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Nanoparticle: An overview of preparations, Characterizations, Evaluations, pharmaceutical aspects and Applications

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ABSTRACT: Nanoparticles are solid colloidal particles ranges from 1 nm - 100 nm. Biodegradable natural or synthetic polymers are the building blocks of nanoparticles. Two types of nanoparticles i.e nanosphere which is matrix type and nanocapsule which is reservoir type are formed depending upon to the method of preparation. Nanoparticles can offer significant advantages over the conventional drug delivery in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules. This review mainly focuses on methods of preparation, characterisations, Evaluations, pharmaceutical aspects and applications.

KEYWORDS: Nanoparticles, colloidal particles, Biodegradable, controlled release, pharmaceutical aspects

I. INTRODUCTION

Nanoparticles are solid colloidal structures or drug carrier composed of synthetic or semisynthetic polymers. Nanoparticles size ranges above molecular dimention and below microscopic ones ie generally greater than 1 nm to below 100 nm. They consist of macro- molecular materials in which the active ingredients (drug or biological active materials) is dissolved, entrapped or encapsulated or adsorbed.[1,2]

The term nanoparticle is a combined name for both nanospheres and nanocapules. Nanospheres are solid core spherical particulates which contain drug embedded within matrix or adsorbed onto the surface (matrix type) while nanocapsules are the vesicular system in which drug is essentially encapsulated within the central core surrounded by a unique polymeric membrane (reservoir type).[1,2,3]

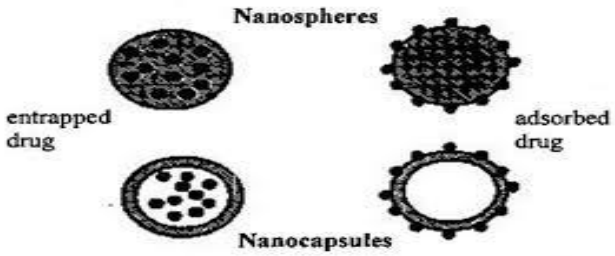

Fig.1: Nanospheres and nanocapsules with the mode of drug entrapment.

It was realized that the nanoparticles loaded bioactives could not only deliver drug(s) to specific organ within the body but delivery rate in addition could be controlled as being bystanders, burst controlled, pulsatile or modulated. The possibilities and potentials further prompted the work and as a result a great deal of related information covering preparation methodologies, characterization, engineering, bio- fate and toxicology has been gathered. The understanding that relates to the biodistribution in particular has propelled and motivated the development of functionally designed nanoparticulates.

The first reported nanoparticles were based on non-biodedradable polymeric systems (Polyacrylamide, polymethyl methacrylate, polystyrene etc). The possibilities of chronic toxicity due to tissue and immunological response towards non-degradable polymeric burden, their use for systemic circulation could not be considered. Soon the bio- degradable polymers were taken up and nanoparticles based on poly (cynoacrylate) were extensively studied. The polymeric nanoparticles can carry drug(s) or

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proteinaceous substances, i.e. antigen(s). These bioactives are entrapped in the polymer matrix as particulates enmesh or solid solution or may be bound to the particle surface by physical adsorption or chemically. The drugs may be added during preparation of nanoparticles or to the previously prepared nanoparticles.[1,3]

Novel drug delivery systems have several advantages over conventional multi dose therapy. For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems using nanoparticles. Nanoparticles can offer significant advantages over the conventional drug delivery in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules.[3,12]

Advantages of Nanoparticles [1,3,4,9]

- Nanoparticles can deliver the drug even in the smaller areas of the body.
- Site specific drug delivery can be achieved by attaching target ligands to the surface of molecules .
- They help in enhancing the bioavailability by increasing the aqueous solubility of poorly soluble drugs.
- They are useful in all routes of administration namely Oral, Parenteral, nasal, ocular etc.
- Controlled release of drugs can be achived.

