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Nanoparticulate systems as drug carriers: the need

Abstract: Development of nanoparticles for drug delivery has progressed by leaps and bounds over the last few decades, facilitating the possibility of an efficacious therapy for some fatal diseases. This development has stemmed from either the unsuitable physicochemical characteristics of the existing drug molecules, such as limited solubility and hence poor bioavailability, or the inadequacy of the conventional delivery systems to provide safe and efficient delivery. This chapter focuses on the precise need for the development of these novel nanoparticulate drug carriers and reasons for their popularity with the drug delivery scientists. The text also discusses the various strategies, including different formulation and targeting approaches, which have been adopted to overcome the challenges presented by the inherent properties of the drug molecules. Examples of nanoparticulate drug delivery systems which have already gained market approval have been cited in the discussion, wherever applicable.

Key words: nanoparticulate drug carriers, solubility, bioavailability, targeting, nanoemulsions, nanocrystals, nanoparticles.

1.1 Introduction: nanoparticles for drug delivery

The last decade of drug delivery research has witnessed a boom in the development of the nano-drug delivery systems. The major drivers responsible for the initiation of this new revolution were the development

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of a plethora of varied nano-drug delivery systems, not only by the academic institutions but also by industrial organizations. This led to the availability of a huge database comprising several research papers and patents from all over world, describing these new dosage forms. Numerous funding agencies and industries actively promoted research into nanoparticulate drug delivery vehicles and huge investments were made to this end. All these diverse and concurrent efforts created an awareness about the immense potential of these new drug delivery systems, which were then looked upon as therapeutic regimens of the future.

There are many reasons behind the development and success of nanoparticulate drug delivery systems. A few years ago, the entire attention of pharmaceutical industry was focused on the novel developments in designing various dosage forms, primarily due to expiry of the existing patents, a surfeit of poorly soluble drug candidates and the problems of non-specificity from conventional dosage forms. Under these circumstances, the development of nanoparticulate drug delivery systems gained huge momentum due to a number of diverse factors listed in the following section of this chapter.

- The pharmaceutical industries were poised to provide quality products to the patient, at the same time increasing or maintaining their profitability. However, this process demanded extensive scientific innovation and financial support. Development of new chemical entities and their transition from the laboratory to market required the company to expend as high as 800 million US dollars [1]. Apart from a huge investment, the development of the new drug was also an extensively time consuming process with very limited success rates.
- Research progress in the drug discovery area resulted in the development of various poorly soluble drug candidates. The solubility limitations of these drug candidates, in turn, lead to poor bioavailability and lower therapeutic efficacy [2, 3]. In such situations, formulation of these therapeutic molecules into nanoparticulate delivery systems was observed to improve their bioavailability and hence elicit the desired therapeutic effects from these candidates. The nanoparticles also received a prominence due to other probable benefits like biodegradability, biocompatibility, high encapsulation characteristics and probability of surface functionalization [1–3].
- Nanoparticles were found to exhibit several advantages for parenteral drug delivery; counter to the aggregation phenomenon commonly observed with microparticles, the smaller size of nanoparticles endowed them with better distribution profiles during systemic

administration. Nanoparticles enabled an effective systemic circulation, thus leading to better therapeutic outcomes. Better systemic circulation was found to be specifically important for cancer therapies, where nanoparticles could infiltrate through the vasculature of tumor tissue and provide targeted therapeutic effects [4].

- First pass metabolism is one of the key concerns for many commercial and upcoming drugs. This phenomenon accounts for their low bioavailability and reduced efficacy at the site of action. In this regard, nanoparticulate drug delivery vehicles were particularly advantageous because of their likelihood in being modulated for site specific delivery/targeted delivery. Apart from their specificity, nanoparticles were also found to mitigate drug related side effects and dose related toxicities, resulting in enhanced bioavailability of the encapsulated agent and excellent patient compliance [1, 3, 5].
- Owing to their small size, nanoparticles were found to effectively traverse many biological barriers. Of significant importance is their ability to permeate the blood brain barrier (BBB). Although brain administration is an effective route for the treatment of various brain diseases, it is severely limited due to the highly impermeable nature of the BBB. Because of their potential to cross this barrier, numerous publications have demonstrated the effectiveness of nanoparticles for targeting various central nervous system disorders [6]. Nanospectra Bioscience, Texas, USA, has recently initiated a clinical trial of nanoparticle based 'nanoshells' for the treatment of brain tumors [7].
- The size of nanoparticles offers distinct advantages when compared with conventional dosage forms. The tunable size of these systems greatly influences the release profile of the encapsulated active component, so a formulator could thus control the drug release at the site of action [8, 9].
- Nanoparticles were found to be highly versatile systems to encapsulate and delivery not only chemical drug moieties but also nuclic acid therapeutics (DNA, siRNA), and imaging and diagnostic agents, for site-specific delivery and detection. Various ligands can be attached to the surface of nanoparticles to guide them to specific locations within the body [9, 10].

Thus nanoparticulate drug carriers found applications in several diverse quarters of drug delivery research and, due to their tunable properties, they were foreseen as the future of the pharmaceutical and biotechnology industry.

