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Recent Advances and Application of Nanotechnology in Drug Delivery Systems: A Review

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Abstract

Advances in nanotechnology have significantly become an effective approach for achieving efficient drug targeting for various diseases by circumventing all the shortcomings of conventional drug delivery systems. Most of the available drugs now are lipophilic in nature and this stands as challenging aspect faced for scientists to formulate and deliver for better efficacy, so nanoparticles, nanosuspension, nanocapsules are used now days to deliver these drugs with greater bioavailability and also have been adopted to improve the solubility of poorly soluble drugs. The use of nanotechnology is a universal formulation approach to increase the therapeutic performance of drugs in any route of administration. Nanotechnology will affect our lives tremendously over the next decade in very different fields, including medicine and pharmacy. This review article describes the preparation methods, physicochemical properties, characterization, applications, clinical advantages, and recent development of nanoparticles and their potential in drug delivery systems.

Keywords: Nanoparticles; Bioavailability enhancement; Nanocrystals; Drug delivery system

Introduction

Poorly soluble drugs (including BCS class 2 drugs) have low bioavailability and /or erratic absorption; hence these are general problem in pharmaceutical drug formulation [1]. Low saturation solubility combined with decreased dissolution rate is the major obstacle preventing sufficiently high blood levels of poorly soluble drugs. The classical approach to deal with this issue is to generate various salts of a poorly water soluble drug so as to improve solubility while retaining biological activity. Alternatively prodrug or analogs with enhanced solubility were also used. Saturation solubility could be increased by using solubilization, non-specific or specific complexation (eg., addition of PEG or cyclodextrins) and solvent mixture (eg., ethanol-water, up to 20% ethanol are possible). The problem with these formulation approaches are poor bioavailability, lack of fed/fasted equivalence, lack of optimal dosing, presence of extra excipients that pose limitation with respect to dose escalation finally leading to poor patient compliance [2].

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In order to overcome these discrepancies, micronization technology was used for poorly soluble drugs by colloid and jet mills. It increases dissolution by increasing surface area as particle size is reduced significantly to sub-micronic size but does not change saturation solubility. Next step was to transform microsized to nanosized particle. Nanoparticles are defined as particulate dispersion or solid particles with size range of 10- 1000nm. The drug is dissolved, entrapped, encapsulated or attached to nanoparticle matrix [3].

Depending upon method of preparation, nanoparticles and nanocapsule can be obtained. Drug nanocrystals of nanometer size range are with crystalline character. Nanosuspensions consist of drug nanocrystal in aqueous vehicle in presence of suitable surfactant and/or polymer as stabilizer. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site specific action of the drug at the therapeutically optimal rate and dose regimen [4]. The advantages of using nanoparticles (Table 1) as a drug delivery system include the following:

1. Particle size and surface characteristics of nanoparticles can

Route of Administration	Disadvantages of conventional formulation	Benefits of Nanoparticles
Oral	Slow onset of action/poor absorption	Fast onset of action/ good absorption
Ocular	Lacrimal-wash off low bioavailability	Higher bioavailability/ dose consistency
Intravenous	Poor dissolution/non specific action	Rapid dissolution/tissue targeting
Intramuscular	Low patient compliance due to pain	Reduced tissue irritation
Inhalation	Low bioavailability due to low solubility	Rapid dissolution/high bioavailability/dose regulation

Table 1: Benefits of Nanoparticles.

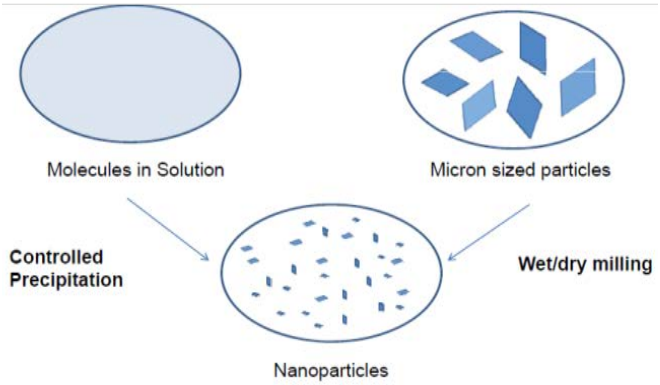

Figure 1: Techniques of nanoparticles preparation.

be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively 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 achieved by attaching targeting ligands to surface of particle or use of magnetic guidance.
5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.
6. Increasing dissolution rate through nanonization [5].

