International Journal of Pharmacology and Pharmaceutical Sciences 2015; Vol: 2, Issue: 5, 60-69.

Home Page: http://ijppsjournal.org
International Journal of Pharmacology and Pharmaceutical Sciences

Review Article ISSN: 2394-613X

Polymeric Nanoparticles Drug Delivery to Brain: A Review

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Abstract
This work represents review of literatures covering various aspects of the Central Nervous System (CNS) targeted drug delivery using polymeric nanoparticles with respect to targeted drug delivery to CNS and its need, barriers of CNS, which prevents the entry of therapeutics, various strategies used to manipulate drugs to cross the blood brain, and blood cerebral spinal fluid barriers. Central nervous system disorders are the major worldwide public health problem. The central nervous system is one of the most delicate and sensitive micro environments of the body. It is protected by the blood-brain barrier (BBB) regulating its homeostasis. Several strategies are currently being required to enhance the delivery of drugs across the BBB. Generally the size ranges of nanoparticle which are from 10 to 1000 nm (50–300 nm generally). The use of small particles as drug carriers for targeted delivery has been studied over a long duration of time. Polymeric Nanoparticles have been shown to be promising carrier options for the delivery of drugs in the CNS system because of their potential both in encapsulating drugs, hence it protect them from excretion and metabolism, and in delivering active agents across the BBB without producing any damage to the barrier. Different types of polymers have been used and different strategies like surface modification have been used to increase the retention time of nanoparticles. The use of biodegradable polymeric nanoparticles (NPs) for controlled drug delivery has shown significant therapeutic potential. The development of other useful polymeric NPs to deliver a spectrum of chemotherapeutic, diagnostic, and imaging agents for various applications. Polymeric nanoparticles signify one of the most motivating challenges for the technical world being investigated as drug delivery systems for effective complete and local delivery of therapeutics to the central nervous system.

Key words: Polymeric nanoparticles, targeted drug delivery, nanoparticles, micro fluidics. Brain drug delivery, central nervous system, brain blood brain barrier.

INTRODUCTION

Nanotechnology consists of the creation of useful materials, devices, and systems through the alteration of such small scale matter; nanoparticulate systems have gained increasing interest within therapeutics. Polymer nanoparticles are the particles of less than 1µm diameter that are prepared from natural or synthetic polymers. Nanoparticles have the ability to deliver a wide range of drugs to different areas of the body for sustained periods of time. The smaller size of nanoparticles is integral for systemic circulation. Composed of synthetic or semi-synthetic polymers. Biodegradable polymeric nanoparticles ie. polylactic acid (PLA), polyglycolic acid (PGA), polylactic glycolic acid (PLGA), and polymethyl methacrylate (PMMA) phospholipids hydrophobic core[1]. They also exhibit a good potential for surface modification via chemical transformations, and provide excellent pharmacokinetic control, and are suitable for the entrapment and delivery of a wide range of therapeutic agents[1,2].This polymeric coating is thought to reduce immunogenicity, and limit the phagocytosis of nanoparticles by the reticuloendothelial system, resulting in increased blood levels of drug in organs such as the brain, intestines, and kidneys[3]. They may be formulated to encapsulate several classes of therapeutic agents including, but not limited to, low molecular weight compounds[4]. Natural polymers like proteins or polysaccharides have not been widely used for this purpose since they vary in purity, and also require cross linking that could denature the enclosed drug. The most commonly used polymers for nanoparticles have been poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly-ε-caprolactone (PCL), and their co-polymers, poly (lactide-co-glycolide)(PLGA).

Additional nanoparticles are polymer-based, meaning they are made from a natural polymer such as polylactic acid (PLA), poly-D, L- glycoloide (PLG), polyactide-co-glycolide (PLGA), and polycyanoacrylate (PCA). A number of studies have found that polymeric nanoparticles may in fact provide better results for drug delivery measured up to with lipid-based nanoparticles because they may increase the stability of the drugs or proteins being transported. Polymeric nanoparticles may also include valuable control release mechanisms. In current years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in drug targeting to particular organs/tissues as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides, and genes in spite of development of various synthetic, and semi-synthetic polymers, natural polymers still enjoy their popularity in drug delivery, and some of them are listed as [5]. Gums (Ex. Acacia, Guar, etc.), Chitosan, Gelatin, Sodium alginate and Albumin.

