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POLYMERIC NANOPARTICLES FOR DRUG DELIVERY APPLICATIONS

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Abstract:
Polymeric nanoparticles are dispersions or solid particles with size in the range of 1nm to 1000 nm that can be loaded with active components. It includes both nanospheres and nanocapsules. They represent a convenient drug delivery system in the form of a controlled and targeted release. The usage of polymeric nanoparticle in drug delivery is a way which is targeted to optimize drug effects meanwhile minimizing side effects. Since they are minute in sizes, they represent a distinct physio-chemical as well as biological attributes such as an enhanced reactive region also it is capable of crossing cells and tissue barriers, which make them a best material for bio-medical applications. Because of such properties of polymeric nanoparticles, it has attracted the attention of a vast audience in bio-science. The present review focuses on applications of polymeric nanoparticles for drug delivery.
***KEYWORDS**: Polymeric, Nanoparticle, Drug Delivery, Nanospheres, Nanocapsules, Applications*

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1. INTRODUCTION:

1.1 Nanoparticles as Drug Delivery Carriers

In recent years, we have observed the unprecedented growth and development of research in the area of nanotechnology for biomedical applications and more specifically drug delivery. The submicron-size objects, due to their unique properties and large surface to volume ratio, have become an important class of materials capable of improving pharmacologic activities of conventional therapeutics.[1-3] Only careful and thoughtful design of these nanoparticles could lead to development of smart drug delivery vehicles, capable of increasing the stability and bioavailability of the drug as well as providing controlled release at the desired site and time of action.

Nanoparticles as drug delivery carriers could be classified into a variety of different groups. The most general way of classification is based on the nature of the material – organic vs. inorganic, similarly as specific placement of the drug molecule within the nanoparticles. Organic nanoparticles differ significantly from inorganic nanoparticles mainly due to the principles of their fabrication and their intermolecular interactions. While most of the organic nanoparticles (e.g. liposomes, surfactant and polymeric micelles, polymersomes) are formed from at least several molecules through a self-assembly driven mechanism,[5-7] inorganic nanoparticles (e.g., gold and iron oxide nanoparticles, quantum dots) are synthesized through the inorganic salt precipitation resulting in a formation of three dimensional structures of linked atoms. The much stronger interatomic interaction of the inorganic nanoparticles contrasts with a more dynamic-like structure of the organic nanoparticles.

Furthermore, a drug or a medicinal compound of interest could be dissolved in certain region, entrapped/encapsulated in the core, or attached on the surface of nanoparticles. Organic nanoparticles such as the polymeric/surfactant1micelles or liposomes have the ability of the drug encapsulation inside the core of the structures with the surface being functionalized with targeting molecules. The inorganic nanoparticles usually display interesting optical, magnetic or fluorescent properties within the solid structure that make them attractive as imaging or diagnostic particles, and the active and/or targeting compounds are functionalized on their surfaces. [1]

