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NANOPARTICULATE DRUG DELIVERY SYSTEMS - AN UPDATE

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ABSTRACT

Nanoparticles are considered as one of the novel promising carrier systems. Nano technology deals with fabrication, manipulation as well as use of materials in nanometres range. The ability to penetrate cells and cross blood–brain barrier is a distinct characteristic of nanoparticles and they are easily destroyed. Nanoparticles can be fabricated from biodegradable or non-biodegradable materials. In the present review, various types of nanoparticles and their characteristics, formulation and fabrication of different nanoparticles, characterization of nanoparticles, applications, challenges to be overcome with the use of nanomedicines and future perspectives were elaborated. Polymeric nanoparticles have numerous applications; yet, there are challenges related to the synthesis of polymeric nanoparticles which are required to be addressed before such formulations can be completely used & adapted into applications. Research in the field of nanoparticulate DDS have witnessed remarkable growth and progresses. However, only limited nano drug formulations developed by both academia as well as biopharmaceutical industry have been granted approval for clinical use. Similarly, very few reports are available related to scale-up production of polymeric nanoparticles. Improvement and changes in the physicochemical characteristics provide a new dimension to more effective, beneficial and safer nanoparticulate DDS. Nanoparticulate systems have been emerged as a promising platform to achieve targeted or site-specific drug delivery.

Keywords: Nanoparticles, fabrication, characterization, applications

INTRODUCTION

Nanoparticles are considered as one of the novel promising carrier systems. Nano technology deals with fabrication, manipulation as well as use of materials in

nanometres range. Nanoparticles are described as particles whose three dimensions are limited within a range of 1 - 100 nm **[1–4]**. The optical, mechanical, electrical, magnetic and chemical properties can be modified by varying the size of nanoparticles **[5, 6]**. The ability to penetrate cells and cross blood–brain barrier is a distinct characteristic of nanoparticles and they are easily destroyed **[7-9]**. Nanoparticles can be fabricated from biodegradable or non-biodegradable materials **[10]**. Different types of nanoparticles include polymeric nanoparticles, solid–lipid nanoparticles, gold nanoparticles, silver nanoparticles, magnetic nanoparticles, nanocrystals, mesoporous silica nanoparticles, carbon nanotubes, fullerene nanoparticles and albumin nanoparticles. Nanoparticles have not been accepted extensively because of their toxicity **[11]**.

The solubility of poorly aqueous soluble drugs, therapeutic efficacy of certain drugs as well as their safety parameters can be enhanced by encapsulation of such drugs within the nanoparticles. **[12-15]**. The significant surface area-to-volume ratio of nanoparticles permits them to absorb high amounts of drugs **[16]** as well as to be spread with ease all through the bloodstream **[17]**.

Advantages of nanoparticles [18-20]

- Targeted & controlled drug release at specific site and reduction in fed/fasted variability
- High drug loading, smaller dose and dose proportionality, lesser side effects, biochemically inert, superior compatibility, non-toxic, non-immunogenic & biodegradable
- Ease of scale up and sterilization, enhance solubility of poorly aqueous soluble drugs, thereby improve drug bioavailability
- Valuable in the diagnosis of various diseases and ease of penetrability into cell walls, stomach epithelium, blood vessels as well as blood brain barrier
- Adaptability for various modes of administration, ease of controlling critical parameters of nanoparticles and avoidance of coalescence results in improved physical stability
- Decline of drug leakage due to decreased movement of incorporated drug molecules
- Static solid/liquid interface enables surface modification.
- Polymeric nanoparticles make an exemplar drug delivery system for the preparation of vaccines, antibiotics, contraceptives and treatment of cancer.

Disadvantages

- Potential toxicity, artificially fabricated nanoparticles may comprise a new category of non-biodegradable pollutants.
- Sophisticated strategies and methods are to be developed in order to assess the impacts of exposure to nanoparticles and nanoparticle aerosols.
- Poor oral drug bioavailability and instability in systemic circulation and insufficient tissue distribution as well as toxicity.

TYPES OF NANOPARTICLES [21-26]

Lipid-based drug carriers - Liposomes

A liposome is a spherical vesicle bilayer phospholipid membrane used to deliver drugs or genetic material into a cell. Liposomal formulations of daunorubicin (Dauno Xome) and doxorubicin (Myocet, Doxil) are approved for the treatment of AIDS-related Kaposi's sarcoma and metastatic breast cancer. Further, several liposomal drugs are in the progress of being evaluated in clinical trials **[27]**.

