached to tartaric acid.

The nanoparticles, prepared using equimolar amounts of the PLLA-PEG and PDLA-PEG stereoisomers, are shaped as discs with PEG chains sticking out from their surface.

Their hydrophobic/hydrophilic content seems to be just right for applications in cancer and gene therapies. Such nanospheres are prepared by dispersing the methylene chloride solution of the copolymer in water and allowing the solvent to evaporate.

5. Poly (isobutyl cyanoacrylate) nanocapsules:

Intragastric administration of insulin-loaded poly (isobutyl cyanoacrylate) nanocapsules induced a reduction of the glycemia to normal level in streptozotocin-diabetic rats and is alloxan-induced diabetic dogs. The hypoglycemic effect was characterized by surprising events including a lag time period of 2 days and a prolonged effect over 20 days. Insulin is a very hydrosoluble peptide and should be inactivated by the enzymes of the gastrointestinal tract. Thus, the reason why insulin could be encapsulated with high efficiency in nanocapsules containing an oily core and why these nanocapsules showed so unexpected

biological effect remained unexplained. Nanocapsules can be prepared by interfacial polymerization of isobutyl cyanoacrylate. Any nucleophilic group including those of some of the aminoacids of insulin could initiate the polymerization of such a monomer. In this case, insulin could be found covalently attached to the polymer forming the nanocapsule wall as it was recently demonstrated with insulin-loaded nanospheres.

6. Poly(γ-benzyl-L-glutamate)/poly(ethylene oxide):

Nanoparticles have been widely investigated as the drug carriers. Biodegradable poly (D, L-lactide) polybutyl cyanoacrylate and poly(□-caprolactone) are widely being used to prepare nanoparticles. The advantages of the nanoparticles are the reduced drug toxicity, the improvement of biodistribution, and the increased therapeutic efficacy. Diblock copolymers have been studied in the sustained release system as an alternative drug carrier since they are known to form a micelle structure. Hydrophilic-hydrophobic diblock copolymers exhibit amphiphilic behavior and form micelles with core-shell architecture. These polymeric carriers have been used to solubilize hydrophobic drugs, to increase blood circulation time, to obtain favorable biodistribution and to lower interactions with the reticuloendothelial system. The nanoparticles are obtained from poly (γ-benzyl-L-glutamate)/poly(ethylene oxide) [PBLG/PEO] diblock copolymer, which forms a hydrophobic inner core and a hydrophilic outer shell of the micellar structure, by adopting dialysis procedure. Their results indicate that only 20% of the entrapped drug was released in 24 h at 37ºC and the release was dependent on the molecular weight of the hydrophobic polymer.

7.Chitosan-poly(ethylene oxide) nanoparticles*:*

Hydrophilic nanoparticle carriers have important potential applications for the administration of therapeutic molecules. Most of the recently developed hydrophobic-hydrophilic carriers require the use of organic solvents for their preparation and have a limited protein-loading capacity. A new approach for the preparation of nanoparticles made solely of a hydrophilic polymer, to address these limitations. The preparation technique, based on an ionic gelation process, is extremely mild and involves the mixture of two aqueous phases at room temperature. One phase contains the polysaccharide chitosan (CS) and a diblock copolymer of ethylene oxide and polyanion sodium tripolyphosphate (TPP). It was stated that the size (200-1000 n) and zeta potential (between + 20mv and +60mv) of nanoparticles can be conventionally modulated by varying the ratio CS/PEO-PPO. Furthermore, using bovine

serum albumin (BSA) as a model protein, it was shown that these new nanoparticles have great protein loading capacity (entrapment efficiency up to 80% of the protein) and provide a continuous release of the entrapped protein for up to 1 week.

- **Methods of Preparation of Nanoparticles**[23-25]

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides, and synthetic polymers. The selection of matrix materials is dependent on many factors including:

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,

e) Biocompatibility and toxicity;

f) Drug release profile desired; and

g) Antigenicity of the final product.

Nanoparticles have been prepared most frequency by three methods:

(1) Dispersion of preformed polymers

(2) Polymerization of monomers; and

(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.

1. Dispersion of preformed polymers*:*

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D, L-glycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylate) (PCA), This technique can be used in various ways as described below.

2. Solvent evaporation method:

In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water (o/w) emulsion. After the formation of the stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed, and polymer concentration. In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.

3. Coacervation or ionic gelation method:

Much research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin, and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan nanoparticles by ionic gelation. The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block copolymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. In this method, a positively charged amino group of chitosan interacts with negatively charged tripolyphosphate to form coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing a transition from liquid to gel due to ionic interaction conditions at room temperature.

➢ Characterization of Nanoparticles[16-22]

Nanoparticle characterization is necessary to establish understanding and control of nanoparticle synthesis and applications. The primary characterization of NPs is the size of the newly formed particles.

