Chapter 1
Introduction

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1.1. Lung Cancer and Associated Challenges

Lung cancer stands as the top most common cancer worldwide (mainly in the United States). According to the American Cancer Society, the chances of overall survival for 5 years is only 16-25 % (Distant stage cancer only 6 %). Lung cancer has been reported to have the highest mortality rate (31.8 %) compared to other cancers. Among lung cancers, 80-85 % are non-small cell lung cancer (NSCLC). First-line treatment of lung cancer includes surgical removal or radiation therapy. However, complete eradication is seldom achieved and thus followed with chemotherapy. Also, among approved anticancer drugs, 65 % of drugs exhibit poor aqueous solubility and low permeability, thus not achieve the desired therapeutic outcomes. This necessitates high dose requirements and frequent administration. Non-selective drug distribution to all major organs also reduces the drug availability at the target site and experiences systemic toxicity or severe adverse effects. Therefore, strategies to improve the cellular bioavailability of anticancer drugs are required to obtain better therapeutic effects and minimize adverse effects.

1.2. Nanomedicine for Anticancer Drug Delivery

Several formulation strategies emerged to improve the solubility and subsequent bioavailability of drugs which included design of solvates, co-crystals, pro-drugs, inclusion complex, solid dispersion and various nano-particulate systems like quantum dots, nanoclusters, nanorods, nanotubes, micelles, dendrimers, DNA nano-carriers, liposomes, nanofibers, etc. These systems can be prepared using synthetic polymers or natural polymers or combination and can be equipped with metallic compounds like gold, silver, iron oxide, metal mollybdate etc. The resultant products may exhibit superior characteristics, lower dose, reduced dosing frequency, retarded drug rejection

and thus results in an efficient, economic, flexible, and highly bioavailable dosage form. Though many nanoparticles system are available worldwide as drug delivery system but still suffer from lower drug load, circulation instability, complicated manufacturing and premature drug release (Gad et al., 2018). Recently, nanocrystals have gained an increasing interest and found superior over other nanocarriers owing to their higher drug payload capacity, reduced excipients use, better chemical stability, lower toxicity, easy scale up and large batch manufacturing (Malamatari et al., 2018). Nanocrystals have also advantageous over other dosage forms like self-emulsifiers, cyclodextrin based inclusions, solid dispersions, and solid-lipid nanoparticles as it overcame the requirement of larger amount of excipients for their formulation, eliminate the possible excipients based toxicity and conquer low drug loading in nanocarriers (Hou et al., 2017).

1.3. Drug Nanocrystals

Design of "Drug Nanocrystals" is a universal approach for improving the delivery of drugs with poor aqueous solubility and low permeability. Nanocrystals came into existence since start of 1990s with the first marketed product in 2000. Drug nanocrystals are pure drug particles stabilized using either a surfactant or a polymer or combination of both to avoid Ostwald ripening and obtain a stable colloidal particle. US FDA has received more than 82 submissions of product related to nanocrystals (Chen et al., 2017). According to the US FDA, materials would be considered as nanosized if at least one dimension is of approximately 1– 100 nm [3]. In another definition, a particle with volume median diameter (D50) < 1 mm and a volume diameter 90 % undersize (D90) < 2.5 mm can be considered as nanosized (Malamatari et al., 2018). Preparation of drug as nanocrystals is a simple, straight forward, efficient and a versatile option for modifying solubility and dissolution velocity, capable to reach

