International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.7, No.4, pp 616-628, 2014-2015

Nanotechnology for Controlled Drug Delivery System

Sarmistha Saha[1,2], Ravada Ramesh[1]

[1]Dr. H. L. Thimmegowda College of Pharmacy, Kengal, Channapatna, Ramanagaram, 562161, Karnataka, India
[2]Research Scholar, Pacific University, Airport Road, Pratap Nagar Extension, Debari, Udaipur, 313024, Rajasthan, India.

Abstract: Application of biopharmceutics concepts in formulation development has revolutionized strategy for dosage form design. Nanotechnology has become an essential element of pharmaceutical sciences and finds multiple applications in drug delivery systems in enhancing therapeutic performance of drugs. Many of the current "nano" drug delivery systems are pedigree of conventional dosage forms like nano suspensions, nano emulsions, and nano micelles.
Nanosuspension is an approach used to deliver water insoluble and hence poorly bioavailable drugs where the drug is reduced to submicron range thereby increasing its dissolution rate and hence its bioavailability. Nanoemulsions are O/W (expand) or W/O (expand) emulsions, having droplet size from 20-200nm that are transparent and do not have the tendency to coalesce. They show great esthetic appeal and skin feel and find their application in transdermal delivery of drugs, topical application for systemic drug delivery, oral delivery of proteins and delivering drugs through parenteral and intranasal routes. Nanomicelles are self-assembling nanosized (usually with particle size within a range of 10 to 100 nm) colloidal dispersions with a hydrophobic core and hydrophilic shell. These are currently used as pharmaceutical carriers for solubilizing hydrophobic drugs and provide drug delivery platform to be exploited for multiple routes of administration. All of these nano formulations couple the advantage of maximizing therapeutic benefits with minimized side effects and improved safety, since they have enormous potential of being targeted at cellular level.
This review describes various aspects of nano drug delivery systems in terms of their formulation, characterization, potential benefits and risks, and pharmaceutical applications in drug delivery.

Introduction

Nanotechnology is science and technology conducted at the nanoscale, that is, at the scale of about 1 to 100 nanometers and it can be used across all the other science fields including life sciences and healthcare[1]. The ideas and concepts behind nanoscience and nanotechnology were given by Physicist Richard Feynman also known as Father of Nanotechnology. He described the idea of creating things out of tiny pieces, instead of making things smaller in his lecture - "There's Plenty of Room at the Bottom" at an annual American Physical Society meeting in Pasadena, California on Dec. 29, 1959[2].

Nanomedicine is one of the most intensive areas of research in nanotechnology and is applied widely for the prevention, diagnosis and treatment of diseases. It is utilized in pharmaceutical sciences with the objectives of reducing toxicity and minimizing side effects of drugs by targeting them to the specific site of action and by reducing their This review describes various aspects of nano drug delivery systems in terms of their formulation, characterization, potential benefits and risks, and pharmaceutical applications in drug delivery

dose through improved bioavailability; reducing dosing frequency by controlling drug release into the human body; and improving shelf life by enhancing their stability. This ultimately contributes to increased safety, efficacy, patient compliance, and extended shelf life of drugs and finally reduced healthcare costs [3-5].

There are many thrust areas where drug delivery systems can be developed using nanotechnology such as depot preparations, TDDS particularly for cancer, enhanced bioavailability through improved dissolution and absorption and more. This article focuses on application of nanotechnology to conventional biphasic liquid dosage forms such as suspensions, emulsions and micelles in improving their performance in drug delivery.

Nanosuspensions

A pharmaceutical nanosuspension is a biphasic liquid system in which insoluble solid drug particles of submicron range are uniformly dispersed in an aqueous vehicle. The dosage forms are colloidal in nature and are usually stabilized using surfactants and polymers and are meant to be administered through various routes such as oral, parenteral, topical, nasal, ocular and more[6].