A range of materials have been employed for delivery of bioactive agents. Pharmaceutical Scientist borrowed polymers intended for other non-biological uses. A polymer used in controlled drug delivery formulations must be chemically inert, non-toxic, and free of leachable impurities. It must also have an appropriate physical structure with minimal undesired aging, and be readily processable. Some of the polymeric materials are Cellulosic, Poly (2-hydroxy ethyl methacrylate), Poly (N-vinyl pyrrolidone), Poly (methyl methacrylate), Poly (acrylic acid), Polyacrylamide, Poly (ethylene-co-vinyl acetate), Poly (ethylene glycol), Poly (methacrylic acid). However, in recent years additional polymers are designed primarily for medical applications, and have entered the arena of controlled release of bioactive agents. Barrier like BBB, BCF, and BTB restrict access to brain cells of blood–borne compounds, and facilitates nutrients essential for normal metabolism to reach brain cells. This regulation of the brain homeostasis results in the inability of some small and large therapeutic compounds to cross the BBB[6]. Nanoparticulate drug delivery systems have been extensively studied in recent years for spatial and temporal delivery especially in tumour and brain targeting[7]. Nanoparticulated polymer-based systems provide potential solution to improve therapeutic efficacy and diagnosis sensitivity. Using these nanocarriers, they have found that the pore size in mucus is larger than previously estimated, about 0.5 microns, and that unexpectedly large nanoparticles larger than 100 nm that are densely coated with PEG can diffuse rapidly through the brain[8]. Targeted drug delivery is a means of concentrating drugs at a specific site relative to other parts of the body[9]. It compensates the rest of the body from toxic effects of the drug and is also a potential means of improving therapeutic index[10]. These nanoparticles are fairly stable and can be stored at room temperature for an extended amount of time[11]. The delivery of drugs to the CNS is of prime importance for treating specific neurological disorders and various diseases such as meningitis, encephalitis, degenerative diseases such as alzheimer's, parkinson's, and tumors such as glioblastoma[12]. The major problem in treating such CNS disorders is due to their inability to surpass the natural CNS protective barriers, which is mainly the blood brain barrier (BBB) and the blood cerebral spinal.

Anatomy and physiology of brain

Blood brain barrier structural and functional barrier, which impedes, and regulates the influx of most compounds from blood to brain formed by brain microvascular endothelial cells (BMEC)**,** Astrocyte end feet**,** Pericytes**,** Regulates passage of molecules in and out of brain to maintain neural environment. Responsible for metabolic activities such as the metabolism of L-dopa to regulate its concentration in the brain. The blood brain barrier is a highly sophisticated organ that acts as the biological equivalent of a computer firewall: it selectively allows nutrients into the brain, while keeping out harmful components[13].

The blood brain barrier function results from a combination of this:

A physical barrier: - Tight junctions between cells reducing flux via the intercellular cleft or paracellular pathway.

A transport barrier: - A specific transport mechanism mediating solute flux and the targeted transport mechanism provided that the endogenous function of the transporter and its endogenous ligand(s) is not influenced by the technology in a major way.

Blood brain barrier physiology: -

The blood brain barrier blocks all molecules except those that cross cell membranes by means of lipid solubility (such as oxygen, carbon dioxide, and ethanol). Despite weighing only about 3 pounds, the brain consumes as much as 20% of the oxygen and glucose taken in by the body. Nervous tissue in the brain has a very high metabolic rate due to the sheer number of decisions

and processes taking place within the brain at any given time. This organ is protected against various harmful substances due to the presence of two types of barriers: the blood-brain barrier and the blood cerebrospinal fluid barrier[14]. Fig.1 represents the blood brain barrier, CSF, and brain-CSF. Many drugs are unable to pass the barrier since 98% of them are heavier than 500 Dalton hormones generally do not penetrate the brain from the blood except at the "circumventricular organs.''As antibodies are too large to cross the blood brain barrier infections of the brain when they do occur can be very serious and difficult to treat.

