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Review Article

Role of Novel Drug Delivery Systems in Bioavailability Enhancement: At A Glance

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ABSTRACT
Novel drug delivery systems (NDDS) are one of the most strategies which enable to overcome the problems related to drug bioavailability. It is the rate and extent to which a drug becomes available to the target tissue after its administration. Most of the new drugs used today have poor bioavailability and are required to be administered at higher doses because only a small fraction of the administered dose is absorbed in the systemic circulation and able to reach the target site. This results in the wastage of major amount of drug and lead to adverse effects. Pharmaceutical technology mainly focuses on enhancing the solubility and permeability of drugs with lower bioavailability. Nanotechnology is the concept used in NDDS that enables a weight reduction of drug particles accompanied by an increase in stability and improved functionality. Various approaches such as nanosuspensions, liposomes, niosomes, nanoemulsions, cubosomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), cyclodextrins, phytosome etc., are used for the enhancement of bioavailability. The present review focuses on the different approaches used for bioavailability enhancement along with their advantages and disadvantages.

Keywords: Bioavailability Enhancement; Novel Drug Delivery Systems; Solubility

INTRODUCTION

Bioavailability of the drugs can be enhanced using novel drug delivery systems by transport the drug to the place of action, hence, its influence on vital tissues and undesirable side effects can be minimized so the accumulation of therapeutic compounds in the target site increases and consequently, the required doses of drugs become lower at a predestined rate i.e., offers controlled rate, slow and target delivery[1,2]. Recent developments in nanotechnology have shown that nanoparticles (structures smaller than 100 nm) have a great potential as drug carriers. These nanostructures exhibit unique physicochemical and biological properties (e.g., an enhanced reactive area as well as an ability to cross cell and tissue barriers) due to their small sizes, which make them a favorable material for biomedical applications. Nanoparticles have greater surface area to volume ratio, means more surface is exposed which results in faster dissolution of nanoparticles in solution, resulted in greater bioavailability, smaller drug doses and less toxicity. In traditional drug delivery systems such as oral or intravascular delivery, the drug or therapeutic molecules are distributed throughout the body through the systemic blood circulation, so the majority of molecules does not reach their targets and subsequently, stay in the body causing side effects. The drug and therapeutic molecules have a short plasma half-life, poor stability in serum and potential immunogenicity, and insolubility in water, which results in their rapid clearance of the mononuclear phagocytic system (MPS) and limits their efficiency. Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.

The NDDS like liposomes, niosomes, bilosomes, phytosomes etc., which pass the presystemic metabolism, reducing adverse effects due to the amassing of drugs to the nontargeted areas and improve tissue macrophage distribution in the pediatric and geriatric patients[2,3]. This aids in protection from physical and chemical degradation like increased the solubility, permeability, stability, sustained delivery[4]. The dissolution rate of a drug can be shown by the Noyes–Whitney equation and it is also directly corresponding to the surface area as particles are reduced to a minute size. Hence, the saturation solubility and dissolution rate of poorly water soluble drugs is augmented. Lipophilic drugs from oral route become rate limiting step for dissolution and absorption. Intestinal drug absorption solubility and intestinal permeability can be well explained by the Biopharmaceutics Classification System (BCS)[5] (Figure 1). The present review article deals with different novel drug delivery systems as carriers for enhancing the bioavailability of the poorly soluble drugs.

Different Novel drug delivery systems in drug bioavailability enhancement

Nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they can be successfully used as

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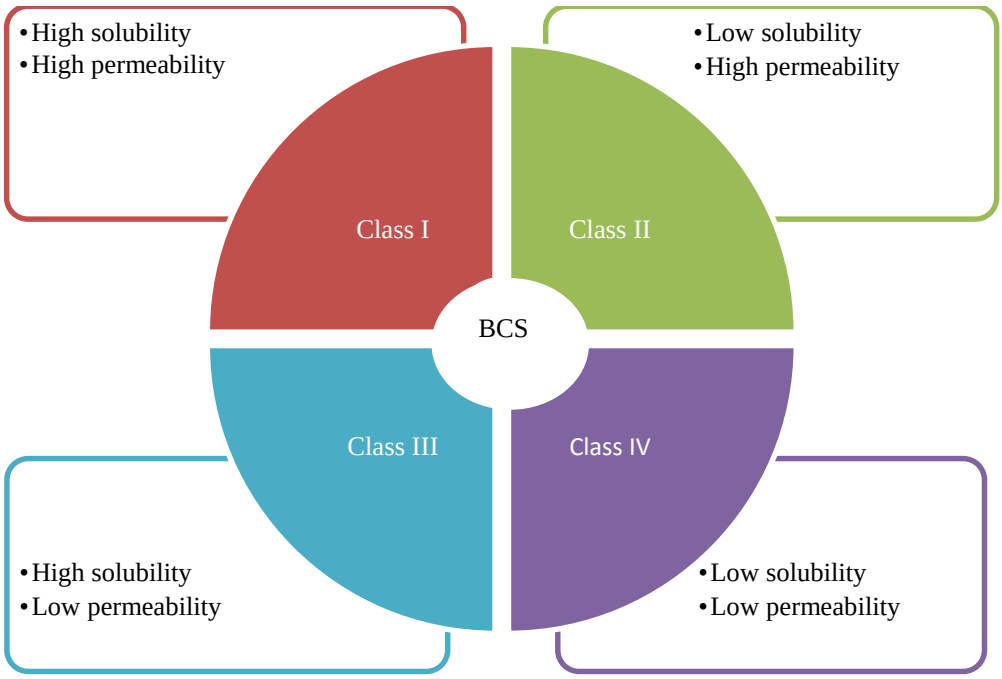

Figure 1: Biopharmaceutics Classification System (BCS)

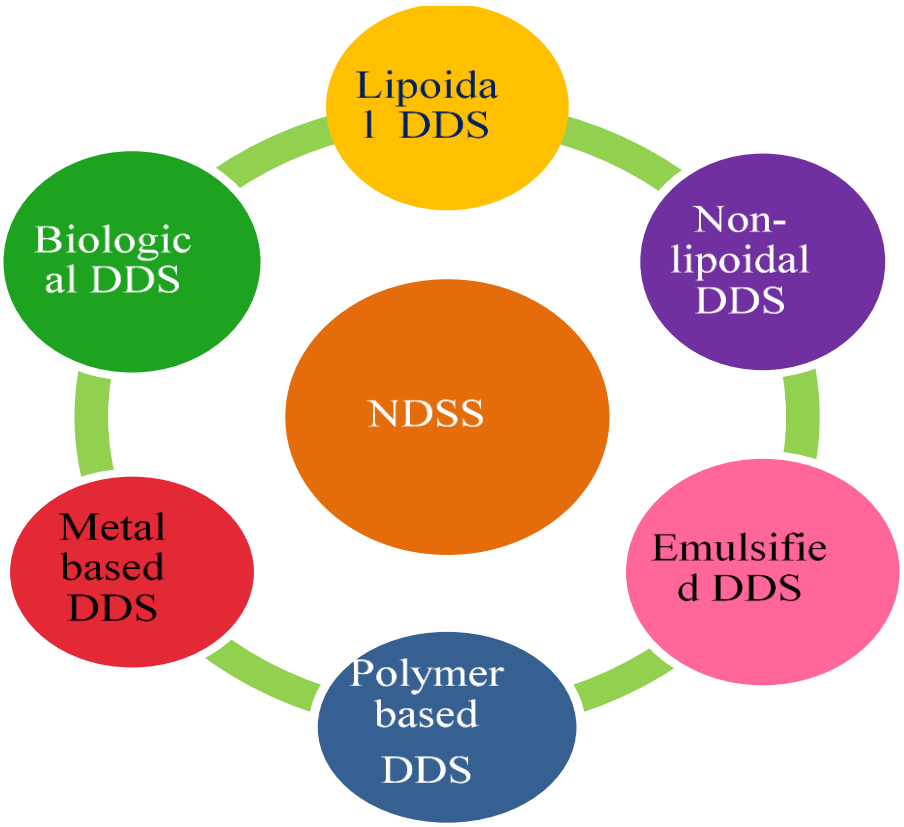

Figure 2: Classification of Novel Drug Delivery Systems (NDDS) on the basis of composition