1.2 Need: solubility, bioavailability, targeting and more

Drug transport through a biological barrier largely depends upon its solubility. Solubility exhibits an important influence on drug permeation and absorption. The solubility of drugs has been a concern for formulation scientists because of the difficulties in developing oral and parenteral delivery systems for poorly soluble drugs. Though the pharmaceutical sector is witnessing vast advances in drug discovery and its therapeutic horizon is expanding, it is the existing drug molecules and novel drug candidates that pose major solubility problems. Various reports indicate that approximately 40% of the drugs which are currently in the market have poor water solubility [11]. About one-third of the drug candidates in the pharmacopoeia exhibit the same solubility limitations. Low water solubility in turn hampers adequate absorption and hence leads to low therapeutic efficacy [12]. The solubility constraint of drugs and novel drug candidates is thus one of the major obstacles to the development of therapeutically effective drug delivery systems.

Nanoparticles made from natural/synthetic polymers, lipids, proteins and phospholipids have received greater attention due to higher stability and the opportunity for further surface modifications [13]. They can be tailored to achieve both controlled drug release and disease-specific localization, either by tuning the material characteristics or by altering the surface chemistry [14]. It has been established that nanocarriers can become concentrated preferentially in the tumor mass, sites of inflammation, and at sites of infection by virtue of the enhanced permeability and retention (EPR) effect of the vasculature. Once accumulated at the target site, hydrophobic biodegradable polymeric nanoparticles can act as a local drug depot, depending upon the make-up of the carrier, thus providing a reservoir for continuous supply of encapsulated therapeutic compound at the disease site, such as, a solid tumor. These systems, in general, can be used to provide targeted (cellular/tissue) delivery of drugs, to improve oral bioavailability, to sustain drug/gene effects in the target tissue, to solubilize drugs for intravascular delivery, or to improve the stability of therapeutic agents against enzymatic degradation (nucleases and proteases), this being especially relevant for protein, peptide, and nucleotide based agents [13,15, 16]. Thus, the advantages of using nanoparticles for drug delivery result from two main basic properties: their small size and the use of biodegradable materials.

Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over conventional dosage forms as drug

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delivery carriers [17]. A further advantage over conventional drug delivery systems is their better suitability for intravenous (i.v.) delivery. The smallest capillaries in the body are 5–6 μm in diameter. Therefore the size of particles being distributed into the bloodstream must be significantly smaller than 5 μm, without forming aggregates, to ensure that the particles do not lead to an embolism. Additionally, some types of cells permit the uptake of only sub-micron particles and not their larger counterparts. Generally nanoparticles have relatively higher intracellular uptake compared to microparticles and are available to a much wider range of biological targets due to their small size and relative mobility. Desai et al. found that 100 nm nanoparticles had a 2.5 fold greater uptake than 1 μm microparticles, and 6 fold greater uptake than 10 μm microparticles in a $CaCo^{-2}$ cell line [16]. Secondly, the use of biodegradable materials for nanoparticle preparation allows sustained drug release within the target site over a period of days or even weeks.

With regards to the material of formulation, biodegradable nanoparticles formulated from polymers and lipids have been developed for intracellular sustained drug delivery, especially for drugs with an intracellular target [13, 16]. Rapid escape of these nanoparticles from the endo-lysosomal compartment to the cytoplasmic compartment has been demonstrated [13, 17]. Additionally, they were demonstrated to effectively sustain the intracellular drug levels, thus allowing a more efficient interaction with the cytoplasmic receptors. Thus, nanoparticles could serve as effective delivery vehicles for drugs with cytoplasmic targets.

To summarize, nanoparticles have proven advantages over the conventional dosage forms. They offer a reliable alternative to the pharmaceutical industry to improve the therapeutic effects of existing drugs, elicit better effect from new chemical entities and to deliver sensitive molecules like proteins, peptides, DNA and RNA.

1.3 Specific nanoparticulate strategies for overcoming solubility and bioavailability limitations

1.3.1 Nanoemulsions

Nanoemulsions are optically isotropic and thermodynamically stable systems of two immiscible liquids – typically water, oil and

surfactant(s) – in which one liquid is dispersed as droplets in another liquid. Emulsions with nanoscopic droplet sizes (typically in the range of 20–200 nm) are often referred to as nanoemulsions [18]. Nanoemulsions offer enhanced solubilization capacity for poorly soluble drugs, increased drug loading, and in turn lead to a higher bioavailability of the formulated therapeutic moiety. Various GRAS (generally regarded as safe) approved, saturated and unsaturated fatty acids and nonionic surfactants are commonly used for formulating the nanoemulsions. The formulation of nanoemulsions can either involve appropriate energy inputs (ultrasonication, high pressure homogenization, microfluidization) or may be a spontaneous process. There are a few commercial products like Estrasorb® and Flexogan® which are based on nanoemulsion technology [19, 20]. Estrasorb® is estradiol topical emulsion developed by Novavax and is recommended for the reduction of vasomotor symptoms in menopausal women. Estrasorb® is composed of soyabean oil, water, polysorbate 80 and water and is based on micellar nanoparticle technology. This technology proves that poorly water soluble molecules like estradiol can be successfully formulated and commercialized using nanoparticulate delivery vehicles [20, 21].

