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A Literature Review on Development and In-Situ Evaluation of Nanocrystal Formulation of Docetaxel Anticancer Drug

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Abstract: ***The purpose of this perusal is to nanocrystal formulation of the anticancer drug and enhance its biological activity can be augmented by Docetaxel. Docetaxel is used to treat advanced or metastatic (that has spread) cancer and other cancer in patients who have previously received other cancer medicines that did not work well. It is a strong chemotherapy drug; also has small side effects. Nanodimension changes physical properties of Docetaxel which were used in pharmaceutics to develop a new innovative formulation principle for poorly soluble drugs: the drug nanocrystals. Docetaxel solubilized in a Tween 80/ethanol solution in inhibiting tumor growth without toxicity. Due to their particle size, nanocrystals (nanosuspension) have the great advantage of being intravenously injectable, reaching 100% bioavailability. The nanocrystal formulation of Docetaxel drug provides an achievements in improving the bioavailability of poorly soluble drugs which accounts for nearly 40 % newly discovered drug molecules and its nanocrystal efficacy is more than 98% according to their administration route, describes the methods developed to overcome physicochemical and stability - related problems, that are able to modify the drug delivery, penetrate targeting specific organs or cells, and enhance the bioavailability. The primary mechanism of docetaxel action is direct bonding to the β - subunits of tubulin, promoting the stabilization of tubulin polymerization and inhibition of microtubule depolymerization. Nanocrystal formulation of docetaxel is a rapidly metabolized drug; enhancing its in vivo circulation may benefit its therapeutic efficacy.***

Keywords: In - situ, Nanocrystal, nanocrystal formulation, Docetaxel, anticancer drug, nanodimension, nanomedicine, nanoscience, nanotechnology, taxane, cancer, nanoparticle, microtubules, pharmacokinetics, Cancer Immunotherapy, vivo circulation, drug delivery, targeting cells, metastatic

1. Introduction

1.1 Docetaxel (DTX)

Docetaxel (DTX), a typical taxane, has been approved as a first - line anti - tumor drug in clinical treatments. Like other taxanes (paclitaxel, cabazitaxel, etc.), docetaxel primarily operates its anti - tumor efficacy by disrupting the microtubular network, inducing a sustained block at the metaphase–anaphase boundary during cell division. As a compound belonging to BCS IV, the only commercially available formulation containing docetaxel is intravenous injection (such as Taxotere® and Docetaxel®), in which polysorbate 80 and dehydrated alcohol are used as cosolvents. Oral administration is the safest and most convenient administration route. Over the past decades, researchers have launched numerous strategies, such as nanoparticles, to enhance the oral bioavailability of docetaxel; however, low bioavailability still hinders the development of oral formulations for docetaxel. Considering docetaxel is a rapidly metabolized drug, enhancing its in vivo circulation may benefit its therapeutic efficacy (Meng Cheng, et al., 2021). Docetaxel (DTX) is a second generation taxane, derived from the inactive 10 - deacetyl baccatin III, extracted from the European Yew tree (Taxus baccata). DTX has better water solubility, pharmacokinetic profile, and anticancer activity than paclitaxel (Zhao, P et al., 2012). Nanotechnology has been extensively studied and exploited for cancer treatment as nanoparticles can play a significant role as a drug delivery system. Compared to conventional drugs, nanoparticle - based drug delivery has specific advantages, such as improved stability and biocompatibility, enhanced permeability and retention effect, and precise targeting. In addition, nanoparticle - based drug delivery systems have been shown to play a role in overcoming cancer - related drug resistance. The mechanisms of cancer drug resistance include overexpression of drug efflux transporters, defective apoptotic pathways, and hypoxic environment. Nanoparticles targeting these mechanisms can lead to an improvement in the reversal of multidrug resistance (Acharya, S., et al., 2012).

