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Review Article

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A Review on Recent Trends and Various Preparation Techniques of Polymeric Nanoparticles

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ABSTRACT

From the past 33 years, so many technologies for reduction of particle size are investigated to develop the drug delivery. Present a lot of latest techniques have been recognized in the pharmaceuticals. Polymeric nanoparticles (PNPs) are defined as particulate dispersions or solid particles with small size in the mean range of 10-1000nm, it protects the drug against in-vitro & in-vivo degradation it releases the drug in a controlled and sustained way and also gives the possibility of drug targeting. The uses of polymeric nanoparticles are a worldwide advance to enhance the poorly soluble drugs therapeutic performance in several administration routes. A number of procedures to make polymeric nanoparticles have been modified like nanoprecipitation technique, solvent evaporation technique, dialysis technique, supercritical fluid technology etc. In this review mainly focused on different preparation methods for PNPs, routes of nanoparticles administration and recent patents on PNPs.

Keywords: Polymeric nanoparticles; Controlled release; Drug delivery; Patents

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INTRODUCTION

At present area there are many techniques recognized in the research of pharmaceuticals. The solid colloid particles which are approximately in size of 10-1000 nm that are prepared from bio degradable and bio compatible controlling where drug undergoes capsulation, dissolved, entrapping and get adsorbed to nanoparticle matrix [1-4]. These are called polymeric nanoparticles (PNPs) depending upon the methods of preparation nanoparticles, nanocapsules and nanospheres are obtained [5].

Nanospheres: The particles in which the matrix system (monolithic type) in which the drug is physically and equally dispersed/adsorbed surfaces with in the particles are called nanospheres.

Nanocapsules: the system in which the inner core cantains active drug dissolved form and also may be adsorbed on to surface of capsule and in which the drug is cramped into cavity surrounded by single polymer membrane. The polymeric nanoparticles are fastly growing and playing a major role in a broad spectrum of areas ranging from photonics, electronics, sensors, biotechnology, conducting materials, medicine, environmental technology and pollution control [6-12]. For easy delivery of drug to the specific target the PNPs act as vehicles. These are particularly investigated in drug targeting and drug delivery due to their size and it results in prolonged circulation in blood[13].

Advantages of PNPs [14,15]:

- Toxicity of drug is minimized along with adverse drug reaction
- Increased bioavailability of the drug
- The concentration of drug delivered to site of action is high
- Efficient and effective development in oral and intravenous administration method
- Any pharmaceutical agents' stability can be inexpensively enhanced and it can be easily made-up in huge quantities by a multitude of techniques.

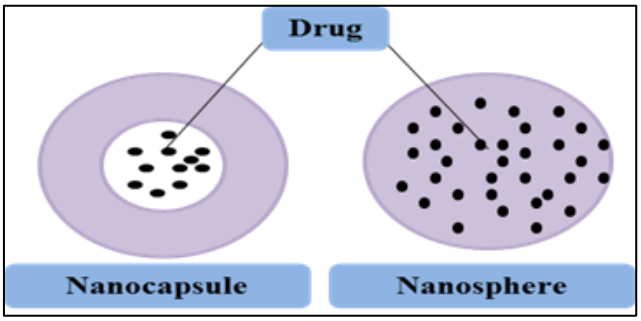

Figure: 1 Difference between Nanocpasule and nanosphere

Limitations

Due to their small size and large surface area the use of nanoparticles have some limitations

- The use of nanoparticles in dry and liquid form is not easy due to particle aggregation
- The lesser particle size results outcome in partial loading of drug and explodes release. These experimental harms have been sorted out previous to nanoparticles can be used clinically or commercially available [16].

Polymers used in Nanoparticle preparation

The polymers that are used in preparation of nanoparticles should be compatible with body.

Natural polymers:

The frequently used natural polymers in PNPs preparations are [17-19].

