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NANOPATICLES AND NANOCAPSULE

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ABTRACT:

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 include 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 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[1-4].

Theory: [10-12, 15]

- **Ideal Properties Of Polymeric Based Nps :**[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 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 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.

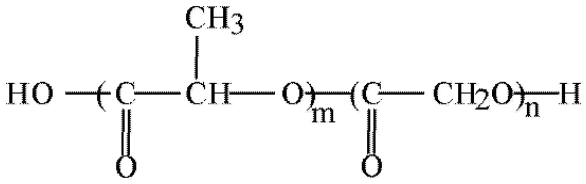

Figure 1. Poly (lactide-co-glycolide) PLG

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 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 blood stream. 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 have 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 have 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 (isobutylcynoacrylate) nanocapsules:***

Intragastric administration of insulin-loaded poly (isobutylcyanoacrylate) nanocapsules induced a reduction of the glycemia to normal level in streptozotocin diabetic rats and is alloxan induced diabetic dogs. The hypolglycemic 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 isobutylcyanoacrylate. 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 nanosphers .

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

Nanoparticles have been widely investigated as the drug carriers. Biodegradable poly (D,L-lactide) polybutylcyanoacrylate 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 reticuloendothelial system. The nanoparticles are obtained from poly(γ-benzyl-L-glutamate)/poly(ethylene oxide) [PBLG/PEO] diblock copolymer, which form a hydrophobic inner core and a hydrophilic outer shell of micellar structure , by adopting dialysis procedure. Their results indicate that only 20% of the entrapped drug was released in 24 h at 37 ^{0}C and the release were dependent on the molecular weight of 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 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.

8. ***Methotrexate-o-carboxymethylate chitosan:***

Nanoparticles of methotrexate (MTX) were prepared using *o*-carboxymethylate chitosan (*o*-CMC) as wall forming materials, and an isoelectric-critical technique under ambient condition. Drug controlled releases were studied in several media including simulated gastric fluid, intestinal fluid and 1% fresh mice serum. It was found that acidic media provide a fast release rate than neutral media. The effect of MTX/*o*-CMC ratio and amount of crosslinking agents of drug release in different media were evaluated. The changes of size and effective diameter of *o*-CMC nanoparticles were detected by SEM and laser light scattering system before and after the drug release. The

author claimed that, the *o*-CMC nanoparticles constitute an attractive alternative to other anticancer drugs and enzyme carriers.

- **Characterisation of Nanoparticles[16-22]**

Nanoparticle characterization is necessary to establish understanding and control of nanoparticle synthesis and applications. The primary characterisation 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 recognised 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 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]

- **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. 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 vesicular system in which drug molecule is embedded in an aqueous or oily cavity surrounded by a single polymeric membrane. Nano- capsule 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 aqueous environment. In particular, liposome have been recognized as an effective nanoparticle drug delivery system and extensively used in research, analytical and therapeutic applications. Liposomes are extensively used as drug carrier.

Their amphilipathic properties make them versatile carrier of either water soluble or lipid soluble drug. Entrapped drug is protected from enzymes and metabolism, and can not 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 targeted site and by decreasing drug concentration in sensitive normal tissues resulting in increased therapeutic index and reduces unwanted side effects.

Stealth liposomes: The major problem with liposomes are, they recognized by immune system as a foreign product and quickly removed from circulation before significant delivery of 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 immune system. The design of such carriers is based on the physico-chemical 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 blood for long time and also offers protection from 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 from silica and alumina. They make the entrapped drug invisible to 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 thermo stable 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 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 external surface can be easily functionalized.

Solid lipid nanoparticles are lipid based submicron colloidal carriers. They require 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.

Drug release mechanisms from the Nano-capsules:

Release of drug from the carrier is important step in nano-capsule based drug delivery system. PH controlled release of drug from carrier is one of the promising approaches to cancer therapy. In this approach acid-sensitive spacers are incorporated between drug and carrier enables release of an active drug from the carrier in a tumor tissue, either in slightly acidic extra cellular tissue fluids or after endocytosis, in endosomes or lyposomes of cancer cells.

In another innovative approach Disulfide bonds are used to assemble nanomolecular capsule around the drug of choice by linking capsule subunit together using disulfide bonds. Disulfide bonds are very stable in blood stream but reduction of the disulfide bond occurs in presence of glutathione. This may be basic principle behind drug release from disulfide nano-capsule. Tumour cells have large amount of glutathione and when nanocapsule reaches tumour site it release drug because of reduction in disulfide bonds.