Yet another example of a nanoemulsion based product is that of Flexogan® developed by AlphaRx, Canada, which is a pain relief cream based on colloidal dispersion of nanoparticles. The oil droplets contain natural pain medicaments like menthol and camphor and as nanoparticles permeating faster through the skin, thereby providing a rapid relief. Once again in this case the nanoparticulate delivery is responsible for a higher bioavailability and quicker onset of action of the encapsulated actives [22].

1.3.2 Nanocrystals

Bioavailability of poorly water soluble drugs is frequently related to the particle size of the drug molecule. Particle size reduction of these drug molecules improves the overall surface area, dissolution properties and thus leads to a higher bioavailability of the drug. Formulating drug nanocrystals is one of the most successful strategies to improve the drug solubility and bioavailability. Numerous methods may be employed to generate the drug nanocrystals which include high pressure homogenization, media milling and nanoprecipitation [12, 23].

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High-pressure homogenization

High-pressure homogenization involves passage of the coarse drug suspension along with a suitable stabilizer through the tiny homogenizer gap at a very high pressure (up to 2000 bar) [23]. This process can be performed in presence of water or non-aqueous media. The non-aqueous medium is specifically useful when there are chances of drug degradation because of aqueous media. The pressure is responsible for the generation of nanoparticles due to various principles, such as cavitation, disintegration and shearing, and based upon these, three important technologies have been designed for nanocrystal production using high-pressure homogenization. The technologies are Piston gap homogenization in water (Dissocubes® technology), Microfluidizer technology (IDD-P™ technology) and Nanopure® technology [12, 23].

Triglide® is the first clinically approved nanocrystal product developed using high-pressure homogenization and is indicated for the treatment of hypercholesterolemia. Triglide® has been produced using the IDD-P™ technology by Skyepharma and has been marketed by Sciele Pharma Inc. [23, 24]. The drug candidate in this product is fenofibrate, a lipophilic compound which is practically insoluble in water. The bioavailability of fenofibrate is severely limited due to its poor water solubility although clinical observations have revealed a higher bioavailability in fed-state patients. This has been attributed to the lipids and associated compounds in the meal which enhance its solubility and hence absorption [25]. In another study, micronization of fenofibrate was found to enhance its dissolution and hence its oral bioavailability. This study also confirmed the reason for nanocrystals of fenofibrate, with a still lower particle size, to further improve its bioavailability, when compared with the micronized form [26].

Media milling

Of all the homogenization methods, media milling has been the most successful in producing drug nanocrystals, primarily due to its simplicity and scalability. Additionally, media milling is also economical compared to the other methodologies. Here, the nanoparticle generation depends upon the shearing forces and impact between the moving beds of milling material and the mixture of drug and stabilizer. Despite a few limitations of this method like drug loss and adhesion, it is still preferred by the pharmaceutical industry for generating drug nanoparticles [11, 27].

Rapamune® is one of the first nanocrystal products developed using media milling technology by Elan Drug Technologies. Rapamune®

consists of sirolimus, a poorly water soluble compound, indicated for prophylaxis of organ rejection in patients receiving renal transplants. Elan termed this technology as NanoCrystal® technology and it involves the particle size reduction of drug to formulate drug nanoparticles [11, 23]. The particle size reduction leads to a higher dissolution, higher absorption and hence enhanced bioavailability. Rapamune® was found to overcome the problems associated with rapamycin, the conventional dosage form of sirolimus. It demonstrated 27% more bioavailability, improved patient compliance and better shelf-life when compared with conventional product. Additionally, the product also met with tremendous economic success [28–30].

Emend® is another successful product of Merck and developed by Elan Drug Technologies. Aprepitant, the active ingredient of Emend®, has poor aqueous solubility (3–7 μg/ml) with moderate permeability ($CaCo^{-2}$ permeability reported at 7.85×10^{-6} cm/s). With the conventional formulation of aprepitant, it was observed that food plays a significant role on the rate and amount of drug absorbed. Emend®, on the other hand, eliminated this requirement and the drug absorption and bioavailability was enhanced by 600%, as compared to the conventional product. This product was also recently approved in Japan, and is now available in US, Europe and Japan 31, 32].

Various other products like Tricor® (Fenofibrate), Megace ES® (Megestrol), Invega®, Sustenna®/Xeplion® (Paliperidone palmitate) are also produced as nanoparticles, by media milling, to overcome the solubility issues. The details of all such products have been listed in Table 1.1.

Nanoprecipitation

The above two methods describe the 'top-down' approach of particle size reduction, aimed to enhance the solubility and bioavailability of drug candidates. These methods are relatively simple and economical; however, the processes possess complexity for formulating sensitive molecules with respect to size and surface control.

In such cases, the 'bottom-up' approach provides an alternative challenging method for generating drug nanoparticles. The approach is specifically useful when there is a need to load a nanoparticle with many active ingredients or the surface of nanoparticle needs to be functionally altered [11, 33, 34].