- Gelatin
- Chitosan
- Albumin
- Sodium alginate

There are many synthetic polymers that are used in PNPs preparation like [20-23]:

- Polylactides(PLA)
- Polyglycolides(PGA)
- Poly(lactide co-glycolides) (PLGA)
- Polyanhydrides
- Poly methyl methacrylate
- Poly vinyl alcohol
- Poly acrylic acid
- Poly acrylamide
- Poly ethylene glycol
- Poly methacrylic acid

Table 1: Advantages and disadvantages of Natural and synthetic polymers [24]

Polymers	Natural Polymers	Synthetic Polymers
Advantages	Easily available	Biocompatibility
	Biocompatibility	
	Biodegradable	
	Less toxic	
Disadvantages	High degree of variability in natural materials derived from animal sources	Toxic
	Structurally more complex	Non degrable
	Extraction process very complicated and high cost	Synthetic process is very complicated and high cost

Ideal polymeric carrier characteristics for nanoparticles:

- Water-soluble
- Easy to synthesize and characterize
- Non-toxic
- Inexpensive
- Biodegradable

- Biocompatible
- Non-immunogenic

Drug release mechanism [25]
The delivery of drug at tissues by polymeric drug carriers is usually by three physic-chemical mechanisms

Diffusion: The polymeric nanoparticles swell by hydration which results in release of drug through diffusion.

Enzymatic drug reaction: Due to the enzymatic reaction the drug gets released at delivery site and releasing the drug from entrapped inside core.

Drug dissociation: In this mechanism the drug dissociation from the polymer and its release/ de-adsorption from the swelled PNPs.

Nanoparticles Preparation techniques

- Nanoprecipitation
- Solvent evaporation
- Emulsification/solvent diffusion
- Dialysis
- Salting out
- Supercritical fluid technology

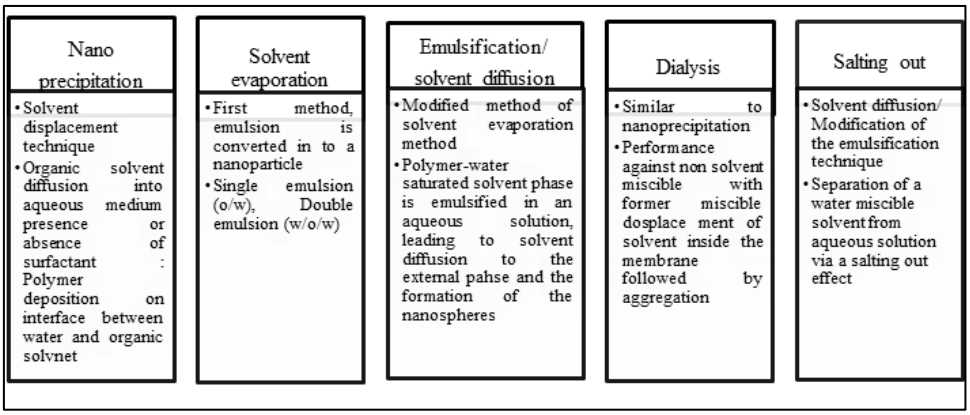

Figure 2: Different nanoparticles preparation method

Nanoprecipitation [26]
The process requires two miscible solvents. Preferably, both the drug and polymer should be dissolved in one solvent but not in the non-solvent (second system). When polymer solution is added to second system, the nanoprecipitation technique occurs by fast desolvation of polymer. The formulation of nanoparticles is immediate and the whole process is done in only one step. The process of nanoprecipitation technique diagram is shown in figure 3 below.

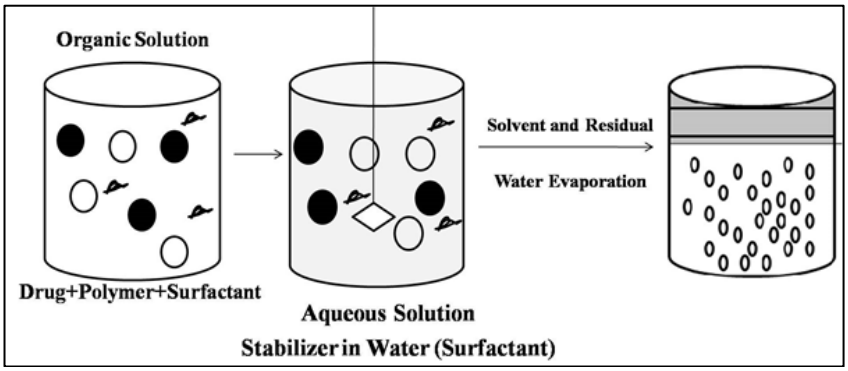

Figure 3: Schematic representation of the nanoprecipitation technique

Solvent evaporation technique [27]

For dissolving the polymer and hydrophobic drug the organic solvents such as ethyl acetate, chloroform and dichloromethane are used. The drug dispersed in polymer solution after that emulsified in an aqueous solution it contains an emulsifying agent or surfactant to produce oil in water emulsion. Following the formation of stable emulsion keep it for evaporation to remove organic solvent is done either by stirring or by evaporator. For the preparation of small uniform size particle size, the ultrasonicator or high speed homogenizer may be needed. The process of solvent evaporation technique diagram is shown in figure 4.