Gliadin nanoparticles

Mucoadhesive gliadin NPs can deliver the antibiotics at the site of infection. Gliadin nanoparticles loaded with clarithromycin & omeprazole were prepared by de-solvation technique.

Solid lipid nanoparticles (SLNs)

SLNs are fostered as an alternative drug delivery system to conventional PMNs. SLNs possess pros of PMNs, liposomes & fat emulsions, however overcome few of their limitations **[28]**.

Polymeric nanoparticles (PMNs) / polymer-drug conjugates

PMNs exemplify remarkable alternative to liposomal drug delivery systems since they exhibit a prolonged shelf-life, good stability upon storage, better than liposomes in targeting them to particular organs or tissues. PMNs are fabricated with the use of preformed polymers such as polylactic acid, or alkyl cyanoacrylates.

Natural: Naturally occurring polymers such as chitosan, albumin & heparin are the choice for the delivery of protein, DNA, oligonucleotides & drugs. In recent times, paclitaxel nanoparticle formulation wherein serum albumin is incorporated as a carrier nm-sized albumin-bound paclitaxel (Abraxane) and further has been applied in clinic to treat metastatic breast cancer.

Synthetic: Amongst synthetic polymers like polystyrene-maleic anhydride copolymer, N-(2- hydroxypropyl)- meth acryl amide copolymer (HPMA), poly-L-glutamic acid (PGA) and polyethylene glycol (PEG), PGA was considered to be the first biodegradable polymer to be utilized for conjugate synthesis.

Polymeric micelles

The functional characteristics of micelles depends on amphiphilic block co-polymers that build to form a nano-sized shell/core

structure in aqueous solutions. Genexol-PM (PEG-poly (D, L-lactide)- paclitaxel), is the first polymeric micelle formulation of paclitaxel.

Dendrimers

Characteristics associated with such dendrimers like their modifiable surface, mono disperse size (1.5-10 nm), multi-valency, available internal cavity & aqueous solubility make them attractive for drug delivery. Cisplatin was conjugated with polyamidoamine dendrimer **[29]**.

Gold nanoparticles [30-35]

The diagnosis of cancer can be much easier by binding gold nanoparticles to a particular antibody for cancer cells. One of the distinct characteristics shown by gold nanoparticles is enhanced light scattering & absorption due to surface-plasmon resonance, that can be tailored by changing shape or size of nanoparticles for various applications. Toxicity concerns limits applications of gold nanoparticles in medicine.

Nanospheres [36, 37]

Nanoparticles were primarily developed as carriers for anti-cancer drugs and vaccines. The strategy of drug targeting was applied to increase tumour uptake.

Viral Nanoparticles

Viruses such as cowpea chlorotic mottle virus, cowpea mosaic virus, bacteriophages and canine parvovirus have been developed for nanotechnology and biomedical applications which comprise drug delivery and tissue targeting.

Carbon nanotubes

Anticancer drugs (methotrexate) and antifungal agents (amphotericin B) have been linked covalently to carbon nanotubes with a fluorescent agent (FITC).

Quantum dots

In recent times, research has been focused towards development of photosensitizing quantum dots for production of radicals upon visible light absorption.

MATERIALS USED IN PREPARATION OF NANOPARTICLES

Poly (ethylene oxide)-poly (L-lactic acid) / poly(benzyl-L-aspartate) [38]

They are used for the preparation of polymeric micelles for the attachment of amino-containing ligands. Such nanospheres have been investigated as carriers for delivery of anti-tumour and anti-inflammatory drugs.

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

Nanoparticles of biodegradable and biocompatible polyester copolymer PLG [Poly(lactide-co-glycolide)] have been formulated by nanoprecipitation process.

Polyphosphazene derivatives

The researchers Allock & co-workers prepared phosphazene polymer derivatives for biomedical applications. PEO-layered poly(organophosphazenes) nanoparticles

have prolonged circulation in blood, consisting of amino acid were developed.

Poly (ethylene glycol) coated nanospheres

PEG-coated nanospheres from PLG, PLA, or other biodegradable polymers such as poly (ε-caprolactone), may be utilized for the delivery of drugs intravenously. Coated nanospheres may serve as the circulation depots of drugs being administered.

