May - June 2018; 7(3): 2969-2981

International Journal of Research and Development in Pharmacy & Life Science
An International open access peer reviewed journal
ISSN (P): 2393-932X, ISSN (E): 2278-0238
Journal homepage: http://ijrdpl.com

Review Article

A Review about various Nanomaterials in Drug Delivery Systems and their Applications

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Keywords: Nanomaterials, nano-suspension, Solid lipid nanoparticles, Liposomes, Hydrogels, Dendrimers, Trans-corneal iontophoresis, Microneedles

Article Information:

Received: March 02, 2018;
Revised: April 21, 2018;
Accepted: May 01, 2018
Available online on:
15.06.2018@http://ijrdpl.com

http://dx.doi.org/10.21276/IJRDPL.2278-0238.2018.7(3).2969-2981

ABSTRACT: Most of drug entities face the problems like reduced absorption, faster metabolism and elimination, toxicity because of drug distribution to other tissues, low drug solubility, unpredictable bioavailability, etc. These issues need to be work out so as to make the novel drug delivery systems for successful therapy. Use of nanotechnology is one of the promising strategies to overcome all of these problems. Distinctive properties of nanomaterials like smaller particles size, high surface area, and ease of suspending in liquids, deeper access across the cells and organelles, flexible optical and magnetic properties are offered by nanoparticles as compared to other micro or macro sized particles. Nanomaterials can be classified into different categories based on their drug delivery system, dimensions, structure and consistency. Various types of nano-formulations (such as nanoparticles, nano-suspension, liposomes, hydrogels, solid lipid nanoparticles, dendrimers, microneedles, ocular insert/disk, trans-corneal iontophoresis) have been used by the researchers for modulating the physicochemical properties and biological activities of the drugs. This review highlights the various types of nanomaterials with their advantages and applications in the pharmaceuticals for enhanced physicochemical properties and better biological activities with reduced toxicity and higher biocompatibility.

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INTRODUCTION

Nanotechnology or nanoarchitecture are vastly appreciated as consuming an unlimited prospective to bring reimbursements to a lot of areas of biomedical research and applications. This is fascinating cumulative investments from administrations and private segment companies in all over the domain. Simultaneously, the use of nanoarchitecture is raising different issues in the secure use, monitoring, as well as ethical areas that will necessitate broad arguments taking place at all stages. Nanoparticulate materials vary considerably from other materials because of two foremost prime factors: the enhanced surface area and quantum effects. These aspects can improve properties like reactivity, strength, electrical features, and *in-vivo* activities. Due to reduction in particulate size, particles are found at the external part in major percentage compared to inner part. For instance, a particulate dimension of 30 nm has approximately 5% of its particles superficially, at 10 nm 20%, and at 3 nm 50% of the particles are on exterior part. A nanosized particulate material has a much greater surface area per unit mass paralleled with bigger particulates, leading to comprehensive reactivity. In tandem with surface area effects, quantum effects may arise to govern the characteristics of material as particle size is compacted to the nanoscale. These can affect the optical, electrical, and magnetic properties of the matter. There *in-vivo* activities can be from enhanced absorption to higher toxicity of nanomaterials [1]. The bulk of marketable nanoparticulate applications in medicine are geared in the direction of drug delivery. In biosciences, nanoparticles are substituting organic dyes in applications that necessitate higher photostability as well as higher multiplexing proficiencies.

There are some new advances in directing and governing the functions of nanoprobes, such as, driving magnetic nanoparticles to the tumour and making them to destroy the surrounding tissue either by releasing the drug load or just heating them. The principal additional development of nanomaterials is to make them multifunctional and manageable by exterior signals or by native surroundings, therefore in actual using them as nano-devices [2].

Different nanosized provisions used for drug transporting schemes with their advantages and applications have been discussed here in this review article.

Types of Nanomaterials

Nanomaterials can be classified by different names based on their structure, dimension, polymeric nature, application in various fields as discussed in the Figure 1.