Nanosuspension is a technological tool applied mainly to unravel the problem of poor solubility and bioavailability of drugs and occasionally to improve drug safety and efficacy by altering their pharmacokinetics. It is used as an alternative approach to lipid systems, when the drug is insoluble in both, water and organic media. Bioavailability is enhanced as the particle size reduction of poorly water-soluble drug to nano range leads to enormous increase in surface area and hence increased rate of dissolution or an increase in saturation solubility due to an increased dissolution pressure. For example, the solubility and dissolution rate and thereby bioavailability of crystalline Simvastatin was increased significantly by preparation of nanosuspension by nanoprecipitation technique at laboratory scale [7]. Similarly, oral bioavailability of olmesartan medoxomil was enhanced by improving its solubility and dissolution rate by preparing nanosuspensions[8]. Nanosuspension may also be used to improve the pharmacokinetic and pharmacodynamic profile and thus therapeutic efficacy of drug upon oral administration. This has been illustrated in case of Atovaquone nanosuspension for improved oral delivery in the treatment of malaria [9] and in case of 1,3-dicyclohexylurea, by subcutaneous route in the treatment of hypertension[10].

Technologies for preparing nanosuspension

Two approaches are generally applied in preparing nanosuspension:

Bottom-up approach- It is based on the principle of first dissolving the drug molecules in a solvent and then building them up to nanosized particles.

Top- down approach-This is based on the principle of breaking down large drug particles to smaller particles that are in nano range.

Bottom –up approach-

Nano precipitation: This technique is an advancement of coprecipitaion method of making suspensions. It involves dissolving the drug in a solvent and then precipitating the dissolved drug molecules from the solvent which further grow up to nanoparticles. Hence this process takes place in two steps viz. nucleation and crystal growth. Care must be taken to control crystal growth at nano level[11]. Precipitation is achieved in four different ways

Precipitation by liquid solvent-antisolvent addition: This method employs adding an antisolvent to the drug solution which is miscible with the solvent in which drug is dissolved. The antisolvent is added in thin stream under continuous stirring or sonication. This creates a large amount of nuclei of supersaturated drug which finally grow to nanosize. It is of utmost importance to control the size of particles and prevent molecular association and crystal growth further. This can be achieved by using stabilizers. Factors that govern the desired particle size include concentration of drug solution used, the type of nonsolvent, agitation or sonication speed and choice of suitable stabilizers [12,13]

Precipitation in presence of supercritical fluid: The most common supercritical fluid is CO_2 and the technique involved is known as Supercritical Antisolvent (SAS) Precipitation. This involves bringing the drug solution in contact with a supercritical fluid which in turn leads to saturation of the liquid solvent and hence precipitation of solute due to anti solvent effect[14].

Precipitation by removal of solvent: Here the drug is first dissolved in an organic solvent. This solvent is then removed by evaporation, either by reducing the pressure or by continuous stirring [15].

Precipitation in presence of high energy processes: This method is applicable for large scale production and employs techniques such as spray drying or freeze drying to produce nanocrystals[16].

Top- down approach

High-pressure homogenization: This methodology employs Microfluidizer to produce nanosuspension which works on anyone of the following principles[17]:

Jet stream: Here two turbulent jet streams of liquid suspension are passed through a homogenization chamber, where these streams impinge on each other and on chamber wall. The particle size reduction results due to high shear forces, particle collision and cavitation forces. The nanosuspensions produced by this method are generally polydisperse in nature and the particle size distribution depends on experimental aspects such as number of cycles, pressure and velocity of the liquid streams[18].

Piston-gap: In this method a liquid dispersion of the active principle containing stabilizer/surfactant is compressed to a pressure ranging from 100 to 2000 bar; and expanded through a homogenization valve consisting of a valve piston, of an impact ring and of a valve seat. The energy generated by the inter-particle impacts,by collision between the particles and the valve piston and with the impact ring,by cavitation and by turbulence leads to particle size reduction in nano range. This technology was developed by R. H. Müller and is described in U.S. Pat. No. 5,858,410, EP 1964605 and is termed as "Dissocubes®"[19,20].

Water reduced or nonaqueous media: This technology is termed as NANOPURE and is used for making nanosuspensions in non aqueous media such as oil or PEG or water reduces media such as glycerol-water or ethanol-water mixtures at low temperatures. Here communition results due to shear forces, particle collision and turbulence but no cavitation. This method is particularly useful for temperature sensitive drugs and for producing nanosuspension in non aqueous media[21].