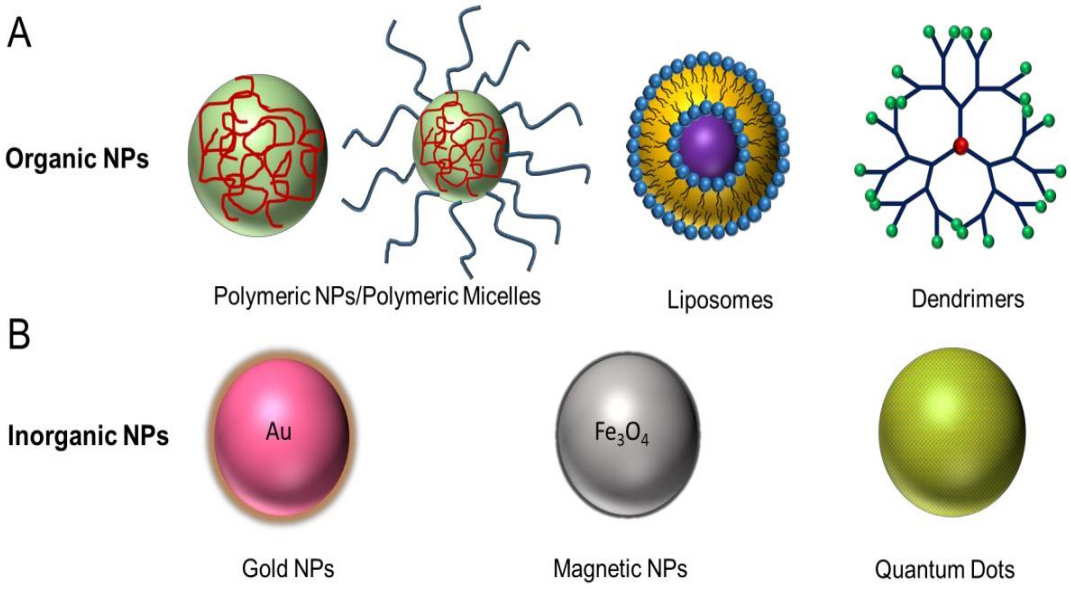

Figure 1.The samples of leading (A) organic and (B) inorganic nanocarrier platforms.[2]

The majority of this thesis focuses on the characterization of organic polymeric nanoparticles for encapsulation of hydrophobic drugs in order to increase drug solubility and oral bioavailability. The surface modification of inorganic nanoparticles with therapeutic polymers is also discussed as an important implementation of improved drug functionality and targeted drug delivery.

1.2 Encapsulation of Hydrophobic Molecules into Polymeric Nanoparticles to Increase Drug Solubility and Bioavailability

The delivery of hydrophobic drug molecules has been considered a tremendous challenge due to their limited aqueous solubility and therefore bioavailability. The poor bioavailability depends on the dissolution kinetics where the dissolution rate is directly proportional to the surface area of the drug mass. Unformulated hydrophobic compounds in aqueous environments quickly form micron-sized or larger precipitates that would result in minimal drug absorption. Nanoparticles have been studied and considered as an effective way of enhancing the solubility of the hydrophobic compounds. Among them polymeric nanoparticles are particularly important due to their ability to provide higher drug loading capacity and greater stability upon dilution in biological fluids when compared with other drug delivery carriers such as surfactant micelles, liposomes, and dendrimers.(Figure 1)2

2. Current Production Methods of Polymeric Nanoparticles

Various methods of producing polymeric nanoparticles have been proposed and developed to date such as supercritical-fluid process, emulsification-based technologies, and nanoprecipitation. However, low drug loading, lack of control over the nanoparticle physicochemical properties, and problems associated with process reproducibility and scalability have still been considered as major hurdles in clinical translation of the polymeric nanoparticle based medicines.[2]

2.1 Supercritical-fluid technology

Supercritical-fluid technology, which involves the use of solvents at temperatures and pressures above their critical point, has been considered as one of the important ways to produce nanoparticles. The attractiveness of the process comes from utilizing environment-safe solvents that minimize the contamination of the final product. Two major super critical fluid technologies, rapid expansion of supercritical solution (RESS) and supercritical antisolvent (SAS) process, have been commonly studied and used.[3]

***(a)* RESS**

In the RESS process, the compounds of interest can be dissolved in a supercritical fluid followed by the expansion of the solution through a nozzle. The most commonly used supercritical solvents are water and carbon dioxide. The major disadvantage of this method is the limited solubility of the high-molecular weight polymers in those solvents that makes it a rather impractical method.3

***(b)* SAS**

The SAS method on the other hand, solves the problem of the limited compound solubility in a supercritical solvent by dissolving the polymer and drug compounds in an organic solvent. The supercritical solvent associates as an anti-solvent to precipitate them. After precipitation, the anti-solvent flows through a vessel removing the residual solvent. The vessel is depressurized and therefore the solid product is collected. Although this method is a continuous process, which is desired for large-scale production, it has a drawback of limited control over the nanoparticle size and surface properties.3

2.2 Emulsification-based technology

The emulsification-based technology is another important nanoparticle formulation technology. Depending on the polymer properties and the miscibility of the organic phase with the aqueous phase, three major emulsification methods have been identified.[4]