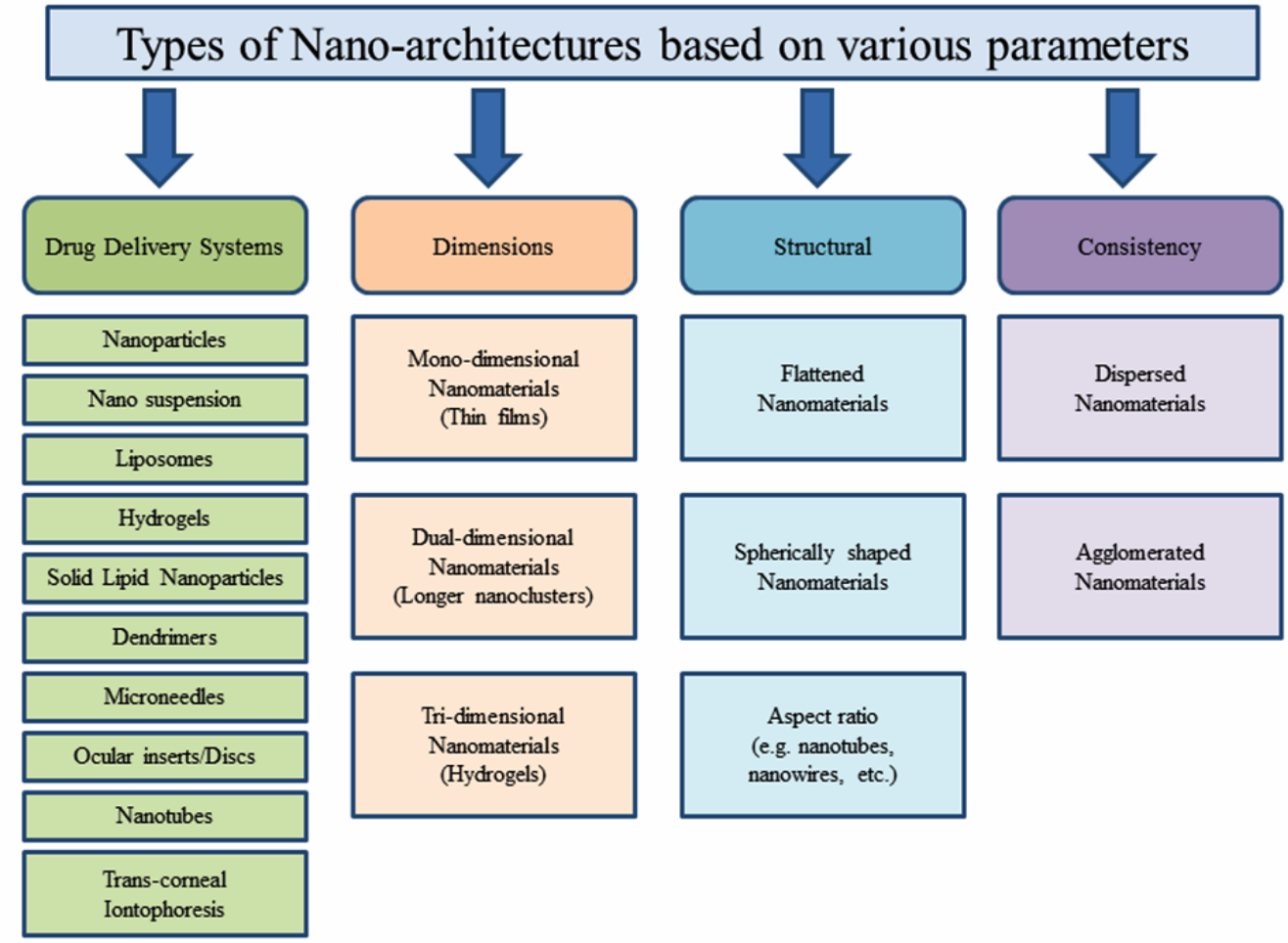

Figure 1: Different types of nanomaterials based on various parameters

Nanoparticles/ Microparticles

Nanospheres and nanocapsules are the two foremost varieties in nanoparticle being used for the delivery of active pharmaceutical ingredients, while the word "Nanoparticles" is a combined face, generally used for different types of polymeric nanoparticulates. Due to vesicular structure, nanocapsules are used as a drug reservoir, which hold the drug within a hydrophilic or hydrophobic liquid core located in the vesicle void and a hard-polymeric shell sealed off it, while, nanospheres are solid or mass of polymer matrix. In case of nanospheres, the drug could be present within the centre of nanosphere or adsorbed superficially over it. So nanosphere may be described as a complete spherical mass of polymer containing drug [3-4]. Polymers having properties like biodegradability and biocompatibility are used for formulating nanoparticulates having nanometeric size range containing drug in the form of encapsulation, entrapment or dissolved within polymeric matrix.

Polymers used for preparing nanoparticles should be harmonious with the body system in the terms of compliance like non-toxicity and non-antigenicity and should be biodegradable and biocompatible [5]. Dubey *et. al.*, reviewed the progress in environmental-friendly polymer nanocomposite material from Poly lactic acid (PLA). They concluded that disposal of large amounts of waste from daily use polymers is among one of the foremost concerns in the current era.

Effective utilization of bio-renewable materials procured from natural sources has been proposed as a potential solution to this problem. Among such different polymers, Poly lactic acid (PLA) which is a bio-degradable polymer resembled quite promotable features, which can be polymerized from sustainable sources as chips sugarcane, starch and corn [6]. Ring-opening polymerization of Lactide monomer considering catalysts such as Al, Sn or Zn is one of the efficient methods for the PLA synthesis [7].

Nanoparticles are useful tool in drug conveyance systems such as: improved bioavailability for low soluble drugs, an extensive potential solicitation range (oral, parenteral, dermal), high pressure homogenization so as an conventional manufacturing process (it permits extensive fabrication), better bioavailability, protection of light and moisture sensitive drugs from the environment, and a controlled release characteristics, perfect candidates for delivery of vaccines, cancer therapy, contraceptives and targeted delivery of antibiotics and can be used in tissue engineering [1, 5].

Liuya *et. al.*, prepared silver nanoparticles through different methods like chemical method, physical method and biological method and studied their applications in various cancer treatment (eg, leukemia, breast cancer, lung cancer, skin cancer hepatocellular carcinoma etc.), as anti-angiogenesis agent, as photosensitizer and radio-sensitizer agent [7]. Sharma *et. al.*, prepared amikacin sulphate nanoparticles for ophthalmic drug delivery through w/o/w emulsion solvent evaporation. Positively charged dual polymers, i.e. Eudragit RL 100 and Eudragit RS 100, were introduced in the blend, with various proportions of polymers and drug and *in-vivo* studies revealed that ophthalmic bioavailability of the nano-formulation was more in comparison to marketed ophthalmic preparation, and nano-formulations were lacking any aggregative effect on the cornea for as long as 12 hours subsequent administration [8].

Brahamdutt *et. al.*, prepared and evaluated tropicamide loaded chitosan nanoparticles through ionic gelation technique for ophthalmic drug delivery. The goal of study was to boost the corneal residence period of tropicamide and *in-vitro* drug release profile revealed sustained release properties of nanoparticulate formulation [9].

Kumar *et. al.*, formulated and evaluated nanoparticles containing artemisinin HCl through solvent evaporation technique for oral drug delivery and concluded that nanoparticles showed a good drug release kinetic as well as optimal particles size range and high entrapment efficiency [10]. Kaur *et. al.*, prepared and evaluated tropicamide-loaded carboxymethyl tamarind kernel polysaccharide nanoparticles through ionotropic gelation method for ocular delivery. The nanoparticulate preparation enjoyed tremendous ophthalmic tolerability, mucoadhesion and corneal permeation as compare to conventional ophthalmic preparations [11].

Nanosuspension

The requirements of nanosuspension as drug carrier form was acknowledged to deliver therapeutic amounts of hydrophobic dosage forms [12]. This method hunts for drugs that show strong binding to hydrophobic receptor sites and consequently yields drug leads that likely to be poorly water soluble [13]. Nanosuspensions applauded themselves as appropriate candidates as: (i) No solvent requirements, (ii) smaller particle size range tolerable for intravenous drug delivery (iii) high loading could be achieved through solid crystal phase, which is acceptable for the animal studies to be accompanied at several multiples of the proposed dose in man. There are two possibilities that we consider for protection of injected nanoparticles: (i) possible vascular obstruction as a function of particle size, number, and its composition (ii) monocyte phagocytic system reaction [1].

Kipp et, al; (2003) prepared taxol nanosuspensions by emulsion templating. A volatile solvent was used for drug dissolution through homogenization process in aqueous solution having appropriate stabilizers, and vaporizing solvent to recover nanosuspensions. To end, with quick homogenizing and precipitation, a stable nanosuspension was obtained [14]. Pharmacokinetic studies of organ drug distribution are dependent on particulate size range and infusion rate. Non-metabolizable particles (<7 µm) are imprisoned in the pulmonary vasculature for longer time period. Alveolar macrophages in the lungs allowed the passing of particle size's (>12 µm) via capillary walls leading to elimination into sputum out of lungs [15]. The broad collateral flow of the pulmonary vasculature might enhance the potential capillaries obstruction through particulates, with expected reduction in flow of blood, if the particulates load is retained sufficiently small. Though, when un-filtered blood having particulates size between 20-500 µm was transfused, blockage of capillaries in the lungs of receiver was indicated. Dacron® wool depth filters of 40- 80 µm size were used to abolish these consequences. It deals with higher loads of particulates in nanosuspension formulation as well as admissibility of particulates of size more than 40 µm from products like them [16].