According to Noyes-Whitney/Nerst-Bruner equation described by Noyes and Whitney in 1897.

$$dx/dt = AD/h(Cs-Xd/V)$$

dx/dt=Dissolution rate,Xd=Amount dissolved,A=particle surface area,D=Diffusion coefficient, V=Volume of distribution,Cs=Saturation solubility,h=effective boundary layer.

Saturation solubility is defined as drug specific constant depending only on solvent and temperature. This definition is only valid for particle size in micrometer range. Further particle size reduction increases surface area and subsequently dissolution rate [6].

Based on this principle many pharmaceutical industries have used nanonization to improve oral availability.In addition to the dissolution rate enhancement described above, an increase in the saturation solubility of the nanosized API is also expected , as described by the Freundlich–Ostwald equation [7].

$$S = S_{\infty} \exp(2\gamma M/ r\rho RT)$$

where S=saturation solubility of the nanosized API, S∞ =saturation solubility of an infinitely large API crystal, .γ is the crystal-medium interfacial tension, M is the compound molecular weight, r is the particle radius, .ρ is the density, R is a gas constant and T is the temperature. Hence decrease in particle size increases saturation solubility (Figure 1).

Techniques for nanoparticle preparation

There are two main techniques which are used in nanoparticles preparation;

1. Bottom up(controlled precipitation)
2. Top down(milling/homogenization)

Various techniques included in Bottom up technology

(i) Solvent evaporation methods

(ii) Spontaneous emulsification or solvent diffusion method

(iii) Production of nanoparticles using supercritical fluid technology.

(iv) Polymerization methods

(v) Nanoparticles by coacervation or ionic gelation.

(vi) Cross linked nanoparticles

Bottom up Top down

Dispersion of preformed polymers

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D,L-glycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylate) (PCA), This technique can be used in various ways as described below [8, 9].

***A. Solvent evaporation method*:** In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water (o/w) emulsion. After the formation of stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration In order to produce small particle size, often a high-speed homogenization or ultra-sonication may be employed [10, 11].

***B .Spontaneous emulsification or solvent diffusion method*:** This is a modified version of solvent evaporation method. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase [12].

Production of nanoparticles using supercritical fluid technology

Conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods require the use of organic solvents which are hazardous to the environment as well as to physiological systems. Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles because supercritical fluids are environmentally safe. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure. Supercritical CO2 (SC CO2) is the most widely used supercritical fluid because of its mild critical conditions (Tc = 31.1 ˚C, Pc = 73.8 bars), nontoxicity,non-flammability, and low price. The most common processing techniques involving supercritical fluids are supercritical anti-solvent (SAS) and rapid expansion of critical solution(RESS). The process of SAS employs a liquid solvent, eg methanol, which is completely miscible with the supercritical fluid (SC CO2), to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting the formation of nanoparticles. Thote and Gupta (2005) reported the use of a modified SAS method for formation of hydrophilic drug dexamethasone phosphate drug nanoparticles for microencapsulation purpose. RESS differs from the SAS process in that its solute is dissolved in a supercritical fluid (such as supercritical methanol) and then the solution is rapidly expanded through a small nozzle into a region lower pressure, Thus the solvent power of supercritical fluids dramatically decreases and the solute eventually precipitates.

This technique is clean because the precipitate is basically solvent free. RESS and its modified between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase [13].

Polymerization method

The polymerization method includes the polymerization in continuous aqueous phase, polymerization in organic phase and the interfacial polymerization. The general mechanism involved is the drug is dissolved in the polymerization medium either before the addition of the monomer or at the end of the polymerization reaction .The nanoparticle suspension is then purified by ultra centrifugation or by resuspending the particles is an isotonic surfactant free medium. During polymerization various stabilizers and surfactant are used [14].

Preparation of nanoparticles by coacervation or ionic gelation method

Different methods are adopted to prepare nanoparticles from these hydrophilic polymers. *Cadvo* and *co-worker* have reported preparing hydrophilic chitosan nanoparticles by ionic gelation [19].In this method the positively charged amino group of chitosan interacts with the negatively charged tripolyphosphate to form coacervates, with size in the nanometer range. These nanoparticles have good association with proteins and their size (200-1000nm) and zeta potential (+20mv and +60) can be modulated. Nanoparticles from hydrophilic polymer can be prepared by the complex coacervation which is the spontaneous phase separation

process that occurs when oppositely charged macromolecules are mixed and it is a result of electrostatic interaction and coacervates from under mild conditions whereas ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction [15, 16].