Based on this approach, the nanoprecipitation method involves the generation of drug nanoparticles by nucleation and growth of the drug

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Table 1.1 Nanoparticle formulations for poorly water soluble drugs (adapted from [11])

Trade name	Drug	Nanoparticle process	Dosage form	Intended therapeutic use	Industry
Triglide®	Fenofibrate	**High-pressure homogenization**	Oral tablet	Hypercholesterolemia	Skye Pharma
Rapamune®	Sirolimus		Oral tablet	Immunosuppression	Elan/Wyeth
Emend®	Aprepitant		Oral capsule	Antiemetic	Elan/Merck
Tricor®	Fenofibrate		Oral tablet	Hypercholesterolemia	Elan/Abbott
		Media milling			
Megace ES®	Megestrol		Oral suspension	Antianorexia, cachexia	Elan/Par Pharmaceuticals
Invega®, Sustenna™, Xeplion®	Paliperidone palmitate		Intramuscular suspension	Schizophrenia	Elan/Johnson & Johnson
Estrasorb®	Estradiol		Topical emulsion	Vasomotor symptoms associated with menopause	Novavax/Graceway
Flexogan®	Camphor, menthol, methyl salicylate		Topical emulsion	Analgesic	AlphaRx
		Nanoemulsion			
BF-200 ALA-gel	5-Amino-levulinic acid		Topical gel	Actinic keratosis for photodynamic therapy	Biofrontera
Restasis	Cyclosporine		Ophthalmic emulsion	Chronic dry eye disease	Allergan

crystals. The nucleation process is triggered by dissolving excess of drug in a suitable solvent, resulting in a super-saturated solution. The supersaturated mixture is then normally added to an antisolvent-stabilized mixture to produce nanocrystals. Various parameters in this process control the ultimate size and surface characteristics. Nanocrystals produced by nanoprecipitation method are presently in preclinical stage and to date these systems have not yet met with clinical or industrial success [11, 33–35].

Though the pharmaceutical industry is witnessing enormous developments in the field of nanoparticulate drug delivery systems, it is still faced with numerous scientific queries and challenges. Limited solubility and poor bioavailability allowed the pharmaceutical industry to look beyond conventional drug delivery systems and that was the primary reason for the nano-drug delivery systems to occupy a significant position in formulation research and development. The development of these technologies is limited to few pharmaceutical industries and continents. Wide-ranging acceptance of the nanoparticle based drug delivery systems is still far from realization. The developed nanoparticulate drug delivery systems need to be investigated for their own unique pharmacological actions and safety profiles. The drug release profiles, *in vitro–in vivo (IVIVC)* correlations, pharmacokinetic and pharmacodyanamic profiles need to be thoroughly established before they can be routinely adopted for clinical applications.

1.3.3 Nanoparticles for targeting

One of the major drawbacks associated with conventional drug delivery systems is their non-specific nature. The conventional dosage forms are generally formulated using an excess of drug as compared to its actual dose because these formulations deliver only a small fraction of this drug to the affected area, while a major part is distributed throughout the body. This random distribution leads to unwanted side effects and toxicities [36]. Nanoparticles are able to provide site specificity and can be targeted to a specific tissue or organ of the body to give the desired therapeutic effect with minimal side effects. The targeting capacity of nanoparticles is one of the most important reasons behind their success. Targeted drug delivery has been proven highly beneficial for the treatment of cancer, since the majority of the anticancer drugs are normally known to harm non-cancerous body cells. [37]. Drug targeting through nanoparticles is usually achieved by their surface functionalization with

various ligands, which can identify and bind to certain cellular receptors of the body [38].

Targeted drug delivery is a broad terminology and has been investigated for decades, specifically for cancer. This research has also been extended to other organs susceptible for site-specific diseases and the following sections of this chapter have been dedicated to these numerous facets of targeted drug delivery. Targeted drug delivery is normally achieved either via active targeting or passive targeting [39].

Active targeting involves direct routing of the drug and/or the delivery system to the diseased biological site to minimize the side effects. RNA interference (RNAi) therapy and monoclonal antibodies are well known examples of this approach. The RNAi approach is a rapidly expanding field and has particularly gained a momentum due to huge investments by the pharmaceutical industry in developing RNAi based therapeutics. This therapy has potential for the treatment of various fatal diseases like cancer, viral infections and various genetic diseases. The details of RNAi therapy are described in Chapter 2 of this book. On other hand, monoclonal antibody-based therapy has been investigated for various diseases, such as cardiovascular disorders, inflammatory disorders and cancer. The antibodies bind only to the specific cells which they are intended to target and stimulate an immunological response against these targeted cells [40, 41].

Passive targeting may be achieved employing drug delivery systems administered via different delivery routes, where the delivery system enhances the effect of the drug utilizing the functions of the targeted site. For example, drug delivery is enhanced through the more permeable cancer tissues as compared to their normal counterparts, due to leaky vasculature and enhanced permeation retention (EPR) effect of the former. Similarly, delivery through nasal, transdermal and intra-uterine routes are also utilized in passive targeting [40, 42].