Boedeker *et al.*, (1994) explored the anaesthetic effect of a lecithin-coated tetracaine-HI nanosuspension. Sonication method was employed to prepare the nanoparticulates, where 80% of particulates were found to be within size range of 100 to 500 nm while none of particulate was >5 µm. Coulter counter method was utilised to determine the particles size. In rat tail, samples (approx. 0.3 cm^3) were injected subcutaneously; to distinguish the local anaesthesia and haemostat was used. Animals served as their own controls by testing both proximally and distally to the injection spot. A 10% lecithin-coated tetracaine nanocrystals injected rats reveal 43.4 ± 1.2 hours (n = 9) tail block distal to the injection spot, whereas 1% tetracaine solution injected rats had 8.5 ± 1.8 hours (n = 5) mean tail block period. So, in tail clamping distal to the injection spot, both animal group showed a progressive response, which neglected the nerve injury as mechanism of local anaesthesia. 10% tetracaine injection receiver rats either died or faced wet gangrene of the tail. No anaesthetic effect was revealed in negative controls of lecithin sheaths without drug and 5% dextrose. Nanosuspensions receiving groups did not indicated any gross native tissue destruction or systemic toxicity [17].

Karan *et al.*, (1996) studied treatment of malignant hyperthermia using Phospholipid-coated nanosuspensions of dantrolene and sodium dantrolene. Particulate size range between 300 -800 nm for nanosuspension of sodium dantrolene and 500 -800 nm for nanosuspension of dantrolene were determined. A faster dissolution consideration of both nanosuspensions was revealed. Pharmacokinetics equivalency was revealed by sodium dantrolene nanosuspension in comparison to solution formulation of the drug.

The dose response curves were measured with strain gauge transducer of forelimb adduction. These were also similar, and concised as therapeutic amount essential for yielding 50% and 95% of the plateau response, plus the magnitude of the plateau response. Almost parallel values were exhibited in normal swine.

Even though the nanosuspension of dantrolene gave a little higher ED_{50} twitch depression than dantrium in malignant hyperthermia-susceptible swine (1.0 ± 0.2 vs. 0.6 ± 0.1 mg/kg), the more significant ED_{95} was statistically equivalent (3.5 ± 0.4 vs. 2.7 ± 0.5). Due to drug dosing near plateau effect, ED_{95} became more significant. In swine models, malignant hyperthermia was treated magnificently with nanosuspensions [18].

Ward and Yalkowski (1993) revealed that due to matched speed of injection with blood flow rate lead to arisen of plug flow. A quick IV bolus (max. 10 mg/kg) of unfiltered dantrolene nanosuspension could be injected in dogs without any fluctuation in pressure of pulmonary artery but compared to dog; swine might be a sensitive model [19].

Donnely *et al*., (2001) studied pharmacokinetics of itraconazole nanosuspension over a 14-day intravenous course of treatment in recipients of allergenic hematopoietic stem cell transplant. Five or six days before transplant, I.V injection of nanosuspension (200 mg) was injected in every 12 hours followed by 200 mg every 24 hours for the next 12 days. Due to inability to reach the study state, five out of six cases were retained the therapeutic level about 500 µg/L for 9 days subsequently end of treatment. Finally it was realised that nanocrystal suspension provided a higher volume of distribution, longer half-life and greater area underneath curve of plasma concentration for 24 hours in comparison to solution formulation Sporanox® [20].

Liposomes

Lipid nanoparticulates have been recommended for the efficient delivery of drugs as a substitute to former controlled drug delivery systems, like polymeric nanoparticulates. Liposomes are extensively preferred to enhance the transportation of numerous anticancer, antibiotics, and antifungal drug entities. On the other hand, the aqueous dispersion of liposome stability is a key concern for numerous types of therapeutical applications. Adding of steroid entities in liposomal arrangements like cholesterol or cholesteryl sulfate is acknowledged to boost the aqueous stability of liposomes. It was revealed that phosphatidylcholine vesicles were extra rigid and sustained severe shear stress with addition of cholesterol. Additionally, the resource of cholesteryl sulphate in the world market place is very limited and costly. There is a necessity to produce newer lipid molecules to prepare stable nanoparticulates and efficient drug delivery system [21]. Yuan *et al*., (2013) prepared iron liposomes, viz. heme liposomes and ferric citrate liposomes, through rotary-evaporated film ultra-sonicating technique.

Characterization properties like entrapment efficiency, structure, particles size distributions and zeta potentials were evaluated. Both kinds of ironic liposomes exhibited stable physical properties. Nourishment with iron-fortified foodstuffs is an efficient technique for treating iron insufficiency ailments. On the other hand, conventional iron agents used to treat anemia of inflammation have slight effect. Outcomes showed that the absorption of iron liposomes was enhanced over that of un-encapsulated ironic agents. Hence, iron liposomes might be preferred to fortify food in handling diseases of iron deficiency [22].

Moghis *et al*., (2010) prepared Z-guggulsulfate [4,17(20)-pregnadiene-3-one-16β-sulfate] sodium and Z-guggullaurate [4,17(20)-pregnadiene-3-one-16β-laurate] and assessed for liposome-based drug conveyancing system. The production of precursor, Z-guggulsterol [4,17(20)-pregnadiene-3-one-16β-ol] was performed with higher yield than other stated production process through combination of some known reactions in few stages. Liposomes were prepared by using the novel synthetic derivatives of guggul lipid. These newer lipid particles might play a convenient role in the improvement of liposomal drug delivery system [21]. Jiang *et al*.. (2010) studied Arg-Gly-Asp (RGD) peptide-modified liposomes for their ability to enhance the delivery of nucleic acids to integrin receptor-expressing cells. RGD modified cationic liposomes loaded with p-glycoprotein-specific siRNAs showed higher delivery to integrin receptor expressing human breast cancer MCF7/A cells, resulting in significant silencing of p-glycoprotein.

Consistent with this, molecular imaging revealed a higher distribution of RGD modified cationic liposomes and siRNA lipoplexes in MCF7/A tumor tissues compared to adjacent normal tissues in a mouse model [23]. Kibria *et al*., (2011) modified liposomal surfaces with both cyclic RGD and octa-arginine to utilize the integrin receptor-binding effects of cyclic RGD and the cell penetrating effects of octa-arginine. The dual ligand modified cationic liposomes showed increased cellular uptake into integrin αvβ3-expressing cells and more effective transfection of luciferase-encoding plasmid DNA [24]. Li *et al*., (2011) studied alkaline amino acid-based cationic liposomes for their potential to enhance the stability of cationic liposomes in serum. Lysinylated cholesterol, histidinylated cholesterol, and argininylated cholesterol were tested, and lysinylated cholesterol and argininylated cholesterol lipid based-cationic liposomes showed more efficient transfection plasmid DNA in serum-containing media [25]. Markov *et al*., (2012) prepared Spermine-tagged cationic lipids and DOPE (1:1 ratio) complexed to EGFP-encoding plasmid DNA or RNA for electro-pulsing into immature dendritic cells or dendritic cell progenitors. Intravenous administration of the nucleic acid pulsed dendritic cells to tumor-bearing mice was found to induce the production of antitumor cytokines, suggesting that cationic liposomes could be used to generate nucleic acid pulsed-dendritic antitumor vaccines [26].