Disadvantages of Nanoparticles [1,3,4,9]

- Nanoparticles can damage the immune system of the body if excessively consumed.
- Oral breathing of fine particles can lead to diseases like Silicosis, cancer and Emphysema.
- Nanoparticles cannot be absorbed through the skin as they cause irritation of the skin surface.
- Small particle size result in limited drug loading and brust release.

Polymers For Nanoparticles

1. **Natural Hydrophillic Polymers**
   (i) **Proteins:** Gelatin, Albumin, lectins, legumin, vicilin
   (ii) **Polysaccharides:** alginate, dextrane, chitosan, agarose, pullulan
2. **Synthetic Hydrophobic polymers**
   (i) **Pre- polymerized polymers:** poly (e-caprolactone) (PEPL), Poly (lactic acid) ((PLA), Poly (lactide-co- glycoside)(PLGA), Polystyrene
   (ii) **Polymerised inprocess polymers:** Poly (isobutyl cynoacylates) (PICA), Poly (butyl cyano acrylates) (PBCA) Polyhexylcynoacrylates (PHCA), Polymethyl (methacrylate) (PMMA).

Natural Hyrophillic polymers are conveniently classified as protein and polysaccharides. These macromolecules have attracted wide interest as biomaterials due to their intrinsic biodegradability and biocompatibility. The polymers of natural origin however suffer some disadvantages including (a) batch-batch variation (b) conditional biodegradability and (c) antigenicity. Parental administration of polymeric nanoparticles gets compromised mainly due to antigenicity. The relevant information for more systemic work to assess safety of carriers based on proteins and polysaccharides are required and should be sincerely considered.

Pre- polymerized polymers are prepolymerized from their monomers and thereafter used for nanocarrier preparation. Polymerized in process polymers are synthesized from monomers during the preparation of nanoparticles. Synthetic polymers have the advantage of sustained release over a period of days to several weeks compared to the relatively shorter duration of drug release of natural polymers. Their other benefits includes the use of organic solvents and the requirement of typical conditions during encapsulation. Polymeric NPs have, therefore been widely investigated as drug delivery systems over the past few decades, including the clinical study of Food and Drug Administration (FDA) - approved biodegradable polymeric NPs such as PLA and PLGA. [4,5]

Methods used of preparation of nanoparticles

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: (i). Size of nanoparticle required. (ii). Inherent properties of the drug, e.g., aqueous solubility and stability. (iii). Surface characteristics such as charge and permeability. (iv). Degree of

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biodegrability, biocompatibility and toxicity. (v). Drug release profile desired and (vi). Antigenicity of the final product. [5]

A. Amphiphillic Macromolecules cross-linking
Heat cross-linking
Chemical cross- linking

B. Polymerization method
Emulsion polymerization
Dispersion polymerization
Interfacial polymerization
Interfacial condentation

C. Polymer precipitation method
Solvent evaporation
Solvent displacement
Salting out

A. Amphiphillic macromolecules cross- linking

Nanoparticles can be prepared from amphiphillic macromolecules, proteins and polysaccharides.The technique involves firstly, the aggregation of amphiphiles followed by further stabilization either by heat denaturation or chemical cross- linking. This process may occur in biphasic o/w or w/o type of dispersed system. The cross-linking method is used for the nano-encapsulation of drug.This method involves the emulsification of Bovine serum albumin (BSV)/ Human serum albumin (HSA) or protein aqueous solution in oil using high pressure homonization or high frequency sonication. The water in oil emulsion so formed is then poured into preheated oil. The suspension in preheated oil maintained above 100 degrees is held stirred for a specific time in order to denaturate and aggregate the protein contents of aqueous pool completely and to evaporate water. Protenacious subnanoscopic particles thus formed where the size of the internal phase globule mainly determines the ultimate size of particulates. The particles are finally washed with an organic solvent to remove any adherent or adsorbed oil traces and subsequently collected by centrifugation. The factors which govern size and shape of nanoparticle are mainly emulsification energy and temperature.