1.2 Description and Molecular Structure of Docetaxel

Docetaxel (DTX) is a lipophilic anticancer agent and a semi - synthetic taxane derived from the European tree Taxus baccata (Zhang H et al., 2016). Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R, 3S) - N - carboxy - 3 - phenylisoserine, N - tert - butyl ester, 13 - ester with 5 β - 20 - epoxy - 1, 2α, 4, 7β, 10β, 13α - hexahydroxytax - 11 - en - 9 - one 4 - acetate 2 - benzoate, trihydrate (Sanofi., Oct 2018). . Docetaxel has the following structural formula:

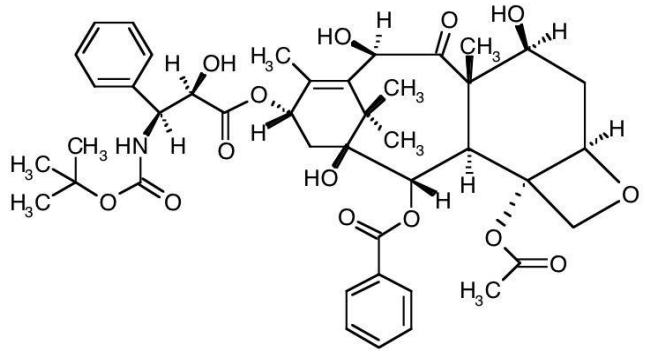

Figure 1.2.: Docetaxal (Molecular Structure) (Purba TS et al., 2019)

Docetaxel is a white to almost - white powder with an empirical formula of $C_{43}H_{53}NO_{14}$• $3H_2O$, and a molecular weight of 861.9 Da. It is highly lipophilic and practically insoluble in water. TAXOTERE (docetaxel) Injection Concentrate is a clear yellow to brownish - yellow viscous solution. TAXOTERE is sterile, non - pyrogenic, and is available in single - dose vials containing 20 mg (0.5 mL) or 80 mg (2.0 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80. TAXOTERE Injection Concentrate requires dilution prior to use. A sterile, non - pyrogenic, single - dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials (Sanofi., Oct 2018). The melting point of DTX is 232ºC. DTX has a partition coefficient (log - P) value of 4.1 and pKa of 10.97 (Thanki K., 2013).

1.3 Drug nanocrystals

Drug nanocrystals are crystals with a size in the nanometer range, which means they are nanoparticles with a crystalline character. Based on the size unit, in the pharmaceutical area nanoparticles should be defined as having a size between a few nanometers and 1000 nm (=1 µm); microparticles therefore possess a size of 1–1000 µm. Dispersion of drug nanocrystals in liquid media leads to so called "nanosuspensions" (in contrast to "microsuspensions" or "macrosuspensions") (Jens - Uwe et al., 2008). Nanocrystals can be adopted by all poorly soluble drugs to defeat their solubility and bioavailability issues. The reduction in particle size to nanometer range adds to the enhanced particle surface, curvature, saturation solubility, dissolution velocity and further reasonable bioavailability. Nanosuspensions are specific and economically conceivable way to deal with tackle the issues of hydrophobic drug, for example, poor solubility and poor bioavailability (S. J. Shankar et. al., 2020). Nanosuspensions are aqueous dispersions comprising of a blend of API and stabilizers, for example, surfactant or polymer in water. These stabilizers help in avoiding the clump of nanoparticles and keep them separate from one another by giving electrostatic/steric repulsion on the surface of nanoparticles (Liversidge M E et al., 2003). Nanosuspension is helpful in enhancement of dissolvability of drugs that are least soluble in water and lipid media (S. J. Shankar et. al, 2020).