Preparation of cross-linked nanoparticles

Polymer nanoparticles cross linked with cross-linking agents such as glutaraldehyde and sodium tripolyphosphate was prepared according to a water-in-oil (w/o) emulsion method using ultrasonication and a cross-linked technique by glutaraldehyde and sodium tripolyphosphate. Drug and Polymer was dissolved in suitable solvent, stirring vigorously and then sonicated at room temperature for 15 minutes. The solution so obtained was poured into a tree necked round bottom flask. Cross-linking agents solution saturated with organic solvents containing surfactant was added slowly to the emulsion by using a dropping funnel and then stirred for 8 hours. The suspension obtained was centrifuged at $1x10^4$ rpm for 15 minutes and washed with suitable solvents like methanol, acetone etc. The polymer nanoparticles in the above procedure were prepared using three different concentration of polymer.

Various techniques in top down technology

Production of nanocrystals by Media milling process

In order to produce nanocrystalline dispersions by the NanoCrystals® technology, a milling chamber is charged with milling media, dispersion medium (normally water), stabilizer, and the drug. The drug particles are reduced in size by shear forces and forces of impaction generated by a movement of the milling media. Small milling pearls or larger milling balls are used as milling media. With a reduction in the size of grinding media in a media mill, the number of contact points is increased exponentially, resulting in improved grinding and dispersing action (i.e. leading to smaller particles). The pearls or balls consist of ceramics (cerium- or yttrium-stabilized zirconium dioxide), stainless steel, glass, or highly cross-linked polystyrene resin-coated beads. A problem associated with the pearl milling technology is the erosion from the milling material during the milling process. Buchmann et al. reported the formation of glass microparticles when using glass as milling material [17]. In order to reduce the quantity of impurities caused by an erosion of the milling media, the milling beads were coated with highly cross-linked polystyrene resin [18]. A perpetual problem is the adherence of product to the large inner surface area of the milling system. The inner surface area is made up of the surface area of the chamber and of all milling beads together. Even in recirculation systems, this product adherence causes a product loss. Of course, this undesirable drug loss can be an issue in very expensive drugs, especially when very small quantities of new chemical entities (NCEs) are processed.

Various marketed formulations are developed using this technology. In 2000 Rapamune was launched by Wyeth as the first product containing sirolimus NanoCrystals[19]. The coated Rapamune tablets are more convenient and show a 27% increased bioavailability compared to the Rapamune® solution. This is an example to compare two formulation strategies. The oral solution shows the principles of co-solvents and surfactants, whereas the tablets shows the nice performance of a particle size reduction technique. Emend® is the second product incorporating the NanoCrystal technology. It was introduced to the market in 2003 by Merck. Emend® is a capsule containing pellets of nanocrystalline aprecipitant, sucrose, microcrystalline cellulose, hyprolose, and sodium dodecylsulfate [20]. The third product is TriCor, a nanocrystalline fenofibrate tablet marketed in 2004 by Abott. Megaace ES, an oral suspension containing megestrol acetate for the treatment of HIV-associated anorexia and cachexia, was launched as a fourth product late in the middle of the year 2005.

High pressure homogenization

The second most frequently used disintegration method is milling by high pressure homogenization.

The two existing homogenization principles (homogeniser types) applied are:

a. Microfluidization (Microfluidics Inc.)

b. Piston-gap homogenisers (e.g. APV Gaulin, Avestin, etc.)

Microfluidization is a jet stream principle; the suspension is accelerated and passes with a high velocity an especially designed homogenisation chamber. In the "Z" type chamber, the suspension changes a few times the direction of its flow leading to particle collision and shear forces. In the second type of chamber, the "Y"-type, the suspension stream is divided into two theoretical Background streams which then collide frontally [21, 22]. The microfluidization technique for drug nanocrystal production has been pursued by the Canadian company Research Triangle Pharmaceuticals (RTP) (meanwhile acquired by SkyePharma PLC) [23]. A disadvantage of the technology is the sometimes high number of passes through the microfluidiser, examples in the various patents describe up to 75 passes. This is not very production friendly. In addition, the product obtained by microfluidisation can contain a relatively large fraction of microparticles (especially in the case of hard drugs) thus losing the special benefits of a real homogeneous drug nanocrystal suspension.

In the knowledge of the potential problems associated with pearl/ball milling and the use of the microfluidization principle, as an alternative a drug nanocrystal technology based on piston-gap homogenisers was developed in the middle of the nineties. A first technology was based on homogenisation of particles in pure water (Müller 1999, the trademark of the product is Disso Cubes® (trade name nowadays owned by SkyePharma) [24]. At the turn of the millennium, the second generation technology was

developed. In comparison to the older method homogenisation of drug particles takes place in non-aqueous media or in dispersion media with reduced water content (i.e. mixtures of water with water-miscible liquids such as water-PEG or water-glycerol (e.g. isotonic suspensions for IV injections). The registered trade name by the company PharmaSol GmbH/Berlin is Nanopure (pure nanocrystals) [25]. Precipitation is the traditional approach to produce nanosized drug material, but having the problem of potential growth of drug nanocrystals to drug microcrystals. The company Baxter introduced a combination technology called NANOEDGE [26].