Poly (isobutyl cyanoacrylate) nano capsules

Nano capsules may be fabricated by interfacial polymerization of isobutyl cyanoacrylate.

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

Nanoparticles are fabricated by the use of biodegradable poly(ε-caprolactone) and poly (D, L-lactide) polybutylcyanoacrylate. Since diblock co-polymers form micelles, they have been used as an alternative drug carrier in sustained release system.

Chitosan-poly (ethylene oxide) nanoparticles

Organic solvents are required for many of the recently developed hydrophilic-lipophilic carriers and possess limited protein-loading capacity. In order to overcome such limitation, nanoparticles are fabricated by ionic gelation using only one hydrophilic carrier which includes mixture of two aqueous phases at room temperature.

METHODS OF PREPARATION

1. Solvent evaporation method [39-43]

In solvent evaporation, the polymer is dissolved in organic solvent (dichloromethane, chloroform or ethyl acetate) followed by dispersion of drug in the resultant solution. Further, the mixture is emulsified in water phase that consists of surfactant (such as tweens, pluronics, poly vinyl alcohol) to make an oil-in-water (O/W) emulsion with the help of mechanical stirring, micro fluidization or sonication. The organic solvent is evaporated after formation of an emulsion by the rise of temperature and reduced pressure with continued stirring **[44]**.

2. Solvent diffusion method / spontaneous emulsification method [45-48]

In solvent diffusion, drug and lipid are mixed in organic, water miscible solvents at higher temperature. The obtained solution is injected rapidly by mechanical stirring into water phase consisting of a surface-active agent.

As temperature reduces, the lipid droplets get solidified to form nanoparticulate suspension of drug. The main pros of such method include ease of handling and its simplicity. Both solvent diffusion and solvent evaporation methods may be applied for hydrophilic or lipophilic active ingredients **[49]**.

3. Nano precipitation method without surfactant [50-52]

It is apt for hydrophobic drugs. Drug solution is combined with anti-solvent by magnetic stirring. Nanoparticle precipitates so formed were subjected to filtration and subsequently product is freeze-dried. By adjustment of process variables such as addition of organic phase into aqueous phase & polymer concentration, the size & drug release were controlled.

4. Supercritical fluid (SCF) technology [53]

SCFs are environmentally safe hence, have no hazardous effects unlike other methods which involve use of organic solvents. SCFs are preferred due to their non-flammability, non-toxicity and low cost. In this, CO_2 is used as an SCF in 2 main techniques (Supercritical anti-solvent technique & Rapid expansion of critical solution (RESS)) because of its mild conditions **[54]**.

5. High pressure homogenisation [55-58]

In case of high-pressure homogenization, the drug is priorly milled by the use of low-pressure homogeniser and followed by addition of aqueous surfactant solution at various concentration levels. Drug is dissolved in molten lipid phase followed by its addition in ethanol. The organic solution, is further transferred to aqueous surfactant solution under stirring at a speed of 500 rpm for the duration of 20 min utilizing a mechanical stirrer. The pre-emulsion so formed, is subsequently homogenised in order to decrease particle size using high pressure homogenizer. Finally, the mixture is cooled to room temperature producing drug-nanoparticles.

6. Dispersion of preformed polymers [59]

It is a conventional technique used to fabricate biodegradable nanoparticles from poly (D, L-glycolide), poly (cyanoacrylate), poly (lactic acid) and poly (D, L-lactide-co-glycolide). In this technique, nanoparticles are formed by the polymerization of monomers in an aqueous solution. Drug incorporation is done by dissolving in polymerization medium or by adsorption onto nanoparticles at the end of polymerization. The resultant nanoparticle suspension is further purified in order to remove different surface-active agents and stabilizers added for polymerization by ultracentrifugation and re-suspending nanoparticles in an isotonic surfactant-free solution. Such technique has been employed for the preparation of poly (alkyl cyanoacrylate) or poly (butyl cyanoacrylate) nanoparticles.

7. Coacervation or ionic gelation method

Hydrophilic polymers like sodium alginate, gelatin and chitosan have been explored in the preparation of biodegradable nanoparticles. Calvo and co-workers established a technique for fabrication of hydrophilic chitosan nanoparticles by the

process of ionic gelation. It encompasses a mix of two aqueous phases consisting of polymer chitosan, a diblock copolymer ethylene oxide or propylene oxide and polyanion sodium tripolyphosphate **[60]**.

