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A Review: Nanoparticulate Drug Delivery System

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ABSTRACT

The nanoparticles have emerged as an amazing drug delivery system consisting of particles size ranging from 1 to 100 nm. There are significant advantages of nanoparticles that make them more potential and effective than conventional drug delivery systems in terms of improved solubility, increased drug bioavailability, high drug carrying capacity, and targeted drug delivery at a specific site of action. The current study topic is undertaken for detailed insight into the nanoparticulate drug delivery system which includes types, advantages, disadvantages, methods of preparation, evaluation, and applications of the nanoparticulate drug delivery system.

INTRODUCTION

In recent decades there has been considerable research interest in the field of pharmaceuticals delivery using nanoparticulate delivery systems as carriers for small and large molecules. Particulate systems such as nanoparticles have been used as a physical approach. Improves pharmacokinetic and pharmacodynamic properties of various classes of drug molecules. Delivering the therapeutic compound to the desired site is a major problem in the treatment of many diseases. Conventional Drug use is characterized by poor and limited biodistribution Lack of Efficacy, Adverse Side Effects, and Selectivity. Targeting cells or specific tissues by individual means engineered drug-attached carriers are more reliable approach in drug delivery systems. Such an approach is known as organization-specific targeting. Size reduction of target formulation and designing its pathway for a suitable drug delivery system is a more basic and successful approach to form the basis of nanotechnology. Nanoparticles have different Conical, hollow cores, spherical, cylindrical, tubular, flat, etc. or irregular, varying in size from 1nm to 100nm. The surface can be uniform or irregular due to surface variations. Some nanoparticles are crystalline or amorphous Single-crystal or polycrystalline solids, discrete or aggregated. The process of synthesis of new drugs, most of which drug candidates are insoluble or sparingly soluble in water, Ruin of the pharmaceutical industry. one of the main reasons for the drug's insolubility is its complexity and Large molecular structure. Reported 65% of new active pharmaceutical ingredients (APIs) are either sparingly soluble or insoluble. because of their Low water solubility and high permeability, they are classified as Class II biopharmaceuticals Classification System (BCS) Resolution Steps are the rate-limiting factor for drug absorption. Pharmaceutical industries currently facing challenges to improve the dissolution properties of poorly water-soluble drugs. This is a crucial component of drug improvement. [1-3]

Advantages of Nanoparticles

1. Nanoparticles can be administered by parenteral, oral, nasal, and ocular routes.
2. Improve stability and therapeutic index and reduce toxic effects.
3. Improve tissue macrophage distribution.
4. Protection from physical and chemical degradation.
5. Enhancement of stability and protection from toxicity.

6. Increased bioavailability.

7. Enhancement of pharmacological activity.

8. Both active and passive drug targeting can be achieved by manipulating the particle size and surface characterization.

9. By attaching specific ligands to their surface, nanoparticles can be used for directing the drug to specific target cells. [1-4]

Disadvantages of Nanoparticles

1. Very costly formulation.

2. Reduced ability to adjust the dose.

3. Requires skills to manufacture.

4. Stability of dosage form is a big issue owing to its nano size.

5. Productivity is more difficult. [1-4]

Types of Nanoparticles

1. Polymeric nanoparticles: The polymeric nanoparticles (PNPs) are prepared from biocompatible and biodegradable polymers in size between 10-1000 nm where the API is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending on the method of preparation, one can produce nanoparticles, nanospheres, or nanocapsules. Nanospheres are matrix systems in which the drug is physically and uniformly dispersed, while nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane. [4]

2. Solid lipid nanoparticles: SLNs are colloidal carrier systems composed of a high melting point lipid having a solid core coated with an aqueous surfactant and BCS class II and IV drugs are used. SLNs use solid lipids instead of liquid lipids, which is different from other colloidal carriers. Lipid pellets for oral drug delivery are a well-known example of using solid lipids as a matrix material for drug delivery.[5]