supersaturation level instead of only thermodynamic solubility (Peltonen and Hirvonen, 2018). Drug as nanocrystals can modify the intrinsic properties of drug to improve solubility, dissolution and bioadhesion. Increased dissolution could be due to nanocrystalline form and can be explained by Noyes-Whitney equation where decrease in size to nano-range is directly responsible for increasing the surface area and thus dissolution. Further, nanocrystals due to polymer used for their stabilization presents them in a highly soluble form being as advantage over crystalline form (Fontana et al., 2018). Nanocrystals based formulation can be administered via different routes (oral, intravenous, dermal, ocular and pulmonary) and found to have numerous advantages like high contact, better permeation, modified drug release, negligible stabilizer linked side effects and no precipitation risk upon administration (Chen et al., 2017). Nanocrystal emerged of great worth which smoothened the delivery of poorly soluble and low permeable drug, thereby boosting the drug bioavailability. Surface modified nanocrystals further can control or preserve crystals morphology or specific polymorphic form as a versatile option for delivery of poor soluble drugs (Tyagi and Subramony, 2018). Anticancer drugs with poor aqueous solubility and low permeability can be easily formulated as sub-micron sized nanocrystals with high drug loading, and greater structural stability. Natural biopolymers as well as synthetic polymers have been widely employed for the stabilization of nanocrystals. The hydrophilic and amphiphilic stabilizers are favored over surfactants and hydrophobic polymers due to their role in stabilizing hydrophobic drugs. Nanocrystals of anticancer drugs depending upon their size and shape can provide antitumor effect via enhanced permeation and retention in the vicinity of the tumor.

In last few years, the combination of two approaches have been utilized for the formulation of drug nanocrystals of desired size range.

Table 1.1 Technology Used for Nanocrystals Formulation

Technology	Owner/Developed by	Method /Mechanism	Drug	Reference
Nanocrystals®	Liversidge et al. owned by Alkermes Plc.	Micronization by Pearl or Bead Milling + HPH/ (Shear Forces and Particle Collision)	Rapamune by Wyeth Pharmaceuticals In 2000	(Salazar et al., 2014)
Dissocubes	Muller and colleagues (1995, 1999), belongs to Skyepharma PLC	Piston-Gap HPH (Cavitation, Shear forces and Particle Collision)	Hydrophobic drugs	(Müller and Junghanns, 2008)
Nanopure®	PharmaSol GmbH in Berlin, Belonging to Abbott Gmbh& Co.	Micronization + Piston-Gap HPH (Shear Forces and Drug Particle Collisions)	-	(Müller and Junghanns, 2008)
Nanoedge	Baxter	Microprecipitation (A Solvent-Antisolvent Technique) + HPH, Sonication, Or Microfluidization	Paclitaxel, Nabumetone, Prednisolone, Carbamazepine, Itraconazole	(Chang et al., 2015; Salazar et al., 2014)
Nanomorph	Auweter et al. belong to Soliqs Abbott Gmbh & Co. Ludwigshafen, Germany	Dissolution-Precipitation	-	(Chang et al., 2015)

Combination Technology (CT)	-	Low Energy Pearl Milling + HPH	Rutin, Hesperidin, Apigenin	(Salazar et al., 2014)
H69 (Pharmasol)	Muller and Moschwitzer, belongs to Smartcrysts® Technology (Abbott/Soliqs, Germany)	Cavi Precipitation + HPH (Cavitation, Particle Collision, and Shear Forces)	Ibuprofen, Resveratrol, Omeprazole, Prednisolone, Hydrocortisone acetate	(Chang et al., 2015; Salazar et al., 2014)
H42	Moschwitzer and Colleagues, Belongs to the Smartcrystal®	Spray Drying + HPH	Amphotericin, Glibenclamide, Ibuprofen, Resveratrol, Hydrocortisone acetate	(Chang et al., 2015; Salazar et al., 2014)
H96	Moschwitzer and Lemke and belongs to Smartcrystal®	Freeze Drying + HPH	Cyclosporin A, Amphotericin, Glibenclamide, Hydrocortisone acetate	(Chang et al., 2015; Salazar et al., 2014)
Wet Ball Milling	Liversidge et al. (Liversidge and Cundy 1995)	Shear Forces	-	(Borchard, 2015)
Rapid Expansion of Supercritical Solution (Ress)	Introduced in 1984 by Krukonis	Solute dissolved in a Supercritical Fluid is quickly depressurized through a nozzle	-	(Chang et al., 2015)

1.3.1. Methods of Preparation

Drug nanocrystals can be formulated using two basic approaches, bottom-up and top-down technologies (Borchard, 2015). In bottom-up methods, drug is dissolved in organic solvent and precipitated by adding to an antisolvent with stabilizer. Whereas, top-down techniques like milling, micro-fluidization, high-pressure homogenization, and probe-sonication brings the larger particles to nano-range (Müller et al., 2011a).