Targeted therapy of cancer

Targeted delivery for cancer is one of the most-investigated areas, with the majority of commercial products belonging to this category. Conventional cancer therapy, i.e. chemotherapy and radiotherapy, are effective in the early stages of cancer detection; however, adverse effects arising from these therapies pose a major challenge [43]. Nanoparticle-based targeted drug delivery provides a huge potential for cancer therapy, primarily due to the favorable dimensions and surface functionalities of these carrier systems. These systems can enter tumor cells and interact

with cellular receptors, and are thus able to inhibit the growth and spread of the cancer. Targeted nanocarriers for cancer facilitate precise cellular and molecular alterations and are hence more effective and less harmful to the normal cells than conventional treatments, including chemotherapy and radiotherapy [44]. Table 1.2 cites some of the nanoparticulate systems, along with their respective oncological indications, which have been developed by various industries.

The majority of nanoparticulate systems for targeted drug delivery to cancers are surface functionalized with appropriate ligands. These ligands facilitate cellular binding, internalization and specific therapeutic effects. Optimization of the process of attachment of the ligand to the nanoparticulate surface is one of the chief factors that govern the precise targeting of nanoparticles. Another important factor includes exclusivity of the targeted ligand to the cancer cells with negligible occurrence on the other healthy cells of the body [43–45]. Some of the common targeting strategies have been listed in Table 1.3.

The past decade has witnessed a sharp rise in the number of targeted drug nanoparticles that have been approved for cancer therapy. Liposomal nanoparticles were the first in this category and were successful in alleviating the adverse effects associated with drugs in conventional dosage forms [43]. An excellent example of this is liposomal doxorubicin,

Table 1.2 Nanoparticle based formulations for targeted cancer therapy (adapted from [1])

Brand	Nanoparticulate carrier	Therapeutic use	Industry
DaunoXome	Liposomal daunorubicin	Kaposi sarcoma	Gilead
Doxil/Caelyx	Liposomal doxorubicin	Cancer, Kaposi sarcoma	Ortho-Biotech, Schering–Plough
Depocyt	Liposomal cytarabine	Cancer	SkyePharma, Enzon
Myocet	Liposomal doxorubicin	Breast cancer	Zeneus Pharma
Abraxane	Paclitaxel Protein-bound nanoparticles	Cancer	Abraxis BioScience, AstraZeneca
Oncaspar	PEG-asparaginase	Leukemia	Enzon
Diagnostic			
Resovist	Iron nanoparticles	Liver tumors	Schering
Feridex/ Endorem	Iron nanoparticles	Liver tumors	Advanced Magnetics, Guerbet

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Table 1.3 Targeted cancer therapy using nanoparticles

Target	Targeting ligand	Therapeutic application	References
HER-2 receptor transferrin receptor (TfR)	Antibody fragments, consisting of only the Fab binding regions	Breast Cancer, Brain Cancer, Colon Cancer	[46–51]
Prostate specific antigen receptor	Whole proteins	Breast Cancer	[50, 51]
Urokinase plasminogen activator receptor	Urokinase plasminogen activator (uPA)	Breast Cancer	[52]
	U11 peptide	Prostate Cancer, Breast cancer	[53–55]
$\alpha_5\beta_3$ integrin receptors	RGD peptide	Breast Cancer	[56–58]
Folate Receptor	Folic acid and modified folic acid	Breast Cancer, Lung cancer, Ovarian Cancer, colon cancer	[59–61]
Sigma receptors	Anisamide	Lung Cancer, Prostate cancer	[62]

which resulted in a significant reduction in the severe cardiotoxicity of the native drug. Doxil® (pegylated liposomal doxorubicin) was the first nanoparticulate product approved for targeted cancer therapy. Pegylated liposomes demonstrated improved pharmacokinetic and pharacodynamic profiles. Polyethyeleneglycol (PEG) coating thus constituted one of the first, commercial targeting strategies [43, 63]. It also afforded additional stability to the nanoparticles and prevented their elimination by reticuloendothilial system (RES). Tagging of PEG on nanoparticle surface, also known as 'steric stabilization' or 'stealth effect', was also reported to improve their blood circulation time and uptake by macrophages [43, 64].

Abraxane® is another commercially successful product for the targeted cancer therapy. Abraxane® (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nm. Paclitaxel, indicated for

breast cancer therapy, is a poorly soluble molecule. There are many formulation challenges associated with paclitaxel like inherent solubility problems and toxicity issues. Moreover, the existing formulation (Taxol®) of this drug exhibits severe adverse effect attributable to its excipient, Cremophor EL. When compared with Taxol®, Abraxane® provided an improved tumor cell penetration of paclitaxel and decreased the occurrence of Cremophor related adverse effects [43, 65, 66].