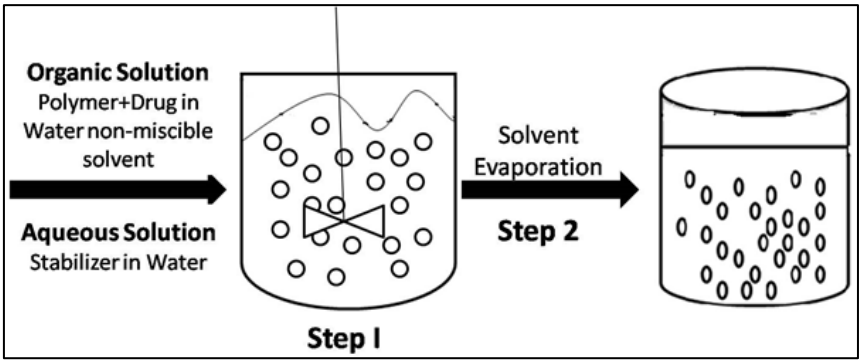

Figure 4: Schematic representation of the Solvent evaporation technique

Spontaneous emulsification/solvent diffusion technique [28]

This is modified technique of solvent evaporation technique. In this technique, a little quantity of water immiscible organic solvents along with water miscible solvent is used as an oil phase. Due to diffusion of immiscible solvents an interfacial turbulence is generated between the two phases leading to produce small size particles. As the water miscible solvent concentration is enhances, the reduction in particle size can be achieved. Both solvent diffusion and solvent evaporation techniques can be used for hydrophilic or hydrophobic drugs. For hydrophilic drugs, a several w/o/w emulsion needs to be produced with dissolving of the drug in the internal aqueous phase.

Dialysis technique [29-37]

Dialysis technique gives a simple and efficient technique for the little, narrow-distributed PNPs preparation. In this technique polymer is dissolved in an organic solvent and positioned it inside a dialysis tube with suitable molecular weight cut off. Dialysis is performed against a non-solvent miscible with the previous miscible. The dislocation of the solvent inside the membrane is followed by the progressive aggregation of polymer due to a loss of solubility and the formation of nanoparticles homogeneous suspensions. At present the mechanism of PNPs formation by dialysis technique is not completely understood. It is thought that it may be based on a mechanism related to that of nanoprecipitation. A number of copolymer and polymer nanoparticles were obtained by this method. Poly (benzyl-l-glutamate)-b-poly (ethylene oxide), Poly (lactide)-b-poly (ethylene oxide) nanoparticles were prepared using DMF (di methyl formalide) as the solvent. The solvent is used in the polymer solution preparation it affects the distribution of particle size and morphology of the nanoparticles. A new osmosis based technique for the PNPs preparation. This is based on the utilization of a physical barrier, especially the dialysis membrane allows the passive transportation of solvents to slowly, the solution which contains polymer is mixing with a non-solvent and the dialysis membrane contains polymer solution. The process of dialysis technique diagram is shown in figure 5 below.

Salting - out technique [38]

In salting - out technique the acetone is chooses as water-miscible organic solvent for the reason that it is a pharmaceutical acceptance with observe to toxicity. In this technique the water soluble polyvinyl alcohol (PVA) adding in a salt solution which is highly concentrated in distilled water (aqueous phase) and the polymer solution in solvent acetone solution (organic phase). Even though acetone is miscible with distilled water in every ratio, the high salt concentration of the aqueous phase prevents mixing. After emulsification process, the addition of distilled water in an adequate quantity causes acetone to diffuse into the aqueous phase, resulting in forming of nanoparticles. The process of salting-out technique diagram is shown in figure 6 below.