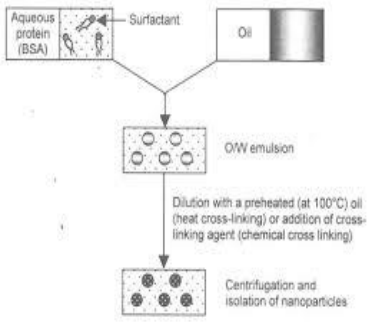

Fig.2: Schematic representation of Amphiphillic macromolecules cress- linking

The high temperature used in the original method restrict to heat sensitivity drug. As an alternative to heat stabilization method a chemical cross- linking agent usually gultaraldehyde is incorporated in to the system.[5,6]

B. Polymerization method [6]

1. Emulsion Polymerization

The process of emulsion polymerization can be conventional or reverse, depending upon the nature of the contineous phase in the emulsion. This process can be:

- *conventional (contineous phase is aqueous i.e o/w emulsion)*
- *Inverse (contineous phase is organic i.e w/o emulsion)*

Two mechanism of emulsion polymerisation are:

-Micellar nucleation and polymerization
-Homogenous nucleation and polymerization

Micellar nucleation and polymerization

In this process The monomer is emulsified in non solvent phase using surfactant molecules. This leads to the formation of

-monomer swallowen micelle
- Stabilized monomer droplets

Polymerization reaction proceeds through nucleation and propagation stage in the presence of chemical or physical initator. Energy provided by initator creats free monomeers in contineous phase which then collide with surrounding unrelative monomers and initate polymerization reaction. The monomer molecules reaches the micelle by diffusion from the monomer droplets through contineous phase, thus allowing polymeerization to progress with in micelles here monomer droplets act as reservoirs of monomers.

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Homogenous nucleation and polymerization

In this process monomer is sufficiently soluble in contineous outer phase.Nucleation and polymerization can directely occur in this phase leading to formation of primary chain called oligomers. In this both micelle and droplets act as monomer reservoir throughout polymer chain length. When oligomers reach certain length They precipitate and form primary particles and stabilized by surfactant molecules provided by micelle and droplets in which the drug will entrapped to form nanoparticles.

2. Dispersion Polymerization

In case of dispersion polymerization , the monomer instead of being emulsified is dissolved in a aqueous medium which acts as a precipitant for subscequently formed polymers. In this type of polymerization the nucleation is directely induced in the aqueous monomer solution and the presence of stabilizer of surfactants is not absolutely necessary for the formation of stable nanospheres. This method is used to prepared biodegradable polyacrylated and polymethyl- methacrylate (PMMA) nanoparticles.[6]

3. Interfacial Polymerization method

In this method a polymer that becomes core of nanoparticles and drug molecule to be loaded is dissolved in volitile solvents. Solution is then placed into a non-solvent for both polymer and core phase.

Polymer phase is seperated at o/w interphase . Resultant mixture instantly turns to milky owing to formulation of nanocapsules.[6]

4. Interfacial complexatation

This method is based on the process of micro-encapsulation. In the case of nanoparticle preparation aqueous polyelectrolyte solution is carefully dissolved in reverse micelles in an apolar bulk phase with the help of an appropriate surface-acting agent. Subsiquently competing polyelectrolyte is added to the bulk which allows a layer of insoluble polyelectrolyte complex to cocervate at the inetrface.[6]

C. Polymer precipitation method [5,12,13,14]

(a). Solvent Evaporation method

Firstly, polymer solutions are prepared in a volatile solvent and emulsion is formulated. The emulsion is converted into a nanoparticles suspension on evaporation of the solvent for the polymer, which is allowed to diffuse across the continuous phase. In the conventional methods, two strategies are used for formation of emulsion: the preparation of single emulsions (e.g. o/w) and preparation of double emulsions (e.g. w/o/w). These techniques utilize high-speed homogenization or ultrasonication or combination of both, followed by evaporation of solvent. Then the solidified nanoparticles are collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants. Finally, the product is lyophilized to obtain free-flowing powder. Normally, a polymer is dissolved in an organic phase containing the surfactant/ stabilizer forms the water phase. This method is a simple method for the preparation of nanoparticles. Although, it is time consuming and possible coalescence of the nano-droplets during the evaporation process may affect the final size and morphology of the particle.

