International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1096-1102 www.ijprajournal.com ISSN: 2456-4494

Recent advancements in various methods in the preparation of polymeric nanoparticles.

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Submitted: 05-04-2022 Accepted: 17-04-2022

ABSTRACT

Nanotechnology is the new emerging technology that is growing very vastly nowadays. The nanoparticles have very many uses in the medical and biomedical fields. Polymeric nanoparticles are one of the types of nanoparticles. Polymeric nanoparticles havea very wide application in curing various types of diseases. This polymeric nanoparticle can easily cruse the BBB (Blood Brain Barrier). This nanoparticle has wide application in cancer treatment. The polymeric nanoparticles are in the size range of 1-1000 nm. These nanoparticles are useful in targeting the disease at the specific site. These nanoparticles act as the controlled as well as a sustained release at the site of action. This nanoparticle can be given via various dosage forms such as gel, i.v. etc. There isa various polymers used for the preparation of these nanoparticles. These polymers are from various sources such as natural as well as synthetic. A natural polymer such as chitosan, alginate, and synthetic polymer such as PLGA, PLA are widely used for the preparation of polymeric nanoparticles.

Keywords- Nanoparticles, Polymeric nanoparticles, Polymer, Natural, Synthetic.

I. INTRODUCTION

Nanoparticles

Nanoparticles are (<1000 nm in size) tiny materials that have specific physicochemical properties different to bulk materials of the same such properties make them very attractive for commercial and medical development. Nanotechnology is a new emerging technology that has been widely applied in the biomedical and medical fields. Has a vast scope in various cancerous diseases. The nanoparticles have a very small size which can easily cross the blood-brain barrier. The nanoparticles are the various types of metal, inorganic, magnetic, polymeric, solid lipid nanoparticles. The nanoparticles are of mostly two types according to their structure one is nano capsule, nanosphere. The nanocapsule and nanosphere are shown in figure1. A nano capsule is defined asa nanoscale shell made from a non-toxic polymer. They are vesicular systems made of a polymeric membrane that encapsulates an inner liquid core at the nanoscale.Nanosphere is small particle size; thus, they are suitable to be administered orally, locally, and systemically. Usually, most nanospheres are prepared using polymers that are biodegradable and biocompatible. They are used as a delivery system to enhance entrapment and release of the drug. Nano (Greek) is extremely small. A nanometer is billionth of A meter or 10^{-9} m. Solid Size particles ranging from 1 - 1000 nm in they consist of macromolecular material. [1]

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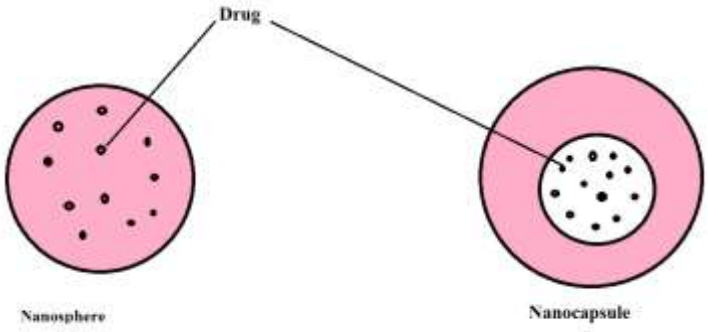

Figure. 1 Types of nanoparticles.

Advantages

1. Higher Stability
2. Higher Carrier Capacity
3. Feasibility of variable routes of administration
4. Feasibility of Variable routes of administration.
5. These are biodegradable, non-toxic & capable Stored for a longer period.
6. Also used Controlled delivery drugs.
7. Reduces dosing frequency[1]

Dis-advantages

1. Posses. limited drug loading capacity
2. On repeated administration, toxic metabolites may be formed during the Polymeric Carriers. biotransformation.
3. Relatively slowly biodegradable which might Cause systemic toxicity

Polymeric nanoparticles

PNPs (polymeric nanoparticles) are particulate dispersions or solid particles with a size range of 10 to 1000 nanometers. The use of particle delivery systems as carriers for tiny and big molecules has sparked a lot of interest in the field of drug delivery. Particulate systems, such as nanoparticles, have been employed to alter and improve the pharmacokinetic and pharmacodynamic aspects of numerous pharmacological compounds using a physical method. Polymeric nanoparticles have been intensively explored as particulate carriers in the pharmaceutical and medical areas, because of their controlled and sustained release qualities, subcellular size, and biocompatibility with tissue and cells, they offer promise as drug delivery methods.[2]

Various Polymersare used for the preparation of polymeric nanoparticles.