8. Double emulsification method

Emulsification and evaporation technique have a drawback of poor entrapment of hydrophilic drugs; therefore, double emulsification method is employed. Initially, w/o emulsion was prepared by the addition of aqueous drug solution to organic polymer solution with constant stirring. Further, the prepared emulsion was added to another aqueous phase with continuous stirring, to form w/o/w emulsion. Finally, the removal of organic solvent was carried out by high-speed centrifugation **[61]**.

9. Emulsion-diffusion technique

The technique patented by Leroux *et al.,* is a modified form of salting out process. Polymer was dissolved in water miscible-solvent (benzyl alcohol, propylene carbonate) followed by saturation with aqueous phase. Polymer-water saturated solvent phase is subjected to emulsification in an aqueous solution consisting of a stabilizer. Lastly, solvent was removed by filtration or evaporation **[62]**.

10. Nano-precipitation / solvent displacement method

Nano-precipitation was first described by Fessi *et al.,* in the year 1989. The precipitation of polymer and drug was achieved from the organic solvent and its diffusion into the aqueous phase with or without the presence of surface-active agent.

11. Salting out technique

It is similar to solvent-diffusion technique. Toxic solvents are not utilized in salting out method. Acetone is commonly used due to its water miscibility and ease of removal. Drug & polymer were dissolved in a solvent, followed by emulsification in water consisting of salting-out agent (electrolytes, like calcium chloride or magnesium chloride, or non-electrolytes like sucrose). Salting out can also be achieved by saturation of water phase using an emulsion stabilizer/ colloidal stabilizer/ viscosity enhancer like hydroxyethyl cellulose or polyvinyl pyrrolidone, PEO, PVA & PLGA. The resultant o/w emulsion was diluted by addition of adequate water in order to permit complete diffusion of organic solvent into aqueous phase, thereby, facilitating formation of nanospheres. It does not need a rise in temperature and require stirring energy to obtain nanospheres of low size range. Limitations of salting out method - extensive nanoparticles washing steps & exclusive application to hydrophobic drug **[63]**.

12. Dialysis

The solution obtained by dissolving drug and polymer {like poly (lactide)-b-poly (ethylene oxide), poly (benzyl-l-glutamate)-b-poly (ethylene oxide)} in an organic solvent was added to a dialysis tube and dialysis carried out in contrast to a non-solvent miscible with the former.

13. Emulsion cross-linking method

A water-in-oil emulsion is made by emulsifying chitosan solution in oil phase. Stabilization of aqueous droplets is done using appropriate surfactant and stable emulsion is cross-linked by suitable cross-linking agent like glutaraldehyde in order to harden obtained droplets **[64]**.

NANOPARTICLES CHARACTERIZATION

Particle size and surface morphology

The particle size and surface morphology of the fabricated nanospheres was carried out using scanning electron microscopic technique.

Measurement of zeta potential / polydispersity index

Zetapotential provides information related to charge on nanoparticles surface and assess stability of colloidal dispersion. It is variable with the composition of particles as well as dispersed medium. Zeta potential is measured by Zeta meter. If zeta potential value is above (± 30mv), more the charge on surface and less will be aggregation. It is used to establish whether the product is adsorbed or encapsulated.

DSC analysis

Habit of powder sample (amorphous, crystalline) & nature of crystallinity can be determined using DSC technique. It provides sharp endothermic peak which evaluate the melting point, crystalline nature and glass transition temperature.

Transmission Electron Microscopy (TEM)

It is a technique used to determine morphology as well as three-dimensional structure of product with high contrast compared to scanning electron microscopy (SEM). In this method, a beam of electrons is transmitted in straight line *via* thin specimen. An image on the imaging device is formed after interaction with the specimen, which can be identified by a photographic film. Physical characteristics of nanoparticles can also be determined by TEM.

Percentage yield

Percentage yield of nanoparticles was estimated by comparing the total weight of nanoparticles obtained against the combined weight of drug & polymer applying below mentioned formula:

$$Percentage\ yield = \frac{Total\ weight\ of\ nanoparticles\ obtained}{Weight\ of\ drug\ +\ polymer}\ x\ 100$$

Surface lipophilicity

Surface lipophilicity governs the concentration of absorbed blood components and it can be opsonin protein. It helps in opsonization (binding of opsonin on surface of nanoparticles). Opsonin's

build connection between phagocytes and nanoparticles. Lipophilicity on nanoparticles surface can be estimated by biphasic partitioning, hydrophobic interaction chromatography, contact angle measurements, adsorption of probes, etc. Explicit chemical groups on nanoparticles surface can be detected by x-ray photon correlation spectroscopy.