Characterization of Nanoparticles

Following are some of the properties which are used to characterize the formulations of drug with nanoparticles.

Particle size

The Particle size and size distribution are the most important characteristics of nanoparticles which has greater importance in determining the performance of nanoparticulate system in vitro as well as the therapeutic effect of the incorporated drug. They determine the in vivo distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Their size was very much affected by their preparation conditions, large particle have a smaller surface area compared to small particles with the same total volume, therefore most of the associated drug cannot be at or near the particles surface and cannot be released. The diffusion distances encountered in large particle are greater which allows drug trapped in the core to slowly diffuse out and also for the release medium to slowly diffuse. Smaller particles also have greater risk of aggregation of particles during storage and transportation of nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability.

Followings are the techniques used for determining the particle size of nanoparticles:

- Electron microscopy
- Electric sensing zone
- Laser diffraction
- Photon correlation spectroscopy (PCS)
- Optical sensing zone

Surface Properties of Nanoparticles

Surface properties including surface charge and surface hydrophillicity / hydrophobicity are important factor for determining particles dispersion in-vitro and their biological fate. When nanoparticles are administered intravenously they are recognized readily by the body immune system and then cleared from the circulation. Apart from the size of nanoparticles their surface hydrophobicity determines the amount of absorbed blood components mainly proteins (opsonins) .The opsonised particles are taken up by the phagocytes as the part of the body's defense system to remove foreign substance. To avoid this in vivo fate, the surface of nanoparticles is an often modified with a hydrophilic polymer, which act as a shield between nanoparticles and opsonins. So it is better to design nanoparticles by surface modifications. When a neutral polymer is applied on the surface charge of nanoparticles is usually neutral or slightly negative, whereas when a cationic polymer is applied, zeta potential of nanoparticles is positive.

The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles . It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. The zeta potential can also be used to determine whether a charged active material is encapsulated within the centre of the nanocapsule or adsorbed onto the surface.

Drug loading

A successful nanoparticle system should have a high drug loading capacity there by reducing the quantity of matrix materials required for administration. Incorporation of drug into the nanoparticles can be achieved two methods; one by incorporating the drug at the time of nanoparticle production or secondly by adsorbing the drug after the formation of nanoparticles including the carrier with the drug solution. Larger amount of drug can be entrapped by incorporation method when compared with the adsorption. In the case of the entrapment method for nanoparticles prepared by polymerization technique, it was found that increase in concentration of the monomer increase the association of drug where as the reverse is observed with the drug concentration in the dispersed solutions. Hence these results indicate that it is important to optimize the amount of monomer available for drug entrapment. Preparation of chitosan nanoparticles under mild conditions by coacervation technique appears to be a very effective way for the delivery of sensitive macromolecules such as Bovine serum albumin, tetanus toxoid, and insulins. The ability of chitosan nanoparticles to encapsulate these molecules was so high that to obtain a desired final protein loading, there was a need to adjust the amount of protein added to the formulation.

Release profiles of drug from nanoparticle dispersion the nature of delivery system used and the interactions between the drug and matrix materials. The release is mainly dependent on either diffusion or erosion of the matrix or both. The rapid initial release (i.e. burst release) of drug is mainly attributed to the fraction of drug, which is absorbed or weakly bound to the large surface area of the nanoparticles rather than due to the release of drug incorporated in nanoparticles.

Drug Release

Drug release from nanoparticles may be any one of the following methods;

a) Desorption of the surface – bound drug.

b) Diffusion through the nanoparticles matrix.

c) Diffusion through the polymer wall of nanocapsules.

d) Nanoparticles matrix erosion.

A combined erosion diffusion process, the following are the methods for the determination of invitro release of drug from nanoparticles.

a) Side by side diffusion cells with artificial (or) biological membranes.

b) Dialysis bag diffusions.

c) Reverse dialysis.

d) Ultra centrifugation.

e) Ultra filtration.

f) Centrifugal ultra filtration

Usually the release study is carried out by controlled agitation followed by centrifugation. Due to the time-consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred.

Crystal morphology

X-ray diffraction analysis in combination with differential scanning calorimetry, scanning electron microscopy is used to determine the polymorphic changes due to impact of high pressure homogenization in the crystalline structure of the drug. Nanosuspension can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high pressure homogenization. An increased amount of amorphous drug fraction could induce higher saturation solubility.