***(a)* Emulsification-solvent evaporation**

This technique was first projected by Gurny et al. in 1981. The polymer and thecompound of interest are first dissolved in water immiscible solvents such us chloroform, methyl chloride or ethyl acetate, and the solution is further emulsified through high-speed homogenization or sonication into the aqueous phase (i.e. water) to form an oil-in-water emulsion. The formation of nanoparticles starts during solvent evaporation that is achieved under reduced pressure or constant stirring.4

***(b)* Emulsification-solvent diffusion**

The emulsification-solvent diffusion technique (first described by Leroux et al.) is a modified method of the aforementioned production process. It utilizes the partially-water miscible solvent or the mixture of a water-immiscible organic solvent and a water-miscible organic solvent that is slowly added into the aqueous phase under constant stirring. Fast diffusion of the water-miscible solvent results in the formation of smaller emulsion droplets and thus smaller nanoparticles. The remaining solvent is then evaporated.4

***(c)* Salting-out**

The third emulsification-based method is called salting-out. In this method, more environment-friendly water-miscible solvents such as acetone or ethanol are used. The direct mixing of the organic phase and the aqueous phase is prevented by saturating the aqueous phase with salts (e.g. ammonium acetate, calcium chloride, magnesium acetate, etc.) that results in phase separation and emulsification. Subsequent dilution of the emulsion results in faster diffusion of the organic solvent. The organic solvents and the salts are then removed by cross flow filtration.

Although, the problem of using toxic chlorinated solvents in emulsification technology can be solved through the use of the modified salting-out method, the scale-up of the emulsification-based methods that demand high-energy homogenization/sonication is rather challenging. Furthermore, the limited drug loading (<20%) and large polydispersity of nanoparticles are other drawbacks of this technology4

2.3 Nanoprecipitation/Solvent displacement

Nanoprecipitation, first proposed by Fessi et al.,has been considered one of the easiest and most economic ways of synthesizing polymeric nanoparticles. The method, also known as the solvent displacement technique, utilizes water-miscible organic solvents (e.g., dimethyl sulfoxide, acetonitrile, acetone, tetrahydrofuran, etc.) to dissolve polymer and hydrophobic drugs, and usually water as an anti-solvent for subsequent precipitation. Both the drug and the polymer are first dissolved in an organic solvent and then added drop-wise to a large amount of a water solution, followed by the organic solvent removal. Alternatively, the organic solution containing both the polymer and the drug compound can be dialyzed against large amount of water until complete removal of the organic solvent is achieved. Although the nanoparticle properties can be controlled by manipulating process parameters such as drug to polymer ratios or species' starting concentrations, the slow mixing of the process results in the limited drug entrapment efficiency as well as relatively large polydispersity in nanoparticle size.[5]

2.4 Flash Nanoprecipitation

Flash Nanoprecipitation (FNP) is a process that was first proposed by Prud'homme and coworkers to reproducibly generate polymeric nanoparticles encapsulating hydrophobic drugs with high drug loading, controllable size, and surface properties. This process manipulates non equilibrium structures of nanoparticles via kinetic control of sophisticated and fast mixing. Therefore, high drug loading could be achieved. The fast mixing results in uniform solvent displacement and nanoparticle properties depend on the competitive kinetics of the polymer micellization and the hydrophobic compound nucleation and growth. A confined impinging jet mixer (CIJ) was first developed for the process. However, the mixer necessities equal momentum of two rapid jet streams that can indeed lead to a relatively fast nanoparticle growth. This pure mathematics limitation has been further resolved by Liu et al. who developed a multi-inlet vortex mixer (MIVM), which gave the flexibility of using multiple compounds of distinct solvent solubilities and manipulating solvent to anti-solvent ratios to achieve various supersaturation rates.