Hydrogels

Hydrogels are 3-dimensional, lyophobic, polymeric systems accomplished of imbibing enormous volumes of water or organic fluids. The complexes consist of homo-polymers or copolymers, which are insoluble due to the occurrence of chemical crosslinks and physical crosslinks, like crystallites or entanglements. Hydrogels bear a resemblance to usual living tissue more than some other class of synthetic biomaterials. This is because their higher water contents and soft constancy which is like to natural tissue. Moreover, the higher aqueous content of the constituents subsidises to their biocompatibility. Consequently, hydrogels can be used as contact lenses, films for biosensors, liners for artificial hearts, constituents for artificial skin, and drug delivery devices. Delivery of drugs to the oral cavity can have useful applications in native oral diseases treatment, like stomatitis, periodontal disease, fungal or viral infections, and cancers of oral cavity.

To improve this native drug delivery, some of key factors play a crucial role such as extended attachment of hydrogels carrying active entity alongside numerous salivary gland secretions flow with baths the oral cavity mucosa [27].

Petelin *et al.*, (1998) checked various hydrogel having ointment base to carry liposomes for delivery of drug into oral cavity tissues with the help of Electron Paramagnetic Resonance (EPR). Orabase® (a sodium carboxymethyl cellulose, pectin and gelatin mixture in a polyethylene- paraffin base), neutralized poly-(MAA-co-methyl methacrylate) and Carbopol 934® were used as a vehicle. Ointment bases were first diluted with phosphate-buffer of pH 7.4 in ratio of 1:4 and liposomes were mixed with each ointment base to formulate a mucoadhesive ointment containing liposomes. Electron Paramagnetic Resonance indicated that poly-(MAA-co-MMA) was the best suitable ointment in relations to stability of liposomes within the ointment, transference of liposomal entangled particles from ointment into oral cavity tissues and washing out time from gingiva [28].

Kitano *et al.*, (1998) suggested 17 β-estradiol (E2) deliveries through a hydrogelic ointment comprising absorption enhancers for the buccal cavity to treat osteoporosis. Because of higher first pass metabolism, the bioavailability of E2 is quite low in oral route of administration. To formulate hydrogelic ointment, E2 and an absorption enhancer i.e. glyceryl monolaurate were dissolved in ethanol and a commercially available carboxyvinyl polymer and triethanolamine aqueous solution were mixed together. This preparation containing E2 was administered via buccal cavity into hamsters for *in-vivo* studies. This formulation-maintained plasma level of E2 up to 300 ng/ml/cm^3 for 7 hours without any crucial alteration in the morphology of buccal membrane after application up to 7 hours [29]. Patel and Amiji (1996) recommended *Helicobacter pylori* infection treatment in peptic ulcer through stomach-specific antibiotic drug delivery. A pH-sensitive swelling hydrogel was prepared for confined delivery of antibiotics in low pH atmosphere of stomach. Freeze dried chitosan- poly (ethylene oxide) was used for preparation of hydrogels. Antibiotics, metronidazole and amoxicillin were assessed for pH dependent swelling properties and drug release pattern in enzyme free simulated gastric fluid of pH 1.2 and intestinal fluid of pH 7.2. After 1 hour, the ratio of swelling was found to be 16.1 in SGF while 8.60 in SIF respectively. Furthermore, the freeze-dried chitosan- Polyethylene glycol established faster release of the trapped antibiotics in SGF due to its extremely permeable matrix arrangements resulting from freeze drying. After 2 hours in simulated gastric fluid, around 65 % of amoxicillin and 59 % of metronidazole were released respectively from hydrogel formulation. The quicker drug release and swelling characteristics revealed by these preparations may be beneficial for site-specific antibiotics transfer in the gastric area, due to the confines of gastric draining period [30].

Lowman *et al.*, (1999) proposed pH-responsive complexation hydrogels oral insulin delivery. To protect the insulin from highly acidic environment of stomach, hydrogels were used as safeguard earlier to its release in the small intestine. Crosslinked copolymers of PMAA with graft chains of polyethylene glycol (P(MAA-g- EG)) were used for preparation of insulin containing hydrogel formulation.

In-vivo studies, using both diabetic and healthy rats revealed that strong dose-dependent hypoglycaemic effects were established in insulin containing P(MAA-g-EG) microparticles via oral route of administration. Fall in blood glucose level was reported in these organisms considerably for minimum 8 hours because of insulin absorption in the gastro-intestinal tract. It was important to note that these effects were detected devoid of the tallying of additives, like protease inhibitors or absorption enhancers [31]. Miyazaki *et al.*, (1998) investigated rectal drug delivery of xyloglucan gels with a thermal gelling property as vehicles. The transition temperature of Xyloglucan was found to be approx. 22-278 C, due to this it behaves like a liquefied material at room temperature while it showed gelling properties at body temperature. When *in vivo* studies were performed on rabbits through rectal administration of xyloglucan gels comprising indomethacin and compared with market formulation of indomethacin suppositories, a well-controlled drug plasma concentration-time profile deprived of decreased bioavailability was reported [32]. Cohen et al. (1997) established an *in-situ* gelling system of alginate having higher amount of guluronic acid for the ocular delivery of pilocarpine. This arrangement considerably prolonged the extent of the influence of pressure reduction properties of pilocarpine up to 10 hours, associated to 3 hours, when solution formulation of pilocarpine nitrate was administered [33].

Solid- Lipid Nanoparticles (SLN's)

Solid Lipid Nanoparticles (SLN) or Nanostructured Lipid Carriers (NLCs) are the newer colloidal drug carrier systems with numerous cosmetic and dermatological properties, like adhesiveness after applied to the skin [1]. These assets convey many other benefits like occlusion and skin hydration, enhanced absorption effects, improvement in active permeation, and controlled release assets [34-35]. SLNs and NLCs structures vary as SLNs were prepared via substituting the liquid lipid of oil-in-water emulsions through a solid lipid, which can convey many benefits in contrast to a liquid core [36]. The idea of NLCs was established via nano-structuring the lipid matrix, to give extra flexibility for variation of drug release, improvement in the drug loading and avoiding its escape. This tactic was accomplished by mixing solid lipids with liquid lipids, rather than greatly refined lipids with comparatively related molecules. The outcome is a reduced amount of ordered lipid matrix with much defectiveness, which can accommodate a high amount of drug [35, 37-38].