1.3.2. Nanocrystals for Intravenous Administration

Nanocrystals can be administered by intravenous route for drug delivery to target site. Owing to its size, nanocrystals are likely to undergo dissolution in systemic circulation however, nanocrystals do not dissolve instantly upon administration instead display sustained and controlled release possibly due to incorporated stabilizers (Lu et al., 2017). Nanocrystal act differently on systemic administration where in one scenario, it bypasses the biological barriers to underwent specialized absorption such as clathrin or caveolae mediated endocytosis while dissolved drug follow passive diffusion. In other scenario, nanocrystals in blood circulation if underwent phagocytotic uptake will disintegrate and dissolve, releasing drug which will come back to circulation due to concentration gradient and will follow passive diffusion (Mohammad et al., 2019a).

In systemic circulation, pure drug nanocrystals without any stabilizers can bind to opsonin, which induce the process of phagocytosis by forming a bridge between hydrophobic surface of nanocrystals and phagocytic cells, followed by removal of nanocrystals by the cells of MPS (Liu et al., 2017). To improve systemic circulation, decrease prior drug release from nanocrystals, and prevent clearance via MPS, a protective coating is required that is usually done with stabilizer. For example, PEGylated stabilizer can cover the hydrophobic surface of nanocrystals providing a stealth layer and a hydrophilic surface which in turn delay recognition by MPS, repel

opsonisation and minimize clearance. As a result uptake via other non-target organs like liver, kidney, lung, spleen etc is decreased to maximize the drug availability at target site (Liu et al., 2017). Therefore, to control the drug release, prolong systemic circulation, and maintain higher drug availability at the target site, surface modification of nanocrystals is required. For this, nanocrystals are usually stabilized with hydrophilic and amphiphilic polymers to obtain colloidal particles with hydrophilic surfaces. The nanocrystals can also be surface coated with lipids, proteins, and targeting ligands to modify release and specify drug delivery.

1.3.3. Nanocrystals for Pulmonary Delivery

Nanomedicine is an emerging solution, which possesses numerous advantages, including dose reduction, improved pharmacokinetic behavior, overcome drug resistance, and provide active as well as passive targeting of drugs to selective regions of the body, organs, or tissue. The systemic administration of nanosized carriers for lung cancer therapy still experiences certain drawbacks that may result in adverse effects and poor therapeutic effects. The drawbacks include; dose dumping or drug leakage, non-specific distribution, and reduced accumulative potential in tumor. Recently, pulmonary delivery has been employed as a potential alternative to overcome the drawbacks of the systemic administration. Pulmonary route is associated with various advantages like availability of large surface area, thin permeable membrane, high blood flow, limited proteolytic activity, low enzymatic action, and extensive absorption vascularization make it an ideal route for drug administration (Elmowafy and Soliman, 2019; He et al., 2020a; Jyoti et al., 2017; Patton et al., 2004; Xu et al., 2019). Pulmonary route offers a non-invasive alternative route for direct and efficient drug delivery to the lungs (Elmowafy and Soliman, 2019), thereby offering advantages of high drug accumulation in lung for localized action, lower systemic toxicity,

enhanced bioavailability by bypassing the first-pass metabolism and improved patient compliance (He et al., 2020a; Jyoti et al., 2017). The pulmonary route has been extensively explored and is a well-established route for the treatment of local symptoms, with minimum concern regarding variation in systemic bioavailability. The use of pulmonary nanocarriers may allow preferential accumulation of drugs in the lung tumor responsible for improved anti-tumor efficacy and reduced toxicity to healthy lung cells and other body tissues and organs. But, limited FDA approved excipients quantity for the pulmonary delivery system is one of the major hindrances towards the development of nanocarriers for pulmonary delivery. Moreover, small hydrophobic molecules have to be effectively delivered to the epithelial layer of the respiratory tract to counter allergic rhinitis or asthma or possible inflammatory response. Therefore, a delivery strategy for effective retention of formulation at the alveolar and epithelial region, alongside enhanced permeability to the epithelial cell membrane, is vital to increase the drug concentration at tumor sites and improve the delivery of chemotherapeutics for the treatment of lung cancer.