3. Gold nanoparticles: Gold nanoparticles can be coated with different materials such as small molecules, biomolecules, and polymers because of these nanoparticles' versatile surface chemistry. As a result, they have numerous applications in a variety of fields,

including catalysis, sensory probes, drug delivery, and therapeutic agents. Recently, gold nanoparticles are known as an ideal modifier for electrode surfaces in electrochemical sensors fabrication. Wide applications of gold nanoparticles for the fabrication of electrochemical sensors are due to their excellent properties such as tenable physiochemical properties, outstanding electrical conductivity, oxidation resistance, high stability, simple preparation, narrow size distribution, excellent biocompatibility, capacity for surface modification, large surface area, and excellent catalytic activities.[6]

4. Magnetic nanoparticles: There are several strategies for the synthesis of magnetic nanoparticles for drug delivery. Particles may be produced that have a core-shell structure, where the core is a magnetic iron oxide (usually magnetite – [Fe3O4] or maghemite [gFe2O3]) and the shell is generally a polymer such as silica, dextran, or PVA, or metals such as gold to which functional groups can be attached via cross-linkers. This type of structure can be synthesised using both ionic and non-ionic surfactant techniques or encapsulated within a structure such as a carbon cage or ferritin protein. These particles can then be functionalized by attaching carboxyl groups, amines, biotin, streptavidin, antibodies, and others.[7]

5. Silver nanoparticles: AgNPs are extensively used in state-of-the-art drug delivery carriers in recent years, because of their facial synthesis methods to functionalize surfaces and tune optical features. AgNPs can be engineered to deliver drug molecules in response to electromagnetic and pH stimuli. A multifunctional drug carrier responsive to photo and pH stimuli has been developed by Fang and co-workers by uniformly coating mesoporous silica on the surface of PdAg nanoplates.[8]

6. Silica nanoparticles: Mesoporous silica materials (MSMs) are a type of mesostructured bioceramics that have shown bioactive behaviour thanks to the presence of silanol groups at their surface and a similar chemical composition to bioactive glasses. The excellent properties of MSNs for biomedical applications have triggered the development of novel advanced multifunctional materials for a broad range of biotechnological applications.[9]

7. Carbons nanoparticles: Carbon nanotubes (CNT)] are considered ideal materials for several applications, ranging from ultra strong fibers to field emission displays. Recently, CNT has generated great interest in biology, where suitably modified CNT can serve as vaccine delivery systems or protein transporters.[10]

8. Liposomes: Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural nontoxic phospholipids. Liposomes are promising drug delivery systems due to their size, hydrophobic and hydrophilic properties (along with biocompatibility). Liposome properties vary greatly depending on lipid composition, surface charge, size, and preparation method.[11]

9. Dendrimer: Dendrimers are novel three dimensional, hyperbranched globular nanopolymeric architectures. Attractive characteristics include nanoscopic size, a narrow polydispersity index, excellent control over the molecular structure, and the availability of multiple functional groups at the periphery and cavities in the interior to distinguish them from the available polymers. Dendrimer applications have been investigated in a wide range of fields. Drug delivery scientists are especially enthusiastic about the possible utility of dendrimers as drug delivery tools.[12]

10. Quantam dots: Quantum dots (QDs) are nano-sized semiconductor crystals that have been found as interesting materials in different areas of science, especially in biology. They are categorized into two distinct groups including cadmium-based (e.g., CdTe, CdSe) and cadmium-free ones (e.g., InP, InAs, CuInS2, Ge, Si, ZnS, and graphene QDs). [13]

METHODS OF PREPARATION:

1) Emulsion-solvent evaporation method: In the emulsion solvent evaporation method, the organic phase is prepared by dissolving the drug and polymer in an organic solvent like dichloromethane. Then aqueous phase is prepared by dissolving the stabilizer in distilled water. The organic phase is added dropwise to the aqueous phase under a high share force of homogenizer to prepare an o/w emulsion. The rotary evaporator is used for the evaporation of the solvent. Then nanoparticles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug. After this water is evaporated by lyophilization and dried nanoparticles are collected in the form of powder.[1][4]