In this thesis we have developed and investigated the integrated process of FNP in the MIVM with freeze/spray-drying (process referred to as Flash Precipitation and Drying - FPaD), which in addition to providing high drug loading can lead to long-term stabilization of the nanoparticles. Producing dry powders prevents further growth of nanoparticles, which can be later conveniently resuspended in aqueous buffers atdesired concentrations for both *in vitro* and *in vivo* studies (Figure 2).

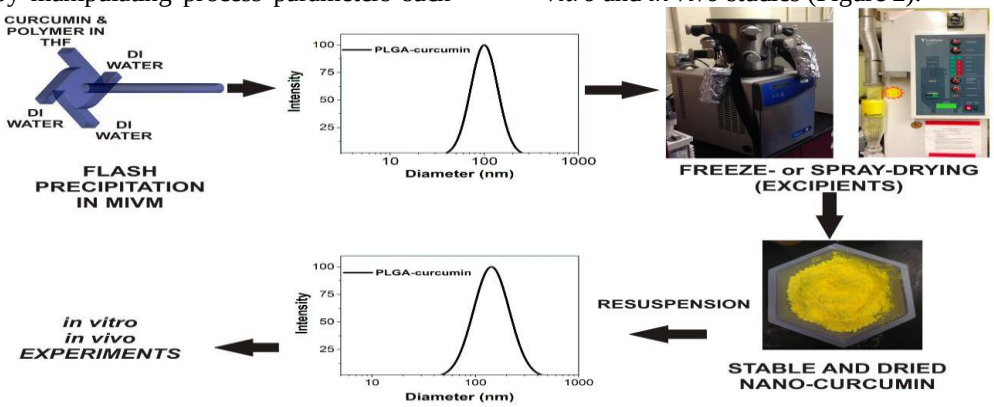

Figure 2.The general FPaD process of producing polymeric nanoparticles encapsulating hydrophobic compounds for in vivo and in vitro studies.[6]

Nanosuspensions are generated via flash nanoprecipitation in the multi inlet vortex mixer (MIVM). The nanoparticles are further freezeor spray-dried together with excipients to obtain stable and dried product that can be conveniently resuspended at desired time and concentration for *in vitro* or *in vivo* animal studies.[6]

3. DRUG RELEASE AND RELEASE KINETICS

Drug release from the carrier-primarily based particulate system depends upon the cross-linking, morphology, size, density of the particulate system and therefore the physiochemical properties of the drug, as well as presence of adjuvant. *In vitro* drug release additionally depends upon pH, polarity and presence of enzymes within the dissolution medium. The release of drug from theparticulate system depends upon completely three different mechanisms:

• Release from the surface of particles.
• Diffusion through the swollen rubbery matrix.
• Release due to erosion.

In the some majority of cases, drug release follows more than one type of mechanism [Figure 2][7].

Mechanism of drug release from particle system

When it connected with the release medium, the drug instantaneously dissolves, thus affecting its release from the surface. Drug entrapped in the surface layers of the particles conjointly follows this mechanism. This type of drug release results to a burst effect.

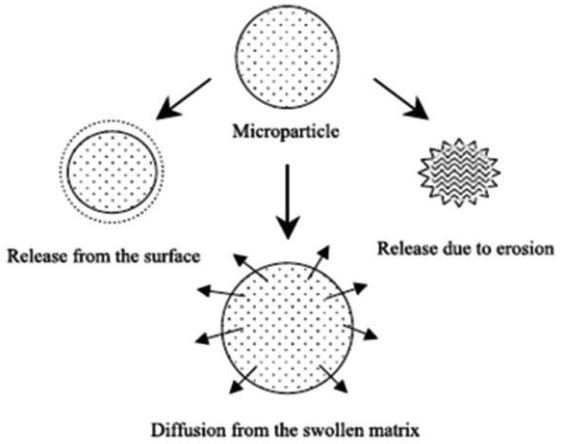

Figure 3. Drug release mechanisms in nanoparticles[8]

Drug release mechanisms in nanoparticles

Drug release through diffusion involves three steps:

• Penetration into the particulate system, that causes swelling of the matrix.
• Conversion of the glassy polymerinto a rubbery matrix.
• Diffusion of the drug within the rubbery matrix.