The drug nanocrystals have emerged as a revolution in the field of pulmonary drug delivery owing to advantages of minimal excipient usage, higher stability, better penetration efficiency, the feasibility of scale-up and ease of preparation (He et al., 2020a; Kumar* et al., 1969). The drug nanocrystals preparation involves minimal use of stabilizers resulting in a carrier with high drug payload (Mishra, 2015; Raghava Srivalli and Mishra, 2016). Nanocrystals are responsible for enhancing the solubility, improving the permeation, providing controlled drug release and better mucoadhesion, subsequently resulting in increased bioavailability of drugs, making it an ideal system for development of anticancer formulation for pulmonary delivery (He et al., 2020a; Kumar* et al., 1969; Kumar et al., 2019a, 2019c). Pulmonary delivery of drug

nanocrystals as dry powders has gained popularity for both local as well as systemic action. Pulmonary delivery of nanocrystals is a non-invasive approach for delivering anticancer drugs into lung cancer cells. Drug nanocrystals offer high drug dissolution, enhanced mucus penetration, good lung tissue distribution, lower mucociliary clearance, and minimal macrophage uptake, on pulmonary administration. Drug nanocrystals escape the clearance mechanism by their size and hydrophilic surface that favor higher dissolution in lung fluid and mucus/epithelial permeation in its free or intact form to reach the tumor microenvironment. Drug nanocrystals display unique advantage of overcoming drug inhomogeneity problems observed with pulmonary delivery of aerosols. Nanocrystals have extra edges over nebulizers due to their higher physical stability towards aerosolization pressure, portability, and ease of use. Nanocrystals can be surface modified for improving the drug retention in the lung on intratracheal administration. Nanocrystals surface can further be functionalized with targeting moiety for specifying the drug delivery to the target site, thereby avoiding off-target distribution and minimizing systemic side effects related to anticancer drugs.

The nanocrystals associated bioavailability improvement on its pulmonary delivery can be due to high dissolution velocity responsible for maintaining a higher concentration gradient and faster drug release, taken up by cells. Smaller nanocrystals obey faster dissolution and higher percentage diffusion, compared to larger nanocrystals, and thus exhibit higher cellular uptake and transport efficiency. However, lungs possess small fluid volume; thus, nanocrystals can follow a different dissolution behavior on pulmonary delivery. Nanocrystals can accumulate to cancerous cells passively via enhanced permeation and retention (EPR) effect, governed by the size of nano-crystals. Better interaction between NC and mesh-like structures of mucus or biological structure might be responsible for enhanced mucus penetration and cellular internalization (He et

al., 2020a). Various other nanocrystals associated advantages are; high permeation for effective anti-tumor activity, and sustained release for maintaining the drug concentration in tumor for longer period of time (Kumar et al., 2019a; Mangal et al., 2017). These drugs absorbed through deep lung tissue into the lymphatic circulation can also target lymph node metastases of advanced lung cancer.