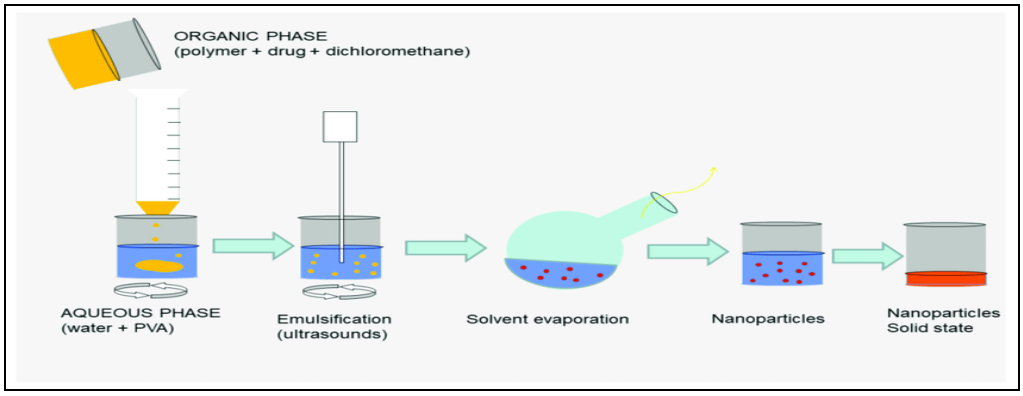

Figure No. 1: Emulsion-solvent evaporation method

2) Solvent diffusion method: This is another widely used method to prepare nanoparticles. The encapsulating polymer is dissolved in a partially water-miscible solvent (such as propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. The polymer-water saturated solvent phase is then emulsified in an aqueous solution containing a stabilizer, resulting in solvent diffusion to the external phase and the formation of nanocapsules or nanospheres, according to the oil-to-polymer ratio. Finally, depending on its boiling point, the solvent is removed via evaporation or filtration. [1][4][14]

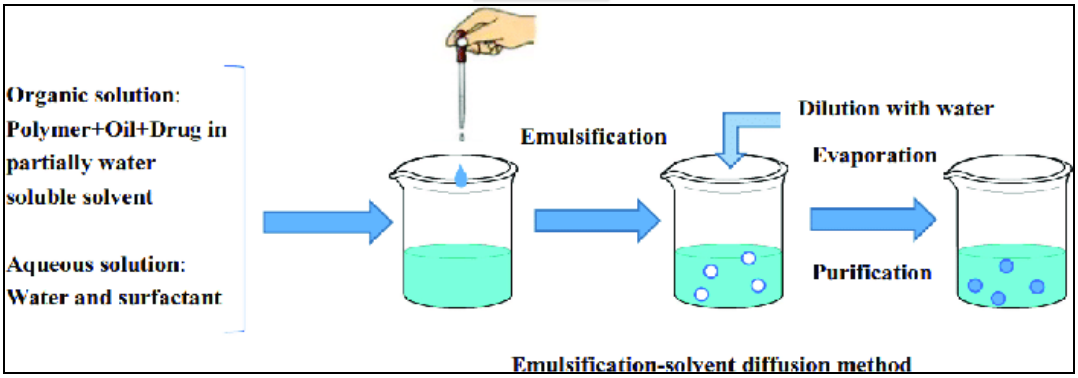

Figure No. 2: Solvent diffusion method

3) Double emulsification method: The emulsion and evaporation method suffer from the limitation of poor entrapment of hydrophilic drug. To encapsulate hydrophilic drugs, the double emulsion technique is used, which involves vigorously stirring aqueous drug solutions into organic polymer solutions to form w/o emulsions. This w/o emulsion is continuously stirred into the second aqueous phase to form the w/o/w emulsion. The emulsion is then subjected to solvent removal via evaporation, and nanoparticles can be isolated via high-

speed centrifugation. Before lyophilization, the formed nanoparticles must be thoroughly washed.[4]