A polymer is a substance or material consisting of very large molecules, or macromolecules, composed of many repeating subunits. Due to their broad spectrum of properties, both synthetic and natural polymers play essential and ubiquitous roles in the manufacturing of polymeric nanoparticles. The polymer word arises from greek which means poly-, "many" + -mer, "part". The polymer is used in the nanoparticles for various purposes most of the time polymers are used for the controlled release, sustained release. The main purpose of the use of polymeric nanoparticles is the target the disease. The polymers are from various sources which are natural, synthetic, semi-synthetic.[3]

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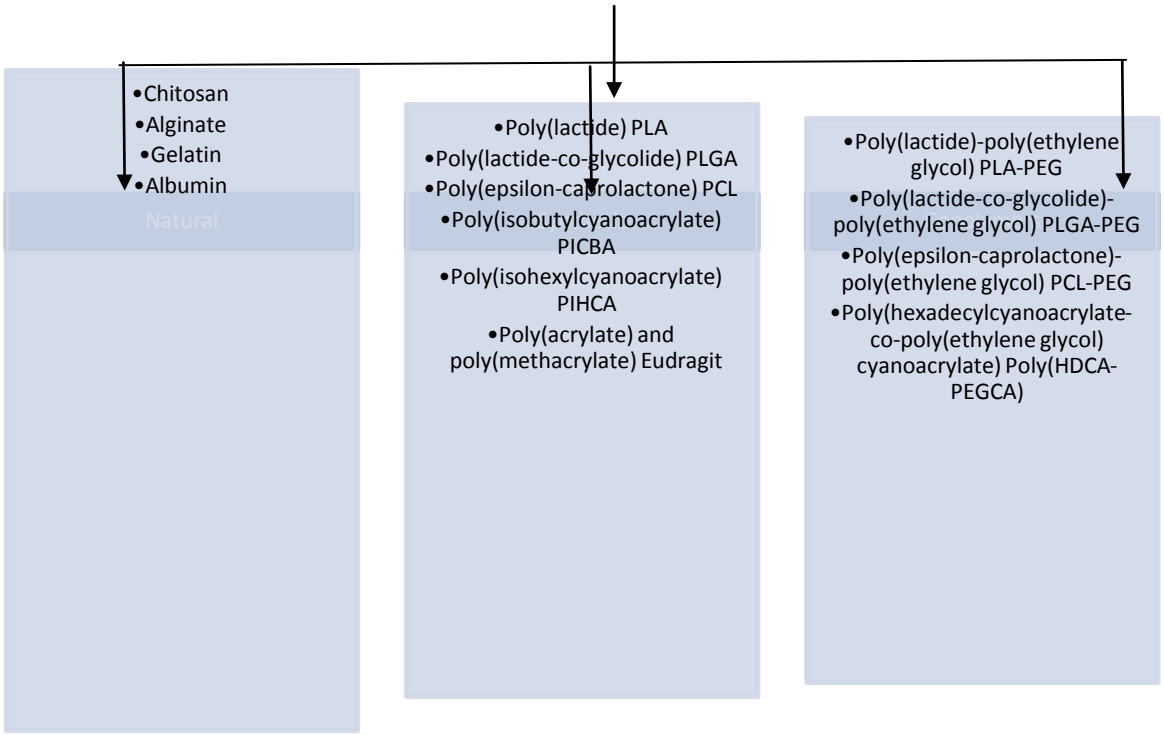

Recent advancement in Preparation of Polymeric Nanoparticles.

In the 20th century, polymeric nanoparticles are invented and various methods for that are invented. This polymeric nanoparticle has been prepared by various methods like nanoprecipitation, solvent evaporation, solvent diffusion, Saluting out, Dialysis, Supercritical fluid technology (SCF), Emulsification/solvent diffusion. In the 21st century, this method has been used with modern technology. Various modern instrument like high-speed homogenizer, peristaltic pump, as well as ultra-centrifugation is used. These methods are used with new high-tech instruments as well as new modern techniques. By using these modern instruments and techniques the production yield, as well as encapsulation efficiency, has been increased. The few cost-effective techniquesreduce the cost of formulation.