1.3.3.1. *How Nanocrystals Escape Ciliary Clearance and Macrophage Uptake?*

The respiratory tract consists of several protection barriers, which include i) a thin film of surfactant, ii) mucociliary system iii) alveolar macrophages iv) tight junctions between epithelium and v) dendritic cells present in airways (Blank et al., 2006). Poorly soluble or hydrophobic drugs are prone to mucociliary clearance or removal by phagocytic alveolar macrophages. Insoluble drug particles >5 μm can be eliminated via mucociliary clearance, dominant in the upper airway, while smaller particles deposit in the deep lungs where mucociliary clearance is less prominent. However, insoluble drug particles ranging from 1 to 5 μm in size may interact with and are cleared by epithelial and immune cells from deep lung depends on drug dissolution, endocytic uptake by epithelial cells, and phagocytosis via alveolar macrophages, dominant in the deep lungs. Thus, the preparation of drugs as nanocrystals can help to prevent clearance by providing a hydrophilic surface and a higher effective surface area exposed to the fluid lining of lungs responsible for faster drug dissolution, increased saturation solubility, and higher drug diffusion to mucous layer (He et al., 2020a). Lung clearance by ciliary action and alveolar macrophage uptake may depends on nanocrystals size and surface characteristics, while pulmonary absorption and metabolism are based on the dissolution behavior of nanocrystals. Nanocrystals >100 nm could translocate across lung epithelium to blood circulation. Nanocrystals of about 500 nm escape from mucociliary clearance and alveolar macrophages responsible for better lung retention

than microparticles (Hu et al., 2017). Moreover, internalized particles are mainly removed from macrophages to lymph circulation after digestion or degradation of the polymer system (Mangal et al., 2017)

1.3.3.2. *Drug Nanocrystals and Particle Deposition Pattern*

The nanocrystals deposition in lungs primarily depends on particle size via impaction, sedimentation, and diffusion. Impaction is observed with particles > 5 μm, administered using dry powder inhaler, where particles adhere to deposit in oropharynx due to high velocity and force used. If particles are large or force is low, particle deposits upper airways, whereas high mass and size particles (1-5 μm) deposits in bronchioles and smaller airways. Sedimentation depends on breathing as slow breathing provides sufficient time for particles to sediment. While diffusion is based on the dissolution of nanocrystals in alveolar fluid, upon coming in contact with lung surfactant layer and also on concentration gradient and Brownian motion (Paranjpe and Müller-Goymann, 2014). Various area of deposition in lungs includes primary bronchi (5-10 μm), secondary bronchi (1-5 μm), bronchioles (1-3 μm) and alveoli (0.5-1 μm) where deposition could occur via impaction, sedimentation, sedimentation, and Brownian motion, respectively. (Paranjpe and Müller-Goymann, 2014). The aerodynamic diameter of the particle should be smaller, ranging 0.5-5 μm for targeting deep lungs. (Ni et al., 2017). Results are contradictory for particles < 500 nm where in a study nanocarriers ranging 50-200nm reported having relatively high pulmonary deposition fraction with 500 and 2000 cm^3 sec^{-1} breathing rate and 5–10 sec. breath-hold (Dandekar et al., 2010). In other study, particles with diameter < 0.5 μm remain suspended in the airstream, and can get exhaled without deposition in the lung (Mangal et al., 2017; Ni et al., 2017). Therefore, nanocrystals of particles 0.1-5 μm are still require to further explore for determining their suitability for pulmonary administration.

1.3.3.3. *Nanocrystals Fate in Lungs*

Localized drug delivery for lung cancer via pulmonary route may minimizes the therapeutic dose, systemic side effects and chances of drug resistance. However, lung physiology is complex with impervious biological barriers including pulmonary surfactant, mucocilliary system, alveolar macrophages and pulmonary epithelium, that attenuates the therapeutic effects of the drugs by restricting their passage (Haque et al., 2016; Newman, 2017). Other barriers to pulmonary delivery may include; airway narrowing, mucus plugging, mucus hypersecreation, and drug degradation by proteolytic enzymes (Newman, 2017). The entrapment of the drug particles in the mucus/surfactant, poor permeation through epithelial barrier, and mucociliary or macrophagic clearance can cause short residence time in the airway, which in turn negatively affect the therapeutic effect of drug. The mucin 3D mesh structure may trap the inhaled drug particles, thus reducing its penetration to the lung epithelium and then subsequently cleared out from the airway. It is therefore important to understand the barriers and fate of drug in the lungs on pulmonary administration.