Supercritical fluid technology

This technique is environmentally safer and useful technique for the PNPs production has aggravated research work on the efficacy of supercritical fluids as high environmental responsive solvents, to generate PNPs potentially with more cleanliness and without any organic solvent trace. Supercritical fluid and dense gas

techniques both are expected to provide attractive and successful techniques to produce particles and to avoid the popular drawbacks of the conventional techniques.

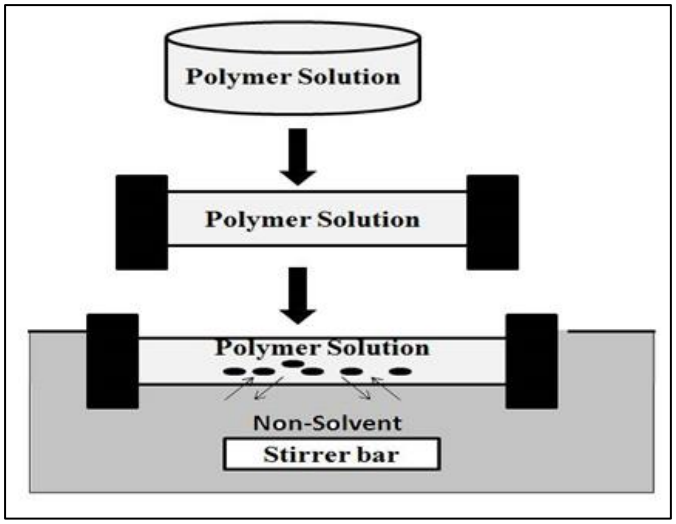

Figure 5: Dialysis technique

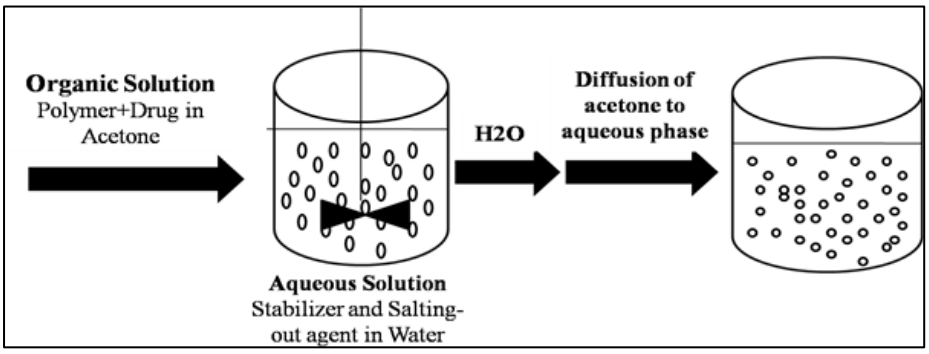

Figure 6: Salting - out technique

Majorly 2 techniques have been developed for the nanoparticles formation by using supercritical fluids:

- Rapid expansion of supercritical solution into liquid solvent (RESOLV).
- Rapid expansion of supercritical solution (RESS)

Rapid expansion of supercritical solution into liquid solvent (RESOLV):

- This method is easy to produce nanoparticles, but important modification to RESS (Rapid expansion of supercritical solution) involves growth of the supercritical solution into a liquid solvent instead of ambient air, named as RESOLV.
- The poly (heptadecafluorodecyl acrylate) nanoparticles having a size of < 50 nm preparation was proposed by Meziani. Although in the formation of polymeric nanoparticles organic solvents are not used in RESS method, the most important compounds gained with proposed method are micro in size rather than nanoparticles that is the major demerit of RESS technique.
- To overcome this demerit, a latest supercritical fluid technology known as RESOLV technique has been developed.

In RESOLV technique the liquid solvent actually inhibits the development of particles in the growth jet, thereby develop it possible to obtain primarily nanosized particles. The process of Rapid expansion of supercritical solution into liquid solvent technique (RESOLV) is shown in figure 7 below.