Various methods, which can be used to study the *in vitro* release of drug, are as follows:

• Side-by-side diffusion cells with a synthetic or biological membrane.
• Dialysis bag method.
• Ultracentrifugation.
• Centrifugal ultrafiltration7.

3.1 ADMINISTRAION OF NANOPARTICLES

The main administration routes for nanoparticles are IV injection, hypodermic or intramuscular injection; peroral administration; and ophthalmic application.

- **Intravenous administration**

Nanoparticles, like other colloidal carrierssuch asliposome, micro-emulsions and erythrocyte ghosts, are taken up by the reticuloendothelial systems (RES) after IV injection and distributed mainly to the liver, spleen and to a lesser degree, the bone marrow; variable amounts may be found in the lungs. All of these organs contain sessile, actively phagocytosing cells. Different phagocytosing cells are found in the blood and lymphatic system, and in the epithelial tissue of the blood vessels. These cells may take up nanoparticles by varying degrees. The sequence of events throughout distribution of nanoparticles and their phagocytosis is not currently known. It is believed that immediately after injection, the particles are coated by the serum components, the opsonins, which act as labels to passively target the nanoparticles to bound certain phagocytic cells.[9]

- **Active targeting**

Active targeting refers to a change within the natural distribution pattern of a carrier particle by deliberate modification of its properties, thereby leading it to specific cells, tissues or organs.

The following methods are mainly used:

• Changes of the surface properties by coating the nanoparticles with surfactants or macromolecules;
• Incorporation of magnetite particles into the particles and application of magnetic field;
• Alteration of surface charge; and
• Attachment of specific antibiotics to the nanoparticle surface.

The first two methods seem to be promising. Coating of nanoparticles with surfactants for instance can

drastically reduce liver uptake from 80% to 30%, and increase in blood concentration can be from 0.14 up to about 40%. Poloxamine 1508 is that the principal agent for reducing liver uptake and increasing blood concentration, whereas polysorbate 80 will increases the concentration in non-RES organs. Alternative surfactants such as poloxamer 184 and 407 have a high targeting capacity to the bone marrow. The chance of bone marrow targeting is size-dependent.[10]

- **Subcutaneous and intramuscular injection**

After subcutaneous and intramuscular injection of C-labelled polymethacrylate nanoparticles in rat, over 99% of the injected radioactivity remains at the injection site. The elimination rate of the administered dose per day within the variety of oligomeric components of the nanoparticulate polymer is found to be lesser in the urine and faeces initially and later elimination is found to be more in faeces.[11]

- **Oral administration**

Nanoparticles are maintained in the gut of rats and mice up to 6 days. Additionally , they are taken up in the intestine and appear in lymph nodes, blood, liver, spleen and at the site of inflammation in the body. Three different mechanisms are possible:

• Intracellular uptake.
• Intracellular-paracellular uptake.
• Uptake via M-cells and Peyer's patches within the gut.[12]

- **Ophthalmic application**

After ophthalmic application to rabbits, polyhexyl cyanoacrylate nanoparticles are eliminated from tears with a half-life of concerning about 15-20 min. Aqueous eye drops, on the opposite hand, have a half-life of 1-3 min. A little quantity of polycyanoacrylate nanoparticles adhere mainly to theconjunctiva, but also to the cornea and to the nictitating membrane of rabbits, and penetrate into the primary two layers of the cell layers.9

3.2 Nanoparticles and targeted drug delivery

The greatest immediate impact of nanotechnologies in cancer medical aid therapy is in drug targeting. The therapeutic indexof nearly all drugs currently being used can be improved if they are more efficiently delivered to their biological targets through appropriate application of nanotechnologies. In the case of central nervous system cancers (brain cancer), many drugs have difficulty in crossing the blood-brain barrier to attack the tumour. Drug-loaded nanoparticles are able to penetrate this barrier, and are been shown to greatly increase therapeutic concentration of antitumor drugs in brain tumours.