delivery tools for currently available bioactive compounds[6]. The way of conjugating the drug to the nanocarrier and the strategy of its targeting is highly important for a targeted therapy. A drug may be adsorbed or covalently attached to the nanocarriers surface or else it can be encapsulated in it. Covalent linking has the advantage over other ways of attaching as it enables to control the number of drug molecules connected to the nanocarrier, *i.e.*, a precise control of the amount of therapeutic compound delivered. Cell-specific targeting with nano carriers may be accomplished by using active or passive mechanisms. The first strategy relies on the attraction of a drug – the nanocarriers conjugate to the affected site by using recognition legends, attached to the

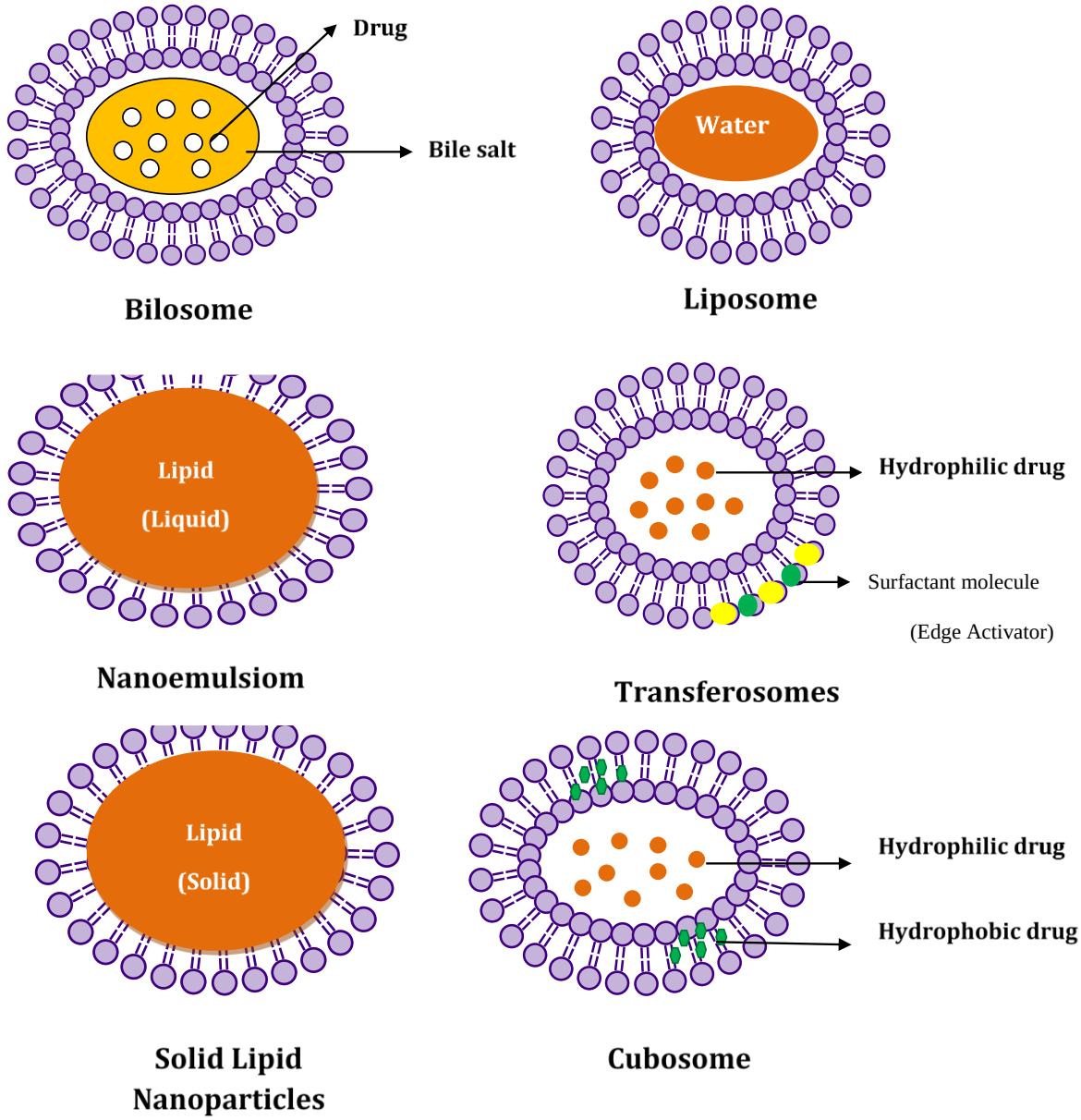

Figure 3: Simplified structures of Novel drug delivery carriers

surface of conjugate antibodies, low molecular ligands, e.g., folic acids, peptides, etc. The active strategy can be also achieved through a manipulation of physical stimuli (e.g., temperature, pH, magnetism). Passive targeting is a result of enhanced vascular permeability and retention (EPR) which is characteristic of leaky tissues of tumors[7]. Nano drug carriers can be divided into two groups: Nanocapsules and nanospherse. Nanocapsules are vesicular systems in which a drug is confined to a cavity surrounded by a membrane and nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Various NDDS used for bioavailability enhancement are categorized on the basis of different compositions are shown (Figure 2)

Lipoidal based drug delivery systems

Liposomes

These were first described by British hematologist Bangham in 1961. These consist of an aqueous compartment enclosed by a lipid bilayer membrane (Figure 3). An outer hydrophobic environment is established due to the linkage of a lipophilic moiety of the player and non-polar part lipophilic or amphiphilic drugs can associate depending upon their geometry and size[8]. However, the hydrophilic drugs or molecules interact with the inner aqueous phase of the vesicles. This bypass characteristic and diversity, composition and construction of liposomes offer a dynamic and adaptable technology for enhancing drug solubility. These can be classified depending upon the size, the number of players and the existence of inner vesicles as: multilamellar large vesicles (>0.5 µm), oligolamellar vesicles (0.1–1 µm), unilamellar vesicles (all size ranges), small unilamellar vesicles (20–100 nm), medium sized unilamellar vesicles, large unilamellar vesicles (>100 nm), giant unilamellar vesicles (diameters >1 µm), multivesicular vesicles (>1 µm)[9]. Another classification based on the method of liposome