Media milling technique: This is one of the most traditional approaches for particle size reduction. A patented technology for making nanosuspensions by applying acoustic energy until said active pharmaceutical compound has been milled to the desired average diameter in the nanoparticle range. It involves the use of media which is actually beads or pearls of various sizes, densities, and material. Most commonly used beads are of zirconium, stainless steel, glass or highly cross-linked polystyrene resin. The pearls are moved by a stirrer, the drug is ground to nanocrystals in between the pearls. The technique utilizes shearing and impact forces (in conjunction with the mill) to reduce the size of the particle. This is the basic technology developed by G. Liversidge and co-workers and nowadays used by the company Nanosystems (presently owned by élan). But this technique has a disadvantage of erosion of mill and there are chances of product contamination[22,23].

Combination techniques: It is a technology by Baxter and is known as NANOEDGE technology. The "NANOEDGE" is a registered trademark by Baxter International Inc., serial number 76322804 , which was filed on 9th October 2001, and the technology is designed to enable water insoluble drugs to become medications. It combines the microprecipitation and high pressure homogenization technique and successfully overcomes drawbacks of both. Initial step is microprecipitation by solvent-anti-solvent technique, which involves addition of anti-solvent to a drug solution containing stabilizers to get precipitates in micro range which are then put to communition by subjecting the slurry to high pressure homogenization. This produces particle in nano range with improved thermodynamics as this step exercises a check on crystal growth of nanoparticles[24].

Applications of nanosuspensions in drug delivery systems

Oral drug delivery

As mentioned in the preceding sections nanosuspensions are prepared mainly with a view to enhance bioavailability of poorly soluble drugs by enhancing their solubility. Currently this approach has been utilized by many researchers for improving bioavailability of drugs via oral route. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are a specific class of anti-AIDS drugs and their use was limited owing to low bioavailability resulting from poor dissolution [25]. "Nevirapine, a BCS class II NNRTI with undesirable

solubility and dissolution kinetics from the dosage form was formulated as nanosuspension by nanoedge method which increased its solubility several times as also its chemical stability" [26].

Similarly, nanocrystalline suspension of poorly soluble drug itraconazole prepared by pearl milling method was found to be promising for oral drug delivery for treatment of fungal infection [27]. Likewise, drugs such as Efavirenz[28] and Furosemide[29] were formulated as nanosuspension for improved oral bioavailability.

Parenteral drug delivery

The key reason to formulate parenteral nanosuspension is either targeting the drug to specific site or prolonging its action. Etoposide-loaded bovine serum albumin (BSA) nanosuspension was formulated for parenteral delivery with an objective of targeting delivery to lung; reduce toxicity, and Etoposide's side effects[30].

GlaxoSmithKline has designed long acting nanosuspension formulation of antiretroviral drug for HIV patients named as GSK1265477 which is under investigation [31]. This investigational HIV integrase inhibitor is designed as a long-acting formulation so that the frequency of drug administration can be reduced which would finally result in improved patient compliance for HIV patients. This approach of a long-acting drug would be specially beneficial in maintenance therapy, or as a means of 'pre-exposure prophylaxis (PrEP)' in HIV negative population.

Ocular drug delivery

These are developed to avoid rapid precorneal elimination and drainage by gravity and to enhance the permeation of drug through cornea and to reduce the frequency of administration by formulating controlled release dosage forms [32]. Itraconazole-loaded chitosan nanosuspension were prepared and evaluated and were found to show significantly higher percentage cumulative permeation for ocular delivery as compared to suspensions available in the market[33]. Pilocarpine loaded eudragit nanosuspension was formulated with aim to improve the availability of drug at intraocular level and to reduce the frequency of drug administration [34].

Pulmonary drug delivery

Nanosuspensions for pulmonary drug delivery are formulated with a view to target the drug to lungs. Fluticasone nanosuspension for aerosol delivery had been investigated as efficient formulation for intranasal (IN) dosing and was found to be efficient for targeting drugs to lungs [35]. Similarly, fluticasone and budesonide nanosuspensions that were prepared for pulmonary delivery also showed deep lung deposition and fast lung absorption[36].