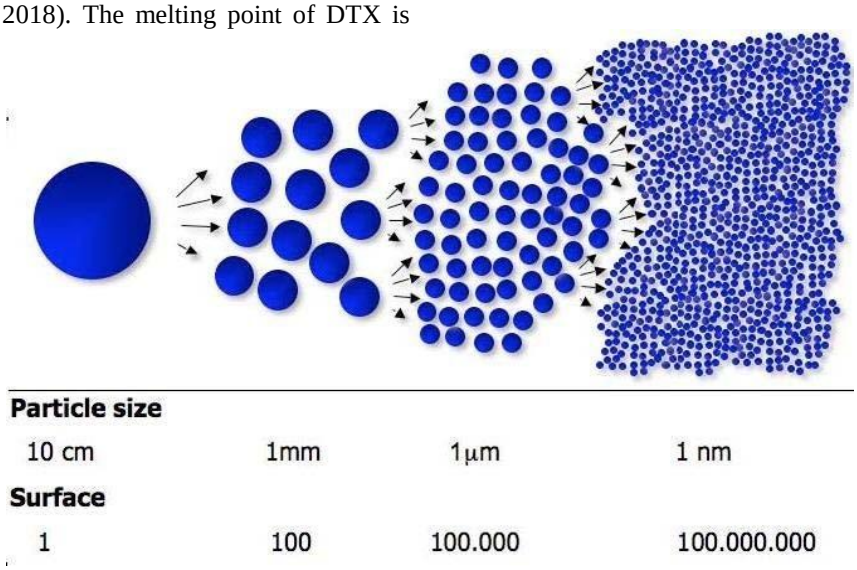

Figure 1.3: Schematic representation of particle size and surface at nano - scale. (Kathirvelu Subramanian, et al., 2008)

1.4 Nanocrystal based Formulation on Docetaxel anticancer drug:

Nanoparticle - based, Tween 80 - free DTX formulations are expected to not only avoid Tween 80 - related side effects but also increase the concentration of DTX in tumors due to the enhanced permeation and retention (EPR) effect. Data from many previous studies demonstrate that nanoparticles of 100−200 nm are most successful in tumor vasculature extravasation. PEGylation is a strategy to render the surface of nanoparticles hydrophilic, thus enabling the nanoparticles to evade early opsonization and circulate longer in the blood (Youssef Wahib Naguib et al., 2014).

1.4.1 Preparation of docetaxel - loaded SLNs:

Docetaxel - loaded SLNs were prepared by the solvent - diffusion method in an aqueous system, as reported elsewhere but with slight modifications 28–30 briefly, 150 mg of tristearin and 10 mg of docetaxel were dissolved completely in a 10 mL mixture of acetone and ethanol (1: 1,

v/v) in a water bath at 70°C. The resulting organic solution was dispersed quickly into 100 mL of an aqueous phase containing 0.01% (w/v) of Tween 80 (F1) or 0.01% (w/v) of TPGS (F2) under continuous mechanical agitation at 400 rpm in a water bath at 70°C for 5 minutes. The resulting pre - emulsion (melted lipid droplets) was ultrasonicated at 30 W for 10 minutes and subsequently transferred into an ice bath to solidify the lipid droplets. The dispersion was then purified by dialysis against distilled water for 12 hours to remove water - soluble impurities (organic solvents and nonadsorbed surfactants) and subsequently centrifuged (1, 600 × g, 5 minutes) to remove large lipid particles and precipitate free docetaxel. The supernatant was lyophilized, redispersed in distilled water, vortex - mixed, centrifuged, and syringe - filtered (Minisart RC15 0.2 µm; Sartorius Biotechnology, Göttingen, Germany) to obtain a docetaxel - loaded SLN dispersion (Hyun - Jong Cho, et al., 2014).

1.4.2 Production of Nanocrystals of Docetaxel drug:

Nanocrystal drugs can be created by "top - down" or "bottom - up" technologies, or combinations of the two.