The best way to increase the effectivity and reduce the toxicity of an antineoplastics drug is to direct the drug to its target and maintain its concentration at the location for an adequate time for therapeutic action to take effect. The potency of drug delivery to various parts of the body is directly affected by particlesize. Nanostructuremediatedrug delivery, a key technology for realisation of nanomedicine, have the potential to enhance drug bioavailability, improve timed release of drug molecules and enable precision drug targeting. Additional benefits of using targeted nanoscale drug carriers are reduced drug toxicity and more efficacious drug distribution. Anatomic features such as the blood-brain barrier, the branching pathways of the pulmonary system and therefore the tight epithelial junctions of the skin make it difficult for drugs to reach out many desired physiologic targets.

Nanostructured drug carriers facilitate to penetrate or overcome these barriers to drug delivery, and it has been shown that the greatest potency for delivery into the pulmonary system is obtained for particle diameter < 100 nm. Larger uptake efficiency has also been shown for gastrointestinal absorption and transdermal permeation, with particles about 100 nm and 50 nm in size, respectively. However, such tiny particles travelling in the pulmonary tract may also have a greater probability of being exhaled. Larger, compartmentalised or multilayered drug carrier architectures could facilitate with delivery to the pulmonary extremities. For instance, the outer layers of the carrier designed may be formulated to biodegrade as the carrier travels through the pulmonary tract. Because the drug carrier penetrates further into the lung, additional shedding will allow the encapsulated drug to be released. Biodegradable nanoparticles of gelatin and human albumin show promise as pulmonary drug carriers.

Advantages of nanostructuremediate drug delivery include the ability to deliver drug molecules directly into cells and the capability to target tumours within healthy tissue. Nanoscale drug delivery architectures are able to penetrate tumours because of the discontinuous, or "leaky," nature of the tumour microvasculature, which usally contains pores ranging from 100 to 1000 nm in diameter. Microvasculature of the healthy tissue varies by tissue type.[13]

Table 1: Therapeutic Applications Of Nanoparticles[12]

Application	Material	Purpose
Cancer therapy	Poly (alkyl cyanoacrylate) nanoparticleswith anticancer agents, oligonucleotides	Targeting, reducing toxicity, enhanced uptake of antitumour agents, improved in vitro and in vivo stability
Intracellular Targeting	Poly (alkyl cyanoacrylate) polyesters nanoparticles with anti-parasitic or antiviral agents	Targeting reticuloendothelial intercellular infections
Prolonged systemic Circulation	Polyesters with adsorbed poly ethylene glycols or pluronics	Prolonged systemic effect, avoid by the uptake of reticuloendothelial system
Vaccine adjuvant	Poly (methyl methacrylate) nanoparticles with vaccines (oral and IM immunisation)	Enhanced immune response, alternate acceptable adjuvant
Peroral absorption	Poly (methyl methacrylate) nanoparticles with proteins and therapeutic agents	Enhanced bioavailability, protection from GIT enzymes
Ocular delivery	Poly (alkyl cyanoacrylate) nanoparticles with steroids, anti-inflammatory agents, anti-bacterial agents for glaucoma	Improved retention of drug/reduced wash-out
DNA delivery	DNA-gelatine nanoparticles, DNA-chitosan nanoparticles, PDNA-poly (D, L-lactide-co-glycolide) nanoparticles	Enhanced delivery and significantly higher expression levels
Oligonucleotides Delivery	Alginate nanoparticles, poly (D, L-lactic acid) nanoparticles	Enhanced delivery of oligonucleotides
Other applications	Poly (alkyl cyanoacrylate) nanoparticles with peptides	Crosses blood-brain barrier