Particles with a very small size (<1000nm), low charge, and a hydrophilic surface are not recognized by the mononuclear phagocytic system(MPS) and, therefore, have a long half-life in the blood circulation which is essential for targeting NPs to target the brain.

Characterization is done by using a variety of different techniques, mainly drawn from materials science.

Common techniques[22]

(1) Electron microscopy [TEM,SEM]

(2) Atomic force microscopy [AFM]

(3) Dynamic light scattering [DLM]

(4) X-ray photoelectron spectroscopy [XPS]

(5) Powder x-ray diffractometry [XRD]

➢ Effect of Characteristics of Nanoparticles on Drug Delivery

1. 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. 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. 100 nm nanoparticles had a 2.5 fold greater uptake than1 μmmicroparticles, and 6 fold greater uptake than 10 μmmicroparticles in a Caco-2 cell line. In a subsequent study, 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 cross the blood-brain barrier following the opening of tight junctions by hyperosmotic 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. Drug release is affected by particle size. Smaller particles have a 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. Smaller particles also have the 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*. 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.

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. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

2. 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. 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. 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 bloodstream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs. Generally, it is IgG, complement 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

1.Surface coating of nanoparticles with hydrophilic polymers/surfactants;

2.Formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, polyoxamer, 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.

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. The zeta potential can also be used to determine whether a charged active material is encapsulated within the center of the nanocapsule or adsorbed onto the surface.

3. Drug loading:

Ideally, a successful nanoparticulate system should have a high drug-loading capacity thereby reduce the quantity of matrix materials for administration. Drug loading can be done by two methods:

- Incorporating at the time of nanoparticles production (incorporation method)

- Absorbing the drug after formation of nanoparticles by incubating the carrier with a concentrated drug solution (adsorption/absorption technique).

Drug loading and entrapment efficiency very much depend on the solid-state drug solubility in the matrix material or polymer (solid dissolution or dispersion), which is related to the polymer composition, the molecular weight, the drug-polymer interaction and the presence of end functional groups (ester or carboxyl). The PEG moiety has no or little effect on drug loading. The macromolecule or protein shows greatest loading efficiency when it is loaded at or near its isoelectric point when it has minimum solubility and maximum adsorption. For small molecules, studies show the use of ionic interaction between the drug and matrix materials can be a very effective way to increase the drug loading.

4. Drug release:

To develop a successful nanoparticulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on:

(1) Solubility of drug

(2) Desorption of the surface-bound/ adsorbed drug

(3) Drug diffusion through the nanoparticle matrix

(4) Nanoparticle matrix erosion/degradation

(5) Combination of erosion/diffusion process

Thus solubility, diffusion, and biodegradation of the matrix materials govern the release process. In the case of nanospheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the drug is faster than matrix erosion, the mechanism of release is largely controlled by a diffusion process. The rapid initial release or ‘burst' is mainly attributed to weakly bound or adsorbed drug to the large surface of nanoparticles. It is evident that the method of incorporation has an effect on release profile. If the drug is loaded by incorporation method, the system has a relatively small burst effect and better-sustained release characteristics. If the nanoparticle is coated by the polymer, the release is then controlled by diffusion of the drug from the core

across the polymeric membrane. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of a drug in polymer membrane become determining factor in drug release. Furthermore, release rate can also be affected by an ionic interaction between the drug and addition of auxiliary ingredients. When the drug is involved in interaction with auxiliary ingredients to form a less water-soluble complex, then the drug release can be very slow with almost no burst release effect; whereas if the addition of auxiliary ingredients e.g., addition of ethylene oxide-propylene oxide block copolymer (PEO-PPO) to chitosan, reduces the interaction of the model drug bovine serum albumin (BSA) with the matrix material (chitosan) due to competitive electrostatic interaction of PEO-PPO with chitosan, then an increase in drug release could be observed .

Various methods which can be used to study the *in-vitro* release of the drug are:

1.Side-by-side diffusion cells with artificial or biological membranes;

2.Dialysis bag diffusion technique;

3.Reverse dialysis bag technique;

4.Agitation followed by ultracentrifugation/centrifugation;

5.Ultra-filtration or centrifugal ultra-filtration techniques.

Usually, the release study is carried out by controlled agitation followed by centrifugation. Due to the time-consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred.

- **Types of Nanoparticles:**[23-30]

1. Liposome

2. Gliadin Nanoparticles

3. Polymeric Nanoparticles

4. Solid Lipid Nanoparticles (SLN)

5. Others-gold, carbon, silver, etc.

6. Nanoparticles and nanospheres

1. Liposomes:[23]

A liposome is a spherical vesicle with a membrane composed of phospholipids bilayer used to deliver drugs or genetic material into a cell. Liposomes can be composed of naturally-derived phospholipids with mixed lipid chains (like the egg, phosphatidylethanolamine), or of pure components like DOPE (dioleolyl phosphatidylethanolamine). The lipid bilayer can fuse with other bilayers (e.g., the cell membrane), thus delivering the liposome contents. By making liposomes in a solution of DNA or drugs, (which would normally be unable to diffuse through the membrane), they can be (indiscriminately) delivered past the lipid bilayer.