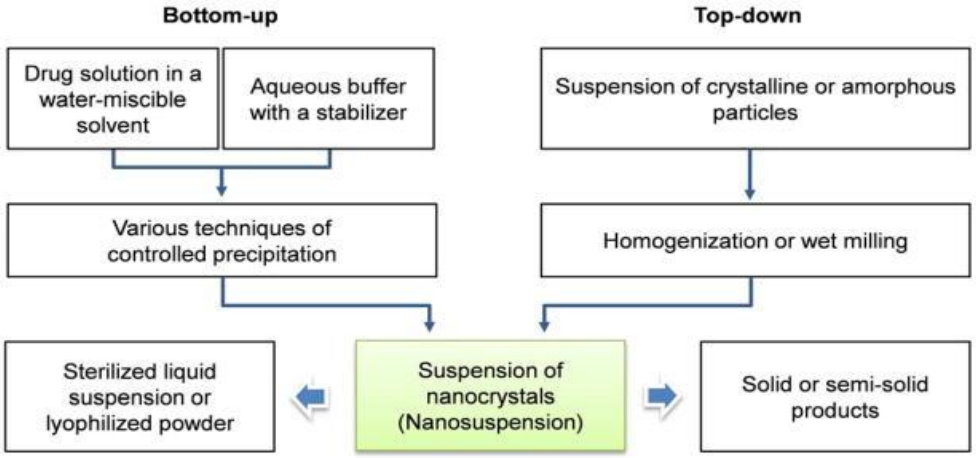

Figure 1.4.2: Schematics of bottom - up and top - down production of nanocrystals can be further processed into sterile products or other dosage forms. (Sun B, et al., 2012)

1.4.2.1 Bottom - up technologies:

The bottom - up approach refers to methods that create small drug particles from drug molecules dissolved in an organic solution. Small drug particles are formed as drug molecules precipitate from solution in the presence of an agent and/or a condition that induces nucleation of the molecules. For example, a non - solvent, which is miscible with the solvent but does not dissolve the drug, is used to induce the nanocrystal formation, in conjunction with various methods to mix the drug solution with non - solvents such as rotation, liquid jets, or multi - inlet vortex mixing. Alternatively, supercritical fluid, ultrasonic waves, or controlled solvent evaporation are employed to induce drug precipitation (Chan H - K, et al., 2011). Particles produced by the bottom - up approach can be crystalline or amorphous. Amorphous nanoparticles produced by a technique called Nanomorph™ achieve higher saturation solubility and faster dissolution rate (Lindfors L, et al., 2007). However, they are prone to partial or complete re - crystallization. (Müller RH, et al., 2011).

2.4.2.2 Top - down technologies:

Top - down approach is based on two basic size reduction methods: wet milling and high - pressure homogenization. The wet milling process applies shear stress on large drug particles by grinding an aqueous suspension that contains a drug and a surface stabilizer using beads or pearls in a milling chamber. The outcome of the milling process is determined by the hardness of the drug, energy input, milling time, and stabilizer concentration (Merisko - Liversidge E, et al., 2003). Microfluidization and piston - gap homogenization are examples of high - pressure homogenization (Müller RH, et al., 2011). Microfluidization is based on the jet stream principle, where the size diminution is achieved by collision of two fluid streams of particle suspension in a Y - type chamber under high pressure. The high shear forces, turbulent flow, and cavitation generated during this passage can reduce the particle size to the nanometer range (Shegokar R, et al., 2010).

1.5 Bioavailability of Docetaxel Nanocrystal drug

Nanotechnology has prompted the rise of another field called nanomedicine, which includes the utilization of nanotechnology in drug development, improves and offers many all the more energizing guarantees of new diagnoses and cures (Vivian S W Chan, 2006). To date, there are over 10 products based on nanocrystals that have been approved by the FDA for oral administration (like Rapamune®, Emend®), and intramuscular injection (such as Invega Sustenna® and Aristada®). (Mohamed A. I. et al., 2019). The bioavailability of a drug depends on its ability to dissolve in biological fluids, cross membranes, and efficiently reach its pharmacological target. In the biopharmaceutical classification of drugs, drugs of this class of group are characterized by poor solubility, but have a good ability to cross membranes. Thus, to improve the bioavailability of this class of drug, it is necessary to increase drug solubility and the drug dissolution rate (Maria R G et al., 2018). In particular, for nanocrystals, it is possible to consider the following scenarios:

- A decrease in particle size leads to an increase in surface area available for the interaction with the dissolution media, and thus an increase in the particle dissolution rate, in accordance with the modified Noyes - Whitney law.