Determination of drug entrapment efficiency

After the process of centrifugation, the concentration of drug entrapped in a lipid matrix is determined by the collection and further analysis of supernatant using UV spectrophotometer. If the concentration is zero, it indicates that all drug is entrapped within lipid matrix. The drug entrapment efficiency is calculated by using the below mentioned formula.

$$Drug\ entrapment\ efficiency\ \left(\%\frac{w}{w}\right) = \frac{Total\ amount\ of\ drug\ -\ Amount\ of\ drug\ in\ supernatant}{Total\ amount\ of\ drug}\ x\ 100$$

$$Drug\ loading\ (\%\ w/w) = \frac{Initial\ drug\ -\ free\ drug}{Mixed\ lipid}\ x\ 100$$

***In-vitro* drug release**

In-vitro drug release studies are performed using USP type II dissolution apparatus operated at an agitation speed of 50 rpm & 37 ± 0.5 ºC temperature. Such profiles are utilized to determine controlled release potential as well as drug release from lipid nanoparticles. Dru release pattern depends upon factors such as concentration of lipid phase, surfactant and aqueous phase. Aliquot volumes (5 ml) of dissolution medium were withdrawn at particular time intervals and the similar volume of fresh dissolution medium was replaced back into flask to maintain constant volume. Samples withdrawn were subjected to analysis using UV spectrophotometer.

Table 1: Recent investigation explored in the field of nanomedicines

S. No.	Active ingredient/ Excipient	Category	Method of preparation	Polymers used	Result	References
1.	Ketoprofen	Nonsteroidal anti-inflammatory drug (NSAID)	Double emulsification-solvent evaporation technique	Poly D, L-Lactic-Co-Glycolic Acid (PLGA), Polyvinyl Alcohol (PVA)	Exhibited sustained release profile of ketoprofen up to 24 hours.	[65]
2.	Piroxicam	Nonsteroidal anti-inflammatory drug (NSAID)	Nanoprecipitation technique	Nanoparticles of quinoa starch	Quinoa starch found to enhance the rate of piroxicam release with improved anti-inflammatory activity.	[66]
3.	N-Acetylcysteine	Mucolytic, anti-inflammatory & hepaprotective agent	Nanoprecipitation method	PLGA 50:50, Resomer RG 502, RG 504, RG 505	Increased entrapment efficiency	[67]
4.	Puerarin	Isoflavones (Source- Radix puerariae)	Ionic gelation method	Chitosan	Sustained-release effect, significantly improved the bioavailability of Purerarin	[68]
5.	Sandostatin LAR® (Octreotide)	Acromegaly	Solvent evaporation method	Poly (lactic-co-glycolic acid) (PLGA)	Maximized microsphere yield, minimized residual solvent	[69]
6.	Curcumin	Natural antioxidant (Source- Curcuma longa)	High-pressure homogenization by antisolvent crystallization	HPMC, PVP K-30	Acquired better solubility and dissolution rate with high-pressure homogenization.	[70]
7.	Curcumin	Anticancer, antioxidant, anti-inflammatory, anti-microbial & antiviral effect	High pressure homogenization using antisolvent crystallization	Poloxamer 188, Soluplus®	Due to concentration of stabilizer dissolution rate of curcumin was controlled.	[71]
8.	Amphotericin B	Antifungal	Supercritical fluid processing	Polyvinyl Alcohol (PVA)	Obtained stabilized formulation.	[72]

CHARACTERIZATION [73-77]