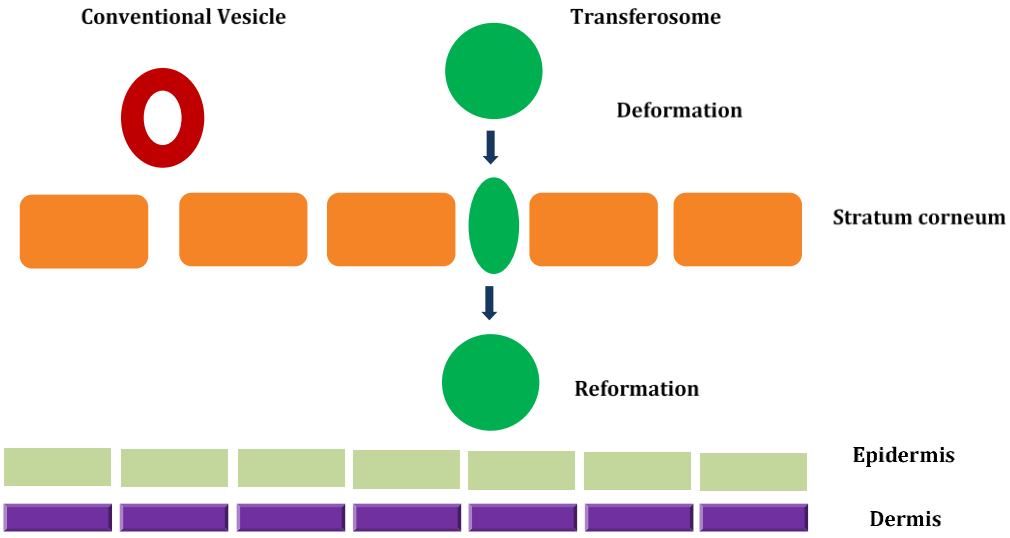

Figure 4: Penetration of Transferosome (ultradeformable vesicle) across Stratum corneum

preparation is reverse-phase evaporation lipid vesicles (REV) - single or oligolamellar vesicles made by reverse-phase evaporation method (MLV-REV), multilamellar vesicles made by the reverse-phase evaporation method, stable plurilamellar vesicles (SPLV), - frozen and thawed multilamellar vesicles (FATMLV), MLV, VET- vesicles prepared by extrusion methods, dehydration-rehydration vesicles (DRV) [15]. Few liposomal formulations available in the market are AmBisome™, DaunoXome™ and Pevaryl™. Liposomal formulations when administered orally, rapid degradation of liposomes occurs due to the pH of the stomach, intestinal enzymes and bile salts. Cefotaxime (acid labile drugs), liposomal formulation provides enhanced intestinal permeation and temporary protection from the hostile acidic environment of the stomach for the drug[10]. The treatment of human carcinomas can be enhanced significantly through the use of a liposomal delivery system, with reduced toxicity of vincristine, a lipophilic drug widely used[11]. While phospholipid-based liposomes enhances the bioavailability of poorly soluble drugs, including peptides and proteins. For instance, Cyclosporin A (CyA) proliposomes were formulated by spraying a solution of CyA, egg lecithin and Cremophor EL® in a methanol/chloroform mixture onto lactose in order to obtain a free-flowing powder. Liposomes formed resulted in enhanced bioavailability and absorption of CyA liposomes was nine times higher than that of the free drug solution and four times higher than for a marketed sample of micro emulsion[12]. In another study, the Zaleplon proliposomes were prepared by film deposition method using spray dried mannitol as carrier at varying ratios of (hydrogenated soyphosphatidylcholine) HSPC and cholesterol. This formulation was optimized with dicetyl phosphate and stearylamine to obtain negative and positive charged vesicles respectively. *In vivo* study confirmed the two to fivefold enhancement in bioavailability in comparison with control formulation[13]. The highest oral bioavailability of 8.5% and 11.0% was achieved by SGC-liposomes in non-diabetic and diabetic rats, respectively, when these were prepared by a reversed-phase evaporation method containing bile salts, sodium glycocholate (SGC), sodium taurocholate (STC) or sodium deoxycholate (SDC)[14].

Cubosomes

These are solid nanoparticles (10-500 mm in diameter) having honeycombed (cavernous) structures. The cavernous structures separates two internal aqueous channels and a large interfacial area and bicontinous cubic phases are optically isotropic, very viscous and solid like liquid crystalline substance with cubic crystallographic symmetry[15]. Cubic phases were produced at 25 ºC in water monoolein-alcohol mixtures. Ethanol was found to be more efficient than propanol and butanol. In the composition range of 49 to 56 wt% water, 31 to 40 weight% mainline and 10 to 13 wt% transparent, low-viscosity (flowing) phase that ethanol[16]. According to curvatures, Schwarz discovered 3 types of minimal surface and studied in cubic phases, while Luzzati *et al.*, (1993) proposed three structures of cubosomes (i) Pn3m (D-surface) (Diamond surface), (ii) Ia3d (G-surface) (Gyroid surface), and (iii) Im3m (P- surface) (Primitive surface) in terms of nodal surfaces[17]. Cubic liquid crystals are transparent and isotropic phases that are physically stable in excess water representing a unique system for the production of pharmaceutical dosage. These can be manufactured by two distinct technologies: a) Top down technique: Over the last two decades, most cubosome research mainly based on top-down technique. In this technique firstly bulk cubic phase is produced and then dispersed by high energy processing into cubosome nanoparticles. Bulk cubic phase resembles a clear, rigid gel formed by water swollen crossed linked polymer chains where as cubic phases exhibit liquid crystalline structure and have a single thermodynamic phase. Rupture of these cubic phases occurs in a direction parallel to the shear direction and the energy required is proportional to the number of tubular network branches that rupture. The yield stress is shown by the cubic phases and that yield stress, increased with increasing amounts of surfactants

and oils forming player. However, Warr and Chen suggested that cubic phases may behave as lamellar phases during dispersion with increasing shear. At high oscillatory frequencies, cubic phases become highly elastic[18-20]. Where as in the bottom-up technique nanostructure building blocks are prepared from the precursors and then assembled into the final material. Cubosomes are formed by dispersion or inverse micellar phase droplets in water at 80°C, then by slow cooling aids droplets to gradually crystallize into cubosomes[21]. In the following cases, Cinnarizine (CZ) cubosomes formed from phytantriol resulted into longer duration sustained-release and oral bioavailability was increased by cubosomes (21%) when compared to a CZ suspension (9%) and oleic acid emulsion (12%)[22]. In another instance, Simvastatin-loaded cubic nanoparticles were prepared using glyceryl monooleate/poloxamer 407 and the oral bioavailability was increased 2.41 times than micronized simvastatin crystal powder[23]. While Flurbiprofen (FB) loaded cubosomes showed that Tmax of FB cubosome F2 was increased about 1.6-fold as well as men residence time (MRT) also significantly longer (P<0.001) as compared to FB Na eye drops[24].

Transferosomes

These are ultraflexible lipid supramolecular aggregates, which easily penetrate the mammalian skin intact. Conventional drug carriers are not suitable for transdermal delivery, because of their poor skin permeability, breaking of vesicles, leakage of drug, aggregation and fusion of vesicles. "Transfer some" are promising NDDS which are capable of transdermal delivery of low as well as high molecular weight drugs[25] (Figure 4). These have at least one inner aqueous compartment, surrounded by a lipid bilayer and "edge activators" such as sodium cholate, sodium deoxycholate, span 80 and Tween 80 which are attached to the vesicular membrane[26]. Long *et al.,*[27] prepared and evaluated the entrapment efficiency of capsaicin transfersomes, the entrapment efficiency reached 96.7% and in vitro cumulative penetration rate of capsaicin was higher in transfersomes than in cream and suspension in rats. A similar study was done by Patel *et al.,*[28] formulated the transferosome for transdermal delivery of Curcumin. Tween 80 and Span 80 were used as surfactants and the higher entrapment efficiency was found to be 89.6±0.049 as compared to plain drug gel.