- An increase in the particle curvature (particularly pronounced for colloidal particles) leads to an increase in dissolution pressure, according to the Kelvin's equation.
- Increased solubility leads to an increased concentration gradient at membranes, and thus subsequently to higher penetration or permeation through membranes.
- High penetration through membranes is also favored by high adhesion to biological membranes of nanocrystals, favored by their size, but adhesion can be also improved by the coating with mucoadhesive polymer.
- Nanocrystals can be administered by intravenous injection (nanosuspensions) and are able to efficiently reach the target tissue or organ with 100% bioavailability.
- Targeting can be promoted by coating nanocrystals with molecules that are able to interact with specific substrates.
- Nanocrystals have been developed to deliver drugs under different administration routes. The following paragraphs present several examples of the most important administration routes for which a nanocrystal formulation has been developed with an improvement in drug bioavailability (Maria R G et al., 2018).

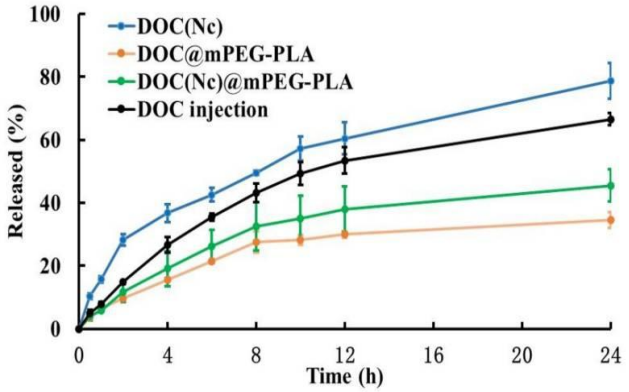

Figure 1.5: Release profiles of different formulations (Meng cheng et al., 2021).

1.6 Benefits of Docetaxel Nanocrystal technology for poorly soluble drugs:

- Diminished particle size, enhanced drug dissolution rate, enhanced rate and extent of absorption, enhanced bioavailability of the drug, area under plasma versus time curve, peak drug level, onset of time, decreased variability and lowered fed/fasted impacts.
- Compounds that are insoluble in water and soluble in oil can be formulated as nanosuspension, then again, nanosuspension can be utilized with lipoid systems and effectively formulate compounds that are insoluble in both water and oil.
- Nanoparticles prolongs the contact time of drug by adhering on to the gastrointestinal mucosa thus increase its absorption.
- Nanosuspension has got many routes of administration such as parenteral, oral, dermal, ocular and pulmonary makes it most convenient.
- Nanosuspension of nanoparticles offers different favorable circumstances over conventional ocular dosage forms, incorporating lower in the measure of dose, upkeep of drug release over a delayed timeframe, decrease in systemic toxicity of drug, improved drug absorption because of longer residing time of nanoparticles on the surface of cornea, higher concentration of drug in the infected tissue, and suitability for inadequately water - soluble drugs, and smaller particles are preferred endured by patients over bigger particles.
- Nanosuspension has got resistance to hydrolysis, oxidation and also posses' increased physical stability to settling.
- Decreased administration quantities need for intramuscular, subcutaneous, and ophthalmic use. (S. J. Shankar et. al., 2020).

1.7 Drug delivery system of Docetaxel Nanocrystal Drug:

1.7.1 Oral Drug Delivery:

Oral delivery is the first choice in drug therapy, because of safety, patient compliance, ease of production, and scalability, though the principal limitations are related to drug bioavailability. Nanocrystals may improve bioavailability through an increase in solubility and particle dissolution, and through an increased gradient concentration at membranes and adhesion to the gastrointestinal wall (Maria R. G. et al., 2018). By using standard manufacturing strategies, drug nanoparticle can be basically joined into different dosage forms like fast melts, capsules and tablets (S. J. Shankar et. al., 2020).

1.7.2 Intravenous Drug Delivery:

Due to their particle size, nanocrystals have the great advantage of being intravenously injectable, reaching 100% bioavailability. Nanocrystals in the range of 100–300 nm can be injected intravenously without any unwanted effect, such as the obstruction of small capillaries. Consequently, nanoparticles circulate in the bloodstream and dissolve according to their dissolution properties, and then are able to reach the target tissue (Maria R. G. et al., 2018).