The mixture obtained with solid and liquefied lipids required to be rigid at least at 40°C to ensure that it didn't melt down at room temperature when used as drug delivery system. Benefits of using lipids as transporter systems for dermatological purposes were connected to their physiological and sound endured nature, which lessens the possibility of toxicological harms and indigenous irritancy [35-36]. A variety of very different lipids with normally renowned as harmless status has been used to yield SLNs and NLCs, ranging from extremely refined lipids, like tristearin in SLNs, to blends of mono, di, and triacylglycerols in NLCs, together with polyacid acylglycerols and monoacids [1, 39]. Jingyi et al., (2017) formulated solid lipid nanoparticles (SLNs) through a newer synthetic surfactant and organic solvent free manner using sodium caseinate, stearic acid, pectin and water.

Fourier transforms infrared spectroscopy and fluorescence was used for evaluation of any physiochemical incompatibility among all the ingredients to be used for the preparation of SLNs. In simulated gastrointestinal environments, the comparison between prepared SLNs and conventional SLNs formulated with organic solvents was performed in terms of stability. The outcomes of study exhibited a better physiochemical stability in terms of small particle size and improved stability in case of SLNs formulated from solvent free method in comparison to conventional formulations of SLNs [40].

Arif *et al.*, (2017) prepared curcumin-loaded solid lipid nanoparticles by micro emulsion and ultra-sonication techniques to conclude the action of Curcumin-loaded SLNs on liver-spleen scintigraphy. In the subsequent steps of study, a radioisotope Technetium-99 m (^{99m}Tc) was labelled on SLNs loaded with Curcumin. The *in-vivo* studies were executed with scintigraphic methods using New Zealand rabbit to perform a comparison with Phytate colloid. The data obtained from the study revealed that Technetium-99 m (^{99m}Tc) labelled SLNs containing curcumin were promising imaging agent. ^{99m}Tc-labeled Curcumin-loaded could be used as a novel radiopharmaceutical substitute to ^{99m}Tc-labeled composites for spleen and liver imaging [41]. Pooja *et al.*, (2016) prepared wheat germ agglutinin (WGA)-coated SLNs to improve oral paclitaxel delivery. WGA bound to N-acetyl-D-glucosamine and sialic acid presenting on the cell surface throughout the intestine, leading to prolonged residence time [42]. Baek *et al.*, (2012) had developed the surface-modified paclitaxel loaded SLNs with hydroxypropyl-β-cyclodextrin (HPCD). This dextrin is known to solubilize the drugs and prevent oxidation of lipids. The HPCD-coated SLNs showed a paclitaxel encapsulation percentage of 71% with a mean size of 251 nm. The Caco-2 cell uptake of paclitaxel from SLNs was 5.3-fold greater than the Taxol formulation. The C_{max} and lymph node concentrations of SLNs (1.44 mg/mL and 11.12 ng/mg, respectively) were higher than those of the control solution (0.73 mg/mL and 0.89 ng/mg, respectively) after oral paclitaxel application at 25 mg/kg [43].

Tsai *et al.*, (2011) developed SLNs for improving brain drug distribution and oral bioavailability of Apomorphine. A 13-fold higher bioavailability was shown by SLNs than reference solution at an orally dose of 26 mg/kg. In the striatum, distribution of Apomorphine, also improved while using SLNs. In rat model of Parkinson's disease induced by 6-hydroxydopamine, the contralateral rotation number increased from 20 to 115 after oral SLN administration [44].

Xue *et al.*, (2013) encapsulated berberine by SLNs with a particulate size and entrapment efficiency of 77 nm and 58%, respectively. A single oral dose (50 mg/kg) in rats achieved a significant improvement of AUC by SLNs (179 mg h/L) compared to solution (86 mg h/L) [45]. Fan *et al.*, (2013) prepared salmon calcitonin-loaded SLNs by linking with peptide ligand (CSKSSDYQC), which shows attraction with goblet cells on the epithelium, (IRQRRRR), which is a cell probing peptide. The protective efficacy of SLNs on calcitonin against pancreatin was examined. Most of the free calcitonin was degraded within 15 minutes. A very slow degradation rate was found for SLNs. The permeability across the Caco-2 cell monolayer for nonconjugated, CSKSSDYQC and IRQRRRR SLNs was 2.1-, 5.9-, and 4.7-fold higher than that of the free control. The bioavailability of CSKSSDYQC (12.4%) and IRQRRRR SLNs (10.1%) was greater than that of unmodified SLNs (5.1%), suggesting the effectiveness of peptide conjugation for the enhancement of oral protein delivery [46].

Dendrimers

These are macromolecular system made up of a succession of subdivisions around an interior core. These are smart systems for drug delivery since their nano size range, ease of manufacturing and functionalization, and capability to exhibit numerous copies of surface assemblies for biological recognition progressions [47]. These sphere-shaped polymers possess monodisperse, symmetrical structure, which gives several unique properties [48]. Three main components may be distinguished in their architecture: a central core, branches that are composed of repeated monomeric units radially attached to the core, and functional end groups on the surface. All three elements perform critical functions, affecting the size, shape and properties of the dendrimer. The size of the macromolecule is determined by its generation, which refers to the number of recurring layers of branched monomers attached to the core [49-50]. Michał *et al.*, (2017) studied dendrimers as nanocarriers for nucleoside analogues. Dendrimers can be used as drug carriers in two ways: by the covalent bonding of therapeutic compounds, or by forming stable complexes, based on electrostatic forces, between ionized moieties of drugs and dendrimers. The latter method includes both surface interactions and encapsulation within dendritic scaffold. Use of dendrimers as drug delivery devices show that these macromolecules, usually after surface modification, can serve as effective nano-carriers of nucleoside analogues both in complexed and conjugated form [51].

Wenjie *et al.*, (2016) studied about synthesis and applications of dendrimers based magnetic iron oxide nanoparticles. The dendrimer-based magnetic iron oxide nano-particulates have been functionalized in numerous biomedical areas, including MRI, drugs and genes delivery, biosensors, protein immobilization, and bio-separation [52]. Devaraj and Rajkumar (2017) synthesized Triazole-based novel dendrimers with bile acid surface groups through click chemistry by divergent approach and characterized by spectral data. The cytotoxicity of bile acid dendrimers was evaluated based on their effect on cell growth with C6 glioma cell lines by MTT assay method.

The cytotoxicity of bile acid dendrimers was studied and showed that proliferation of cancer cells was inhibited significantly with increase in the concentration and generation of dendrimers. All the dendrimers exhibited excellent anticancer activity. Higher-generation dendrimers exhibited better anticancer activity than the lower-generation dendrimers [53]. Lokesh *et al.*, (2017) studied the approaches of encapsulation and conjugation using dendrimers of G4 PAMAM containing berberine. The formulations prepared through encapsulation and conjugation of berberine and evaluated for particulates size and zeta potentials. The average particles size of both approaches was found to be 100-200 nm and zeta potential nearby to the PAMAM G4 dendrimer. The percentage entrapment efficiency and conjugation of both approaches were found to be 29.9% and 37.49% respectively, showing that conjugation has high drug payload. Water and phosphate-buffer pH 7.4 were used as media for *in-vitro* drug release studies.