Nanoemulsions

Nanoemulsions are heterogeneous but clear and transparent dispersions of two or more immiscible liquids, stabilized by an interfacial film of surfactant molecules in which internal phase is present in nano size range. These are isotropic in nature and thermodynamically stable. "Nanoemulsions are also referred to as miniemulsions, ultrafine emulsions and submicron emulsions"[37].

The above mentioned attributes of nano emulsions, that is, increased surface area, optical clarity and transparency and thermodynamic stability makes them important tool for answering some of key issues in drug delivery systems. The clarity and transparency of nanoemulsions is exploited for delivering products that can offer good esthetic appeal, skin feel and patient compliance [38]; the resulting large surface area of nanoemulsions is applied to augment the dermal, transdermal and mucosal transport or permeation of various drugs [39]. Ropinirole, an antiparkinson drug was formulated as nanoemulsion for percutaneous delivery [40]. The resulting increased surface area is also utilized in improving oral bioavailability of hydrophilic as well as hydrophobic drugs. A hydrophobic drug, Paclitaxel was formulated into nanoemulsion for enhancing its oral bioavailability [41]. The long-term colloidal stability of nanoemulsions is a solution to impart long shelf-life to many pharmaceutical products.

Technologies for preparation of nanoemulsion [42]

Several methods have been suggested to prepare nanoemulsion. Formation of nanoemulsion system requires a high amount of energy which is availed either by using mechanical homogenizers or the by

employing chemical energy resulting during phase transition. Some methods used for the preparation of nanoemulsion are –

Phase Inversion Method: Phase inversion is a phenomenon by which dispersed phase gets converted to continuous phase and continuous phase gets converted to dispersed phase; and it is used as an important tool to produce emulsion made of very fine droplets. This can be brought about either by transitional inversions which involves a spontaneous change in the surfactants arrangements at the oil-water interface (HLB value of system is changed) or by a change in temperature of the system, or electrolyte concentration. Another method is known as catastrophic inversion which is effected by changing the volume fraction of the phases [43,44].

Sonication Method: Use of low frequency ultrasound is one of the successful methods for preparing emulsion at laboratory scale [45,46] and is known as ultrasonic emulsification. It takes place via two mechanisms.

Application of an acoustic field to produce interfacial waves which leads to eruption of the oil phase into the aqueous phase as droplets [47].
Application of low frequency ultrasound causing acoustic cavitation. Only small batches of nanoemulsion can be prepared by this method[48].

High Pressure Homogenization: As discussed about nanosuspensions, high pressure homogenization (HPH) is a mechanical process, which involves forcing a fluid product through a narrow gap (the homogenizing nozzle) at high pressure hence subjecting the liquid product to very high shear stress, resulting in the formation of nano-scaled emulsion droplets.

For producing nanoemulsion, the fluid consisting of a system having oil phase, aqueous phase and surfactant or co-surfactant is passed through the homogenizing nozzle [49]. The pressure is applied with the help of homogenizer. The major drawback associated with this method is poor productivity and component deterioration due to generation of too much heat. Another limitation is that only O/W liquid nanoemulsion of less than 20% oil phase can be prepared.

Micro fluidization: This method is similar to as discussed in nanosuspensions. A coarse emulsion is first obtained by processing the two phases along with surfactant in an inline homogenizer. This coarse emulsion is further passed into an interaction chamber micro fluidizer to obtain the desired droplet size nano emulsion [50].

Applications of nanoemulsion

Oral delivery

Nanoemulsions have been explored to be delivered via the oral route for enhancing the bioavailability of drugs, for increasing the stability of drugs in GIT and to achieve sustained release profile.

“Nanoemulsions containing Saquinavir (SQV), an anti-HIV protease inhibitor, were formulated for enhanced oral bioavailability and brain disposition. Here, the drug SQV was dissolved in different types of edible oils rich in essential polyunsaturated fatty acids (PUFA) to constitute the internal oil phase of the nanoemulsions. The external phase consisted of surfactants Lipoid®-80 and deoxycholic acid dissolved in water.” [51] “Nanoemulsions of Ramipril were formulated with minimum surfactant concentration that could improve its solubility, stability and oral bioavailability” [52]. Curcumin, a natural bioactive compound was developed as novel organogel-based nanoemulsions to improve its bioavailability and make it suitable for oral delivery. Here, the oil phase employed was curcumin organogel and Tween 20 was employed as the emulsifier [53].