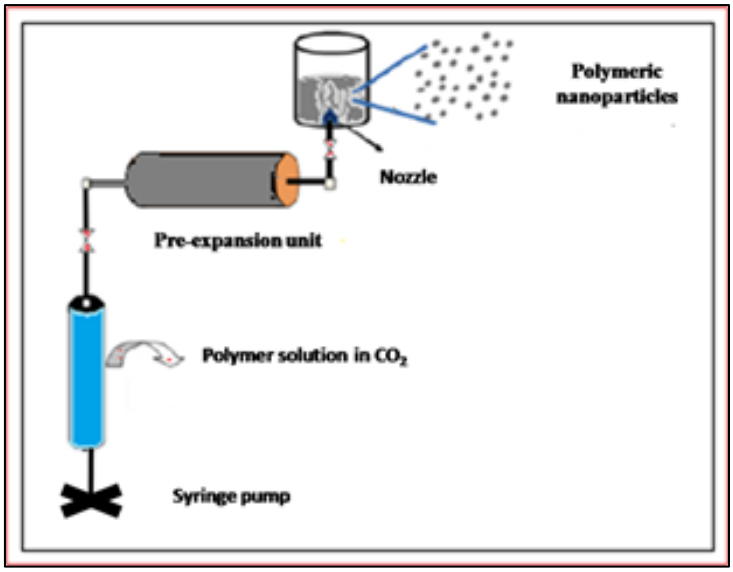

Figure 7: Rapid expansion of supercritical solution into liquid solvent technique

Rapid expansion of supercritical solution (RESS):

- In this conventional RESS technique, in a supercritical fluid the solute is dissolved primarily to produce a solution, then the rapid expansion of the solution across a capillary nozzle into ambient air.
- The great saturation escorted by the rapid pressure decrease in the expansion, and the outcome is homogenous nucleation and thus, the well-dispersed particles are formed.
- The obtained outcome from experiments of various model solutes for the RESS development it indicates that particles having both nano and micro sizes are there in the expansion jet.
- In the PNPs production till now a small no of studies were conducted by using RESS. From the rapid expansion of CO2 solution, the poly (perfluoropolyetherdiamide) were produced
- The RESS experimental equipments consist of three main units: i) high pressure stainless steel mixing cell, ii) syringe pump and finally iii) preexpansion unit.
- A polymer solution in CO2 is prepared at established temperature. Before the solution leaves the nozzle, using syringe pump, it is pumped to the pre-expansion unit and isobarically it is heated to the pre-expansion temperature.
- The supercritical solution is now permitted to expand through the nozzle, at ambient pressure. The concentration and degree of saturation of the polymer have a considerable effect on the particle size and morphology of the particles for RESS. The process of Rapid expansion of supercritical solution technique diagram (RESS) is shown in figure 8 below.

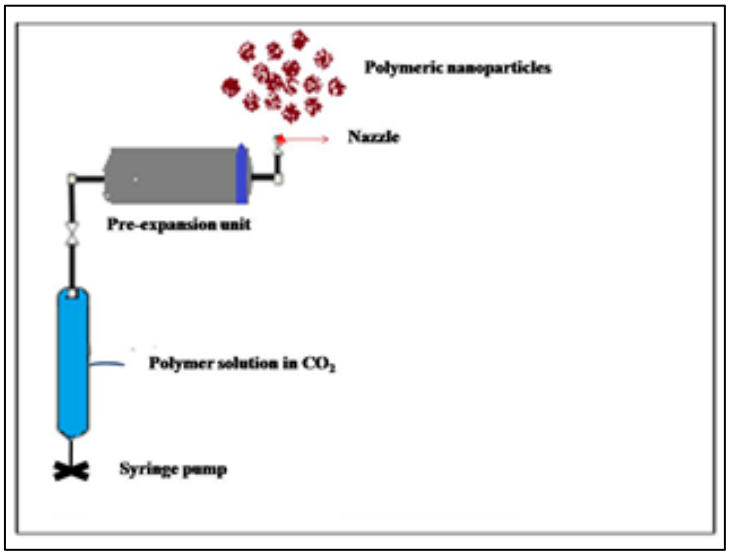

Figure 8: Rapid expansion of supercritical solution technique

Physicochemical characteristics of nanoparticles

The physicochemical characterisation of nanoparticles are tabulated

Drug loading:

Nanoparticulate system drug loading can be prepared by two various techniques:

- Incubation technique
- Incorporation technique

Incubation technique: Adsorbing the drug after the nanoparticles production by incubating the carrier with the drug solution.

Incorporation technique: Incorporating at the time of nanoparticles production.