Within 24 hours, the percentage drug release in water was 72% and 98%, while it was 80% and 98% in case of phosphate-buffer pH 7.4 respectively and concluded that conjugation could be a superior choice for drug delivery using dendrimers [54]. Joel *et al.*, (2015) investigated effects of iontophoresis on PAMAM permeation and its delivery into the cornea and influence of these dendrimers in Dexamethasone transcorneal iontophoresis and investigated the potential of polyamidoamine (PAMAM) dendrimers in combination with iontophoresis for delivery of Dexamethasone in the cornea. PAMAM dendrimers were well-defined and enormously repeatedly diverged synthetic globular constructions. These constructions could be readily amended through enhancing the dendrimer generation, or by varying their surface groups. The potential of dendrimer's interaction with bio membranes or their consumption through cells could be enhanced by these amendments. The study revealed that PAMAM complex's iontophoresis signified the favourable approach for sustained and targeted topically or ophthalmic drug delivery [55].

Ashok *et al.*, (2017) reviewed the usefulness of dendrimers for cancer diagnosis and anticancer drug delivery system and concluded that dendrimers could be used for fluorescence-based imaging, ligand-based therapy, contrast agent in X-rays and CT scan imaging, photo thermal therapy, boron capture therapy, photodynamic therapy and as imaging agent in diagnosis purposes [56].

Microneedles

Micro sized needles are designed to invade dermal layers intended for drug delivery [57]. These devices are longer enough to pierce stratum corneum however too tiny to provoke pain receptors that are situated in the dermis [58]. Microneedles have numerous benefits including painless, low possibility of infection, negligible invasiveness, easy disposal, also the facility to enhance transcutaneous flux of drugs [59]. Microneedles considerably lessen these issues as these do not provoke pain receptors. Although the use of microneedles is considered advantageous, nevertheless several concerns have also been raised regarding their use. There are valid concerns that creating microscopic pores in the skin can lead to bacterial and fungal infections. Also, ingress of allergens can result in hypersensitivity reactions. In addition, there are potentials for misuse and abuse of microneedles. More importantly, the use of microneedles does not always result in the achievement of therapeutic drug concentration [58-60].

Lee and Jung (2012) proposed drawing lithography as an exclusive improved process for the construction of a microneedle directly from two-dimensional planar substrates, so overcoming a subtractive progression limitation. Drawing lithography used the gelatinous assets of a polymer in the glass transition phase for fabrication. Elastic distortion of polymer stuff in the glass transition state and the three-dimensional microneedle assemblies were then fabricated via stretching distortion [61]. Blinded pain revisions in human volunteers indicated that pressing a set of 400 microneedles, 150 μm in length, dermally was considerably less painful than introducing a 26-gauge hypodermal needle [62]. Another comprehensive study revealed that microneedle size significantly affected pain scores, quantity of microneedles similarly exaggerated pain scores, thickness and tip angle of microneedle had weak possessions on pain score over the series of conditions studied [63]. Ma *et al.*, (2011) firstly studied the insertion behaviour of the spine of caterpillar, *Parasa consocia*. Taking advantage of the SEM and microcomputed tomography system, it was found that this kind of spine is a hollow tapered needle with a side-open tip and measured the insertion force of caterpillar spine into fresh mouse skin. It was found that the average insertion force was only about 173 μN, which was higher than that of mosquito's fascicle into human skin [64].

Gupta *et al.*, (2009) carried out a clinical study in patients having Type-1 diabetes and assessed bolus transport of lispro insulin via hollow microneedle as compared to catheter infusion set. The use of microneedles managed the speedy insulin absorption and lessening in glucose level. Bolus insulin transfer followed by intake of a standardized feed in the subsequent stage of the study showed that microneedles were helpful in dropping postprandial glucose level [65]. Chong *et al.*, (2013) prepared siRNA loaded onto individual steel microneedles. The siRNA aiming the corresponding (luciferase/GFP) gene was coated against microneedles and conveyed to mouse footpad. Quantification of corresponding mRNA and intravital imaging of corresponding expression in the external dermal linings established efficient *in-vivo* gene silencing after delivery of siRNA via microneedles [66].

Zhu *et al.*, (2017) studied rapidly separating microneedles through structural optimization for effective pharmaceutical drug delivery. The study investigated numerous important structural aspects backing the performances of drug delivery by rapidly separating microneedles. *In-vivo* and *in-vitro* studies exhibited drug delivery above 95% within 30 seconds by using optimized rapidly separating microneedles having 500 mm-long solid PLA microneedles, 250 mm-long overlap and 500 mm-long dissolving microneedles. *In-vivo* studies revealed that, optimized rapidly separating microneedles loaded with insulin considerably lowered the blood glucose level by attaining the equal therapeutic effect as injection in diabetic mice treatment, so superior than conventional microneedles [67].

Jeon *et al.*, (2013) matched the efficiency of MFR with intra-dermally injection of *Botulinum toxin* A for the management of crow's feet. Treatment with Microneedles headed to slow and continued development in the skin's wrinkles that was higher to Botox injection [68]. Gold *et al.*, (2016) reported the special effects of microneedles fractional radio-frequency management on dermal rejuvenation and testified in terms of wrinkle lessening, skin constriction, and lifting of the middle and lower face in most of patients, without any adversative effects detected during study [69].

Machekposhti *et al.*, (2017) prepared microneedle with biocompatible polymer for dermal or topical conveyance of Tranexamic acid. The Tranexamic acid biocompatible polymer microneedle was fabricated from PVP and methacrylic acid, using the lithography method. The required mechanical strength to pierce skin was attained by optimizing the ratio of PVP to methacrylic acid. Acute dermal toxicity was done, and drug diffusion in skin layers was simulated by calculating the diffusion coefficient of tranexamic acid in interstitial fluid (plasma).

The biocompatible polymer microneedle was fabricated at 60 °C. Needles could sustain 0.6 N that was enough to pierce stratum corneum. 34% of the released drug was locally effective and the rest permeated through the skin. This polymer microneedle had no dermal toxicity [70]. Anastasia *et al*., (2017) prepared 16 separate microneedle groups (microneedle height 600 mm), with aqueous mixtures of 15% w/w Gantrez1 S97 and 7.5% w/w PEG 10,000 Da. Penetration levels in an authenticated dermal model were nearly 500 mm. 10 human volunteers efficaciously inserted the microneedles patches in their skin, following proper instruction, as per defined by transepidermal water loss measurements. The average insertion level ranged stuck between 300 mm and 450 mm over the zone of the larger patches. So it was not considerably dissimilar to a sole unit microneedle patch self-applied by same volunteers was promising. Microneedle sizes considerably longer than 1 to 2 cm^2 would be needed if this technique was to be effectively turned to hospitals for delivery of drugs and recommended that usage of larger patches by patients could be fruitful, possibly introductory to the opportunity for a major enlargement of the extent of the market for transdermal drug delivery [71].