Novel nanoemulsion drug-delivery system (NEDDS) that would encapsulate a standard-model protein drug – bovine serum albumin (BSA) was also developed to improve drug stability.[54]

Bioavailability of Paclitaxel, a potential anticancer agent against solid tumors was increased multifold by development of O/W nanoemulsion. Here Capryol 90 was used as dispersed phase, water was employed as dispersion medium and Tween 20 as emulsifier. The results also highlighted improved cellular uptake, higher in vitro antitumor activity and achievement of sustained release profile [55].

Lipid nanoemulsions size less than 100nm was prepared by spontaneous nanoemulsification and used as coating agent for conventional tablets containing hydrophilic drug. Fluid bed coater was used for the same. The nanoemulsion coated tablets showed delayed and zero-order release of the drug theophylline [56].

Ocular delivery

Nanoemulsions are used in ocular delivery with the purpose of enhancing ocular bioavailability by extending the precorneal residence time of a drug. In situ nanoemulsion gel of Dorzolamide hydrochloride were developed for ocular delivery [57]. "Novasorb, an advanced pharmaceutical technology was used for improving ocular drug delivery using the cationic nanoemulsion." [58] Nanoemulsions of Timolol for ocular administration were prepared and compared with the aqueous solutions of same drug. The results indicated that drug formulated in nanoemulsions resulted into significant reduction in corneal opacity and improvement indrug permeation as compared to the aqueous counterpart [59].

Transdermal or Percutaneous route

This is an effective mode for delivering hydrophobic drugs to systemic circulation via skin. Nanoemulsions easily penetrate the pores of the skin and reach the systemic circulation. They provide better application property and stability in comparison to cream and ointment. Also they show marked benefit over chemical skin penetration enhancers and organic solvents as they are nontoxic , and do not irritate or sensitize skin [60,61]. Many antihypertensive drugs which show extensive first-pass metabolism and low oral bioavailability were formulated as nanoemulsion to be administered via transdermal route [62]. Caffeine was formulated into W/O nanoemulsion and evaluated for its anticancer property when delivered via transdermal route [63]. Nanoemulsions proved to be potential vehicles for improved transdermal delivery of celecoxib [64].

Nasal route

Nanoemulsions are administered by nasal route to bypass the first-pass effect in liver. Nitrendipine (NDP), a potent antihypertensive molecule, shows low oral bioavailability due its extensive first-pass metabolism. NDP was formulated into a nanoemulsion for its intranasal delivery where Caproyl 90® based nanoemulsion system was developed using Tween 80 as the surfactant, Transcutol P® as solubiliser and Solutol HS-15® as cosurfactant [65]. The nasal route has been explored by researchers for brain targeting [66] and vaccine delivery [67]. Risperidone was targeted to brain by formulating the drug into mucoadhesive nanoemulsion and administering it via nasal route [68]. Olanzapine mucoadhesive nanoemulsions were formulated for delivering the drug via intranasal route for targeting the same to brain [69]. Nasal nanoemulsions were also evaluated as potential candidate for administering mucosal influenza vaccines [70]. Nasal immunization with a Recombinant HIV gp120 and nanoemulsion adjuvant produces Th1 polarized responses and neutralizes antibodies to primary HIV Type 1 Isolates [71]. Needle-free nasal hepatitis B vaccine composed of recombinant hepatitis B surface antigen (HBsAg) in a novel nanoemulsion (NE) adjuvant (HBsAg-NE) was investigated to provide an alternative booster administration for the parenteral hepatitis B vaccines [72].

Parenteral delivery

Parenteral nanoemulsions are employed for delivering nutritional supplements, [73] vaccines and for drug targeting. Inventions are patented for delivery of vaccines by parenteral route where O/W nanoemulsions containing small lipid particles are able to carry both hydrophilic and lipophilic immunogens.These vaccines are shown to exhibit improved immune response [74]. Carbamazepine (CBZ) is used in the treatment of generalized tonic-clonic and partial seizures where local point of treatment is brain. O/W nanoemulsion of CBZ stabilized by 1-O-alkylglycerol/lecithin were formulated and evaluated for brain targeting via intravenous administration [75]. Intravenous nanoemulsion of thalidomide (THD) was formulated using hydrophilic emulsifier polysorbate 80 with the purpose of achieving desired concentration of thalidomide in plasma using comparatively lower dose [76].