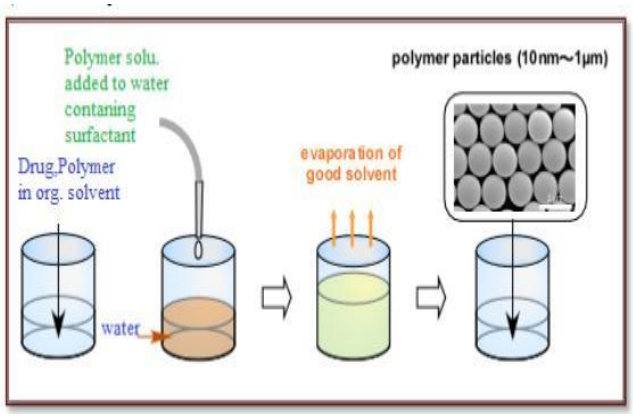

Fig 3: Schematic representation of solvent evaporation method

(b). Solvent displacement

This method is also known as Nano precipitation method.This method is based on the interfacial deposition of a polymer after displacement of a semipolar solvent, miscible with water, from a lipophilic solution. Rapid diffusion of the solvent into non-solvent phase results in the decrease of interfacial tension between the two phases, which increases the surface area and leads to the formation of small droplets of organic solvent. Nano precipitation system comprises of three basic components: the polymer (synthetic, semi synthetic or natural), the polymer solvent and the nonsolvent of the polymer. Organic solvent (i.e., ethanol, acetone, hexane, or dioxane) which is miscible in water and easy to remove by

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evaporation is selected as the polymer solvent. Due to this reason, acetone is the most commonly employed polymer solvent in this method sometimes, it consists of binary solvent blends, acetone with small amount of water, blends of acetone with ethanol and methanol. On the other hand, the non-solvent phase consisting of a non solvent or a mixture of non-solvents is supplemented with one or more naturally occurring or synthetic surfactants.

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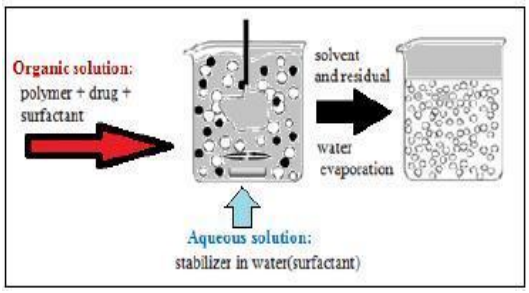

Fig.4: Schematic representation of Solvent displacement method

(c). Salting-out

Salting out method based on the separation of a water-miscible solvent from aqueous solution via a salting-out effect. Polymer and drug are initially dissolved in a solvent which is subsequently emulsified into an aqueous gel containing the salting- out agent (electrolytes, such as magnesium chloride and calcium chloride, or non electrolytes such as sucrose) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyethylcellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of solvent into the aqueous phase, thus inducing the formation of nanospheres. Several manufacturing parameters can be varied including stirring rate, internal/external phase ratio, concentration of polymers in the organic phase, type of electrolyte concentration and type of stabilizer in the aqueous phase This technique used in the preparation of PLA, Poly (methacrylic) acids, and Ethyl cellulose nanospheres leads to high efficiency and is easily scaled up. Salting out does not require an increase of temperature and therefore may be useful when heat sensitive substances have to be processed. The greatest disadvantages are exclusive application to lipophilic drug and the extensive nanoparticles washing steps**.**

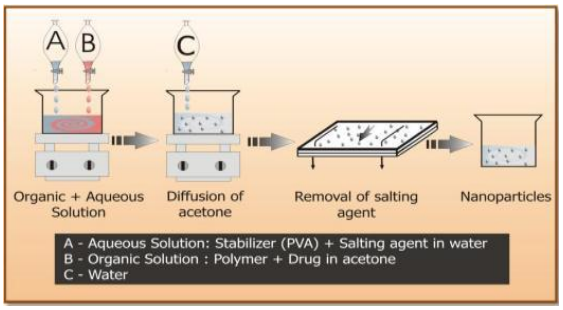

Fig.5: Schematic representation of salting-out method.