Ocular inserts/ disks

Eye drops are the most functional pharmaceutical dosage forms in the management of ophthalmic diseases preferably affecting the anterior segment of the eye. However, ocular bioavailability of the drugs instilled topically is extremely poor, being lower than 5% of the total dose [72]. To overcome the drawbacks of the conventional eye drops, ocular drug delivery systems, such as ocular inserts, could be applied as a therapeutic alternative to treat the ocular diseases. Ocular inserts are solid or semi-solid devices, usually elaborated using natural or synthetic polymers, to be inserted in the conjunctival sac to deliver the drug in the anterior segment of the eye [73]. The polymeric matrix controls the transfer of therapeutic concentrations of the drug straight in the target tissues and provides its prolonged release, increasing its ocular residence time and bioavailability. As a consequence, the ocular inserts are capable of improving the glaucomatous patient compliance due to the efficacy of the therapy and the reduced frequency of administration [74]. Inserts have been categorized, on the root of their physical and chemical properties, as solubility. Ocular inserts typically deliver drugs through a diversity of techniques at a predetermined rate, controlled, but required elimination from the eye while 'empty'. Soluble inserts, as well commonly defined by various authors as erodible, are monolytic polymeric systems that go through slow dissolution while releasing the drugs, and no removal requirements [75].

DeSouza *et al*., (2016) prepared and characterized chitosan and brimonidine tartrate based Ocular inserts. *In-vitro* biocompatibility study was investigated against ARPE-19 and MIO-M1 cells. Then *in-vivo* biocompatibility study was too performed using the chorioallantoic membrane. Ocular Inserts delivered the controlled release of drug deprived of a burst effect for 30 days. Inserts did not prompt an injurious consequence to ocular cells, demonstrating their biocompatibility characteristics. These were well tolerated *in vivo*, signifying the lack of noxiousness. They could be prospective delivery methods to lessen the intraocular pressure and to encourage neuroprotective possessions in glaucomatous patients [72].

Everaert *et al*., (2017) prepared and optimized HPMC based ocular inserts with sustained release properties as carriers for thermolabile medicaments. Sodium fluorescein and lysozyme were selected as model drugs to attain the slower drug release kinetic. Primarily burst release was produced in the process of rehydration due to low penetration into the insert because of HMW albumin. SV40-human corneal epithelial cells with PrestoBlue® were selected for evaluation of biocompatibility of a viscous HPMC solution, negligible cytotoxic reactions were detected [76]. Lee *et al*., (1999) formulated and evaluated ocular inserts comprising tropicamide and phenylephrine. Gelfoam® based ocular insert having phenylephrine (1.7 mg) and tropicamide (0.6 mg) was prepared and assessed for pupil's dilatory action in rabbits. *In-vivo* outcomes confirmed that the mydriatic actions created by the projected device were superior and extended than that produced by eye drops having an equivalent quantity of phenylephrine and tropicamide. The consequences conveyed in this study, suggest that Gelfoam® could be used as a drug transporter in case of ophthalmic route of drug delivery system [77].

Colo *et al*., (2001) tested linear poly-(ethylene oxide) (400 kDa) through gel-forming erodible inserts for ophthalmic controlled conveyance of ofloxacin *in-vitro* and *in-vivo*. Ocular inserts having diameter 6 mm, 20 mg in weight containing 0.3 mg of Ofloxacin, were manufactured through powder compression. *In-vitro* drug release pattern was primarily controlled by means of insert erosion. The time of erosion scale was varied via compounding poly-(ethylene oxide) with Eudragit L100, 17% neutralized or 71% neutralized. The rate of insert erosion was governed by strength of inter-polymer interaction and hydrophilic-hydrophobic equilibrium of compounds. Bioavailability enhancement had been attributed to poly-(ethylene oxide) mucoadhesion or improved tear liquid viscosity [78]. Earlier studies of the current authors on gel-forming erodible inserts, grounded on poly(ethylene oxide) (400 kDa), for ophthalmic controlled delivery of ofloxacin has been extended to inspect the effects of poly(ethylene oxide) molecular weight, ranging between 200–2000 kDa, on insert characteristics significant to therapeutic effectiveness. *In-vitro* drug release from inserts prepared by poly-(ethylene oxide) molecular weight 200,400 and 900 was largely controlled through erosion of insert, while with poly-(ethylene oxide) 2000 was mostly diffusion-controlled in a primary stage, trailed by an erosion-controlled stage. Poly-(ethylene oxide) 2000 was inappropriate as an insert, because the formulated gel spilled from the eye, due to extreme swelling. The poly-(ethylene oxide) 400 and poly-(ethylene oxide) 900 inserts had presented a prospective for topical management of endophthalmitis [79].

Shivakumar *et al*., (2007) formulated brimonidine tartrate containing reservoir-type ophthalmic inserts through solvent casting method for administrating once a day. The core loaded with drug was prepared through forming a hydro-alcoholic solution of hydroxyl propylmethyl cellulose (5% w/v) and glycerine (40% w/w). A 3^2 factorial design was used to formulate the controlled rate membranes of cellulose acetate butyrate consuming polyethylene glycol-600 as plasticizer. The adjacent settlement of the investigational and the estimated values verified the validity and the robustness of the mathematical models produced.

A decent relationship between the *in-vitro* and *in-vivo* drug release information was detected when the optimized preparation was assessed in a rabbit model [80].

Trans- Corneal Iontophoresis

Trans-corneal iontophoresis comprises use of a direct electrical current delivering ionized antibiotic deep down into the ocular tissues. Idyllically, the aqueous solution of drug is introduced into a cylinder-shaped eye cup constrained by the corneal limber region. A charged platinum electrode similar as medicine is positioned in connection with a drug solution in the eye cup. Another electrode oppositely charged is linked to the rabbit's ear. The electrical current is continued at 0.8 mA for not more than 10 min. Surface resistance of corneal epithelium overcomes by direct current, driving the drug through the semipermeable corneal epithelium and into the corneal stroma and aqueous humor [81]. The strategy of an iontophoretic scheme comprises manageable direct electric stream that finishes an electrical circuit in the body. The nature and charges of electrodes used for electric transmission is significant. Usage of platinum electrodes basically abolishes ionic discharge, electrode deprivation, and noxiousness. Electrode charges, whether cationic or anionic, were determined by the charge of molecules in the drug itself. Hence, the drug carrying medium should have negligible unnecessary ions. In investigational animal models, iontophoresis of diluents alone (antibiotic-negative vehicle controls) were neither bactericidal nor toxic [82-83]. The drug salts has been ideal for iontophoretic delivery since of the greater charge density and solubility. Before and after iontophoresis, additional considerations, like pH, conductivity, and ionic strength of the medication solution, should be calculated [81].