Nanomicelles

Nanomicelles are nanosized aggregates of amphiphilic monomer units. Ampiphiles are the molecules having polar or hydrophilic as well as nonpolar or hydrophobic groups. They have ability to orient themselves as clusters when added above critical micelle concentration in a solvent. They form regular micelles in a hydrophilic solvent and reverse micelles in hydrophobic solvent.

Nanomicelles like other nano liquid systems are an answer to enhancing solubilization properties of poorly soluble drugs. Normal or regular micelles where the micellar core is made up of non polar group are suited predominantly for hydrophobic drugs, while, reverse micelles where the micellar core is made up of polar groups are primarily suited for the encapsulation and delivery of hydrophilic drugs. The amphiphilic nature of these micelles can be exploited for targeting drugs to specified sites by attaching ligands to them.

Technologies for preparing Nanomicelles

Grafting polymerization: Nanomicelles are prepared mostly by employing technology of grafting polymerization. For example, nanomicelles were developed as novel drug carrier through grafting polymerization of hydroxyethyl starch (HES) and d,l-lactide. Through self-emulsification combined with solvent evaporation, HES-g-PLAs self-assembled into micelles with uniform sizes ranging from 65 to 130 nm, depending upon the chain length of PLA [77]. Self-associating cellulose-graft-poly (ε- caprolactone) (cellulose-*g*-PCL) copolymers were successfully synthesized via homogeneous ring-opening polymerization (ROP) of ε-CL onto softwood dissolved pulp substrate in ionic liquid 1-N-butyl-3-methylimidazolium chloride. The micelle size and critical micelle concentration (CMC) was controlled by varying the grafting ratio of PCL. [78]

Co precipitation method: Particle size control is a drawback of this method. This method has been illustrated by forming nanomicelles in water-saturated organic solutions of $HFeCl_4$ and $HClO_4$ which showed a stable, almost stoichiometric, composition *[79]*.

Solvent pH change solubilization method: It is easy to control the size of nanomicelles as compared to copreciptation or polymerization technique. This was very well illustrated by formulation of Camptothecin in sterically stabilized phospholipid nano-micelles [80].

Applications of nanomicelles in drug delivery: The key application of nanomicelles in drug delivery is for the purpose of targeted drug delivery. Hydrophobic anticancer drug doxorubicin (DOX) was formulated for nuclear targeting using PV7, as a vehicle [81]. Nanomicelles based on cationic mPEG2000-PLA3000-b-R15 copolymer were proved to be safe and efficient nanocarriers for *in vivo* targeted delivery of therapeutic siRNA[82]. Magnetic nanomicelles have been explored as potential platform for dual targeted drug delivery in cancer therapy [83].

Nanomicelles have also been employed in improving solubility and bioavailability. Solid dispersions of α-mangostin were formulated to improve its aqueous solubility through self-assembly of Nanomicelles[84].

Characterization of Biphasic Liquid Nanosystems [85, 86]

Mean Particle Size and Particle-Size Distribution [87]

These parameters are evaluated as they influence important properties of biphasic liquid nanosystems such as saturation solubility and dissolution velocity [88, 89]. Also, they play important role in governing physical stability and biological performance of nanosuspensions, nanoemulsions and nanomicelles.

The technologies used to measure mean particle size and particle-size distribution are as following:

Dynamic Light Scattering (DLS) also known as Photon Correlation Spectroscopy (PCS)

In this method, dynamic fluctuations of intensity of scattered light is measured which in turn is used to determine the velocity distribution of particles movement. Many researchers have employed Malvern Zetasizer Nanoseries nano-ZS for determination of particle size in their nanosuspension [85-87]. This technique has been employed to determine average diameter of nanoemulsions[90,91] and nanomicelles[92,93].