2. Gliadin nanoparticles:[24]

In an effort to improve bioavailability anti-H.pylori effects of antibiotics, mucoadhesive gliadin nanoparticles (GNP) which have the ability to deliver the antibiotics at the sites of infection were prepared. GNP bearing clarithromycin (CGNP) and omeprazole (OGNP) were prepared by desolvation method. In vivo gastric mucoadhesive studies confirmed the strong mucoadhesive propensity and specificity and specificity of gliadin nanoparticles towards the stomach. Gliadin nanoparticles show a higher tropism for the gastrointestinal regions and their presence in other intestinal regions is very low. This high capacity to interact with the mucosa may be explained by gliadin composition. In fact, this protein is rich in neutral and lipophilic residues. Neutral amino acid can promote hydrogen bonding interaction with the mucosa whereas the lipophilic components can interact within the biological tissue by hydrophilic interaction. The related protein gliadin possessing an amino and disulfide groups on the side chain has a good probability of developing bonds with mucin gel.

3. Polymeric Nanoparticles:

Polymeric nanoparticles have been invented by Speiser et al. They represent interesting alternative as drug delivery systems to liposomes. They usually exhibit a long shelf life and a good stability on storage. These are superior to liposomes in targeting them to specific organs or tissues by adsorbing and coating their surface with different substances. Nanoparticles can be prepared either from preformed polymers, such as polyesters (i.e. polylactic acid) or from a monomer during its polymerization, as in the case of alkyl-cyanoacrylates. Most of the methods based on the polymerization of monomers consist in adding a monomer into the

dispersed phase of an emulsion, an inverse microemulsion, or dissolved in a non-solvent of the polymer.

4. Solid Lipid Nanoparticles (SLN):[25]

Solid lipid nanoparticles have been developed as the alternative delivery system to conventional polymeric nanoparticles. SLNs are sub-micron colloidal carriers (50-1000nm) which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. SLNs combine advantages of polymeric nanoparticles, fat emulsions, and liposomes, but avoid some of their disadvantages. They are biodegradable, biocompatible and non-toxic.

5. Gold Nanoparticles May Simplify Cancer Detection:[26]

Binding gold nanoparticles to a specific antibody for cancer cells could make cancer detection much easier.

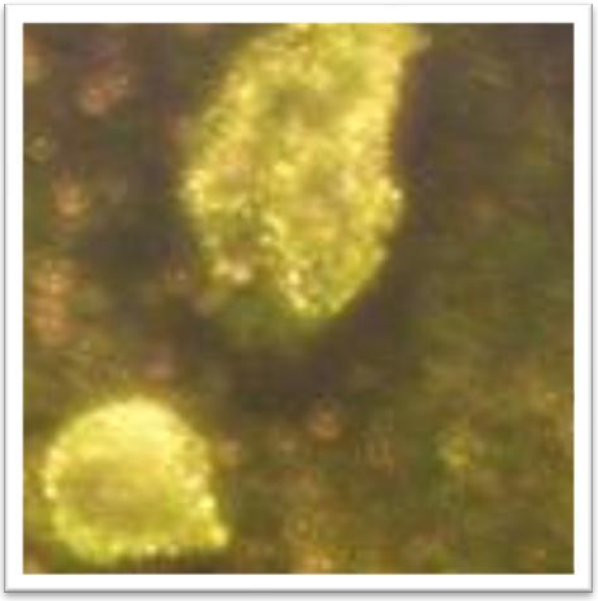

Figure 2: Gold nanoparticles stick to cancer cells and make them shine

"Gold nanoparticles are very good at scattering and absorbing light. Many cancer cells have a protein, known as Epidermal Growth Factor Receptor (EFGR), all over their surface. By conjugating, or binding, the gold nanoparticles to an antibody for EFGR, suitably named anti-EFGR, researchers were able to get the nanoparticles to attach themselves to cancer cells. Gold nanoparticles don't stick as well to noncancerous cells. The

results can be seen with a simple microscope. In the study, researchers found that the gold nanoparticles have 600 percent greater affinity for cancer cells than for noncancerous cells. The particles that worked the best were 35 nanometers in size. Researchers tested their technique using cell cultures of two different types of oral cancer and one nonmalignant cell line. The shapes of the strong absorption spectrum of the gold nanoparticles are also found to distinguish between cancer cells and noncancerous cells.