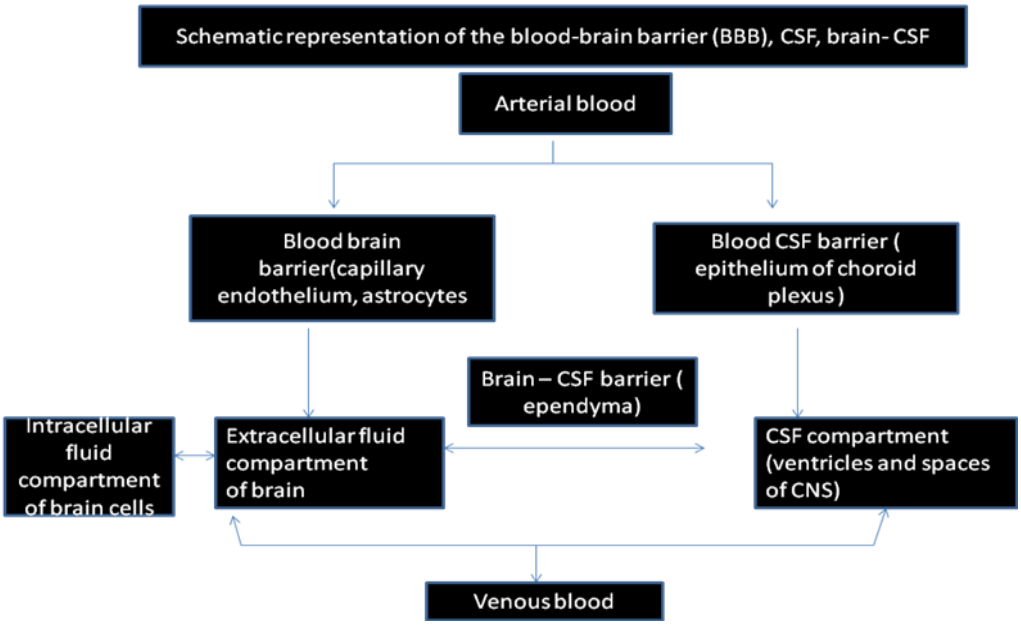

Figure1: Schematic representation of blood brain barrier, CSF, Brain CSF

Why to target a drug

To obtain a desired therapeutic response.

The correct amount of drug should be transported and delivered to the site of action with subsequent control of drug input rate.

To avoid distribution of a drug to other tissues which seems to be unnecessary, wasteful, and a potential cause of toxicity.

Drug Targeting to the Brain

Polymer-based nanotechnologies are proposed to be an alternative for drug administration delivery and targeting to those of conventional formulations. The blood brain barrier is frequently a rate-limiting factor in determining permeation of a drug into the brain. In this study, the surface-engineered long-circulating PLGA nanoparticles (NPs) were assessed for brain-specific delivery[13]. Drug delivery to the brain is limited due to the presence of the blood brain barrier (BBB), which restricted the delivery of a wide variety of drugs to the brain. The BBB consists of endothelial cells with tight junctions that line the cerebral capillaries. Thus, tight junctions in the epithelium of the brain endothelial eliminate paracellular pathways of solute across the BBB. In addition to tight junctions, many efflux transport pathways like p-glycoprotein and active organic acid present in brain endothelial cells remove unwanted substances[15].The example of using nanoparticulate pharmaceutical carriers has been well established over the past decade both in pharmaceutical research and in the clinical setting. Drug carriers are expected to stay in the blood for a long time, and accumulate in pathological sites with affected and leaky vasculature (tumors, inflammations, and infarcted areas) via the enhanced permeability, and retention (EPR) effect, and facilitate targeted delivery of specific ligand-modified drugs and drug carriers into poorly accessible areas[16].

The various approaches of vectoring the drug to the target site can be broadly classified as

Passive targeting

Active targeting (receptor mediated targeting and Physical targeting **)**

Passive targeting: - Passive Targeting Systems that target the systemic circulation are generally characterized as 'passive' delivery systems (i.e. targeting occurs because of the body's natural response to physiochemical characteristics of the drug or drug-carrier system).