Laser diffraction

Laser diffraction is a technique to measure particle size distribution. It involves passing a laser beam through the sample and measuring the angular variation in intensity of light scattered. Larger the size of particles smaller will be the angular variation. This angular scattering intensity data is further analyzed and the size of the particles calculated using the Mie theory of light scattering. This technique is particularly employed for characterization of solid lipid nanoparticles [94, 95].

Coulter counter

This instrument works on the Coulter Principle. This involves immersing a tube with a small aperture on its wall into a beaker containing sample. The sample is prepared by dispersing the particles (the size of

which is to be analyzed) in a low concentration electrolyte. The tube is subjected to an electric field as the current is allowed to pass through the two electrodes, one of which is inside the aperture tube and the other outside the aperture tube; and the impedance between the electrodes is measured. As a particle passes through the aperture, it displaces a volume of electrolyte equivalent to its volume resulting in short-term change in the impedance across the aperture. This change is measured as a voltage pulse, where the pulse height is proportional to the volume of the sensed particle [96].

Particle Morphology

X-ray diffraction analysis

X-ray diffraction provides exact molecular geometry of crystals and is a predominant tool in characterization of pharmaceutical solids and suspensions. The principle involves use of constructive interference of monochromatic X-rays and the crystalline sample and employing Bragg's law to study the lattice structure in the crystalline material [97- 99] .

Scanning Electron Microscopy (SEM)

Scanning Electron Microscope (SEM) produces extremely high magnification images at high resolution up to nano range and hence is successfully used in characterizing nanosuspensions. It works on the principle of scanning the surface of specimen by an electron beam that is generated by an electron cathode and the electromagnetic lens of the column. Electrons are emitted from the specimen by the action of the scanning beam and collected by a suitable positioned detector and reflected as image on screen after suitable magnification [98,100].

Particle Charge (Zeta Potential)

The zeta potential (ζ) is a function of the surface charge which develops when any material is placed in a liquid. The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion. Hence it becomes an important tool for understanding the state of the nanoparticle surface and predicting and controlling the long term stability of the nanodispersions[101]. The zeta potential values are calculated by determining the particle's electrophoretic mobility.

Rheological behavior

Brookfield viscometer is most commonly employed method for determining rheological behavior of nanosystems[102].

Commercial Application

Many nanosuspensions, nanoemulsions and nanomicelles are being successfully launched in the market and many are at clinical trial stage. A few of the marketed preparations are mentioned in table (Table 1).

Table 1: List of nanotechnology based oral formulations in pharmaceutical market and in clinical trials [103].

Product	Drug	Dosage form	Company/alliance	Commercial/therapeutic benefits
Rapamune	Sirolimus	Tablet	Wyeth Pharmaceuticals – Elan Drug Delivery	Enabled development of tablet dosage form over previous oral solution. Enhanced patient compliance.Greater bioavailability as compared to solution.
Megace ES	Megestrol acetate	Nano-suspen-sion	Par Pharmaceuticals- Elan Drug Delivery	1/4th Reduction in dose volume as compared to previous oral suspension (from 20 mL to 5 mL). Elimination of variability because of food effect.
Emend	Aprepitant	Capsule	Merck-Elan Drug Delivery	Higher oral bioavailability.

Tricor	Fenofibrate	Tablet	Abbott Laboratories	Dose reduction. Elimination of variability. because of food effect
Panzem NCD	2-Methoxy estradiol	Nanosuspension	EntreMed Inc.	Being evaluated in Phase II clinical trial. Douse reduction and higher oral bioavailability.
Sandummine Neoral	Cyclosporine	Soft gelatine capsule	Novartis	Increased bioavailability of cyclosporine as compared to earlier oily formulation. Sandimmun1 and reduction in inter and intra-individual pharmacokinetic variability.
Gengraf	Cyclosporine	Hard gelatineCapsule	Abbott Laboratories	Less expensive than Neoral.

Conclusion

Nanotechnology has gained its place in mainframe drug delivery system particularly in enhancing bioavailability of poorly soluble drugs, achieving controlled release, and drug targeting. It has resulted in increased efficacy and safety as well as improved patient compliance. Much work has been carried out in areas of nanoemulsions and nanosuspensions and many products are successfully launched in the market. But nanomicelle still remains a thrust area for commercial exploitation and has wide scope in formulating targeted drug delivery systems.

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