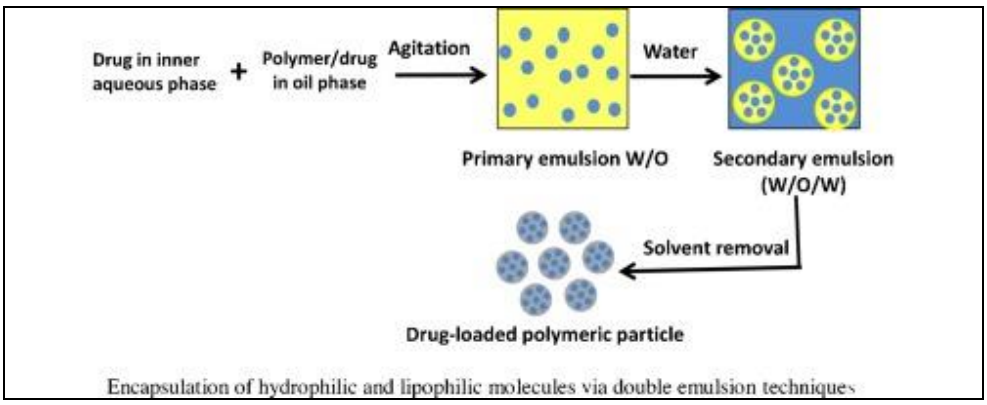

Figure No. 3: Double emulsification method

4) Salting out method: Salting out is based on the separation of a water-miscible solvent from an aqueous solution via a salting out effect. Polymer and drug are initially dissolved in acetone before being emulsified into an aqueous gel containing the salting-out agent (electrolytes such as magnesium chloride, calcium chloride, and magnesium acetate, or non-electrolytes such as sucrose) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyethylcellulose. This oil/water emulsion is diluted with enough water or aqueous solution to promote acetone diffusion into the aqueous phase, resulting in the formation of nanospheres.[1]

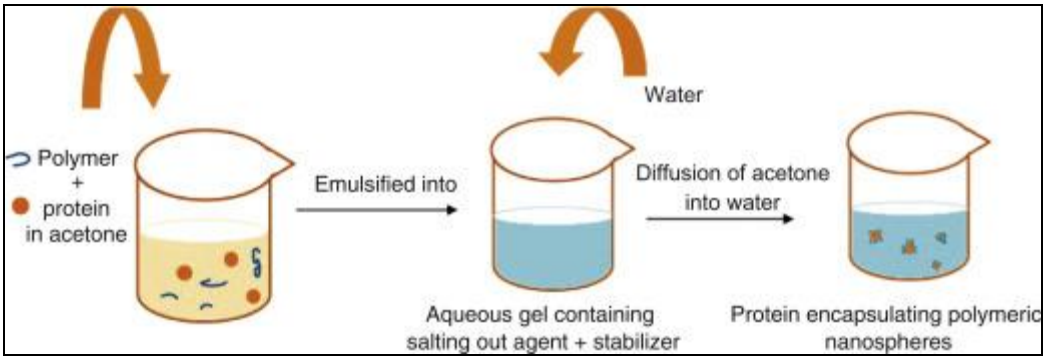

Figure No. 4: Salting out method

5) Nanoprecipitation/Solvent displacement method: Solvent displacement involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of surfactant. Polymers, drugs, and or lipophilic surfactants are dissolved in a semipolar water-miscible solvent such as acetone or ethanol. The solution is then poured or injected into an aqueous solution

containing a stabilizer under magnetic stirring. Nanoparticles are formed instantaneously by rapid solvent diffusion.[4]