Active targeting: - Active targeting exploits modification or manipulation of drug carriers to redefine its biofate. The natural distribution pattern of the drug carrier composites is enhanced using chemical, biological, and physical means, and that it approaches and is identified by particular biosites. Active transport systems can be divided into carrier-mediated transcytosis (CMT), absorptive mediated transcytosis (AMT), or receptor-mediated transcytosis (RMT). The facilitation of the binding of the drug –carrier to target cells through the use of ligands or engineered homing device to increase receptor mediated localization of the drug and target specific deliver of drug is referred to as active targeting[13]. Fig. 2 shows drug targeting delivery to brain i.e. active targeting and passive targeting.

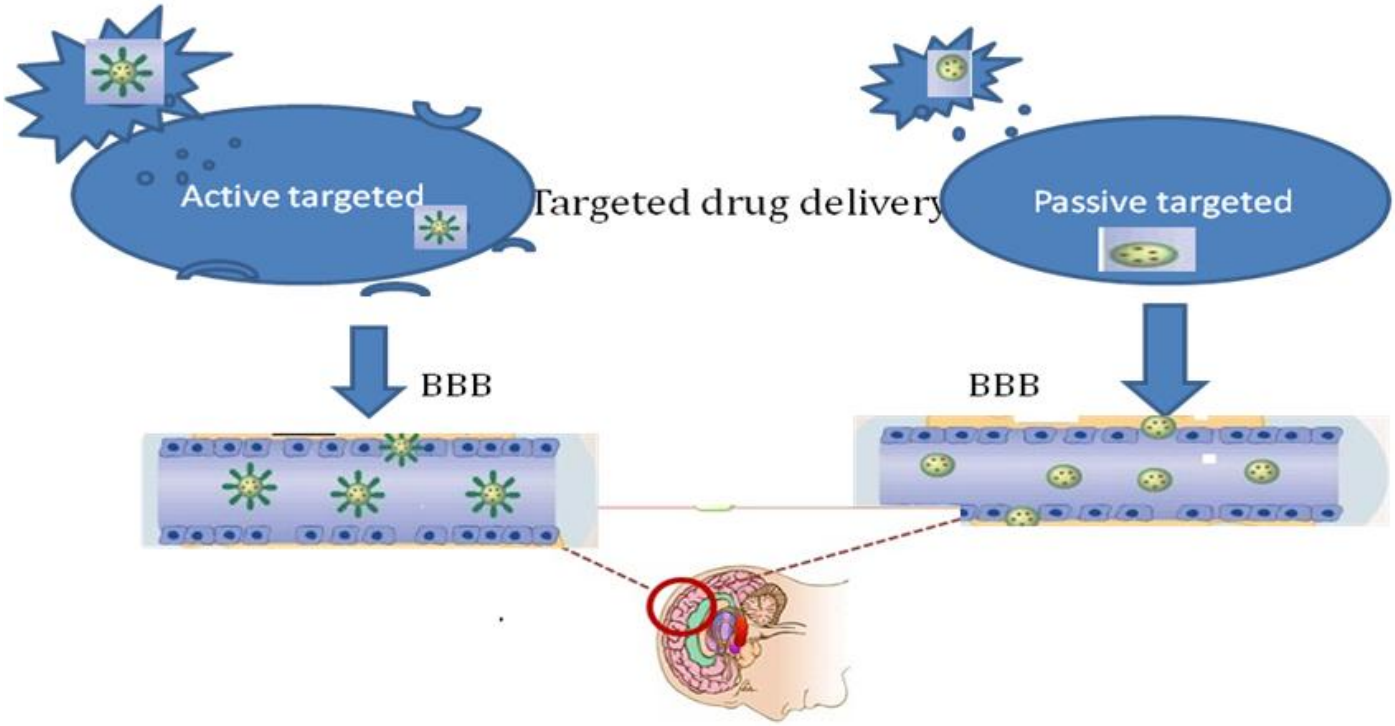

Figure 2: Drug targeting delivery to brain

Obstacle of Drug Delivery to Brain

The blood brain barrier (BBB) is a diffusion barrier, which impedes influx of most compounds from blood to brain while supplying the brain with the required nutrients for proper function. Unlike peripheral capillaries that allow relatively free exchange of substances across/between cells, the BBB strictly limits transport into the brain through both physical (tight junctions) and metabolic (enzymes) barriers. The BBB is mainly formed by brain capillary endothelial cells (BCEC) although other cells such as astrocytes, pericytes, and neuronal cells also play an important role in the function of the BBB[16].