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).[15]

Characterstics/Evaluation of nanoparticles

Particle size and Morphology

Particle size and Particles surface morphology determine the in vivo distribution, biological fate, toxicity and targeting ability of nanoparticle system. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. The particle size and morphology of nanoparticles can be determined using numerous commercially available instruments such as Scanning Electron Microscopy(SEM), Dynamic Light Scattering(DLS), Nano Sight(NTA), Transmission Electron Microscopy(TEM).[16]

Specific Surface

The specific surface area of freeze-dried nanoparticles is generally determined with the help of sorptometer. The equation given below is used in calculation of specific surface area:

$$A = {}^{6}/_{\delta d}$$

Where, A= specific surface area, δ is the density and d is the diameter of particle.[18]

Surface Charge and Electrophoretic Mobility

The nature and intensity of of the surface charge of nanoparticle is very important as it determine their interaction with the biological environment as well

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as their electrostatic interaction with bioactive compound.

The surface charge of colloidal particles or nanoparticles can be determined by measuring the particle velocity in an electric field. Laser Light Scattering technique i.e Laser droppler anemometry or Velocimetry has become available as fast and high resolution technique for the determination of nanoparticle velocities.

The surface charge of colloidal particles could also be measured as electrophoretic mobility. The charge composition critically decides the biodistribution of drug carrying nanoparticles. Generally Electrophoretic mobility of nanoparticles is determined in phosphate buffer(ph 7.4) and human serum.[18,19,27]

Density

The density of nanoparticles is determined with hilium or air using a gas pycnometer. The value obtained with air and with hilium may differ noticeably from each other. The difference is much more pronounced due to specific area and porosity of the surface.[27]

Surface Hydrophobicity

Surface hydrophobicity has an important influence on the interaction of colloidal particles with the biological environment(eg, protein adsorption and cell adhesion). the Hydrophobicity and Hydrophillicity collectively determine the bio-fate of nanoparticles and their contents. Hydrophobicity regulates the extent and type of hydrophobic interactions of nanoparticulates with blood components.

Several methods including hydrophobic interaction Chromatography. Two-phase partition,adsorption of hydrophobic fluorescence or radiolabelled probes and contact angle measurement have been adopted to evaluate surfave hydrophobicity.[7]

Molecular weight measurement of nanoparticles

The molecular weight of polymer and its distribution in the matrix can be evaluated by gelpermeation chromatography(GPC) using a refractive index detector.[18]

Drug Content/Entrapment of drug

After Centrifugation amount of drug present in supernatant(w) is determined by UV-Spectrophotometry.[28]

$$\% \text{ drug entrapment } = \frac{W-w}{W} * 100$$

Where, W= Total amount of drug used in preparation of nanoparticles w=drug present in supernatant.

Yield of Nanoparticles

The yield of nanoparticles was dictated by looking at the entire load of nanoparticles framed against the combined load of the copolymer and drug.[28]

$$\% \, yield = \frac{Amount\ of\ Nanoparticle}{Amouunt\ of\ Drug + Polymer} \times 100$$

Drug- excipient compatibility study

It is performed by FT-IR spectrophotometer. FT-IR spectra of drug, polymer and formulations are analyzed seperately then correlated for incompatibility.[5,29]

Pharmaceutical aspects of Nanoparticles[16,25,35,36]

From the pharmaceutical point of view nanoparticles prepared from different methods should be free from potentially toxic impurities, should be easy to store and administer, finally should be sterile if parenteral use is advocated.

So main three important process parameters are performed before releasing them for clinical trials.

-Purification
-Freeze drying
-Sterilization

Purification:

Different types of nanoparticles prepared from diverse range of methods may yield impurities in the nanoparticles suspension including organic solvents, residual monomers, polymerization initiators, electrolytes, stabilizers and large polymer aggregates. The most commonly reported methods used for purification are:

-Gel filtration

Remarks: High molecular weight substances and impurities are difficult to remove

-Dialysis

Remarks:High molecular weight substances and impurities are difficult to remove and time consuming process.