The nanocrystals fate on pulmonary administration may depends on particle size, shape, surface and lung fluid volume that determines drug dissolution and permeation across biological barrier in lungs to reach tumor site. Drugs nanocrystals can achieve a higher dissolution rate, as explained by Noyes-Whitney equation (Kumar et al., 2019a). Smaller nanocrystals (about 250 nm) exhibit better lung distribution and significantly higher dissolution, faster diffusion and increased permeation than nanocrystals > 500 nm. Small-sized crystals reported to have higher displacement and better cell cytoplasm-cell nucleus uptake. Middle (500 nm) and large sized nanocrystals (1000 nm) can retain in the epithelial layer of the lung, showing lower distribution to other organs than lung (He et al., 2020a). The particles < 5 μm showed higher penetration

potential than larger particles (Hu et al., 2015). The pore size of mucus mesh (200-300 nm) also reported to prevent the penetration or retain the nanocrystals of size more than 300 nm, where small-sized nanocrystals may effectively penetrate (He et al., 2020a). Therefore, particle size and surface modification of drug nanocrystals can alter its bio-distribution, although the exact mechanism is still unclear (Lu et al., 2016a).

1.3.4. Lipid Equipped Nanocrystals

Lipid based nanomedicine is a versatile platform for the delivery of both hydrophilic as well as hydrophobic drugs (Dabbagh et al., 2017). Lipid nanosystems exhibits high systemic stability, prolonged blood circulation, good biodistribution, minimum adverse effects, and can overcome biological barriers (Chiong et al., 2013; Deniz et al., 2010; Haeri et al., 2011). Moreover, the surface of lipid nanosystems can be modified to alter the physicochemical and pharmacokinetics behavior, provide stealth property, and controlled drug release. Nanocarriers of anticancer drugs exhibiting prolonged residence in the respiratory tract can provide controlled drug release in lung maintaining the therapeutic concentration of drug at the desired site for a longer period. Consequently, it may ensure superior therapeutic performance while minimizing the extrapulmonary side/toxic effects. Lipid based nanosystems of optimum size, charge, and other surface characteristics may significantly improve the drug delivery to lung and modulation of these particle characteristics may influence particle deposition and therapeutic responses. lipids nanomedicine besides increasing the drug adsorption, distribution and permeation, also protects the encapsulated drugs and other therapeutics from degradation and clearance prior reaching the target site (Li et al., 2020a). Lipid nanomedicine are low irritant to lung parenchyma, provide high drug retention in lung, better drug diffusion and bioavailability (Dabbagh et al., 2017). The surface functionality of lipid nanomedicines also provides the scope of receptor mediated

targeting, which may bestow the intracellular drug delivery capability to these nanocarriers (Keum et al., 2021).

The pulmonary surfactant system of lung consists of lipids, dipalmitoylphosphatidyl-choline (DPPC), and hydrophobic surfactant proteins (SP-B and SP-C) as the first barrier to the localized drug delivery to the lung. Upon inhalation, drugs particles contact the pulmonary surfactant layer that has critical effect on the drug half-life and its in-vivo fate. However, these surfactants could also be utilized as an effective carrier for delivering therapeutics to the deep lung tissues. Inhalable lipid nanomedicine consisting of phospholipids similar to endogenous pulmonary surfactant interact with the pulmonary membrane, show minimum clearance, prolonged adherence, superior retention at the mucosal surface, and better permeation across the mucosa (Hidalgo et al., 2015; Nafee et al., 2018). A lipid nanosystem consisting of lung surfactant-mimic phospholipids like dipalmitoylphosphatidylcholine (DPPC) and dipalmitoyl-phosphatidylglycerol (DPPG) observed to be safe, stable, and inhalable as dry powders for drug delivery to the deep lung region (Gomez et al., 2020). Addition of molecules like cholesterol, PEG, Cryoprotectant (mannitol, lactose), etc. in lipid nanocarriers may further enhance the nanocarriers stability and ensures particles with desired aerosolization performance (Szabová et al., 2021) (Ji et al., 2016).