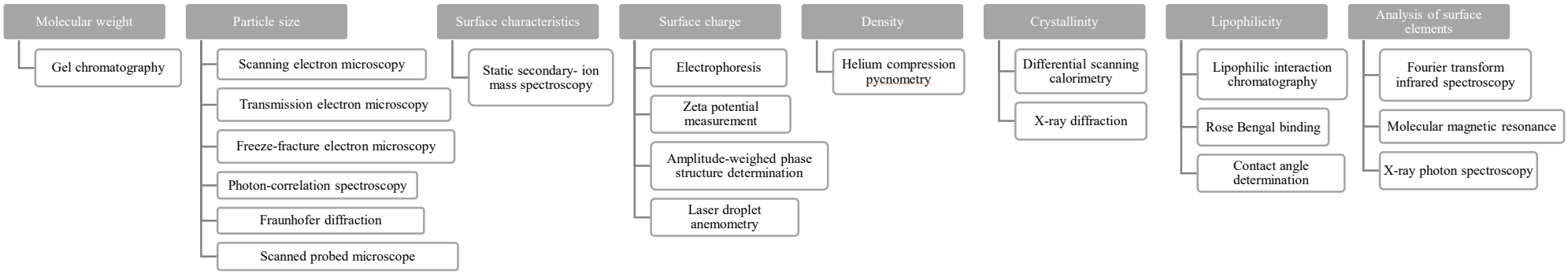

Figure 1: Characterization methods of nanoparticles

Kinetic study

In order to find out kinetic as well as mechanism of drug release, the results of *in vitro* drug release study of nanoparticles was fitted with different kinetic equations such as zero order (cumulative % release vs. time), first order (log % drug remaining vs. time), Higuchi's model (cumulative % drug release vs. square root of time). R^2 & k values were computed for the linear curve obtained by regression analysis of above curves.

Stability of nanoparticles

The stability of nanoparticles was determined by the storage of optimized formulation at temperatures 5 ºC ± 1 ºC & 25 ºC ± 2 ºC, 40 ºC ± 2 ºC, 75% ± 5% RH in a stability chamber for the duration of 6 months. Further, the samples were analysed after specified time intervals as per ICH Q1A guidelines for their drug content, rate of drug release ($t_{50\%}$) and any modifications in their physical appearance.

APPLICATIONS [78-79]

- Target at a tumour site as a drug carrier
- Long circulating and site-specific nanoparticles
- Nanoparticles as antituberculosis drug carrier
- Nanoparticles for delivery into brain
- Oral delivery of nanoparticulate proteins and peptides
- Nanoparticles for gene delivery
- Solid lipid nanoparticles as cosmeceuticals
- Nanosphere blood cleansing

CHALLENGES [80]

Biological Barriers to drug delivery

In order to achieve therapeutic efficiency, the drugs in systemic circulation are required to cross the biological barriers to reach at the target site. Blood-Brain-Barrier constrains the diffusion of aqueous soluble drugs or large molecules inside cerebrospinal fluid and it is the main hindrance for the treatment of several types of brain disorders like brain tumour. Therefore, it is an important challenge for the drug delivery.

Lipophilic drug delivery

Lipophilic drugs are difficult to be delivered at target site. Hence, different solvents & surfactants like tween, cremophor & polysorbate are used to improve drug distribution but, they cause several harmful side-effects.

Nanoparticles components and characteristics

Selection of ingredients for the formulation of nanomedicines is of much significance. The therapeutic efficacy and safety depend upon the chosen target moiety or drug since they could modify several factors which influence high bioavailability like partition coefficient, biodistribution & cellular uptake.

Production challenges

Nanoparticles are made up of many ingredients with spatial arrangements. Nano formulations are adversely affected, if any subtle change happens in the constituents or process. The main challenge during production is reproducibility. The formulations must be greatly reproducible.

Regulatory challenges

Attainment of regulatory approvals for nanomedicines poses many obstacles. Currently, regulatory authorities such as United States Food and Drug Administration (USFDA), European Medicines Agency (EMA) examine a novel nanoparticulate system on a product basis. The complex structure of nanoparticles makes it difficult to compare with standard drugs.

CONCLUSIONS AND FUTURE PERSPECTIVES [81-82]

In the present review, various types of nanoparticles and their characteristics, formulation and fabrication of different nanoparticles, characterization of nanoparticles, applications, challenges to be overcome with the use of nanomedicines and future perspectives were elaborated. Similarly, very few reports are available related to scale-up production of polymeric nanoparticles. Synthesis of polymeric nanoparticles at a laboratory scale occur only as a proof of concept of technology. Priorly, USFDA has taken more time to take a decision for the clinical trials and the regulatory authority framed new set of guidelines for extra preclinical testing procedures. Perhaps, nanoparticles found to have highest potential both at socio-economic level. Improvement and changes in the physicochemical characteristics provide a new dimension to more effective, beneficial and safer nanoparticulate DDS. Nanoparticulate systems have been emerged as a promising platform to achieve targeted or site-specific drug delivery.

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