Magnetic field can be used for drug release. A focused magnetic field selectively activates the magnetic particle present in the nanocapsules. The magnetic field energy is converted to heat by magnetic particles causing a rapid temperature increase with resulting drug release. Incorporation of magnetic nanoparticle is not only useful for producing hyperthermia and magnetically guided drug release but also it gives enhanced and targeted Magnetic Resonance Imaging (MRI).

Characterizations of the nanocapsules:

The sample preparation for examining the morphology, size range and structural information of the nanocapsules with selected anticancer drug in it involve dispersing them in hexane and deionised water respectively. A few drops of the liquid containing the dispersed nanocapsules are studied using transmission electron microscopy. Chemical absorption can be studied using Fourier transform infrared spectroscopy (FTIR). A simple experiment can be performed to study retention of magnetism of magnetic particle when encapsulated in hybrid nanocapsules. This experiment involves application of external magnetic field to the container holding the nanocapsules. The intensity with which nano capsules gets attracted towards magnetic field may determine the magnetism of nanocapsules

In vivo evaluation:

- Drug distribution
- Drug delivery
- Efficacy

Following are various methods that can be used for characterization of nanocapsules:

- Transmission Electron Microscopy
- Electron Scanning Environmental Microscopy
- Raman Spectroscopy
- Thermal analysis

Generally the drug release behaviour depends on a various factors including particle size, surface properties, degradation rate, and interaction force of the drug binding to the surface. Therefore it is necessary to study characterization of nanocapsules which gives evidence to move to the next step of the drug development which is *in vitro* testing.

- ***In vitro* evaluation:**

***In vitro* cytotoxicity assessment** of nanocapsules with anticancer drug in it can be done on human carcinoma cells. Assay involves seeding of approximately 500 to 1000 human carcinoma cells per well in a 96 well plate in 200 µL growth medium. After one day nanocapsule formulation have to be added at the indicated concentration and incubated for 4 days at 37°C. Sulforhodamine B assay can be used to measure tumour cell survival.

Result can be obtained by fitting the data to a sigmoidal dose response. Alternatively cytotoxicity can be measured on different hepatoma cell lines by calculating IC50 that is the 50% inhibiting concentration. In this experiment cells will be incubated for specific time with increasing concentration of nanocapsules drug against standard drug. Cells viability can be measured by neutral red assays. Results can be plotted with Excel software.

- **Rationale:**

It is important to study effectiveness of nanocapsules formulation of anticancer drug in killing the cell line tested. Research has shown that some cell lines which are relatively insensitive to the anticancer drug can be killed with low concentration when capsulated in lipid formulations. It indicates that there could be difference between efficacies of drug when encapsulated. Therefore cytotoxicity assessment is necessary not only to determine therapeutic effects but also to study therapeutic profile of drug formulation.

- **Intracellular accumulation of drugs:**

107 cells can be used to study the intracellular drug accumulation. The experiment involves incubation of nanocapsules containing drugs for 2 hours at concentration of 1, 10 and 50 µmol/L. Immediately after incubation cells are washed twice with ice cold Phosphate Buffer Saline (PBS), harvested by scraping in ice cold PBS, centrifuged and resuspended in 1 ml milli-Q 800 µL sample will have to dry by overnight centrifugation under vacuum and cell pellets formed will be digested in 65% v/v nitric acid at 75ºC for 2 hour. After dilution in water drug content can be analyzed by non flame atomic absorption spectroscopy.

- **Rationale:**

There exists the direct relationship between accumulation of drugs in cells and cytotoxicity. The accumulation of drug in cells treated with nanocapsules was found to be more than in cells treated with the free drug. This test is important to determine minimum effective concentration of drug when encapsulated.

- ***In vitro* drug release:**

It involves five different sets of experiments. They include three different temperatures 40, 37 and 20°C and two different pH 5.3 and pH 7.4. Each experiment has similar procedure with 3.0 mg of the drug encapsulated in nanocapsules sealed in a dialysis membrane tube. The dialysis tube is submerged into 10 ml of Na2HPO4-KH2PO4 buffer solution which is placed in test tube with a closer. The test tube with closer is placed in a water bath maintained at 40°C, 37°C and 20°C. The release medium is withdrawn at predetermined time intervals.

And the amount of free drugs in the buffer solution can be quantified using Lambert-Beer law.

➢ **Rationale:**

The release of drug from nanocapsules varies with temperature and pH. This test conducted at different temperature and pH may find the drug release response depends on temperature and pH. This test is important to study Lower Critical Solution Temperature (LCST) for hybrid nanocapsule.

➢ ***In vivo* evaluation**

In vitro testing of product is only one phase of the clinical development. The next phase is testing its performance in the intended application environment that is, *In vivo* assessment.