Pharmacosomes

These are amphiphilic complexes of drugs (containing an active hydrogen atom) with lipids and drugs are bound covalently, electrostatically or by hydrogen bonds to lipids and form ultrafine vesicular, micellar, or hexagonal aggregates. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without spacer chain[29-31]. Similar to other vesicular systems, these have targeted drug delivery, leading to reduction of drug toxicity with no adverse effects which reduce the cost of therapy by improved bioavailability of medication especially in case of poorly soluble drugs. These are suitable for incorporating both hydrophilic and lipophilic drugs to improve their solubility, bioavailability and minimize the gastrointestinal toxicity of various drugs. So, developing the drugs as pharmacosomes may prove to be a potential approach to improve the bioavailability of drugs and also to minimize the GI toxicity. This approach has successfully improved the therapeutic performance of various drugs, *i.e.*, pindolol mallet, bupranolol hydrochloride, taxol, acyclovir, etc.[32,33]. Zhang and Wang proved that the pharmacosomes can improve the ability of a drug to cross the blood–brain barrier and act as a promising drug-targeting system for the treatment of central nervous system disorders[34]. In another study, *in vivo* behavior of didanosine pharmacosomes was evaluated in rats. The study revealed liver targeting and sustained-release effect in rats after i.v. administration. It was also found that there was targeting in the lung and spleen and that the drug elimination from the target tissues was slow[35].

Solid lipid Nanoparticles (SLN)

Solid lipid nanoparticles were introduced as a colloidal carrier system in 1991. These are aqueous dispersions of solid lipids ranging between 50-1000 nm. These nanoparticles have the combined advantages over polymeric nanoparticles, fat emulsions and liposomes simultaneously, thereby avoiding some of their disadvantages[36]. A clear advantage of solid lipid nanoparticles (SLNs) over polymeric nanoparticles is the fact that the lipid matrix is made from physiologically tolerated lipid components, which decreases the potential for acute and chronic toxicity[37]. SLNs combine the advantages of polymeric nanoparticles, fat emulsions and liposomes[38]. They are melt-emulsified nanoparticles depending on type of lipids used and solid at room temperature[39]. SLNs were prepared by an ultrasound-solvent emulsification technique. The production technique mainly involves high pressure homogenization and microemulsion technique[40]. To manufacture SLN, hot high pressure homogenization above melting point of lipid and subsequent crystallization is recommended, but cold high pressure homogenization[41] (high pressure milling of lipid suspensions) for thermo labile drugs also exists. Other production methods for SLN are the precipitation[42-44], Lipid nanopellets, lipospheres[44] and dispersing by ultrasound[45,46] are differ normally in particle size distribution. One of the major advantages of SLN over other systems is the reduction in acute and chronic toxicity (10-100 fold decrease) due to the presence of physiologically tolerated lipid components[47,48]. SLN proved to be promising strategy in bioavailability enhancement, as in case of Clozapine atypical antipsychotic drug, with very poor oral bioavailability (27%) due to first pass metabolism. Clozapine SLN prepared using stearylamine resulted up to 2.91-fold increase in AUC $_{(0-l)}$ and clearance was decreased (up to 2.93-fold)[49]. SLN formulations with a lipid matrix of glyceryl monostearate have also been prepared for Vinpocetine by an ultrasonic solvent emulsification technique. An oral pharmacokinetic study conducted in male rats showed that SLNs produced a significant improvement in the bioavailability of Vinpocetine compared with Vinpocetine solution[50]. Venishetty *et al.,* (2012) prepared N-carboxymethyl Chitosan (MCC) coated carvedilol loaded SLN to protect the rapid release of

Table 1: Drug bioavailability enhancement by Novel Drug Delivery Systems (NDDS)

S.N.	NDDS	Drug	Method	Application	Ref
1.	Liposome	Silymarin	Ethanol injection method	Increased the bioavailability of silymarin by adopting buccal liposomal drug delivery system	66
2.	Cubosomes	Rifampicin	Pressure ultrafiltration method	Enhance bioavailability of Rifampicin (Antituberculosis drug)	67
3.	Transferosomes	Curcumin	Hand shaking method	To improve the oral bioavailability of curcumin	68
4.	Pharmacosomes	Aspirin	Conventional solvent evaporation technique	To improve the solubility, bioavailability and dissolution of aspirin	69
5.	Solid lipid Nanoparticles (SLN)	Vinpocetine	ultrasonic-solvent emulsification technique	Improve cerebral circulation and metabolism in the treatment of various types of cerebrovascular circulatory disorder	70
6.	Nanostructure lipid carriers (NLC)	Breviscapine	Thin film homogenization method	Improve sustainable release of breviscapine drug	71
7.	Niosomes	Celecoxib	Thin film hydration technique	Provides prolonged drug release and improved site specificity of drug	72
8.	Bilosome	Hepatitis B vaccine	Film hydration method	Successful induction of mucosal and systemic immunity	73
9.	Nanoemulsion	Ramipril	Spontaneous emulsification method	Enhanced solubilisation of Ramipril (antihypertensive drug)	74
10.	Nanosuspension	Aphidicolin	High pressure homogenization technique	Drug targeting against leishmania infected macrophages.	75
11.	Self emulsifying drug delivery systems (SEDDS)	Indomethacin	Oil in water emulsion method	Improvement in vitro drug dissolution and enhanced the in vivo drug absorption	76
12.	Polymeric nanoparticles	Daunomycin	Non-covalent (biotin-streptavidin) coupling procedure	To increase bioavailability of Daunomycin	77
13.	Dendrimers	Naproxen	Solvent deposition technique	Enhancement of both drug dissolution and in-vitro release rates.	78
14.	Carbon nanoparticles	Camptothecin	Combined hydrothermal synthesis and hard templating method	Sustainable release of camptothecin (anticancer) drug	79
15.	Silica nanoparticles	Paclitaxel	Polyethyleneimine coated MSN method	Enhance the delivery of this hydrophobic anticancer drug to pancreatic cancer cells	80
16.	Cyclodextrins	Betamethasone	Phase solubility method	Enhance drug entrapment efficiency	81
17.	Phytosome	Silybin Phytosome TM	Siybin from silymarin marinum	Improved drug bioavailability of these nutraceutical, antioxidant herbal drugs	82

carvedilol in an acidic environment and to avoid intraduodenal administration. The study showed that MCC coated SLN followed sustained release and there was a significant improvement in bioavailability[51].

Nanostructure lipid carriers (NLC)

A second generation of lipid nanoparticles was developed and were called nano structured lipid carriers (NLC) are prepared not only from solid lipids but from mixtures of solid lipids with liquid lipids (oils)[52]. SLN is having pure solid lipids whereas NLC contain a certain percentage of additional liquid lipids leading to imperfections in the

crystal lattice. These nanoparticles are produced by, high pressure homogenization, microemulsion template, solvent diffusion, reverse micelle-double emulsion, homogenization followed by ultrasonication, solvent injection and a recently introduced membrane contractor techniques[53]. Zhuang *et al.,*[54] prepared Vinpocetine (VIN) NLC using high pressure homogenization method. The oral bioavailability study of VIN was carried out using Wister albino rats and the relative bioavailability of VIN–NLC was found to be 322% compared with VIN suspension. In another instance, testosterone undecanoate (TU) loaded NLC were produced using hot high pressure homogenization method and results showed that 30% increase in drug loading capability as well as bioavailability was also enhanced in comparison to Andriol Testocaps®[55].