BCEC (Brain microvascular endothelial cells) have specific characteristics such as tight junctions, which prevent paracellular transport of small and large (water soluble) compounds from blood to the brain. Furthermore, transcellular transport from blood to brain is limited as a result of low vesicular transport, high metabolic activity, and a lack of fenestrate. The function of the BBB is to exclude toxic exogenous compounds from the brain, and to nourish the brain with essential nutrients such as ions, glucose, amino acids, purines, nucleosides, peptides and proteins. Several influx mechanisms exist at the BBB, which can be divided into active or passive BBB transport mechanisms. Passive diffusion depends on lipophilicity and molecular weight. Furthermore, the ability of a compound to form hydrogen bonds will limit its diffusion through the BBB. Transport of hydrophilic compounds via the paracellular route is limited while lipophilic drugs smaller than 400 - 600 Dalton can enter the brain via the transcellular route. Active transport systems can be divided into carrier-mediated transcytosis (CMT), absorptive mediated transcytosis (AMT), or receptor-mediated transcytosis (RMT). CMT is used for the transcytosis of nutrients such as glucose, amino acids and purine bases. Examples are the hexose transporter, which transports glucose and mannose, and the amino acid transporters, which can be roughly subdivided into anionic, cationic or neutral amino acid carriers. CMT is selective and the transport rate is dependent on the occupation rate of the carrier. AMT is initiated by the binding of polycationic substances to negative charges on the plasma membrane. This process does not involve specific plasma membrane receptors. Upon binding of the cationic compound to the

plasma membrane endocytosis occurs followed by the formation of endosomes. Peptides and proteins can undergo transport to the brain via RMT. Examples of receptors involved in RMT are the insulin receptor, the transferrin receptor, and the transporters for low-density lipoprotein, lepton and insulin-like growth factors. In general, RMT occurs in 3 steps. [13, 16]. Receptor-mediated endocytosis of the compound at the luminal (blood) side, Movement through the endothelial cytoplasm and Exocytosis at the abluminal (brain) side of the brain capillary endothelium. P-glycoprotein (Pgp). Pgp is a trans-membrane protein, located at the apical membrane of the BCEC. (Brain microvascular endothelial cells).

Approaches of Drug Targeting Delivery to Brain

To overcome the multitude of barriers restricting CNS drug delivery of potential therapeutic agents numerous drug delivery strategies have been developed.

These strategies generally fall into one or more of the following categories: invasive, non-invasive or miscellaneous techniques. Fig.3 schematic representation of approaches of brain drug delivery.