These benefits of Abraxane® are due to the natural property of its key ingredient, albumin, to transport the lipophilic molecules through non-covalent binding. Albumin, a predominant plasma protein, binds to the glycoprotein receptor gp60 and maintains the transendothelial oncotic pressure gradient by regulating the transport of bound/unbound plasma components such as fatty acids, steroids, thyroxine, and amino acids. The receptor subsequently binds to caveolin-1 with successive formation of caveolae, a key determinant of transcellular endothelial permeability. Albumin is accumulated in breast, lung, head, neck and prostate cancer by binding with the secreted protein acid rich in cystein (SPARC). SPARC-albumin interaction supports the accumulation of albumin in tumor and increases the effectiveness of albumin-bound paclitaxel (nab-paclitaxel). The success of nab nanoparticles has paved a way for their use in different types of cancer, and a large number of clinical trials, utilizing these nanoparticles, are presently in progress [43, 67–70].

Brain targeting

The drug development for the treatment of central nervous system (CNS) disorders has been increasing; however, the preclinical and clinical successes are still far from reality. The global market for drugs for central nervous system (CNS) diseases is limited due to various reasons like high cost of drug development, a very high risk to benefit ratio, a limited understanding of these diseases and the formulation intricacies for brain delivery [71]. Other difficulties in efficiently treating CNS disorders include the limited number of available drugs and lack of a broad understanding of the etiology of brain diseases. Examples of the diseases in this category (see Figure 1.1) include Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, HIV infection of the brain and brain tumors [71, 72].

However, in the past few years, there has been a tremendous improvement in drug discovery for CNS diseases. According to a report from the Pharmaceutical Research and Manufacturers of America (PhRMA), approximately 313 diverse drugs for various CNS disorders

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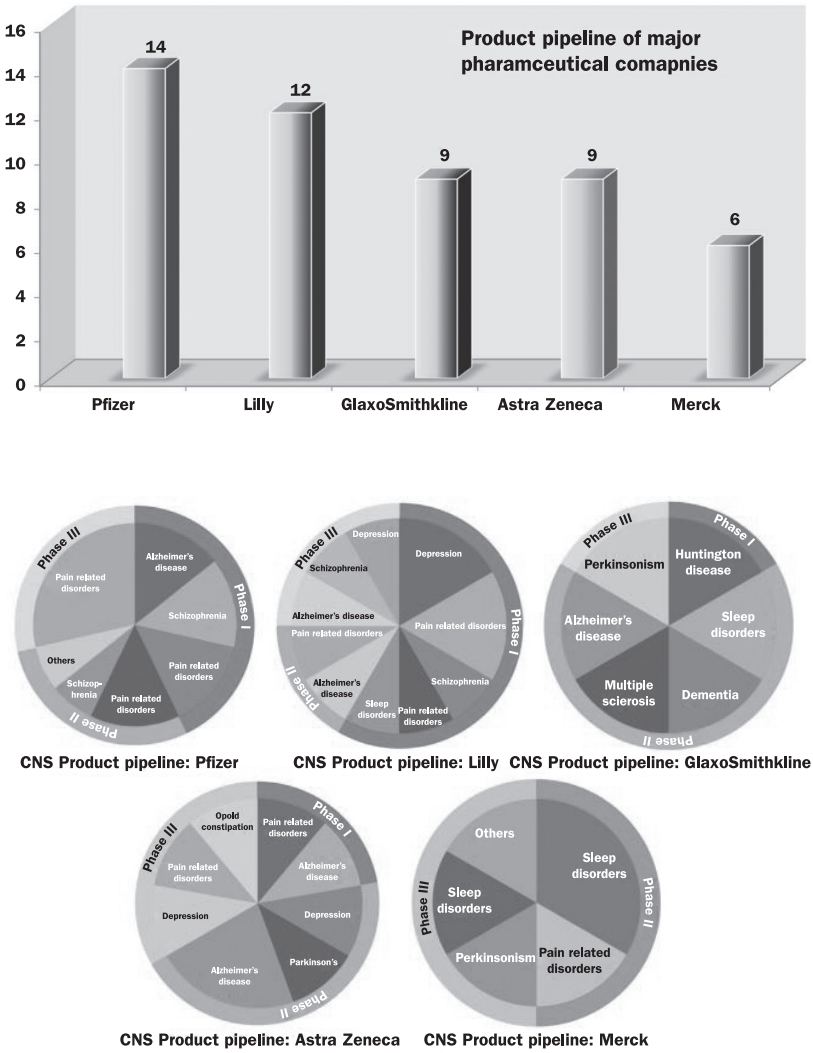

Figure 1.1 An overview of market progress in CNS drug development (Data is based on the press information released by respective pharmaceutical companies till July 2012)

(majorly addiction and depression) are currently in research and production pipeline. Additionally, the Tufts Center for the Study of Drug Development states that approximately 1747 drugs are in development for various other CNS disorders like multiple sclerosis and epilepsy [73].