There are several animal systems with which drug delivery, distribution and efficacy in pre clinical trial can be measured and explored.

2. NANOSPHERE BLOOD CLEANSING[26,27]

Intravenously injected into victims of radiological, chemical or biological attack, biodegradable nanospheres circulate through the bloodstream, where surface proteins bind to the targeted toxins. They are removed from the bloodstream by a small dual-channel shunt, inserted into an arm or leg artery that circulates the blood through an external magnetic separator. Strong magnets in the shunt immobilize the iron-based particles, and clean blood flows back into the bloodstream.

Potential Applications

- Biological toxin exposures
- Radiological toxin exposure and radioprotection
- Internal hemorrhage
- Brain swelling
- Stroke therapy
- Cancer therapy
- Acute trauma leading to kidney failure

➢ **Status**

- In vitro and in vivo trials ongoing
- Magnetic filter prototype developed
- Many nanospheres formulations tested in vitro
- A strong team of scientists, engineers and medical doctors from Argonne National Laboratory and The University of Chicago Hospitals

➢ **Advantages over current methods:**

- This system offers a number of advantages over existing methods to clean human blood of radioactive and other hazardous materials. Current medical procedures to detoxify human blood are restricted to a few types of toxins and are mainly limited to dialysis and filtration.
- In addition, currently available treatments can take several hours to complete, require the turnover and filtration of large volumes of blood, are rather inefficient at removing toxins and can be risky for the patient. For

these reasons, current methods are mostly restricted to patients with kidney failure and certain types of drug overdoses.

- Alternative treatments exist, such antibodies and chelators substances that combine with and neutralize toxins. These treatments can be used for specific kinds of toxins, but they are inefficient and can cause serious side effects, such as allergic reactions and organ failure.

Solid lipid nanoparticles [29, 30]

Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research, as well as in other varied sciences. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers. This review presents a broad treatment of solid lipid nanoparticles discussing their advantages, limitations and their possible remedies. The different types of nanocarriers which were based on solid lipid like solid lipid nanoparticles, nanostructured lipid carriers, lipid drug conjugates are discussed with their structural differences. Different production methods which are suitable for large scale production and applications of solid lipid nanoparticles are described. Appropriate analytical techniques for characterization of solid lipid nanoparticles like photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry are highlighted. Aspects of solid lipid nanoparticles route of administration and their biodistribution are also incorporated. If appropriately investigated, solid lipid nanoparticles may open new vistas in therapy of complex diseases.

Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity. Over the years, they have emerged as a variable substitute to liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. However, the scarcity of safe polymers with regulatory approval and their high cost have limited the wide spread application of nanoparticles to clinical medicine.

To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting wide attention of formulators world-wide. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes and polymeric nanoparticles). They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials.

SLNs are attracting major attention as novel colloidal drug carrier for intravenous applications. The SLNs are sub-micron colloidal carrier which is composed of physiological lipid, dispersed in water or in an aqueous surfactant

solution. The Pubmed search till the date indicates the trends in SLN research, so if systematically investigated, SLNs may open new vista in research and therapy.

Advantages and Problems of SLNs and Other Nanoparticles:

SLNs combine the advantages and avoid the drawbacks of several colloidal carriers of its class. Potential disadvantages such as poor drug loading capacity, drug expulsion after polymeric transition during storage and relatively high water content of the dispersions (70-99.9%) have been observed. The drug loading capacity of conventional SLN is limited by the solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of the lipid matrix. If the lipid matrix consists of especially similar molecules (i.e. tristearin or tripalmitin), a perfect crystal with few imperfections is formed. Since incorporated drugs are located between fatty acid chains, between the lipid layers and also in crystal imperfections, a highly ordered crystal lattice can not accommodate large amounts of drug. Therefore the use of more complex lipids is more sensible for higher drug loading.

- **Nanostructure lipid carriers (NLC):**

NLC were introduced to overcome the potential difficulties with SLNs. The goal was to increase the drug loading and prevent drug expulsion. This could be visualized in three ways. In the first model, spatially different lipids (like glycerides) composed of different fatty acids are mixed. The use of spatially different lipids leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal and thus provides more room for accommodation of guest molecules. The highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids (oils). This model is called imperfect type NLC. Drugs showing higher solubility in oils than in solid lipids can be dissolved in the oil and yet be protected from degradation by the surrounding solid lipids. These types of NLC are called multiple types NLC, and are analogous to w/o/w emulsions since it is an oil-in-solid lipid-in-water dispersion.