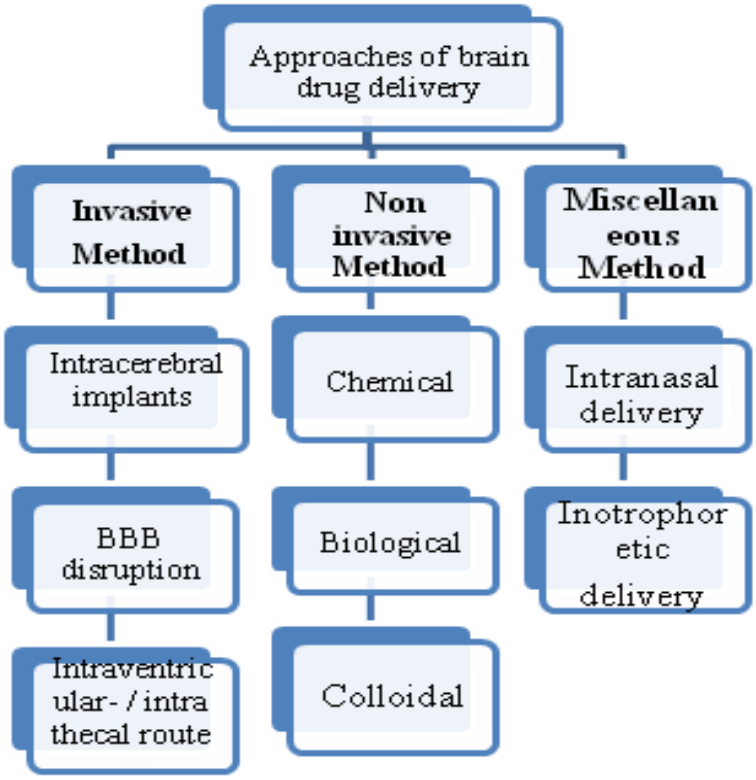

Figure 3: Schematic Representation of Approaches of Brain Drug Delivery

Invasive method is generally only low molecular weight, lipid-soluble molecules and a few peptides, and nutrients that can Cross this barrier to any significant extent either by passive diffusion, or using specific transport mechanisms. However, these methods entail that drugs are administered directly into the brain tissue. BBB disruption temporary breaks down the BBB by sugar solution (mannitol). The endothelial cells shrink the opening of the tight junctions[17-18]. The effects last for 20-30 minutes, and are useful in cerebral lymphoma, malignant glioma, and disseminated CNS germ cell tumours[19]. Side effects include physiological stress, transient increase in intracranial pressure, and unwanted delivery of anticancer agents to normal brain tissues. A variety of non-invasive brain drug delivery methods have been investigated that make use of the brain blood vessel network to gain widespread drug distribution. Non-invasive systemic delivery of the drugs to the brain remains a challenge that gives rise to the development of new drug-targeting technologies[18]. The non-invasive systemic delivery of the drugs to the brain always remains a challenge that gives rise to the development of new drug-targeting technologies[19]. Non-invasive techniques usually rely upon drug manipulations which may include alterations such as prodrugs, lipophilic analogues, chemical drug delivery, carrier-mediated drug delivery, receptor mediated drug delivery etc. For this reason different approaches have been developed in order to overcome this barrier. Polymeric nanoparticles represent one of the most stimulating challenges for the scientific world being investigated as drug delivery systems for effective systemic and local delivery of therapeutics to the CNS[20].

Table 1: Conventional drug delivery to BBB (various drug available)

Brain diseases	Drug	Animal Model Used	Result	Reference
Alzheimer's disease/Dementia	Rivastigmine (Exelon),Donepezil hydrochloride(Aricept),	Mice, Mouse	Abnormal metabolism of b-amyloid.	[21]
Parkinson disease	Co-beneldopa (benserazide+levodop) Levodopa,Dopamine Agonists	Mouse	Evidence of increased motor complications other adverse events.	[22]
Brain tumor	Doxorubicin		Accumulation of NP in the tumour site and contralateral hemisphere.	[23]

Polymeric Nanoparticles As Drug Delivery Device For Brain Targeting (CNS)

Polymeric Nanoparticles have shown the most potential for CNS drug delivery. Polymeric nanoparticles are nanoparticles which are prepared from polymers. Polymeric nanoparticles have attracted researchers in targeting drug molecules to brain[16]. It is known that between the blood streamline and the central nervous system there is a barrier known as the blood brain barrier (BBB). The BBB allows only the exchange of ions in order to maintain a constant osmotic pressure and the passage of nutrients. Its role is to protect the brain and the spinal axis from any chemical or bacteriological threats. The protection offered by the BBB comes at a certain value because it is impossible to get drugs through the barrier, so the therapy for the central nervous system is very difficult. In the brain endothelial cells are packed more tightly together due to the existence of tight zonulae occludentes junctions between them. The blood brain barrier recognizes therapeutic agents as foreign particles and doesn't allow their passage. Because of the blood brain barrier, finding a way to deliver bioactive substances to brain has become a real challenge. One of the methods to achieve drug delivery to the central nervous system is to entrap the drugs into nanoparticles. Because of their reduced size, nanoparticles are able to pass through the vascular endothelium of the BBB. There are several studies that showed good result in the treatment of brain tumors by drugs loaded with nanoparticles[24]. The method of preparation of nanoparticles, nanospheres or nanocapsules are depending upon the drug that is dissolved, entrapped, encapsulated or attached to a nanoparticle that can be obtained. As time has progressed biodegradable polymeric nanoparticles have attracted significant consideration as potential drug delivery devices in observation of their function in drug targeting to particular organs/tissues as carriers of DNA in gene therapy. Now a days, these polymers are designed primarily for medical applications and have entered the controlled release of bioactive agents[25].