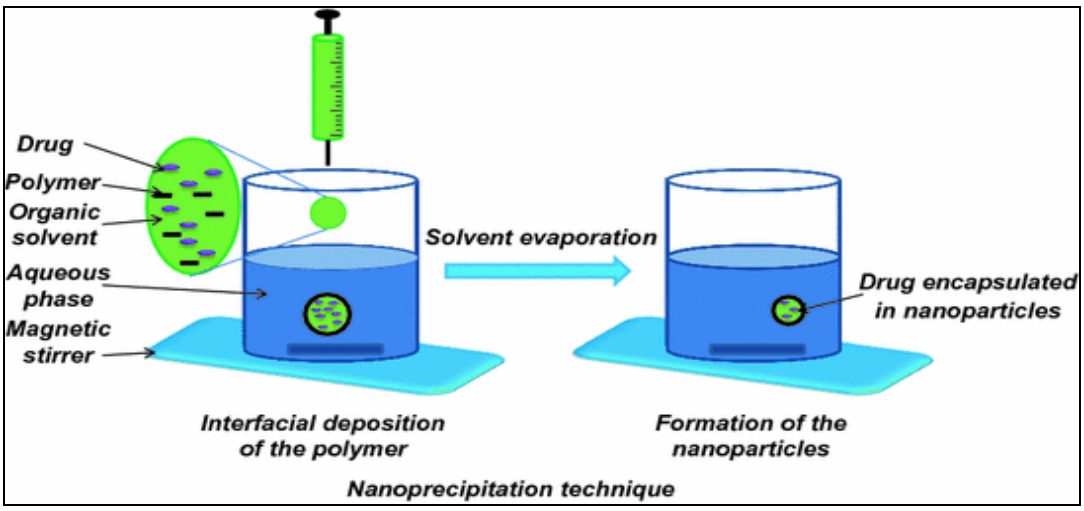

Figure No. 5: Nanoprecipitation/Solvent displacement method

6) Dialysis: Dialysis offers a simple and effective method for the preparation of small, narrow-distributed polymeric nanoparticles. Polymer is dissolved in organic solvent and placed in a dialysis tube with the appropriate molecular weight cut off. Dialysis is carried out against a non-solvent miscible with the former. The displacement of the solvent inside the membrane is followed by progressive polymer aggregation due to loss of solubility and the formation of homogeneous nanoparticle suspensions. At the moment, the mechanism of PNP formation via dialysis is not fully understood.[6]

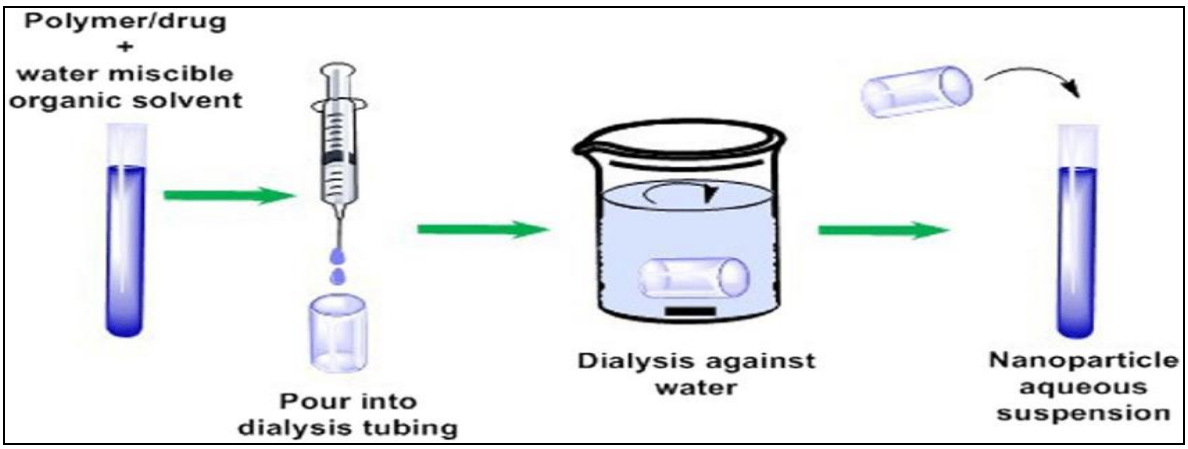

Figure No. 6: Dialysis

7) Supercritical fluid technology: The solute is dissolved in a supercritical fluid to form a solution, followed by the rapid expansion of the solution across an orifice or a capillary nozzle into the ambient air. The high degree of supersaturation, combined with the rapid pressure reduction during expansion, causes homogenous nucleation and, as a result, the formation of well-dispersed particles. Mechanistic studies of various model solutes for the RESS process show that nanometre and micrometer-sized particles are present in the expansion jet.[4]