- **SLN Preparation**

SLNs are made up of solid lipid, emulsifier and water/solvent. The lipids used may be triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), and steroids (cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combination (Pluronic F 68, F 127) have been used to stabilize the lipid dispersion. The combination of emulsifiers might prevent particle agglomeration more efficiently. A clear advantage of SLN is the fact that the lipid matrix is made from physiological lipids which decreases the danger of acute and chronic toxicity. The choice of the emulsifier depends on the administration route with a suitable number of emulsifier suitable for parenteral administration.

Applications of Nanoparticulate Drug Delivery Systems [31-36]

1. Medicine:

The biological and medical research communities have exploited the unique properties of nanomaterials for various applications (e.g., contrast agents for cell imaging and therapeutics for treating cancer). Terms such as biomedical nanotechnology, bionanotechnology, and nanomedicine are used to describe this hybrid field. Functionalities can be added to nanomaterials by interfacing them with biological molecules or structures. The size

of nanomaterials is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both in vivo and in vitro biomedical research and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug-delivery vehicles.

2. Diagnostics:

Nanotechnology-on-a-chip is one more dimension of lab-on-a-chip technology. Biological tests measuring the presence or activity of selected substances become quicker, more sensitive and more flexible when certain nanoscale particles are put to work as tags or labels. Magnetic nanoparticles, bound to a suitable antibody, are used to label specific molecules, structures or microorganisms. Gold nanoparticles, tagged with short segments of DNA can be used for detection of genetic sequence in a sample. Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots, into polymeric micro beads. Nanopore technology for analysis of nucleic acids converts strings of nucleotides directly into electronic signatures.

3. Drug delivery:

The overall drug consumption and side-effects can be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach reduces costs and human suffering. An example can be found in dendrimers and nanoporous materials. They could hold small drug molecules transporting them to the desired location. Another vision is based on small electromechanical systems: NEMS are being investigated for the active release of drugs. Some potentially important applications include cancer treatment with iron nanoparticles or gold shells. A targeted or personalized medicine reduces the drug consumption and treatment expenses resulting in an overall societal benefit by reducing the costs to the public health system.

4. Tissue engineering:

Nanotechnology can help to reproduce or to repair damaged tissue. This so called “tissue engineering” makes use of artificially stimulated cell proliferation by using suitable nanomaterial-based scaffolds and growth factors. Tissue engineering might replace today’s conventional treatments, e.g. transplantation of organs or artificial implants. On the other hand, tissue engineering is closely related to the ethical debate on human stem cells and its ethical implications[35, 36].

5. Tumor targeting using nanoparticulate delivery systems[31-34]

The rationale of using nanoparticles for tumor targeting is based on 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 targeting by ligands on the surface of nanoparticles;

6. Long circulating nanoparticles:

To be successful as a drug delivery system, nanoparticles must be able to target tumors which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so-called “stealth” particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by

the MPS. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production of nanoparticles.

7. Reversion of multidrug resistance in tumour cells:

Anticancer drugs, even if they are located in the tumour interstitium, can turn out to be of limited efficacy against numerous solid tumour types, because cancer cells are able to develop mechanisms of resistance. These mechanisms allow tumors to evade chemotherapy. Multidrug resistance (MDR) is one of the most serious problems in chemotherapy. MDR occurs mainly due to the over expression of the plasma membrane pglycoprotein (Pgp), which is capable of extruding various positively charged xenobiotics, including some anticancer drugs, out of cells . In order to restore the tumoral cells' sensitivity to anticancer drugs by circumventing Pgp-mediated MDR, several strategies including the use of colloidal carriers have been applied. The rationale behind the association of drugs with colloidal carriers, such as nanoparticles, against drug resistance derives from the fact that Pgp probably recognizes the drug to be effluxed out of the tumoral cells only when this drug is present in the plasma membrane, and not when

8. Nanoparticles for oral delivery of peptides and proteins:

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 to200 times that of skin. 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; and (d) mucus layer and epithelial cell lining itself.

9. 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 beclassified into those utilizing specific binding to ligands or receptors and those based on nonspecific adsorptive mechanism. The surfaces 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.

10. Nanoparticles for drug delivery into the brain:

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells 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.

11. SLNs as gene vector carrier:

SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. The lipid nucleic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nucleic acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

12. SLNs as cosmeceuticals:

The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The *in vivo* study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% SLN to a conventional cream. SLN and NLCs have proved to be controlled release innovative occlusive topical. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations.

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, 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.