Saturation solubility and dissolution velocity

Nanosuspension increases the dissolution velocity and saturation solubility. Size reduction leads to increase in the dissolution pressure. An increase in solubility that occurs with relatively low particle size reduction may be mainly due to a change in surface tension leading to increased saturation solubility.

Applications of nanoparticles in drug delivery

Parenteral administration

Nanosuspensions have been found to increase the efficacy of parenterally administered drugs. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above [27].

Oral administration

Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can be explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood and the increased dissolution velocity of the drug. Aqueous nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as tablet or hard gelatin capsule with pellets. The aqueous nanosuspension can be used directly in the granulation process or as a wetting agent for preparing the extrusion mass pellets. A similar process has been reported for incorporating solid lipid nanoparticles into pellets[27].

Ophthalmic drug delivery

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids[27].

Bioavailability enhancement

Nanoparticles and nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane.

Target drug delivery

Nanoparticles can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems [24, 27]. Some of the target drug delivery of nanoparticles and nanosuspensions are summarized in Table 2.

Formulation type	Drug	Polymer used	Research Out come
Polymeric Nanoparticles	Dalargin	Poly(butylcyanoacrylate) and polysorbate-80	Intravenous delivery showed higher concentration in capillary endothelium and cerebral neurons [28].
	Nimodipine	Methoxy poly(ethylene glycol)-poly(lactic acid)	Intranasal administration showed greater concentrations in blood, CSF and brain tissues [29].
	Loperamide	Poly(d,l-lactide-co-glycolide) (PLGA)	Higher BBB concentration with sustained release profile [30].
	Estradiol	Chitosan	Prominent blood and CSF concentration after intranasal administration [31].
	Paclitaxel Biotinylated Poly lactic acid-poly ethylene	glycol	Increased anti-tumoral activity [32].
	Tacrine	Poly(n-butyl cyano acrylate) (surface functionalized by 1% polysorbate-80)	higher brain concentration after intravenous administration in rats [33].
	Loperamide	Poly(d,l-lactide-co-glycolide), peptide Gly-l-Phe-d-Thr-Gly-l-Phe-l-Leu-l-Ser(O-betad glucose)-CONH(2)	Effective carrier of Loperamide for brain targeting when administered intravenously [34].
	Amphotericin B	Poly(lactic acid)-b-poly(ethylene glycol) and polysorbate 80	Enhanced concentration in mice brain [35].
Nanoemulsion & Nanogel	Risperidone	Capmul MCM as the oil phase along with mucoadhesive polymers	Intranasal with high cerebral and CSF concentration [36].
	Olanzapine	Capmul MCM and chitosan	High cerebral as well as CSF concentration [37].
	Paclitaxel	Pine-nut oil containing high concentrations of essential polyunsaturated fatty acid (PUFA)	Showed higher cytotoxic effect in human glioblastoma brain tumor cells [38].
Nanosuspension and Solid lipid Nanoparticles	Saquinavir	Edible oils rich in essential polyunsaturated fatty acids (PUFA) and surfactant Lipoid-80 and deoxycholic acid.	Enhanced oral bioavailability and brain concentration achieved effective antiretroviral therapy [39].
	Sumatriptan	Polyunsaturated fatty acids (PUFA) and surfactant Lipoid-80 and deoxycholic acid and chitosan	High brain as well as CSF concentration [40].
	Indinavir	Nanosuspension were prepared by high pressure homogenization	Increased central nervous system concentration of drug due to enhanced Biodistribution [41].
	Atovaquone	ApolipoproteinE apoE) stabilized by polysorbate80, poloxamer 184, or poloxamer 338	Improved uptake into brain and reduced T. gonadi infection [42].
	Camptothecin	Stearic acid, Soybean lecithin and Poloxamer 188	Showed effective drug targeting with promising sustained release profile along with dose reduction and decreased systemic toxicity [43].
	Etoposide	Tripalmitin as solid fat	Better drug concentration in dalton's lymphoma when injected by subcutaneous, intravenous or intraperitoneal routes [44].
	Temozolomide	Stearic acid, Lecithin, Poloxamer188, Tween 80	Achieved higher cerebral concentration with least cardiac and nephro cytotoxicity [45].

Table 2: Various Nanoformulations with its research outcome.

Conclusion

Development in nanotechnology has tremendously change the approach of drug delivery system with effective means of drug targeting by circumventing all the shortcomings of conventional delivery system. Recent advancement shows that it really proves to be a boon in the field of medicine, pharmacy and modern science.

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