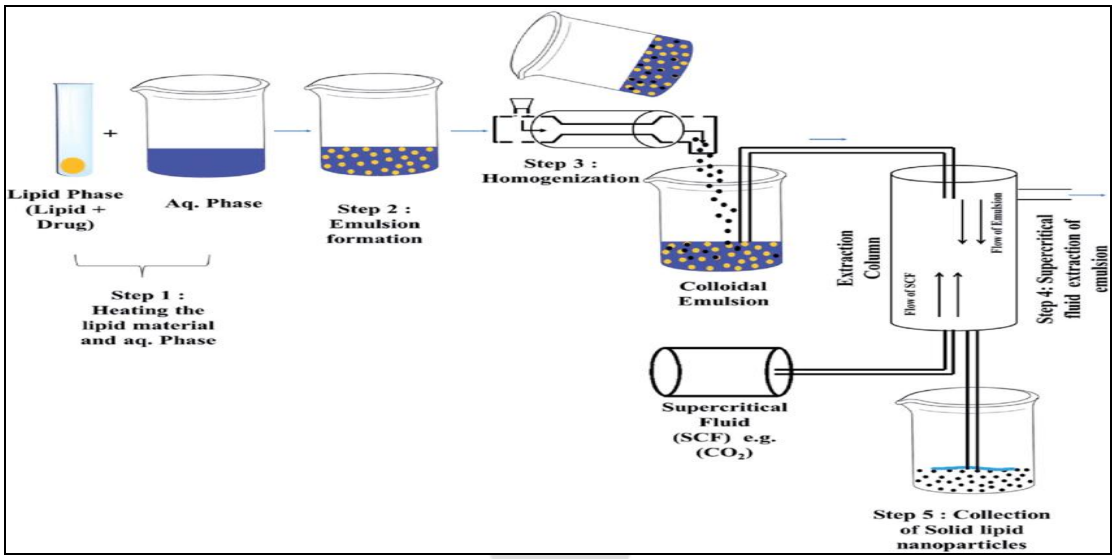

Figure No. 7: Supercritical fluid technology

EVALUATION PARAMETERS OF NANOPARTICLES:

1. Percentage yield: The yield of nanoparticles was determined by comparing the whole weight of nanoparticles formed against the combined weight of the polymer and drug.[15]

$$\% \text{ yield} = \frac{\text{weight of nanoparticles} \times 100}{\text{Weight of drug + polymer}}$$

2. Drug Entrapment Efficiency: The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 5^0c.The supernatant solution was then decanted and dispersed in phosphate buffered saline pH 7.4. As a result, the procedure was repeated twice to completely remove the unentrapped drug molecules. The amount of drug entrapped in the nanoparticles was calculated by subtracting the total amount of drug used to prepare the nanoparticles from the amount of drug in the aqueous medium. [16][17]

$$\text{Drug entrapment Efficiency (\%)} = \frac{\text{Amount of released from lysed nanoparticles}}{\text{Amount of drug initially taken To prepare the nanoparticles}} \times 100$$

3. Particle size: Particle size distribution and morphology are the most important parameters of the characterization of nanoparticles. Morphology and size are measured by electron microscopy. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affects drug release. Smaller particles offer a larger surface area. As a result, most of the drug loaded onto them will be exposed to the particle surface leading to fast drug release. On the contrary, drugs slowly diffuse inside larger particles. As a drawback, smaller particles tend to aggregate during the storage and transportation of nanoparticle dispersion. Hence, there is a compromise between the small size and maximum stability of nanoparticles.[15][17]

4. In vitro release study: In vitro drug release studies were performed in USP type 2 dissolution apparatus at a rotation speed of 50rpm. The prepared nanoparticles were filled in a capsule shell immersed in 900ml of phosphate buffer solution in a vessel and temperature was maintained at 37± 0.2 ^{0}C. The required quantity (1ml) of medium was withdrawn at specific time periods and the same volume of dissolution medium was replaced in the flask to maintain a constant volume. The withdrawn sample was analyzed using a UV spectrophotometer.[16]