Table 2: Various advantages and disadvantages of the NDDS which are used for the enhancement of bioavailability

NDDS	Advantages	Disadvantages	Ref.
Liposomes	Encapsulate both hydrophilic and lipophilic drugs and protect them from degradation PEGylated liposomes have advantages such as increased bioavailability and the targeted delivery to the organs or tissues that most need them. These regulate the membrane permeability and thus do not allow the leakage of solute.	Production cost of liposomes is high and they are less stable. Oxidation and hydrolysis like reaction may occur in phospholipid. Phagocytes in human body see liposomes as invaders and devour these liposomes, which may thus go waste.	163
Nano-suspensions	Cost-effective and technically simpler alternative. Good reproducibility in case of large-scale production. Increase in dissolution rate and saturation solubility. Efficient release of hydrophobic drugs	Not ideal for intravenous administration Not suitable for cytotoxic drugs with small therapeutic indices. Require stabilizers for their stability purpose. Leakage of encapsulated drug during storage.	164
Niosomes	These can be successfully used for oral administration of peptide or protein drugs such as insulin to eliminate or reduce the need to use injection as the mode of administration. These increases the stability of entrapped drug as they are osmotically active and stable. These lead to enhancement of skin permeation as well as improvement of oral bioavailability of poorly soluble drug. Structure of the noisome is designed in such a way that these vesicles can entrap hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drug.	Sometimes lead to leakage of entrapped drug. Though niosomes are biocompatible. However sometimes, non-ionic surfactants interact with components of the system and formulation form precipitates	165
Solid lipid nano-particles (SLN)	They possess adhesive properties that make them adhere to the gut wall and release the drug exactly where it should be absorbed. These improve the bioavailability of lipophilic drugs by minimizing first pass metabolism These include high biocompatibility, controlled release, and no problems with multiple routs of administration, such as oral, intravenous, pulmonary and transdermal administration.	Particle growth. Unpredictable gelation tendency. Unexpected dynamics of polymeric transitions.	166, 167

Table 2: Various advantages and disadvantages of the NDDS which are used for the enhancement of bioavailability

NDDS	Advantages	Disadvantages	Ref.
Nanostructured lipid carrier (NLS)	Drug loading can be increased, drug inclusion is improved. These are much easily processed in comparison to traditional dosage forms, e. g. tablet, capsule or pellet. These lead to improvement in topical delivery as they are highly concentrated and are already creamlike that can directly be applied to the skin.	Low capacity to load hydrophilic drugs due to partitioning effects during the production process and only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix	168
Nano-emulsions	These eliminate variability in absorption there by increasing the rate of absorption. These are effective transport system as compared to macro emulsions because these nanoemulsions have much higher surface area and free energy and also do not possess problems of inherent creaming, flocculation, coalescence and sedimentation, which are commonly associated with macro emulsions. These show rapid and efficient permeability of the drug moiety thus there is significant increase in bioavailability. Since nanoemulsions are formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route	Stability is influenced by environmental parameters such as temperature and pH Formulation requires very expensive instruments such as homogenizers and ultrasonicators are to be used.	169
Self emulsifying drug delivery systems (SEDDS)	Protection of sensitive drug substances Selective targeting of drug(s) toward specific absorption window in GIT, protection of drug(s) from the hostile gut environment. Controlled drug delivery profiles Enhanced oral bioavailability enabling reduction in dose Reduced variability including food effects More consistent temporal profiles of drug absorption	Chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT.n Consequently, the safety aspect of the surfactant vehicle had to be considered.	170
Cubosomes	Excellent solubilizers when compared with conventional lipid or non-lipid carriers, a These carriers are having high drug carrying capacity for sparingly water-soluble drugs. These protect sensitive drug from enzymatic degradation and *in-vivo* degradation, such as peptides and proteins. The liquid crystalline nanoparticles enhances the bioavailability of water-soluble peptides.	Bulk cubic phases are difficult to handle and difficult to apply to human skin. The cubic phase is hygroscopic on human skin as judged by instrumental tests such as the sorption-desorption test.	171

Table 2: Various advantages and disadvantages of the NDDS which are used for the enhancement of bioavailability

NDDS	Advantages	Disadvantages	Ref.
Bilosomes	Increase the bioavailability of enclosed bioactive substance and act as penetration enhancers Bile salts (commonly used as penetration enhancers) in bilosome formulation could stabilize the membrane against the detrimental effects of bile acids in GI tract	Limited to enhancement of oral delivey of vaccines mainly	172
Transfero-somes	Suitable for transdermal drug delivery Ultra-deformable vesicles can squeeze itself through a pore, many times smaller than its size owing to its elasticity	Transfersomes are chemically unstable because of their predisposition to oxidative degradation. Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles. Transfersomes formulations are expensive	173
Pharma-cosomes	As the drug is covalently bound to lipid, membrane fluidity has no effect on release rate, but depends upon the phase-transition temperature of the drug lipid complex. No leaching of drug takes place because the drug is covalently bound to the carrier. Drugs can be delivered directly to the site of infection. Suitable for both hydrophilic and lipophilic drugs. High and predetermined entrapment efficiency of drug and carrier are covalently linked together. No need of removing the free un-entrapped drug from the formulation which is required in case of liposomes. Improves bioavailability especially in case of poorly soluble drugs.	Synthesis of a compound depends upon its amphiphilic nature. It requires surface and bulk interaction of lipids with drugs. It requires covalent bonding to protect the leakage of drugs. Pharmacosomes, on storage, undergo fusion aggregation as well as chemical hydrolysis.	174
Carbon nano-particles	Ease of cellular uptake, high drug loading, thermal ablation	The toxic potential of carbon nanotubes can result from the high length to diameter ratio and the toxicity of the sole material, which is graphite. In addition, some impurities, such as residual metal and amorphous carbon, contribute to the level increase of reactive oxygen species (ROS), thus, inducing the oxidative stress in cells	175
Dendrimer nanocarriers	Highly promising platforms because of their modularity, tailoring their physicochemical and biological properties to achieve precise targeted outcomes.	Short plasma circulation times Low drug loadings Difficulties in controlling drug release and scaling up of multifunctional dendrimers.	176
Cyclo-dextrins	Improve water solubility, hydrolytic or photolytic stability of drugs for better loading properties Provide a number of potential sites for chemical modification They possess low toxicity and low pharmocological activity. They protect the included/conjugated drugs from degradation	stabilization of active compounds, reduction in volatility of drug molecules masking of malodours and bitter tastes	177

Table 2: Various advantages and disadvantages of the NDDS which are used for the enhancement of bioavailability

NDDS	Advantages	Disadvantages	Ref.
Polymeric nano-particles	These have Biodegradability and sustained release property,	Poor stability in biological fluids Sometimes become toxic	178
Phytosomes	It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit. As the absorption of active constituent(s) is improved, its dose requirement is also reduced. Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed. Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile. Added nutritional benefit of phospholipids	Phytoconstituent is rapidly eliminated from phytosomes	179

Non-lipoidal based drug delivery systems

Niosomes

In the year 1972, it was reported that niosomes are the vesicular system composed of non-ionic surfactants with or without the presence of cholesterol or other lipids with subsequent hydration in aqueous media[56,57]. These are closed lipid bilayer structures which mimic biological membrane[58]. They surpass instability of liposomes due to oxidative and hydroxylation degradation of unsaturated fatty acids and ester bindings of phospholipids[59]. Earlier oral administration of drugs was considered to be the primary cause of the enhanced bioavailability but later showed that the lipophilic nature of the niosomal formulation and the effect of the nonionic surface-active agent on the permeability of the gastrointestinal membrane. The average 2-fold increased relative oral bioavailability found with respect to the free solution in acyclovir from rabbit's niosomal dispersion[60]. Depending upon vesicle size, niosomes are divided into three groups: Small Unilamellar Vesicles (SUV, Size, 0.025-0.05μm), Multilamellar Vesicles (MLV, Size, >0.05μm), Large Unilamellar Vesicles (LUV, Size, >0.10μm)[61]. Drugs like minoxidil and acyclovir have been encapsulated into a non ionic vascular system for enhancing bioavailability of these drugs[62,63]. Pratap *et al*.,[64] observed that niosomal formulation prepared by the thin film method followed by sustained release pattern significantly increased in the area under the curve (AUC_{0-24}: 41.56 μg/ml h) as compared to free griseofulvin (AUC_{0-24}: 22.36 μg/ml h). In this case, Acelofenac loaded Niosomes were formulated by hand shaking method. Drug release was customized and extended over a period of 72 h in all formulations. Optimized niosomal drug formulation release was 79.56% ± 0.42 over 72 h[65].