3.3 Polymeric Nanoparticles as Nutraceutical Agents

Although there'sno official accepted definition of nutraceuticals, they're mostly referred to as pharma-foods, a powerful toolbox to be used as a complement to the diet and before prescribing medications, in order to enhance health and prevent and/or treat pathologic conditions. Subjects might be people who may not yet be eligible for conventional pharmaceutical therapy. There is widespread inconsistency and confusion within the definition of "nutraceuticals". Substances from same sources are classified differently, like as plant-derived drugs, for example, digitalis from foxglove leaves is in the group of the medicinal products, whereas extracts from green tea leaves are considered as nutraceuticals (Figure). Relating to the legislation, in the United States of America, the FDA regulates dietary supplements, which include nutraceuticals, under the Dietary Supplement Health and Education Act of 1994 (DSHEA). In distinction to Canadian regulations, analysis studies in humans to prove dietary supplement safety/efficacy, aren't required by the FDA prior to marketing. The present European regulations consider nutraceuticals as belonging to the same category as food supplements. The Directive 2002/46/EC on food supplements and novel foods, that was recently modified by the new European Parliament and Council Regulation (EU) 2015/2283, defining new foods categories, completes the classification of food supplements, however it still does not mention the term 'nutraceutical'

The use of nutraceuticals for certain pathologies has been reported. Some nutraceuticals may be used to reduce some of the main cardiovascular risk factors, such as altered blood glucose levels, hypertension and hypercholesterolemia . The most frequently often cholesterol-lowering and blood–pressure lowering substances found in nutraceuticals are the following: berberine, beta-glucans, sterols, isoflavones, mono unsaturated fatty acids and monacolin K (also

referred as lovastatin) from extracts of red yeast rice fermented by *Monascus purpureus* or the use of potassium, magnesium, L-arginine, vitamin C, cocoa flavonoids, beetroot juice, coenzyme Q10, melatonin and aged garlic extract. In the case of the glucose metabolism and type 2 diabetes mellitus (T2D) the study suggests that increasing omega-3, omega-6 or total polyunsaturated fatty acid (PUFAs) has very little or no effect on prevention and treatment of T2D, but randomized controlled trials suggest that viscous dietary fiber at a median dose of ~13.1 g/day may offer beneficial effects on glycemic control and, thus, an enhanced cardiovascular disease risk profile. In addition, vitamins, mainly vitamin C and vitamin D, has been recommended as nutraceuticals to reduce periodontal risks or improve periodontal health. Riboflavin, coenzyme Q10, magnesium, butterbur, feverfew, and ω-3 PUFAs are recommended for adults with migraine. Still, the evidence of the efficacy of nutraceuticals for the treatment of pediatric migraine is limited. Multiple nutraceuticals have been considered useful, not only to treat some pathologies, but also to mitigate disease-related symptoms.

In osteoarthritis, a chronic disease, the nutraceuticals could represent promising alternatives for the relief of pain,wherever the conventional pharmacological approachesto pain relief and joint repair haven't always been safe for long term use.[14]