5. Kinetic study: For estimation of the kinetic and mechanism of drug release, the result of in vitro drug release study of nanoparticles was fitted with various kinetic equations like zero order, first order and Higuchi's model and R^2 and K values were calculated for the linear curve obtained by regression analysis of the plot. [15]

APPLICATIONS OF NANOPARTICULATE DELIVERY SYSTEMS:

1. Nanoparticles for Brain Delivery

Antibiotics, antineoplastic agents, and a variety of neuroleptic drugs all face challenges crossing the blood-brain barrier. One solution proposed to overcome this barrier is drug delivery to the brain via nanoparticles. The hexapeptide dalargin, the dipeptide kyotropin,

loperamide, tubocurarine, and doxorubicin have all been successfully used for brain targeting using nanoparticles. [3][18]

2. Nanoparticles for Gene Delivery

Gene therapy is a method of treating disease that involves inserting genetic material/DNA into cells and either replacing a defective gene or modifying the expression of a gene. Nanoparticles emerged as the most promising vehicles for clinical gene therapy due to their size, shape, surface, and biological behaviours. Gene therapy has received a lot of attention as a promising strategy for treating a variety of gene-related human diseases, including cancer, haemophilia, hypercholesterolemia, neurodegenerative diseases, and autoimmune diseases.[2][19][20]

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

Targeting strategies for improving nanoparticle interaction with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be divided into two types: those that use specific binding to ligands or receptors and those that use a nonspecific adsorptive mechanism. Cell-specific carbohydrates on the surface of enterocytes and M cells may serve as binding sites for colloidal drug carriers containing appropriate ligands. Certain glycoproteins and lectins bind to this type of surface structure selectively via a receptor-mediated mechanism. Various lectins, including bean lectin and tomato lectin, have been studied to improve oral peptide adsorption.[2][18]

4. Nanoparticles for vaccine delivery

Nanosomic systems with molecular-targeting and diagnostic imaging capabilities are emerging as the next generation of functional nanomedicines to improve therapeutic outcomes.[19]

5. Nanoparticles in diagnostic medicine

Very interesting study on the subject of nanoparticles in diagnostic medicine. They used to antibody-conjugate, hydrophilic, magnetic nanocrystals as smart nanoprobes for the ultrasensitive detection of breast cancer via Magnetic Resonance Imaging (MRI). MnFe2 O4 nanocrystals employed as MRI-contrast agents for MRI were synthesized by thermal decomposition.[1][20]

FUTURE OPPORTUNITIES AND CHALLENGES

The nanoparticles have already been used successfully as drug delivery systems. Nanoparticles provide massive advantages regarding drug targeting, and delivery and with their potential to combine diagnosis and therapy as one of the major tools in Nanomedicine. The following techniques present numerous technical challenges: - Virus-like systems for intracellular systems, biomimetic polymer architecture, drug control, functions (of active drug targeting, bioresponsive triggered systems, systems interacting with the body smart delivery), nanochips for nanoparticle release, carriers for advanced polymers for therapeutic peptide/protein delivery Drug delivery techniques were developed to deliver or control the amount and rate of administration. Most major and established internal research programs on drug delivery that are formulations and dispersion containing components down to nano sizes.

CONCLUSION

Nanoparticulate drug delivery is opening a prospective future in pharmaceutics. Nanoparticles enable new techniques in imaging and sensor technology and perfect for building better systems. It delivers drugs to small areas of the body. The current pharmaceuticals are characterized by low bio-availability which is results in higher patient costs and inefficient treatment and also more likely increased risks of toxicity or even death. A nanoparticle drug delivery system will help to lower drug toxicity, reduce the cost of treatments and improve bioavailability. Nanotechnology drug delivery also makes it possible for drugs to permeate through cell walls, which is of critical importance to the expected growth of genetic medicine over the next few years. Some recently found health risk shreds of evidence limit their utilization in pharmacy and the medical field.

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