Bilosomes

Bilosomes are the novel, innovative drug delivery carriers produced by incorporating deoxycholic acid into the membrane of niosomes[83]. Incorporation of bile salts (commonly used as penetration enhancers) in niosomal formulation could stabilize the membrane against the detrimental effects of bile acids in the gastrointestinal tract while conventional vesicles like liposomes and niosomes, can cause dissolution and undergo enzymatic degradation in the GI tract. These bile salts stabilized vesicles are known as blossoms. These show various advantages, including biocompatibility as they are produced from naturally occurring lipids. Bile salts along with lipid content increase the bioavailability of enclosed bioactive substance and act as penetration enhancers. These have been found to increase the bioavailability of drugs as they can readily absorb through the small intestine into the portal circulation (hepatic circulation). Through this circulation, they approach to liver and release the drug, so also found to be an effective tool in drug targeting to liver[84]. This delivery system exhibits inherent adjacent properties when associated with an antigen. These allow only a small quantity of an antigen to be effective and both cellular and humoral immune responses can be induced. Shukla *et al*.,[85] showed that HBsAg loaded bilosomes produced both systemic as well as mucosal antibody responses upon oral administration. Arora *et al*.,[86] developed and characterized mannosylated bilosomes loaded with Hepatitis B surface antigen for dendritic cell targeting to provide enhanced bioavailability with

extended humoral, cell mediated and mucosal immune responses.

Emulsified Drug Delivery System

Nanosuspension

Nanosuspensions are part of nanotechnology and consists of the pure poorly water soluble drug without any matrix material suspended in dispersion. One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like itraconazole, simvastatin, and carbamazepine, which are feebly soluble in both aqueous and nonaqueous media, belonging to as classified by biopharmaceutical classification system. Formulation as nanosuspension is an attractive and promising alternative to solve these problems. This approach is most suitable for the compounds with high log P value, melting point and dose[87,88]. Cui *et al*,[89] demonstrated the increased in bioavailability *in vivo* test, the maximum concentration (Cmax) and area under curve ($AUC_{0\rightarrow12}$) values of nanosuspension in rats were approximately 6.1-fold and 5.0-fold greater than that of commercial tablets. In another study, 1.5-fold and 1.8-fold higher bioaviability by nanosuspensions of dried itraconazole (ITZ) prepared by spray drying method than sporanox pellets (commercial product) respectively[90].

Nanoemulsions

Nanoemulsions are dispersions of shear-induced ruptured nanoscale droplets. It can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000nm. It is very likely that nanoemulsions played commercially important role; since they can typically formulate using significantly less surfactant than is required for nanostructured lyotropic microemulsion phases[91]. Nanoemulsions are kinetically stable, even for several years. The term sub–micron emulsion (SME)[92], mini-emulsion[93] and ultra-fine emulsion[94] are used as synonyms. It has to be considered that these novel nanoemulsions again are fluid systems where the production is not easy to handle. Different techniques for the production of nanoemulsions are High pressure homogenization (HPH) where, disruptive forces are responsible for conversion of coarse emulsion into nanoemulsion and Low energy emulsification methods **(**LPH) where, condensation forces are utilized for this purpose[95]. A narrow size distribution can be obtained using Micro fluidization technique, where emulsions are forced through micro channels in the central chamber of the microfluidizer using high pressure pump[96,97]. A heterogeneous distribution of droplet size is achieved using Ultrasonication technique (destructive) that use ultrasound energy to disrupt macroscopic droplets. Lipophilic drug entrapped lipid nanoemulsions improved bioavailability of drugs by increasing drug absorption through the gastrointestinal tract[98]. Ramipril nanoemulsions were prepared comprising of sefsol 218, tween 80, carbitol, oil, surfactant, co-surfactant, aqueous phase and standard buffer solution (pH 5) respectively. The absorption was increased 2.94 times as compared to conventional capsules and 5.4 times compared to drug suspensions. Hence, it's used for geriatric and pediatric patients[99]. Nanoemulsions containing Saquinavir (SQV) were prepared by the ultra-sonication method for the improving SQV oral bioavailability. SQV was dissolved in different types of edible oils rich in essential polyunsaturated fatty acids (PUFA) as internal oil phase while external phase consisted of surfactants Lipoid®-80 and deoxycholic acid dissolved in water of the nanoemulsions. Flax-seed and safflower oil-containing nanoemulsions, formulated with deoxycholic acid, improved the oral bioavailability and brain uptake of SQV as compared to the aqueous suspension formulation[100]. Further bioavailability of ezetimibe was increased using nanoemulsion formulation of ezetimibe containing capryol 90, tween 20, PEG 400 and double distilled water. The absorption of ezetimibe from nanoemulsions, increased bioavailability was 3.23-folds and 4.77 folds as compared to drug suspension and conventional tablet respectively[101]. Cefuroxime axetil nanoemulsion was formulated utilizing campul, soya lecithin, deoxycholic acid, pluronic F127 and distilled water by using sonication method. *In vivo* studies indicated that $AUC_{0\text{-}24}$: 325.3 were increased for nanoemulsions as compared to $AUC_{0\text{-}24}$: 165.3 there by showing improved oral bioavailability[102].

Self emulsifying drug delivery systems

Emulsion system used for bioavailability enhancement are generally having their own set of complexities, including stability and manufacturing problems associated with their commercial production. Therefore, such problems may be surpassed by using self-emulsification systems[103]. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drugs, lipids, oils and surfactants sometimes including hydrophilic cosolvents or cosurfactants. It has the ability to form fine oil in water (o/w) emulsions or micro/ nano emulsions upon gentle agitation following dilution with the aqueous phase in the GI tract[104]. Self-emulsifying drug delivery systems are a cardinal technique for enhancing bioavailability of poorly soluble and permeable drugs. For instance, SEDDS of Coenzyme Q10 (CoQ10) were developed through construction of pseudo-ternary phase diagram. *In vivo* studies of optimized formulation was performed and compared to powder formulation of CoQ10, significant increased in the Cmax and area under the curve (AUC) of CoQ10 compared to powder formulation of CoQ10 ($P < 0.05$). Thus SEDDS are effective oral dosage for improving oral bioavailability of lipophilic drug, CoQ10 improving dissolution and solubility[105]. Self-microemulsifying drug delivery systems' (SMEDDS) indicates the formulations forming transparent microemulsions with oil droplets ranging between 100-250 nm**.** Zhai *et al*.,[106] prepared curcumin-loaded SMEDDS and *in situ* absorption property was evaluated in intestines of rats, results showed significant increase in oral bioavailability by SMEDDS compared with curcumin suspension. In another illustration absorption of exemestane (is a novel, very potent, orally active, selective, and irreversible steroidal aromatase inhibitor) from SMEDDS resulted in about 2.9-fold increased in bioavailability compared with the suspension[107]. 'Self-nano-emulsifying drug delivery