Various methods for the preparation of polymeric nanoparticles.

Methods:

1. Desolvation Technique
2. Dialysis Technique
3. Ionic Gelation Technique
4. Nanoprecipitation Technique
5. Salting Out Technique
6. Solvent Evaporation Technique
7. Spray Drying Technique
8. Supercritical Fluid Technique.

1) Desolvation technique:

In the preparation of polymeric nanoparticles, the desolvation process is commonly applied. This method may be used to change the charge and pH of a wide range of polymers by adding a desolvating agent such as ethanol or a strong organic salt solution. In a brief, the hydrogen ion concentration is modified by continuously adding ethanol at a controlled rate of 1ml/min to a protein solution containing drug while constantly stirring until the solution becomes turbid. The coacervates are also toughened by the addition of glutaraldehyde, a cross-linking agent. The lowest needed glutaraldehyde content of roughly 40% is used for the creation of stable nanoparticles, with a reaction time of 24 hours. Nanoparticles are purified by centrifugation to remove the free drug and excess cross-linking agent after ethanol is removed by evaporation under pressure. To obtain a fine powder of

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nanoparticles, the nanosuspension is freeze-dried with 5% mannitol added as a cryoprotectant. [Multi-Criteria Decision Making Approach][4]

2) Dialysis Technique:

The dialysis procedure provides a straightforward and efficient method for generating small, narrowly distributed PNPs. [c2]. In this method, dialysis tubes or semipermeable membranes with a suitable molecular weight cut-off (MWCO) are used as a physical barrier for the polymer [pnp2] The polymer is dissolved in an organic solvent and poured into a dialysis tube with the appropriate molecular weight cutoff. Dialysis is done using a non-solvent that is miscible with the former miscible. The displacement of the solvent into the membrane is followed by increasing polymer aggregation and the production of homogeneous nanoparticle suspensions due to a loss of solubility. The nanoparticles' shape and particle size distribution are affected by the solvent used to prepare the polymer solution. [5]

3) Ionic Gelation Technique:

The ionic gelation method is also known as coacervation. Nanoparticles obtained from ionic gelation procedure are synthesized in totally aqueous media. Natural polymers such as chitosan and alginates, rather than hazardous chemical polymers, are used in the oral administration system to improve the drug's penetration effect, enzyme inhibitory ability, and mucoadhesive property. Briefly, the drug and polymer are dissolved in a weakly acidic medium or water-dependent on their solubility, and the resulting solution is dropped into the solution containing counter ions and stabilizer while being constantly stirred. The complexation of oppositely charged species leads to gelation and precipitation, resulting in spherical-shaped particles. By sonicating the resulting solution, the particle size is decreased to the nanometer range. To obtain a fine powder of Nanoparticles, the nanosuspension is freeze-dried with 5% mannitol as a cryoprotectant.[6]

4) Nanoprecipitation Technique:

Solvent displacement is another name for nanoprecipitation. In the presence or absence of a surfactant, it entails the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium. The polymer, in this case, PLA, is dissolved in a water-miscible solvent with an intermediate polarity, resulting in nanosphere precipitation.

This phase is injected into an aqueous solution that has been agitated and contains a stabilizer as a surfactant. Polymer deposition on the water-organic solvent interface, caused by fast solvent diffusion, results in the instantaneous formation of a colloidal suspension. Phase separation is accomplished with a fully miscible solvent that is also a non-solvent of the polymer to assist the creation of colloidal polymer particles during the first step of the process. When a small amount of non-toxic oil is added into the organic phase, the solvent displacement method allows for the development of nanocapsules. When nanocapsules are manufactured, high loading efficiencies for lipophilic drugs are commonly observed due to the oil-based central chambers of the nanocapsules. This simple technique is only suitable for water-miscible solvents with a high enough diffusion rate to generate spontaneous emulsification. Even if some water-miscible solvents cause some instability when mixed with water, spontaneous emulsification does not occur if the coalescence rate of the produced droplets is sufficiently high. Although acetone/dichloromethane (ICH, class 2) is used to degrade pharmaceuticals and enhance trapping, dichloromethane increases mean particle size42 and is hazardous. Because the solvent is miscible with the aqueous phase, this approach is only suitable for lipophilic pharmaceuticals, and it is not an effective way to encapsulate water-soluble medications. This approach has been used on PLGA36, PLA43, PCL44, and poly (methyl vinyl ether-co maleic anhydride) (PVM/MA), among other polymeric materials. Because entrapment efficiencies of up to 98 percent were achieved, this approach proved ideally suited for the inclusion of cyclosporin A. According to the solvent displacement method, highly loaded nanoparticulate systems based on amphiphilic h-cyclodextrins were developed to enhance the parenteral administration of the weakly soluble antifungal drugs Bifonazole and Clotrimazole.[7]