Lipid nanomedicine also increases the drug retention in lungs and minimized the drug clearance, maintaining higher drug concentrations at the target site by many folds compared to the free drug (Ji et al., 2016; Poyner et al., 1995). Lipid nanosystems of about 167.46 ± 2.05 nm consisting of lipid DOPC and cholesterol for inhalation delivery demonstrated time dependent uptake in airway epithelial cells via the caveolae pathway (Komalla et al., 2020). Lipid nanosystems observed safe, well tolerated and not induce signs of local inflammatory effects in the respiratory tract in a murine

inhalation model (Nassimi et al., 2010). The lipid nanosystems may alter the drug pharmacokinetics and exhibit an extended clearance half-life of approx. 10.5 hours (Patel et al., 2016). Lipid based nanocarriers may overcome mucus barrier owing to their role in penetrating through the thick mucus layer and its biophysical interactions with the mucin. The low interaction with the mucin and high diffusivity and penetration through a considerably thick mucus layer favor drug delivery. The surface charge may predominantly influence the interaction with the mucin layer more than the particle size (Alp and Aydogan, 2020). Lipid nanoparticles that are smaller than the mucus pore size can penetrate through it, while larger size lipid nanoparticles exhibit longer lung retention time ensuring efficient and prolonged drug delivery in the pulmonary region (Huang et al., 2020). Moreover, the small sized lipid nanoparticles can have wide distribution in lung on aerosolization for pulmonary administration. Lipid nanosystems ranging between 150 to 300 nm were employed for pulmonary administration that showed deep lung deposition, prolonged retention, high mucus penetration and minimum toxicity (Esmaeili et al., 2016; Moreno-Sastre et al., 2016; Torge et al., 2017).

Based on these advantages of lipid nanosystems, nanocrystals can be modified with lipids to obtain a hybrid system with merged benefits. The Lipid-coated nanocrystals have dual advantages of nanocrystals as well as lipid nanoparticles, providing high payload, control over drug release via increasing the drug diffusion path causing improved systemic circulation, superior stability, higher lung retention, lower clearance and better membrane fluidity.

1.3.5. Nanocrystals Market

Nanocrystals provide opportunities for pharmaceutical manufacturers to extend the patent life of their products. Elans NanoCrystals technology have been utilized for enhancing the drug bioavailability by improving the solubility and permeability of drug

and can provide quicker onset of action, improved dose proportionality, increased dose uniformity, fewer side effects, more predictable therapeutic response, elimination of food effects, higher safety, and greater efficacy. First four products based on nanocrystals were produced by Elan nanosystems using Nanocrystal technology that involved pearl milling. Rapamune by Wyeth Pharmaceuticals (Madison, NJ; 2000), Emend® by Merck (Winehouse Station, NJ; 2001), Tricor® by Abbott Laboratories (2004) and Megace ES® by Par Pharmaceutical Companies, Inc. (2005) were the former products marketed as dosage form (Müller and Junghanns, 2008). Many products incorporated with drug nanocrystals are now available in market. Some of them are enlisted in Table 1.2.

Recently, Ireland's Alkermes Aripiprazole Lauroxil NanoCrystal Dispersion (AL_{NCD}), a novel investigational product for improving drug dissolution and treatment of schizophrenia was accepted for filing by the U.S. Food and Drug Administration, June 30, 2018 (Ehret et al., 2018). A new invention involving use of nanocrystal technology by Scientists at the University of Nebraska Medical Center is reported which involved modification of dolutegravir into nanocrystals (Keenan, 2018). Prepared nanocrystals were able to penetrate hidden HIV reservoirs with facilitated entry into lymph nodes, bone marrow and persisted for months showing an extended life. Formed delivery system released drug only in surrounding tissues on entering the macrophages and was able to withstand temperature variations inside body. SILCRYST™ nanocrystals by Smith and Nephew's used in Acticoat™ dressings showed sustained release of silver ions upto 7 days and demonstrated to have broad spectrum antimicrobial activity (Fong and Wood, 2006). Ryanodex brought in market by Eagle Pharmaceuticals as nanocrystalline suspension of dantrolene was able to obtain rapid response in less than 1 min for life threatening malignant hyperthermia (Yang et al., 2023).