Fishman *et al*., (1984) used iontophoretic method for delivering gentamicin in various parts of eye in aphakic rabbit. After 30 min of iontophoresis, highest drug concentrations viz. in the cornea (71 pg./ml) and in the aqueous humor (78 ~g/ml) were attained. Highest concentrations of gentamicin viz. 10.4 ± 0.4 µg/ml in vitreous humor were found at around 16 hours, having amount of drug overhead the minimal inhibitory concentration sustained 24 hours subsequent iontophoresis [84]. Grossman *et al*., (1990) revealed that on using iontophoretic tactic on 2 % of agar containing 10 % Gentamicin gave rise to greater and additional controlled concentration of drug in aqueous humor and cornea as compared to amount of drug achieved via injection in subconjunctival [85].

Rootman *et al*., (1988) proposed delivery of Tobramycin using transcorneal iontophoresis in rabbit to treat investigational bacterial keratitis. They used 1000 colony forming units (CFU) of *P. aeruginosa* intrastromal injection for inducing infection, which leads to bacterial growth of around 10^7 CFU/ Cornea within 22 hours after infection. When treated with Tobramycin using transcorneal iontophoresis at 22 and 27 hours after infection, 6 log in CFU/ Cornea were reduced in compared to untreated controls and on around 67% of the corneas bacteriologically sterile 32 hours post-infection. No conventional formulation of tobramycin was able to provide sterile or bacteria free corneas except Tobramycin using transcorneal iontophoresis I rabbit model [86].

Hobden *et al*., (1990) suggested the fluoroquinolone's hydrated shields for curing investigational aminoglycoside resistant *P. keratitis*. In comparison to untreated eyes, decline of around 4 log CFU per cornea was achieved by using ciprofloxacin (25 mg/ml) containing hydrated shields. When treating with norfloxacin shields hydrated, just 2 log CFU per cornea declination was detected [87].

Binstock *et al*., (2005) evaluated a hydrogel loaded with dexamethasone gathered over a portable iontophoresis instrument. Dexamethasone permeability into the eye after a short transcorneal and transscleral iontophoresis was assessed. Healthy rabbits were used to study iontophoresis of dexamethasone phosphate by using drug laden disposable HEMA hydrogel sponges and portable iontophoresis device. The intensity of electric current 1 mA for 1 min and 4 min was used for corneal iontophoretic. 30 times more dexamethasone level was obtained in rabbit cornea in single iontophoresis process used for 1 min as compared to quick administrations of eye drops [88].

Barza *et al*., (1987) examined the effectiveness of trans-scleral iontophoresis of gentamicin in rabbits for the treatment of *P. endophthalmitis*. They revealed considerably lesser amount of bacterial colonies in the vitreous after two periods of iontophoresis followed by an intravitreal injection of gentamicin than the injection alone [89]. Berdugo *et al*., (2003) tested oligonucleotide permeation into the cornea by using current density of 1.1 mA/cm^2 for 5 min in rat eyes. After 5 minutes of treatment, fluorescence was sensed superficially in the corneal epithelial lining. Fluorescence of oligonucleotide was sensed over entire corneal layer, after 90 minutes to 24 hours post-iontophoresis [90].

Kamath and Gangarosa (1995) examined the movement of drugs appropriate for iontophoresis, in various pH ranges. By calculating the spot migration, mobility values of drugs were determined by with a paper electrophoresis. The deviation in pH modifies the extreme ionization of drug depend on the pKa and optimal mobility fluctuates of the drug [91]. Different type of drug containing nano-formulations with various polymers have been summarised in table 1 with their application in different drug delivery systems.

CONCLUSION

Nanotechnology uses constituents on an extremely minor scale. Hence, they earn on new properties compared to their bigger forms. This tactic has the prospective to convert face of current drug delivery system scenario. Delivery of therapeutically active compounds to the targeted location is a chief difficulty in treatment of numerous ailments. Limitations of conventional drug delivery systems are inadequate efficacy, reduced bio-distribution, and lack of choosiness. Hot extensions in nanotechnology have presented that nanoparticulates (constructions lesser than 100 nm in at least one dimension) have a countless prospective as drug carriers. Nanocarriers with improved physicochemical and biological possessions are taken up by cells more effortlessly than bigger molecules, so these can be effectively used as transporter tools for presently offered bioactive compounds.

Biodegradable polymers are extensively being used as possible carrier stuff for targeted drug delivery as of its low toxicity and biocompatibility in nature. Naturally occurring polysaccharides have been studied for drug delivery uses as well as in biomedical arenas. Solid lipids nanoparticles, Liposomes, dendrimers, carbon or silicon materials, and magnetic nanoparticles are some examples of nanostructures that have been verified as drug delivery structures. Because of their smaller sizes, these nanocarriers demonstrate exclusive physicochemical and biological characterizations (e.g., an improved responsive area as well as capability to cross cell and tissue obstructions) that make them an encouraging material for delivering therapeutic materials. Cell-specific targeting can be attained by attaching drugs to independently designed carriers.

Table 1: Various types of nanomaterials used in drug delivery systems

Drug	Polymer	Nanomaterial	Applications	Ref.
Amikacin sulphate	Eudragit RS 100 Eudragit RL 100	Nanoparticles	Ocular drug delivery	[8]
Tropicamide	Carboxymethyl tamarind kernel polysaccharide	Nanoparticles	Ocular drug delivery	[11]
siRNA	Arg-Gly-Asp peptides	Liposomes	Human breast cancer treatment	[23]
Tetracaine	Lecithin	Nanosuspension	Anaesthetic action	[17]
Dantrolene and sodium dantrolene	Phospholipids	Nanosuspension	Malignant hyperthermia	[18]
17 β- estradiol	Carboxyvinyl polymer and triethanolamine	Hydrogel	Osteoporosis	[29]
Amoxicillin and Metronidazole	Chitosan and poly(ethylene-oxide)	Hydrogel	*Helicobacter pylori* infection treatment	[30]
Insulin	Polyethylene glycol	Hydrogel	Oral insulin delivery	[31]
Paclitaxel	Wheat germ agglutinin	Solid lipid nanoparticles	Anticancer activity	[42]
Dexamethasone	Polyamidoamine	Dendrimers	Topical and ocular drug delivery	[55]
Insulin	PLA	Rapidly separating microneedles	Insulin drug delivery	[67]
Tranexamic acid	PVP	Microneedles	Topical and ocular drug delivery	[70]
Brominidine	Chitosan	Ocular inserts	Ocular drug delivery	[72]
Phenylephrine and tropicamide	Golfoam ®	Ocular inserts	Local & systemic drug delivery via ocular route	[77]

Conflicting Interest: Nil

ACKNOWLEDGMENT

We are thankful to Department of Pharmaceutical Sciences and Library, Maharshi Dayanand University, Rohtak for providing support and facilities.

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How to cite this article:
Brahamdutt, Arun, Sangwan P, Singh P, Yadav V and Kumar S. A Review about various Nanomaterials in Drug Delivery Systems and their Applications. *Int. J. Res. Dev. Pharm. L. Sci.* 2018; 7(3): 2969-2981. doi: 10.13040/IJRDPL.2278-0238.7(3).2969-2981