5) Salting Out Technique:

A salting-out effect is used to separate a water-miscible solvent from an aqueous solution. Initially revealed a salting-out version of the emulsion technique that eliminates the use of surfactants and chlorinated solvents. The emulsion is made with a polymer-solvent that is normally completely miscible with water, such as acetone, and emulsification of the polymer solution in the aqueous phase is achieved by dissolving a high concentration of salt or sucrose chosen for a strong salting-out effect in the aqueous phase, much like an Ouzoeffect, without using any high-shear forces. Electrolytes such as magnesium chloride, calcium

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chloride, and magnesium acetate are routinely used. The miscibility properties of water with other solvents are modified as these components dissolve in the water. A reverse salting-out effect, obtained by dilution of the emulsion with a large excess of water, leads to the precipitation of the polymer dissolved in the droplets of the emulsion. In fact, upon dilution, migration of the solvent for the polymer from the emulsion droplets is induced due to the reduction of the salt or sucrose concentration in the continuous phase of the emulsion.

This method, which is utilized to make PLA, poly(methacrylic) acid, and EC nanospheres, has high efficiency and may be easily scaled up. The fundamental benefit of salting out is that it reduces protein encapsulant stress. Because salting-out does not require a temperature rise, it may be advantageous when processing heat-sensitive compounds. The most significant drawbacks are the limited application to lipophilic drugs and the lengthy nanoparticle washing process. [8]

6) Solvent Evaporation Technique:

The earliest method for making PNPs from a was solvent evaporation. Polymer solutions are made in volatile solvents and emulsions are created using this process. Dichloromethane and chloroform premade polymer were once used, but they have since been superseded with ethyl acetate, which has a superior toxicity profile. On evaporation of the polymer's solvent, the emulsion transforms into a nanoparticle suspension, which is permitted to diffuse into the emulsion's continuous phase. The manufacture of single-emulsions, such as oil-in-water (o/w), or double-emulsions, such as (water-in-oil)-in-water, (w/o)/w, are the two major techniques utilized in conventional procedures for the formation of emulsions. These procedures use high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either at room temperature or under decreased pressure, using continuous magnetic stirring. After that, ultracentrifugation can be used to collect the solidified nanoparticles, which can then be washed with distilled water to remove any additions like surfactants. The product is then lyophilized. Although solvent evaporation is a simple method for preparing PNP, it is time-intensive, and probable nanodroplet coalescence during the evaporation process can alter the final particle size and shape.[9]

7) Spray Drying Technique:

Spray drying is a well-known process for creating drug powder from a liquid phase that is widely utilized in the pharmaceutical industry. Spray dryers with vibrating mesh technology use rotary atomizers and pressure nozzles to generate fine droplets. To avoid clogging, the drug and polymer are mixed in ultrapure water with tween 80 and filtered through a 0.45 m syringe filter before spray drying. Under the aforementioned circumstances, the resulting solution is spray-dried dried at a range of outlet temperatures between 30 and 55°C. The vibration of the mesh upwards and downwards generated by the piezoelectric actuator driven at an ultrasonic frequency produces millions of perfectly proportioned droplets (i.e., 60 kHz). The new electrostatic particle collector is made up of a grounded star electrode (cathode) and a cylindrical particle collecting device. To collect fine powder, electrodes (anodes) are utilized with great productivity[10]

8) Supercritical Fluid Technique:

The methods described in the preceding subsections use organic solvents, and the need to develop environmentally safer methods for producing PNP has prompted research into the use of supercritical fluids as more environmentally friendly solvents, with the potential to produce PNPs with high purity and no trace of organic solvent. Supercritical fluid and dense gas technology are predicted to provide an intriguing and practical particle generation process that avoids the majority of the shortcomings of previous methods. Indeed, examples of pharmaceutical particle production, formulation, and control using a supercritical fluid and dense gas have been documented.[11]

Two principal processes have been developed for the production of nanoparticles using supercritical fluids:

1. Rapid expansion of supercritical solution and
2. Rapid expansion of supercritical solution into the liquid solvent.

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yield, as well as encapsulation efficiency, has been increased. The few cost-effective techniquesreduce the cost of formulation.

Characterization

1) Particle Size -

The particle size is the major characterization for the nanoparticles. The particle size shows the size range of nanoparticles which is in the range of 1-1000 nm. Various instruments like micro track, maven (Zeta sizer) are used to analyze the particle size.[12]

2) Zeta Potential-

Zeta potential is used to see the charge on the nanoparticle. The nanoparticles should be balanced before administrating them in the body. Zeta potential is measured by the instrument which is used for the particle size.[12]

3) PDI –

Poly Dispersity Index is the uniformity of the nanoparticles. The PDI for the nanoparticles is in the size range of 0-1. The ideal value for the PDI is 0-0.3. [13]

4) TEM-

Transmission Electron Microscopy is used for the analysis of nanoparticles. By using TEM we can analyze the morphology of the nanoparticles.[13]

5) Stability-

The polymeric nanoparticles can be kept in the 2-8 ^{o} C. As per the ICH guideline for stability studies.[9]

6) Entrapment efficiency (EE)

Entrapment efficiency is the amount of drug entrapped to the nanoparticles is determined in the percentage which is ranges from 0-100 %. The entrapment efficiency or percentage of the content was determined using the difference between the initial drug amount and the free or unentrapped quantity of drug in the supernatant in respect to the total quantity contained in the nanocarrier preparation.[14]

$$\text{EE} \quad \% = \frac{\text{Initial weig ht of drug} - \text{Finl weig ht}}{\text{Initial weig ht}} \times 100 [15]$$

7) Compatibility

Fourier Transform Infrared Spectroscopy (FTIR) studies are for determining the compatibility of drugs and a polymer. Spectral analysis of the drug, various polymers, and combinations of the drug with polymers is used to investigate any changes in the chemical makeup of the medicine after it is linked with polymer [15].

8) Scanning electron microscope (SEM)

The SEM is performed on the instrument by spreading the nanoparticles on the slide and observing them under electron microscopy. The SEM study of the particles shows the shape and morphology of the nanoparticles.

Advantages -

1. Increases the stability of any volatile pharmacological substances, which may be made in big quantities simply and cheaply using a variety of ways.[16]
2. In terms of efficiency and effectiveness, they are a major improvement over traditional oral and intravenous administration methods.
3. Delivers a higher concentration of a medicinal substance to a specific area.[17]
4. Polymeric nanoparticles are great candidates for cancer therapy, vaccine delivery, contraception, and targeted antibiotic delivery due to their choice of polymer and ability to adjust drug release from polymeric nanoparticles.[18]
5. Polymeric nanoparticles can easily be integrated into other drug delivery-related processes, such as tissue engineering.

Dis-advantages –

1) The stability issue for the polymeric nanoparticle i.e. they can mostly be stable in the 2-8 ^{o}C.

2) Traces of surfactant can remain in the final formulation which may cause toxicity. [16]

II. CONCLUSION

Polymeric nanoparticles have a wide application in treating various diseases. They have wide application in cancer as well as Alzheimer's disease. The polymeric nanoparticles are the target-specific nanoparticles that can act as the controlled as well as sustained release.These nanoparticles can easily cross the brain barrier because of their nanosized. These nanoparticles are used for ocular as well as transdermal drug delivery.

III. ACKNOWLEDGMENTS

The authors are grateful to the management of Sanjivani college of pharmaceutical education and research Kopargaon affiliated to Savitribai Phule Pune University, India, for providing necessary facilities to carry out this work.

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