systems' is a recent term construing the globule size range less than 100 nm. Self-nanoemulsifying drug delivery system (SNEDDS) for the oral delivery of zedoary turmeric oil (ZTO) were parepered and animal studies were performed. Results showed that when ZTO-SNEDDS were given orally in the rats, both AUC and C_{max} of germacrone (GM), a representative bioactive marker of ZTO increased by 1.7-fold and 2.5-fold respectively compared with the unformulated ZTO[108]. SEDDS can exist in either liquid or solid states. A new approach Solid-SEDDs has been used as an alternative to conventional liquid SEDDS. S-SEDDS are formed by incorporation of liquid/semisolid ingredients into powders/ nanoparticles. These S-SEDDS can be prepared by adsorptions to solid carriers, Spray drying, Melt extrusion, nanoparticle technology, and so on[109]. Choi and co-workers prepared solid SEDDS of dexibuprofen in order to enhance oral bioavailability of the drug and the results showed that the solid SEDDS gave significantly higher AUC and Cmax than dexibuprofen powder[110].

Metal based Drug Delivery System

Silica materials

Silica materials are promising source for drug delivery due to various advantages, can be easily surface modified with several molecules to improve, possess target drug delivery action as well as does not exhibit toxicity in biological system. These are classified as xerogels[111] and mesoporous silica nanoparticles (MSNs), e.g., MCM-41 (Mobil Composition of Matter) and SBA-15 (Santa Barbara University mesoporous silica material)[112]. They exhibit several advantages as carrier systems, including biocompatibility, highly porous framework and an ease in terms of functionalization[113]. These can be easily surface modified with several molecules to improve and target the cellular uptake over surface chemistry[114]. These are carriers among inorganic nanoparticles which most often are chosen for biological purposes. Sol-gel technique is frequently used to form silica xerogels loaded with drugs. A modification of the synthesis conditions, such as the ratio of reagents, temperature, concentration of the catalyst, and pressure of drying, allows to alter properties of xerogels used in controlled drug release[115], Phenytoin[116], doxorubicin[117], cisplatin[118], nifedipine[119], diclofenac[120], and heparin[121] are examples of drugs which have been loaded into xerogels using this technique. The best known types of mesoporous silica nanomaterials are MCM-41 with a hexagonal arrangement of the mesopores and SBA-15 with a well-ordered hexagonal connected system of pores[122]. By these processes, diverse types of drugs, including anticancer drugs[123], antibiotics[124], and heart disease drugs[125], have been embedded into MNSs. The silicalites and mesoporous silica nanoparticles potential application in photodynamic therapy has been also studied[126]. The MSNs properties make them an excellent material for various pharmaceutical and biomedical applications. The structure of MSNs enables the incorporation of both small and large molecules[127], adsorption of DNA, and gene transfer[128]. Zhao *et al*.,[129] have demonstrated the effects of nanoparticles (depending on the surface properties, structure and size) on human red blood cells (RBCs). The uptake of large silica nanoparticles by RBCs showed a strong local membrane deformation leading to a spiculation of RBCs, internalization of the particles, and eventual hemolysis. On the contrary, adsorption of small particles occurred without affecting membrane or morphology of RBCs. Zhanga *et al.,*[130] developed sandwich-like magnetic mesoporous silica nanospheres (M-MSNs) by incorporating superparamagnetic magnetite/polystyrene (Fe_3O_4/PS) nanospheres. This drug carrier showed high adsorption capacity by enhancing salmon sperm DNA as well as rapamycin drug delivery. Zhang *et al.,*[131] synthesized and characterized heparinized multifunctional mesoporous silica nanoparticles, which not only maintains intrinsic functions of baremagnetic and fluorescent mesoporous silica materials such as targeting, imaging, and sustained release of drugs, but also generates several novel activities such as the enhancement of biocompatibility, selective loading drugs, and dual loading of anticancer drug and bFGF. Mesoporous silica nanoparticles (MSNs) have attracted tremendous attention in recent years as drug delivery carriers due to their large surface areas, tunable sizes, facile modification and considerable biocompatibility. In recent years various studies proved the properties of silica nanoparticles as oral drug or gene carrier[132,133]. Silica nanoparticles could also serve as carriers for anticancer drugs such as doxorubicin. It was reported, that mesoporous silica nanoparticles (MSN) release the drug over a period of 20 days in a constant rate[134].

Carbon nanomaterials

Carbo nanomaterials are differentiated into nanotubes (CNTs) and nanohorns (CNH). CNTs are characterized by unique architecture formed by rolling of single (SWNCTs – single walled carbon nanotubes, size - 0.4-2nm in diameter) or multi (MWCNTs – multi walled carbon nanotubes, size-1.4-100nm) layers of graphite with an enormous surface area and an excellent electronic and thermal conductivity[135]. Biocompatibility of nanotubes may be improved by chemical modification of their surface[136]. Carbon nanotubes can be produced small enough to pass through holes in tumours or to transport DNA[137]. Drug release from carbon nanotubes can be electrically or chemically controlled. Nanohorns – a type of the only single-wall nanotubes– exhibit similar properties to nanotubes[138]. CNTs can be used as drug-delivery vehicles or 'nanocarriers' in cancer therapy and other areas of medicine without causing toxicity to healthy tissue while allowing prolonged release of the drug[139]. The poorly water-soluble anticancer camptothecin has been loaded into polyvinyl alcohol-functionalized MWNTs and reported to be potentially effective in treatment of breast and skin cancers[140]. Liu *et al.,*[141] conjugate paclitaxel (PTX), a widely used cancer chemotherapy drug to branched polyethylene-glycol (PEG) chains on SWNTs via a cleavable ester bond to obtain a water soluble SWNT-paclitaxel conjugate (SWNTPTX), the study showed promising role of this chemically functionalized single-walled carbon nanotubes tumor in targeted accumulation in mice and exhibit biocompatibility.

Polymer based drug delivery system

Polymeric nanoparticles

These are drug carriers of natural, semi-synthetic, and synthetic polymeric nature at the nano-scale to micro-scale range. They are collectively named as spheres and capsules. The most of the polymeric nanoparticles with surfactants offer stability of various forms of active drugs and have useful to smart release properties. polymeric particles proved their effectiveness in stabilizing and protecting the drug molecules such as proteins, peptides, or DNA molecules from various environmental hazards degradation[142]. Poly (lactide-coglycolide) nanoparticles are the most studied polymeric nanocarriers used in drug delivery system. Polymeric micelles consist of amphiphillic block copolymers, which can self-assemble to form micelles in aqueous solution. They have a narrow size distribution in the nanometer range and the core shell structure, in which hydrophobic segments are separated from the hydrophilic exterior. Drugs can be partitioned in the hydrophobic core of micelles and the outer hydrophilic layer forms a stable dispersion in aqueous media. Like liposomes, they can also be functionalized with PEG for stealth properties and with targeting ligands including antibodies to the micelle surface. Finally, drug delivery from nanoscale drug delivery systems can also be modulated and triggered by external influence. Ultrasound and magnetism have been used to accumulate chemotherapeutic drugs selectively at tumor sites. The future of nanotechnology in drug delivery will depend on rational design of nanotechnology materials and tools based on detailed and thorough understanding of biological processes. In a study, enhancement of bioavailability of Cefpodoxime Proxetil, Poorly water-soluble drugs were compared by using natural polymers methylcellulose, sodium alginate, and chitosan microparticles[143]. Kolhe *et al*., [144] formulated hydrophilic polymer Kollidon VA64, with surfactants Polyethylene glycol (PEG 4000), polyoxy 35 castor oil (Chremophor EL) and Sorbiton monolaurate (Montane 20PHA) as a plasticizer to improve dissolution and bioavailability enhancement of Efavirenz by Hot Melt Extrusion Technique. The study concluded that bioavailability and solubility were maximum with PEG 4000.