However, the physicochemical characteristics of most of these molecules are unfavorable for their efficient transport through the blood brain barrier (BBB), one of the most difficult biological barriers, which hinder provision of an effective strategy for treating CNS diseases. The BBB consists of different cellular components, such as endothelial cells, pericytes, astrocytes, and microglial cells, interconnected with each other by tight, impermeable junctions. In presence of these natural barriers, drug delivery to the CNS may be performed using invasive methods or non-invasive methods or their combinations. Invasive methods can generate various complications, and are thus adopted only in cases of fatal diseases. In the non-invasive category, nanoparticulate drug carriers have demonstrated great potential for successful therapies [74]. The surface modification of these systems allows them to be directed to specific receptors in the brain while their small size can be exploited for traversing the BBB. Additionally, nanoparticles also prevent structural modification of the drug and can deliver the drug to the desired site in its original form. Other properties of nanoparticles, like biodegradability, low particle size (≈100 nm), prolonged circulation by surface modification, receptor medicated transcytosis, large-scale production ability, possibility for loading of drugs/peptides and the ability to control the release of encapsulated active agent, make them ideal for targeted drug delivery to the brain [72–75]. Table 1.4 indicates various targeting strategies for brain targeting using nanoparticles.

Colon targeted nanoparticles

There is an immense market opportunity for colon targeted drug products and it has been estimated that the US market for products of colorectal cancer will reach $6050 million by 2016, at a Compound Annual Growth Rate (CAGR) of 8.6% [98]. Colon targeted drug delivery has steadily grown for the treatment of various colon specific diseases as well as for the systemic delivery of macromolecules such as peptides. Targeting the colon has become very important for treating diseases like inflammatory bowel disease, Crohn's disease, colon cancer and ulcerative colitis. Our research group has specifically investigated the efficacy of polymeric nanoparticles for colon cancer as well as for ulcerative colitis [99].

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Table 1.4 Examples of brain-targeted nanoparticles at preclinical stage (modified from [76])

Route/Ligand	Nanoparticles	Drug	Therapeutic action	Ref.
Systemic				
Polysorbate 80	PBCA	Dalargin	Pain Relief	[76]
		Kyotorphin	Pain Relief	[77]
		Nerve Growth Factor	Parkinson Disease	[78]
		Rivastigmine	Alzheimer disease	[79]
		Tubocurarine	Anticonvulsant	[80]
		Valproic acid	Anticonvulsant	[81]
		Saquinavir	AIDS	[82]
		Loperamide	Pain Relief	[83]
Maleimide-PEG	Albumin	Aclarubicin	Cancer	[84]
	PLA	Sulpiride	Antipsychotic	[85]
Poloxamer 188	SLN	Campthotecin	Cancer	[86]
Poloxamer 407		Saquinavir	AIDS	[87]
Apo E3, A1, B100 (R)-g7 peptide	PBCA, HSA, PLGA	Loperamide	Pain Relief	[88, 89]
Apo E	HSA	Obidoxime	Acetylcholinesterase reactivator	[90]
Wheat germ agglutinin	PLA	Vasoactive intestinal peptide	Peptide hormone	[91]
Nasal route				
Pluronic F	Polymeric	Zolmitriptan	Migraine	[92]
127	Micelle	Sumatriptan		[93]
	PLGA	Olanzapine	Antipsychotic	[94]
TAT	PCL	Coumarin	Model drug	[95]
Lipid	SLN	Risperidone	Antipsychotic	[96]
Capric glyceride	Nanoemulsion	Clobazam	Epilepsy	[97]

SLN: Solid Lipid Nanoparticles; PBCA: poly (n-butyl cyanoacrylate); HSA: Human Serum albumin; PLGA: poly(lactic-co-glycolic acid), PLA: Poly Lactic Acid, PCL: polycaprolactone, TAT: cell penetrating peptides

Nanoparticles for colon targeting can be formulated using natural or synthetic polymers. There is a wide range of polymers which have been established or are being investigated for their colon targeting potential. The colon targeted nanoparticles have demonstrated their ability to enhance the solubility, absorption and bioavailability of the encapsulated drugs [99, 100]. Additionally, colon targeted nanoparticles have also shown a huge potential for delivering peptides. Etiologies of various colon diseases have shown that macrophages are activated in course of the disease cascade because of immune response by the inflamed cellular structures in the colon. These activated macrophages can efficiently take up the nanoparticles and this governs the accumulation of a large number of nanoparticles in the colon region. This accumulation, in turn, elicits a pronounced therapeutic effect from the colon targeted nano-systems [99, 100].

Literature reports describe the employment of nanoparticles for the colon targeted delivery of various encapsulated moieties. Zheng et al. [101] have reported the incorporation of Thymopentin, a potent immunomodulating drug, into pH-sensitive chitosan nanoparticles coated with Eudragit S100 (ES100) to improve the stability and the oral bioavailability of the encapsulated agent. Uniform nanoparticles with a size of about 175 nm and a moderately high encapsulation of around 76% were formulated. The nanoparticles were found to effectively protect the encapsulated moiety from enzymatic degradation and prolong its degradation half-time. Results of lymphocyte proliferation test and *in vivo* evaluation in rats demonstrated that the nanoparticles could be used as effective vectors for the oral delivery of Thymopentin. Wang et al. [102] have reported the development of Cyclosporine A (CyA) loaded pH-sensitive nanoparticles of ES 100. Various *in vivo* studies conducted by this research group revealed that the nanoparticles increased the absorption of CyA, which could be attributed to a fast stomach empting rate, site specific absorption and lower degradation rate of the entrapped moiety by the luminal contents and the high bioadhesion of nanoparticles to the intestine mucosa. The authors have claimed that the investigation could be helpful for the design of dosage forms for other peptide or protein drugs. Researchers have reported the efficiency of ES 100 nanoparticles as a favorable vehicle for the selective absorption of drugs in the gut, when administered by the oral route. This was proved by encapsulating Rhodamine 6G (Rho) as a model agent. The nanoparticles were evaluated for Rho release profiles, distribution, adhesion and transition in rat gut. It was observed that the nanoparticles decreased the distribution and adhesion of Rho in the stomach but