6. Nanoparticles and Nanospheres:[26, 27]

Nanoparticles were first developed around 1970. They were initially devised as carriers for vaccines and anticancer drugs. In order to enhance tumor uptake, the strategy of drug targeting was employed, and as a first important step, research focused on the development of methods to reduce the uptake of the nanoparticles by the cells of the reticuloendothelial system (RES). Simultaneously, the use of nanoparticles for ophthalmic and oral delivery was investigated.

- **Other:**

1. Gold nanoparticles: These are stabilized by thiol functionality are extraordinarily stable and therefore are great systems for studying nanostructure formation. They have many applications. Because gold nanoparticles are so easy to synthesize they have been studied intensely in recent years.

A common synthesis involves the reduction of a gold salt in the presence of capping agent molecules such as thiols, citrates or phosphines. The functionalities of these capping agents can be altered to yield various chemical properties.

The synthesis of gold nanoparticles with a polymer-thiol monolayer involves the mechanism of particle formation in the presence of bulky ligands. TEM has been used extensively as a way of characterizing the particles. The figure shows an example of TEM imaged particle[26].

2. Nano-capsules based drug delivery system[(28)]

a) Introduction to nanocapsules:

Nano-capsules have been made for many years following the example of nature, using molecules called phospholipids, which are hydrophobic on one end and hydrophilic on the

other. When these molecules are placed in an aqueous environment, they can spontaneously form capsule in which hydrophobic portions are inside. Nano-capsules are the vesicular system in which drug molecule is embedded in an aqueous or oily cavity surrounded by a single polymeric membrane. Nanocapsule may thus be considered as a ‘reservoir system'.

b) Overview of types of nanoparticles used as Nanocapsule in Drug Delivery:

Liposomes are micro- or nanoparticulate vesicles formed by self-assembly of natural molecules such as phospholipids, cholesterol etc or synthetic amphiphiles in an aqueous environment. In particular, liposome has been recognized as an effective nanoparticle drug delivery system and extensively used in research, analytical and therapeutic applications. Liposomes are extensively used as the drug carrier.

Their amphipathic properties make them versatile carrier of either water soluble or lipid soluble drug. The entrapped drug is protected from enzymes and metabolism, and cannot be active until released. The ability of liposomes to alter drug pharmacokinetics makes it as an ideal drug carrier. The increased use of liposome as a drug carrier is due to its ability to increase drug concentration at a targeted site and by decreasing drug concentration in sensitive normal tissues resulting in an increased therapeutic index and reduces unwanted side effects.

Stealth liposomes: The major problem with liposomes are, they recognized by the immune system as a foreign product and quickly removed from circulation before significant delivery of a drug. Recently, lots of research has been done to develop so-called stealth particles, which are invisible to macrophages. Stealth particles are composed of lipid particles that incorporate the polymers like polyethylene glycol (PEG) gangliosides coating. This coating evades the potential impact of the immune system. The design of such carriers is based on the physicochemical concept of steric repulsion. The PEG coating on liposomes reduces the adsorption of steric proteins due to steric hindrance. This approach allows stealth particles to remain in the blood for a long time and also offers protection from the immune system. Stealth particles have ligands on their surface that target receptors expressed on diseased cells. For the disease of vasculature origin, stealth liposomes provide the best therapeutic effect over conventional drug delivery system.

Ceramic Nano-particles are made of silica and alumina. They make the entrapped drug invisible to the immune system and protect from degradation. Although they are stable in a range of temperature and pH their slow dissolution raises questions.

Dendrimers are artificial polymers. The hollow space within it provides great potential for targeted delivery.

Hydrogels are natural polymer amphiphiles where cholesterol groups provide covalent cross-linking. Hydrogels have good bioavailability but are quite unstable.

Micelles are an amphiphilic molecule that includes pluronics. They are thermostable and can carry water-insoluble drugs. It may protect the drug from enzyme and pH action. They can be complexed to ligands combining target ability with stimuli sensitivity.

Nanocrystals are aggregates of molecules with thin surfactant coating. The advantages of nanocrystals include, high dosages can be achieved and poorly soluble drugs can be formulated for improved bioavailability. Both oral and parenteral delivery can be achieved but poor stability is the major limitation with the use of nanocrystals.

Nanotubes are self-assembling sheets of atoms arranged in tubes. Researchers have discovered carbon nanotubes can enter the nuclei of cells and this ability of nanotubes may be used to deliver drugs and vaccines. Nanotubes have large

Internal space and the external surface can be easily functionalized.

Solid lipid nanoparticles are lipid-based submicron colloidal carriers. They require a high amount of surfactants for stability. As compared to the polymer they are less toxic and can be used by various routes like oral, topical or pulmonary.

CONCLUSION:

The foregoing show that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. 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, the 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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