Both incubation & incorporation methods result in:

- Drug chemical bonding in the polymer solution.
- The drug surface adsorption.
- The drug solid dispersion in the polymers.
- The drug solid solution in the polymers.

In this technique the drug is permanently fixed into the matrix and adsorbed onto the surface. Different loading procedures have been promoted to enhance the effectiveness of loading, that is highly depends upon the production techniques more over the polymer and drug physiochemical properties. During the time of particles production the greatest loading can be reached by drug incorporating, however it might be get over-elaborated by method guidelines such as production techniques and bearing of excipients etc.

Table 2: Physicochemical methods for nanoparticles characterization [14]

S.No	Parameters	Method
1	Particle size	Fraunhofer diffraction
		Freeze-fracture electron microscopy
		Photon-correlation spectroscopy
		Scanned probed microscope
		Scanning electron microscopy (SEM)
		Transmission electron microscopy (TEM)
2	Molecular weight	Gel chromatography
3	Density	Helium compression pycnometry
4	Crystallinity	Differential scanning calorimetry (DSC)
		X-ray diffraction (XRD)
5	Surface charge	Zeta potential measurement
		Electrophoresis
		Laser droplet anemometry
		Amplitude-weighed phase structure determination
6	Hydrophobicity	Hydrophobic interaction chromatography
		Contact angle measurement
		Rose Bengal binding
7	Surface properties	Static secondary-ion mass spectroscopy
8	Surface element analysis	X-ray photon spectroscopy
		Molecular magnetic resonance
		Fourier transform infrared spectroscopy (FTIR)

Routes of nanoparticles administration

The major routes of nanoparticles administration are

- Ophthalmic applicaion,
- Intramuscular or subcutaneous injection,
- Intravenous injection,
- Oral administration.

Ophthalmic application

Usually the studies on rabbit's shows that polyhexyl cyanoacrylate nanoparticles are eliminated with half-life of 15-20 min. while aqueous eye drops having 1-3 min. half-life. But little quantity of poly-cyanoacrylate nanoparticles adheres to cornea nicitating membrane of rabbits and penetrate into 2 layers of cells [39].

Intramuscular and subcutaneous injection

By studies in rats it shows the subcutaneous injection of ^{14}C-labelled poly-methacrylate nanoparticles, the 99% of radioactivity leftovers at the ingested site. The removal rate of administered dose is found to be slow in form of nanoparticles than in form of urine & faeces initially but latter it was found to be more in faeces [39].

Intravenous administration

After intravenous injection nanoparticles, like additional colloidal systems example like erythrocyte ghosts, micro emulsions and liposomes are taken up by the reticuloendothelial systems (RES). They are distributed primarily to the spleen, liver and to a smaller amount in bone marrow, and in the lungs varying amounts can be found. Sessile, actively phagocytosing cells are present in all body organs and also lymphatic system, blood system and in the blood vessels. These cells are able to take up nanoparticles by unreliable degrees. The mechanism by which this occurs is still unknown. It is convinced that instantly after injection; the particles are covered by the antibodies present in blood serum, which function as markers to passively aim the nanoparticles to particular phagocytic cells [40].

Oral administration

The oral administration studies in rats and mice are done for around 6 days. which are taken in intestine and occur in lymph nodes, spleen, blood system, liver and at the irritation and inflammation site in the body. 3 different mechanisms are possible [40]:

1. Intracellular - paracellular uptake.
2. Intracellular uptake.
3. Uptake via M-cells and Peyer's patches in the gut.

Therapeutic applications of nanoparticles

Table 3: Therapeutic applications of Nanoparticles

S. No	Application	Material	Purpose
1	Ocular delivery	Poly (alkyl cyanoacrylate) nanoparticles	Improved retention of drug/reduced wash−out
		with steroids, anti−inflammatory agents,	
		anti−bacterial agents for glaucoma	
2	Cancer therapy	Poly (alkyl cyanoacrylate) nanoparticles with anticancer agents, oligonucleotides	Targeting, reducing toxicity, enhanced uptake of antitumour agents, improved *in vitro* and *in vivo* stability
3	Vaccine adjuvant	Poly (methyl methacrylate) nanoparticles	Enhanced immune response, alternate acceptable adjuvant
		with vaccines (oral and IM immunisation)	
4	Intracellular targeting	Poly (alkyl cyanoacrylate) polyesters nanoparticles with anti−parasitic or antiviral agents	Targeting reticuloendothelial intercellular infections
5	Oligonucleotides	Alginate nanoparticles, poly (D, L−lactic	Enhanced delivery of oligonucleotides
	delivery	acid) nanoparticles	
6	Peroral absorption	Poly (methyl methacrylate) nanoparticles	Enhanced bioavailability, protection from GIT enzymes
		with proteins and therapeutic agents	
7	Prolonged systemic circulation	Polyesters with adsorbed poly ethylene	Prolonged systemic effect, avoid by the uptake of reticuloendothelial system
		glycols or pluronics	
8	DNA delivery	DNA - gelatine nanoparticles, DNA - chitosan nanoparticles, PDNA- poly (D,L-lactide-co-glycolide) nanoparticles	Enhanced delivery and significantly higher expression levels
9	Other applications	Poly (alkyl cyanoacrylate) nanoparticles with peptides	Crosses blood-brain barrier
		Poly (alkyl cyanoacrylate) nanoparticles	Improved absorption and permeation for transdermal application
		Nanoparticles with adsorbed enzymes	Enzyme immunoassays

Table 4: Patents on drug delivery system based on Polymeric nanoparticles

S.No	Title	Patent number	Inventors	Year	Ref
1	Polymeric nanoparticles useful in theranostics	WO201312700 A1	Xiao Yu Wu, Alireza Shalviri	2013	41
2	Therapeutic polymeric nanoparticles with mTor inhibitors and methods of making and using same	US8613951 B2	Stephen E. Zale, Greg Troiano, Mir Mukkaram Ali *et. al.*	2013	42
3	Polymeric nanoparticles and a process of preparation thereof cross reference to related applications	WO2013160773 A2	Harpal Singh	2013	43
4	Therapeutic polymeric nanoparticle compositions with high glass transition temperature or high molecular weight copolymers	US8518963 B2	Mir Mukkaram Ali, Abhimanyu Sabnis *et. al.*	2013	44
5	Docetaxel polymeric nanoparticles for cancer treatment	WO2014210485 A1	James Wright	2014	45
6	Polymeric nanoparticles for photosensitizers	US20140170229 A1	Haddadi; Azita, Madiyalakan; Ragupathy, Woo	2014	46
7	Therapeutic polymeric nanoparticles with mTor inhibitors and methods of making and using same related applications	WO2010005726 A2	Stephen E. Zale, Greg Troiano, Mir Mukkaram Ali *et. al.*	2010	47
8	Methods of treating cancers with therapeutic nanoparticles	WO2013044219 A1	Stephen E. Zale, Greg Troiano, Mir Mukkaram Ali *et. al.*	2013	48
9	Polymeric nanoparticles and methods of making and using same	WO2015142605 A3	Young Ho Sung, Greg Troiano, Hong Wang,Maria Figueiredo *et. al.*	2015	49
10	Drug loaded polymeric nanoparticles and methods of making and using same	WO2012166923 A2	Stephen E. Zale	2012	50
11	Drug loaded polymeric nanoparticles and methods of making and using same	US8420123 B2	Greg Troiano, Michael Figa, Abhimanyu Sabnis	2013	51
12	Therapeutic polymeric nanoparticles comprising vinca alkaloids and methods of making and using same	WO2010005725 A2	Stephen E. Zale, Greg Troiano, Mir Mukkaram Ali, Jeff Hrkach, James Wright	2010	52
13	Therapeutic polymeric nanoparticle compositions with high glass transition temperature or high molecular weight copolymers	WO2011084513 A2	Mir Mukkaram Ali, Abhimanyu Sabnis, *et. al.*	2011	53
14	Drug loaded polymeric nanoparticles and methods of making and using same	WO2010005721 A3	Stephen E. Zale, Greg Troiano, Mir Mukkaram Ali, Jeff Hrkach, James Wright	2010	54
15	Polymer nanoparticles coated by magnetic metal oxide and uses thereof	WO2009040811 A2	Shlomo Margel Benny Perlstein Chaya Brodie	2009	55
16	Nanoparticles for drug delivery comprising albumin having a polymer chain coupled thereto	EP2981291 A4	Martina Heide Stenzel, Wei Scarano *et. al.*	2016	56

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