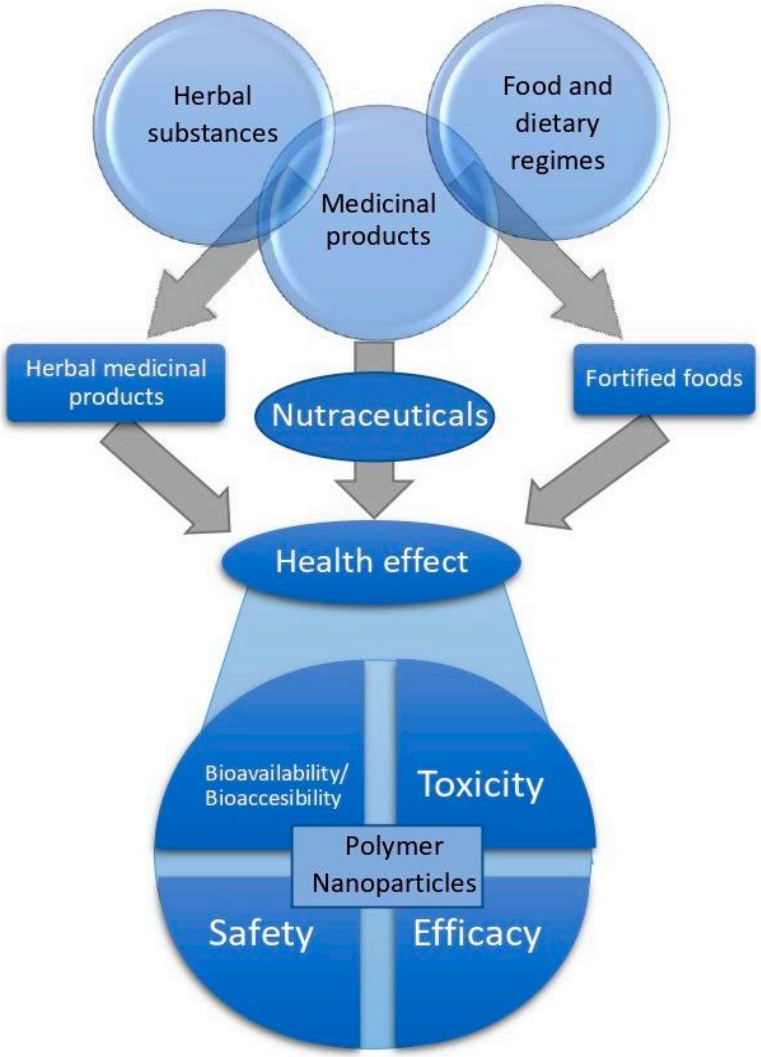

Figure 4.Use of polymeric nanoparticles for nutraceuticals and different bioactive compounds for greater health and medical advantages.[14]

4. Advantages, Disadvantages of polymeric nanoparticles

- **Advantages**

1.Particle size and surface characteristics of nanoparticles can be simply manipulated to achieve both passive and active drug targeting after parenteral administration.

2.They control and sustain release of the drug throughout the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to obtain increase in drug therapeutic efficacy and reduction in side effects.

3.Controlled release and particle degradation characteristics may be promptly modulated by the selection of matrix constituents. Drug loading is comparatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

4. Site-specific targeting can be obtained by attaching targeting ligands to surface of particles or use of magnetic guidance.

5.The system can also be used for various routes of administration including oral, nasal, parenteral, intraocular etc.[15]

- **Disadvantages**

1.Solvent and high-temperature incompatibility for less cost polydimethylsiloxane microchannels. Greater costs and complexities in the fabrication of glass and silicon microdevices.
2.Current methods are not applicable to all categories of nanoparticles. Not all properties can be characterized, like drug encapsulation and release, and signal-tonoise ratio.
3. Higher prices and complexities in the fabrication and operation compared with well plates Might not be reusable and if reusable, it might be difficult to keep sterile.
4. Lack of methods to translate data from small-scale organisms to diffrent species Pharmacokinetics or biodistribution can't be determined.
5.Difficult to build systems at less-cost that are comparable to a batch reactor able to prepare grams or kilograms of nanoparticles.[15]

4.1 Other Nanoparticles Applications

Healthcare/medical

1. Bone growth promoters
2. Biocompatible coatings for implants
3. Sunscreens (e.g. using ZnO and TiO2) / cosmetics
4. Biolabeling and detection (e.g. using Au)
5. Carriers for drugs with less water solubility
6. Fungicides (e.g. using ZnO)
7. MRI contrast agents (e.g. using superparamagnetic iron oxide)
9. Biological binding agents (e.g. for high phosphate levels)
10. Antiviral, antibacterial (e.g. Ag), anti-spore nonchemical creams
11. powders (using surface tension energy on the nanoscale to demolish biological particles)[15]

5. CONCLUSION:

The application of nanoparticles as a drug delivery system is already with great success. Nanoparticles gives us great advantages with regards to drug targeting, drug delivery and with their ability for combining diagnosis and therapy are one of the major instances in Nanomedicine.

There are many technical challenges while developing the following techniques:-

- Architecting of biomimetic polymers
- Virus like systems for intracellular systems
- Control of sensitive drugs
- Functions of bioresponsive triggered systems, active drug targeting, systems interacting with the body, smart delivery and so on
- Nanochips for nanoparticles
- Releasing and carriers for the advanced polymers for delivery of the therapeutic proteins or peptides

Drug delivery systems or techniques were established to deliver and control the amount as well as the rate of drugs released in the body.

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