-Ultra- centrifugation

Remarks: Aggregation of particles and time consuming process

-Cross-flow filtration.

Cross flow filtration A new cross – flow filtration method is used for purification of nanoparticles in industrial point of view. In this method nanoparticle suspension is filtered through membranes, with the direction of fluid being tangential to the surface of the membrane. As a result clogging of filters is avoided.

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Freeze Drying of Nanoparticles

This process involves the freezing of the nanoparticle suspension and subsquent sublimation of its water content under reduced pressure to get a free flowing powder material.

Sterilization of Nanoparticles

Nanoparticles intended for parenteral use should be sterilized to be pyrogen free before they are allowed for administration to animal models or to human one.

The well stabilized method of sterilization for other delivery system like filtration through 0.22 µm membrane filter donot always work for nanoparticles because micro-organism and nanoparticles maybe larger then in size (0.25-10µm). However sterilization in case of nanospheres is best achieved by using aseptic technique throughout their preparation and processing and formation and/or by subsquent sterilizing treatment like autoclaving or Y-irradiation.[35]

***In-vitro* Release**

In-vitro release profile can be determined using standard dialysis, diffusion cell or recently introduced modified ultrafiltration technique.

In- vitro drug release from the nanoparticles can be evaluated in phosphate buffer utilizing double chamber diffusion cells, on a shaker stand. A millipore hydrophillic low-protein binding membrane is placed between two chambers. The donor chamber is filled with nanoparticulate suspension and the receptor chamber with plane buffer. The receptor compartment is assayed at different time intervals for the drug release using standard procedure.[18,30]

Application of Nanoparticles

-Used in targated drug delivery to brain therapy

The brain is one of the least acessible organs for the delivery of drugs due to the presence of the blood-brain barrier (BBB) that controls the transport of endogenous and exogenous compounds. Drugs normally unable to cross the BBB could be delivered to the brain after binding to the surface modified poly (butyl cyanoacrylate) (PBCA) nanoparticles. It has been reported that poly (butylcyanoacrylate) nanoparticles was able to deliver hexapeptide dalargin, doxorubicin and other agents into the brain which is significant because of the great difficulty for drugs to cross the BBB.[2,19,40]

-Nanoparticles for oral delivery of peptides and proteins

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. 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. 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.[15, 40]

-Nanoparticles for gene therapy

Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment. It is reported that following their intracellular uptake and endolysosomal escape, nanoparticles could release DNA at a sustained rate resulting in sustained gene expression. This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morph genic protein.[19,40]

Targeting 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 B12

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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. [19]

-Used in diagnosis and bioimaging

A number of molecular imaging techniques are available such as optical imaging (OI), magnetic resonance imaging (MRI), ultrasound imaging (USI), positron emission tomography (PET) and others have been reported for imaging of *in-vivo* and *in-vitro* biological specimens. The current development of luminescent and magnetic nanoparticles advances bio imaging technologies. Two different types of nanoparticales have been widely for imaging : luminescent nanoprobes for OI and magnetic nanoparticles for MRI.[2,18,38]

- Cancer therapy

It has been shown that nanoparticles nanoparticles have the ability to carry various therapeutic agents including DNA, proteins, peptides and low molecular weight compounds. Among all of them, liposome and polymer based nanoparticulates are the most widely used nanoparticles as drug delivery systems, as these compounds are generally biodegradable, donot accumulate in the body and they are possibly risk-free. For instance, several anticancer drugs, including paclitaxel, 5-fluorouracil, doxorubicin have been successfully formulated using polymers and liposomes as drug delivery system.[2, 38, 39]

Conclusion

The emergence of nanotechnology Is likely to have a significant impact on pharmaceutical field. It has several merits over the conventional drug delivery system in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules. Further more research and development of nanotechnology in Drug targeting to brain, peptides and proteins from oral delivery , nanoparticles for gene therapy, diagnostic and bio imaging purpose , nanoparticles in cancer therapy will be helpful for development of new method for treatment.

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