Dendrimer nanocarriers

The word, dendrimer is derived from the Greek word, Dendron, meaning a tree. The graphical representation of the structure of a typical dendrimer resembles a tree with branches. These have been most heavily explored for their potential as nanocarriers[145]. These are hyper branched structures that comprise of an inner core, a series of branches and outer surface with functional groups. Due to their nanometer size range, ease of preparation and functionalization they are attractive drug delivery systems. Bioactive functional molecules, such as therapeutic agents and imaging probes, can be either directly conjugated to the surface or encapsulated within the void volume of the polymer itself. Due to the presence of internal cavities it is possible to encapsulate therapeutic agents in the inner core. Their properties can be controlled by the functional groups on the outer surface. These are particularly well suited for precise size control and surface functionalization, allowing for their modification with drugs, imaging agents, surface charges, and targeting moieties[146]. These unique properties have made them one of the most promising nanocarrier platforms for biomedical applications, including several recent *in vivo* applications and clinical trials. Typically, given that a drug can be chemically modified, conjugation can confer unique advantages over encapsulation, including increased stability and tailored release kinetics via stimuli-responsive cleavable linkers. Although chemical conjugation confers unique advantages for targeted delivery, it is limited by the need for drugs to chemically modifiable groups. One approach to overcome this limitation has been to form complex drugs either via encapsulation or electrostatic complexation[147]. These can protect drugs from degradation and clearance. This may mean that an improved dosing regimen can be pursued, for example, replacing a daily infusion with a once weekly injection. Kono and coworkers used G3 and G4 ethylenediamine based polyamidoamine (PAMAM) dendrimers with poly (ethylene glycol) monomethyl ether (M-PEG) grafts to encapsulate the anticancer drugs methotrexate (MTX, 5) and doxorubicin (DOX, 6)[148]. Fernández *et al*.,[149] used polyamidoamine (PAMAM) dendrimers to improve aqueous solubility of methyl (5 [propylthio]-1H-benzimidazol-2-yl) carbamate, Albendazole (ABZ). The results obtained show that these polymeric structures have the capacity to enhance the solubility of ABZ, both lipophilic and specific hydrogen bond interactions contributing to the guest-host association.

Biological drug delivery system

Cyclodextrins

These starch derivatives are the most widely investigated for enhancing the solubility, stability, bioavailability and dissolution rate of poorly soluble drugs. The cyclodextrin molecules are relatively large (molecular weight ranging from almost 1000 to over 1500), these molecules can permeate biological membranes easily[150]. These have lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes, resulting in better stability, high water solubility, increased bioavailability or decreased undesirable side effects[151]. One of the unique properties of cyclodextrins is their ability to enhance drug delivery through biological membranes. The increase in solubility also can increase the dissolution rate and thus improve the oral bioavailability of BCS Class II drugs. The success rate of Cyclodextrins for enhancing the dissolution rate of poorly soluble drugs is witnessed by the presence of over 35 marketed drug products incorporating them as excipients. The examples include itraconazole-hydroxypropyl-_cyclodextrin, piroxicam-cyclodextrin and benexate-cyclodextrin[152]. These also exhibited increased nasal absorption of oligopeptide drugs like buserelin[153] and leuprolide[154]. Bioavailability after nasal administration of insulin in rats increased up to 100% with dimethyl β-CD (3–5%)[155]. Nasongkla *et al.*,[156] formed inclusion complexes of β lapachone (β-lap) with cyclodextrin HP β-CD. The result,

demonstrated the maximum enhancement of β- lap solubility to 16.0 mg/ml or 66.0 mM, more than a 400-fold increase over β-lap solubility in water (0.038 mg/ml or 0.16mM).

Phytosome

Phytosome is also called as Phytolipids delivery system which forms a bridge between the convectional delivery system and novel delivery system. It is a newly introduced patented technology developed by Indena to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, which enhances their absorption and bioavailability. The term "Phyto" means plant while "some" means cell-like, often referred as herbosome in certain literature. When treated with water, phytosomes assumes a micellar shape forming liposomal-like structures. In liposomes the active principle is dissolved in the internal pocket or it is floating in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane**.** The Phytosome technology produces a little cell, better able to transit from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood in such a way it protects the valuable components of the herbal extract from destruction by digestive secretions and gut bacteria. It has many advantages over other delivery systems, *i.e.*, phosphatidylcholine present in it, acts as a carrier as well as possessing hepatoprotective effects and stability and bioavailability much better than liposomes. Yanyu *el al*.[157] prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats was increased remarkably after oral administration due to an improvement of the lipophilic property of silybinphospholipid complex. Studies have shown ginkgo phytosome (prepared from the standardized extract of *Ginkgo biloba* leaves) produced better results compared to the conventional standardized extract from the plant (GBE, 24% ginkgo flavone glycoside and 6% terpene lactones)[158]. Grape seed phytosome is composed of oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, *Vitis vinifera*) of varying molecular size, complexed with phospholipids. The main properties of procyanidin flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma, protection against ischemia/reperfusion induced damage in the heart, protective effects against atherosclerosis thereby offering marked protection for the cardiovascular system and other organs through a network of mechanisms that extend beyond their great antioxidant potency[159]. A novel hesperetin was developed by Mukherjee *et al*.,[160] combined and made complex of it with hydrogenated Phosphatidyl choline. They also studied its antioxidant activity and pharmacokinetic studies in CC14 intoxicated rats along. The results of the study showed the phytosome has shown high antioxidant activity. Pharmacokinetic studies have revealed the improved bioavailability of phytosomes than the parent molecule at the same dosage[161]. Das and Kalita[162] developed and characterized Rutin phytosomes (RN-P). In the study, they found that oral bioavailability of Rutin was increased in Phyto-phospholipid complex (phytosomes) and RN-P also able to deliver rutin for a long duration as supported by the results of 24 hours permeation study, for relief in arthritis, rheumatism, athletic aches. The various techniques described can also be used in combination to enhance the bioavailability of the drugs (Table 2).

CONCLUSION

Bioavailability of the drug is the most essential factor that affects the formulation as well as the therapeutic efficacy of the drug. Basic requirement for oral absorption of the poorly aqueous soluble drugs are dissolution and formulation development solubility. Hence bioavailability enhancement of poor water solubility and low permeable drugs persist the most challenging aspects of drug development at formulation level. Particle size reduction, emulsification, cyclodextrin inclusions, etc. are the preferable conventional approaches for improving the dissolution rate of the drug. The advantages and disadvantages of various NDDS are shown (Table 3). Nanosuspensions showed tremendous improvement in the solubility, dissolution kinetics and bioavailability of hydrophobic drugs as well as SLN showed enhanced oral bioavailability. Emulsification technique which includes nanoemulsions, SEDDS, SMEDDS and SNEDDS are used for the improvement of *in-vitro* and *in-vivo* bioavailability. Hence there is a great potential in the development of novel drug delivery systems for bioavailability enhancement and it has proven its potential so far.

Conflict of interest

The authors of the Manuscript titled 'Role of novel drug delivery systems in bioavailability enhancement: At a glance' has no conflict of interest to declare.

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