Table 1.2 Nanocrystals in Market

Drug	Product	Use	Company	Reference
Griseofulvin	Gris-PEG® (FDA 1975)	Antifungal	Novartis, Valeant	(Borchard, 2015; Junyaprasert and Morakul, 2015)
Rapamycin, Sirolimus	Rapamune (FDA 2000)	Immuno-suppressant	Wyeth (Dublin, Ireland), Pfizer	(Shegokar and Müller, 2010)
Aprepitant	Emend (FDA 2000)	Emesis, Antiemetic	Merck, US	(Chang et al., 2015; Möschwitzer, 2013; Shegokar and Müller, 2010, 2010)
Fenofibrate,	Tricor (FDA 2004)	Hypercholesterolemia, Hypertriglyceridemia	Abbott (US), AbbVie	(Chang et al., 2015; Möschwitzer, 2013; Shegokar and Müller, 2010)
Fenofibrate,	Triglide (FDA 2005)	Hypercholesterolemia, Hypertriglyceridemia	Skye Pharma, First Horizon Pharmaceutical	(Borchard, 2015; Chang et al., 2015; Junyaprasert and Morakul, 2015; Möschwitzer, 2013)
Megestrol Acetate	MegaceEs (FDA 2005)	Anorexia, Cachexia, Appetite Stimulant	Par Pharmaceutical	(Chang et al., 2015; Junyaprasert and Morakul, 2015; Möschwitzer, 2013)
Nabilone	Cesamet® (FDA 2006)	Antiemetic	Lilly	(Borchard, 2015; Junyaprasert and Morakul, 2015)
Naproxen	Naprelan®	Anti-Inflammatory	Wyeth	(Junyaprasert and Morakul, 2015)

	(2006)			
Olanzapine	Zypadhera® (EMA 2008)	Schizophrenia	Eli Lilly	(Borchard, 2015)
Paliperidone Palmitate,	Invega Sustenna (FDA 2009)	Schizophrenia	Janssen	(Chang et al., 2015; Möschwitzer, 2013)
Paliperidone	Xeplion (EMA 2011)	Schizophrenia	Janssen-Cilag	(Peltonen et al., 2014)
Brinzolamide	Azopt	Carbonic Anhydrase Inhibitor, Open-Angle Glaucoma	Alcon Laboratories Inc.	(Peltonen et al., 2014)
Methylphenidate HCl	Ritalin LA (FDA 2002)	Anti-psychotic	Novartis	(Shegokar and Müller, 2010)
Dexmethylphenidate HCl	Focalin XR	Attention Deficit Hyperactivity Disorder (ADHD), Narcolepsy	Novartis	(Peltonen et al., 2014)
Itraconazole	-	Antifungal	Huazhong University	(Wan Jiangling et al., 2012)

Ketoprofen	-	Anti-Inflammatory	DENA® mill	(Khan et al., 2019)
Methylphenidate Hcl	Ritalin La	ADHD, Narcolepsy	Novartis	(Peltonen et al., 2014; Shegokar and Müller, 2010)
Morphine Sulfate	Avinza	Analgesic, Psychostimulant	King Pharmaceutical	(Peltonen et al., 2014; Shegokar and Müller, 2010)
TizanidineHcl	Zanaflex	Muscle Relaxant	Acorda	(Peltonen et al., 2014; Shegokar and Müller, 2010)
Guanylhydrazone	Semapimod®	TNF-A Inhibitor	Cytokine Pharmasciences	(Müller and Junghanns, 2008)
Paclitaxel	Paxceed™ (Clinical III)	Anti-inflammatory	Angiotech	(Jarvis et al., 2019)
Thymectacin	Theralux™ (Clinical II)	Anticancer	Celmed	(Jarvis et al., 2019)
2-methoxyestradiol	PanzemNCD (Clinical II)	Ovarian cancer	EntreMed	(Jarvis et al., 2019)
Silver	Nucryst® (Clinical II)	Antibacterial	Nucryst Pharmaceuticals	(Müller and Junghanns, 2008)