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increased these values in the intestine. Additionally, these nanocarriers were reported to control the drug release sites and release rate in the GI tract [103]. Scientists have also investigated the potential of ES 100 to improve oral delivery of HIV-1 protease inhibitors in dogs [104]. Incorporation of a HIV-1 protease inhibitor, HIV CGP 57813, into ES 100 nanoparticles was found to substantially increase the oral bioavailability of this compound after administration to dogs and achieve plasma levels comparable to those obtained in studies conducted in lower animals such as mice [105].

Lung targeted nanoparticles

The lungs present a promising route for drug delivery due to its non-invasive nature and possibility of systemic and local drug delivery. Pulmonary market is expected to increase by up to $24.5 billion by 2015, with a CAGR of 2.8% [106]. There is a growing need for novel therapeutic systems for the treatment of respiratory disease like tuberculosis, pulmonary hypertension, cystic fibrosis, asthma, chronic obstructive pulmonary disease (COPD) and severe acute respiratory syndrome (SARS). Pulmonary route is also being increasingly exploited for the delivery of peptides and vaccines. In view of this enormous need, nanoparticles can provide the right therapeutic option for the treatment of variety of respiratory diseases [107]. Nanoparticle systems in targeted pulmonary drug delivery offers various advantages such as uniform distribution of drug in alveoli, bypassing of first pass metabolism, high solubility, sustained release property, reduced side effects, delivery of macromolecules and improved patient compliance. Lung targeting using nanoparticles can also be achieved through parenteral route. However, researchers have preferred the pulmonary route over the latter [108, 109]. A summary of various nanoparticulate carriers, intended for targeting the lung, has been presented in Table 1.5.

It is thus evident that nanoparticulate drug carriers cater to distinct needs and play definite roles in overcoming the 'lags' encountered with the conventional drug delivery systems. Numerous types of fascinating nanoparticulate drug carriers have stemmed from the research conducted during the last three decades. Also notable is the number of conditions where they may be applied, via different administration routes, for better therapeutic outcomes. With persistence from both academia and industry, some of these systems have successfully accomplished the cumbersome transition from laboratories to clinics. In this book, we intend to provide an overview of these different therapeutic nanoparticles, the challenges

Table 1.5 Examples of nanoparticulate carriers targeted to the lung (modified from [107–109])

Route	Drug	Type of nanoparticle	Application	Ref.
Parenteral	Doxorubicin	Solid lipid nanoparticles	Lung cancer	[110]
	Methotrexate	Albumin	Lung cancer	[111]
	Azidothymidine	Hexylcyanoacrylate	AIDS	[112]
	Diazepam	Hexylcyanoacrylate and albumin nanoparticles	Inflammation	[113]
Lung	Rifampin, isoniazide, pyrazinamide	PLGA	Tuberculosis	[107]
	Rifampin, isoniazide, pyrazinamide	Solid lipid nanoparticles	Tuberculosis	[107]
	Calcitonin	Chitosan labeled PLGA	Parathyroid disease	[107]
	Itraconazole	Itraconazole nanocrystals	Lung infection	[107]
	Amphotericin B	Phospholipid and apolipoprotein	Lung infection	[114]
	Amiloride hydrochloride	Liposome	Cystic fibrosis	[108]
	Secretory leukocyte protease inhibitor	Liposome	Cystic fibrosis	[115]
	Interleukin-4 antisense oligodeoxynucleotides	Polymeric nanoparticle	Asthma	[116]
	Vasoactive intestinal peptide	Protamine nanoparticle	Asthma	[117]
	Indomethacin, ketoprofen	Solid Lipid nanoparticles	Asthma	[108]
	Antisense oligonucleotide 2'-O-methyl-RNA	PLGA nanoparticles	Lung cancer	[118]
	Leuprolide	Liposome	Lung cancer	[108]
	HLA-A*0201-restricted T-cell epitopes from Mycobacterium tuberculosis	Chitosan nanoparticles	Tuberculosis	[119]
	V1Jns plasmid encoding antigen 85B from M. tuberculosis	PLGA-PEI nanoparticle	Tuberculosis	[120]
	Insulin	PLGA, PLGA-PEI, PEI, Chitosan, Alginate	Diabetes	[121]

encountered in their transition to clinical settings, the solutions which may be adopted for surmounting these challenges and the success stories of some of these drug delivery nanoparticles.

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