➢ **BIBLIOGRAPHY:**

1. Tropical journal of pharmaceutical research, June 2006; 5(1):561-573. http://www.tjpr.freehosting.net.(intro)
2. Bhardwaj V, Hariharan S, Bala I ,Lamprect A. Kumar N, Panchagula R et al.Pharmaceutical aspects of polymeric nanoparticles for oral delivery. J Biomed Nanotech 2005; 1: 1-23
3. http://www.altavista.com/web/result?itag=ody&q=nanoparticulated+drug+delivery+system&kgs=1&kls=0

4. http://www.ijpsonline.com/article.asp?issn=0250-474x
5. Drug and te pharmaceutical sciences colloidal drug delivery system volume-66, edited by jorg kreuter Marcel Dekkar, Icn. New York. Basel. Hongkong, page no.219-331
6. Http://www.pharmainfo.net./reviews/solubilization-poorly-soluble-drug-review
7. http://www.pharmainfo.net/e-journal(adv)
8. Http://www.pharmainfo.net./reviews/overview-brain-targeting-drug-delivery-system
9. http://en.wikwpedia.org/wiki/nanomaterials
10. Jain S, Jain NK. Resealed erythrocytes as drug carriers. In: Jain NK, editor. Controlled and Novel Drug Delivery. New Delhi: CBS Publishers and Distributors; 2002. p. 256-7.
11. Lee TW, Robinson JR, Controlled release drug delivery systems. In Gennaro AR, editor.Remington: The science and practice of pharmacy.20th ed. Vol.1 Philadelphia; Lippincot Williams and Wilkinson; 2000 : 903-28
12. Lalla JK, Introduction to controlled release and oral controlled drug delivery systems. The Eastern Pharmacist 1991; 45: 25-28
13. Nanoparticles-Targeting Neurotherapeutic Agents Through The Blood Brain Barrier,Shivakumar H.G, Gowda D.V, Krishna R.S.M, Das. D.
14. http://www.iom-world.org/research/nanoparticles
15. Vyas, S, P and khar, R, K; Edited Targeted and controlled drug delivery. CBS Publishers and Distributers, New Delhi, 2002, 351.
16. Kurihara A, Pardridge W.M.Imaging brain tumors by targeting peptide radiopharmaceuticles through the BBB. Cancer Res. 1999, 54, 6159-6163.
17. http://en.wikwpedia.org/wiki/nanomedicine
18. http://en.wikwpedia.org/wiki/nanotoxicology
19. http://www.pharmainfo.net/nikhil-chandra-loka/publications/nanopharmaceutics
20. http://rss.sciencedirect.com/getMessage?registrationId
21. http://www.sciencedirect.com
22. http://www.pharmainfo.net./reviews/drug-delivery-system
23. Shelly utreja; jain N,K; advance in control and novel drug delivery. Edited by N.K jain ;cbs publishers, new delhi,2001,409.
24. Advances In Nanoparticulate Drug Delivery Systems-Rao G.C.S,Satish Kumar M, Mathivanan N. and Rao M.E.B. 17. Application of nanoparticle in photodynamic diagnosis for colorectal cancer S.J. Yang, C.L. Peng, P.S. Lai, F.H. Lin and M.J. Shieh, University, TW
25. Shoba Rani, R.Hiremath and Hota,A; nanoparticles as drug delivery systems. Indian J.Pharm.Sci.,1999.61(2),69-75.
26. Ravi Kumar; N.V.Majetri;nano and microparticles as controlled drug delivery devices. J.Pharm. Sci;,2000,3(2), 234-258

27. Argonne National Laboratory is a U.S. Department of Energy laboratory managed by UChicago Argonne, LLC
28. Inorganic and organic hybrid nanocapsules based anticancer drug delivery by Amit Pokale, Msc clinical research article, october 2007, page no.18,21-26.
29. Hu LD, Tang X, Cui FD. Solid lipid nanoparticles to improve oral bioavailability of poorly soluble drugs. JPP.2004; 15: 1527-35
30. T. Musumecia, C.A. Venturab, I. Giannonea, B. Ruozic, L. Montenegroa, R. Pignatelloa and G. Puglisia.
31. http://www.pharmainfo.net./reviews/nanoparticles/review
32. http://en.wikwpedia.org/wiki/molecular_nanotechnology
33. http://en.wikwpedia.org/wiki/list_of_nanotechnology_application
34. Ahlin P, Kristl J,Vercer F. Investigation of polymeric nanoparticles as carriers of oral administration. Int J Pharm. 2002; 239 : 113-20
35. Jorg Kreuter; Specialised drug delivery systems. Edited by Praveen Tyle. Marcel Dekker Inc. New York, 1990, 264.
36. Schroeder U, Sommerfeld P, Ulrich S, Sabel B.A, Nanoparticle based researches and applications. J. Pharma. Sci. 1998, 87,1305-1307.