Table 2: List of Nanoformulations Examined for Enhanced Brain Delivery

Formulation	Resources Used	Model Molecule	Compensation	References
Polymeric nanoparticles	PLGA and PCL	Etoposide	Selective distribution with higher brain permeability.	[26]
	PLGA	Imatinib mesylate	Increased the extent of drug permeation to brain.	[27]
	Chitosan	Venlafaxine	Better brain uptake, higher direct transport percentage.	[28]
	PLA-PEG-tween80	AmphotericinB	Drug concentration in mice brain greatly enhanced, Reduced the toxicity of AmB to liver, kidney etc.	[29]
	PBCA-tween 80	Doxorubicin	Augumented accumulation of NP in the tumour site.	[23]

Advantages of Polymeric Nanoparticles

One of the major advantages of nanoparticles is their small size, which allows them to pass through certain biological barriers. A second advantage is that a high density of therapeutic agents can often be encapsulated, dispersed, or dissolved within these nanoparticles, which depending on the preparation process can be engineered to yield different properties and release characteristics for the entrapped agent. Because of the versatility of chemistries and preparation methods in these systems, surface

functionalities can sometimes be incorporated into the nanoparticles. This facilitates additional attractive properties, such as the attachment of 'shielding' ligands that prolong the circulation of the nanoparticles in the blood stream, or the targeting of ligands for interaction with specific cells or tissue[30]. It increases the stability of any volatile pharmaceutical agents easily and cheaply fabricated in large quantities by a multitude of methods. They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness. It delivers a higher concentration of pharmaceutical agent to a desired location polymeric nanoparticles have some advantages over liposomes. It is possible for the drug release profile of polymeric nanoparticles to be modulated and these nanoparticles are more stable in biological fluids. Additionally, the starting polymers are less expensive than phospholipids and manufacturing and the processes are simple and suitable for industrial scale up and polymeric nanoparticles for controlled drug delivery[31].

The blood brain barrier is an important limiting factor for the development of new drugs that can be delivered to the central nervous system[32]. As a drug carrier, NPs have significant advantages like better bioavailability, systemic stability, high drug loading, long blood circulation time and selective distribution in the organs/tissues with longer half life[33].

Moreover, polymeric nanoparticles have been applied in gene therapy to breast cancer cells resulting in ant proliferative effects[34].

Techniques of Preparation

The characteristics of PNPs have to be optimized depending on the particular application.

Preparation Methods of Nanoparticles from Dispersion of Preformed Polymer

Dispersion of drug in preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (D, L-glycolide) (PLG), poly (lactic acid) (PLA), poly (cyanoacrylate) (PCA) and poly (D, L-lactide-co-glycolide) (PLGA). Important terms: Solvent evaporation, Nanoprecipitation, Emulsification/solvent diffusion, Salting out, Dialysis, Supercritical fluid technology. (SCF) [25].

Polymeric Nanoparticles for Targeted Brain Drug Delivery

These polymers poly (alkylcyanoacrylate) nanoparticles with peptide are applicable for crossing the blood brain barrier. The blood brain barrier signifies one of the difficulties for preparation including antibiotics, anti-neoplastic agents, anti-tumor and many other drugs. Polymeric nanoparticles are used for the main purpose for drug delivery to the brain through the BBB ie its drug passes the targeted specific site drugs, and are effectively used for brain targeting via nanoparticles containing the doxorubicin, kyotyropin, loperamide, dipeptide kyotropin, and hexapeptide etc. A preparation of nanoparticles enhanced the brain drug delivery. Superior medication included at the blood brain barrier is as to improve the transportation across the endothelial cell layer, and thus enlarged maintenance in the brain[35]. This review in particular deals on surface modification of PLGA NPs and their possibility of clinical applications including treatment for brain pathologies such as brain tumours, and Lysosomal Storage Disorders with neurological involvement. Since a great number of pharmacologically active molecules are not able to cross the Blood Brain Barrier (BBB) and reach the Central Nervous System (CNS) a new brain targeted polymeric is used[36].

Targeting drugs to the brain by crossing the blood brain barrier (BBB) has been a challenge. In this pursuit many attempts have been made to develop novel drug delivery systems. Tlhe BBB is formed by the tight endothelial cell junctions of the capillaries within the brain, which limits the ability of many drugs to penetrate through the brain tissue in order to enter the central nervous system (CNS). It is known that many regulators of the brain functions such as cytokines, transferins, endorphins and delta sleep inducing peptides pass through the BBB from the vessels into the brain[36]. The treatment of CNS diseases is particularly challenging because the delivery of drug molecules to the brain is often precluded by a variety of physiological, metabolic and biochemical obstacles that collectively comprise the blood brain barrier, blood cerebrospinal fluid barrier, and blood tumour barrier. The present outlook for patients suffering from many types of brain diseases remains poor, but recent developments in drug delivery techniques provide reasonable hope that the formidable barriers shielding the brain may ultimately be overcome. Drug delivery directly to the brain interstitial has recently been markedly enhanced through the rational design of polymer-based drug delivery systems. Substantial progress will only come about if continued vigorous research efforts to develop more

therapeutic and less toxic drug molecules are paralleled by the aggressive pursuit of more effective mechanisms for delivering those drugs to brain targets[37-38].

Diagnostic Features

Nanoparticles covered with polisorbate T-80 have been detected in polymeric nanoparticles in the brain and what proves the substance of endocytosis and/or transcytosis at some extent. These nanoparticles can be directly traced *in vivo* by analytical electron microscopy (AEM). Therefore this type of nanoparticles can be used in the useful examination of the brain[13]. An alternative to these rather complicated methods is to use corticoids loaded nanoparticles. Some of the most promising polymers are PLGA due to their very low toxicity. Gene therapy is a potential method for treating neurodegenerative diseases such as Parkinsons. The controlled delivery of genes responsible for GNDF (Glial Cell Line-Derived Neurotrophic Factor) formation stops the disease evolution and maintains a constant level of dopamine despite the cells lost because of the disease. Also the delivery of genes involved in the tyrosine hydroxylase pathway has shown good results[39-40]. A method to obtain nanoparticles without using a surfactant was proposed by who obtained nanoparticles able to bind DNA without using a surfactant. The nanoparticles have a PMMA core and a shell of PEG and positively charged groups. The PEG chains are both biocompatible and biodegradable and provide stearic stability while the positively charged groups bind DNA. By using these complex structures, the risk of physical desorption is greatly decreased. Such a vaccine is also stable and non-toxic while it is possible to administer it orally [41].

CONCLUSION

The use of nanoparticles in the field of biomedical engineering represents one of the most prominent potential advances in the field in the last few years. Polymeric nanoparticles may signify the most effective nanocarriers for prolonged drug delivery polymeric nanoparticles may overcome stability issues for certain drugs and minimize drug induced side effects. The extent of drug encapsulation/incorporation as well as the release profile from polymeric nanocarriers depends on the polymer type and its physicochemical properties, the particle size, and its morphology. One of the most promising applications of nanoparticles is in gene therapy. The application of nanotechnology in drug delivery has opened various opportunities for the formulation scientists for the better delivery of therapeutic agents to CNS. In addition to enhanced brain transport these systems also provide additional advantages such as extended or controlled release of drugs, protection from degradation before reaching the targeted site leading to decreased dose, and lesser frequency with decreased or no side effects. Delivery of modified viral fragments inside the cells represents one of the most challenging tasks that bioscience undertook in the modern period. Nanoparticles are one of the novel drug delivery systems, which can be of potential use in controlling and targeting drug delivery as well as in cosmetics textiles and paints. Nanoparticle drug delivery system seems to be available and promising strategy for the biopharmaceutical industry.

ACKNOWLEDGEMENT

The authors wish to thank the Correspondent and staff members of Apeejay Stya University Sohna, Gurgaon. For providing support to conduct this work. Special thanks to I.S.F College of Pharmacy, Moga for providing necessary facilities to carry out the work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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