1.7.3 Pulmonary Drug Delivery:

The pulmonary administration of drugs has proven highly successful not only for treating lung pathologies, but also for systemic action, because of the very large surface area available for drug adsorption, as well as the first - pass metabolism effect being avoidable. Fast onset and rapid particle deposition are other advantages (Maria R. G. et al., 2018).

1.7.4 Ocular Drug Delivery:

Drug delivery to eye tissues is particularly problematic because of generally poor drug bioavailability, drug instability, short residence time, poor drug solubility, a low amount of aqueous humor, and the loss of the drug with tears. Nanocrystals can enhance ocular drug permeation, favor controlled release, and promote targeting also guaranteeing fewer or more attenuated side effects than traditional formulations (Maria R. G. et al., 2018). The tear fluid secreted from lachrymal gland has least drug dissolving capabilities that planned as nanoparticles its dissolvability and bioavailability will elevate (Aher SS et al., 2017).

1.7.5 Targeted drug delivery:
Nanoparticles are suitable for targeting specific organs in perspective on their surface properties. Close by this, it is anything but difficult to adjust in vivo conduct by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region - specific delivery of the drug (Kayser O et al., 2005).

1.7.6 Transdermal drug delivery:
Nanocrystals are evolved greatly in the field of transdermal delivery of the drug to overcome the solubility issues of drugs, in this manner expanding the concentration gradient in between the formulation and the skin, subsequently, transdermal permeation of the drug (Sun B et al., 2012).

1.8 SLN for DTX delivery: advances and challenges

In terms of pharmacokinetics, drug stability, anticancer activity, and biodistribution, SLN formulations of cytotoxic drugs have offered better anticancer response than the corresponding free drug solutions. Several studies about DTX - loaded SLN formulations have been published with notable outcomes which are explained in the succeeding sections.

1.8.1 Enhanced stability and controlled release of DTX by SLNs encapsulation
SLNs have enhanced stability and make upgradability to production scale easier in comparison with liposomes. These characteristics of SLNs may be beneficial for various modes of targeting. SLNs develop the origin of drug delivery system, which has storage capability of at least 1 year (Mukherjee S., 2009). SLNs have been used for enhancing the bioavailability and controlled release of encapsulated active substance by altering the dissolution rate in injectable formulations (Wissing S., 2004).

1.8.2 Improved pharmacokinetics and biodistribution of DTXloaded SLN
In accordance with the previous study, DTX - encapsulated SLN demonstrated increased plasma concentrations and AUC as compared with Taxotere®. The co - delivery of DK in SLNs further increased plasma AUC as compared with DTX - encapsulated SLN. F - SLNs showed six times higher concentrations of DTX in the brain in comparison with available formulations of DTX. (Venishetty V. K., et al., 2012).

1.8.3 Antitumour activity with reduced systemic toxicity by SLN: one step further
Most of the cytotoxic anticancer drugs have very poor ability to bind specifically to tumour site and this is the most vital challenge to achieve better anticancer treatment (Kummar S., et al., 2006). The enhanced antitumour activity of DTX - loaded SLNs could be due to optimal particle sizes of SLNs and extended mean residence time (MRT) of DTX (Zhang P., et al., 2010).

1.8.4 Delivering on a promise: SLNs carry DTX to tumours
To enhance cytotoxicity of cancer cell selectively, one recent approach that has gained attention is the targeted therapy. This strategy designs cancer cell specific moiety on drug delivery system that allows molecular targeting of cancer cells avoiding lethal damage to healthy cells. Folic acid functionalized SLNs have been reported to exhibit active tumour targeting. Folate receptors (FRs) are over expressed in wide range of cancers; folic acid binds FR with high affinity and results in internalization of receptor via receptor - mediated endocytosis (Sumera, et al., 2017).

1.9 Advantages and Properties of Drug Nanocrystals:

The main reasons for the increased dissolution velocity and thus increased bioavailability are:
The size reduction leads to an increased surface area and thus according to the Noyes - Whitney equation to an increased dissolution velocity.

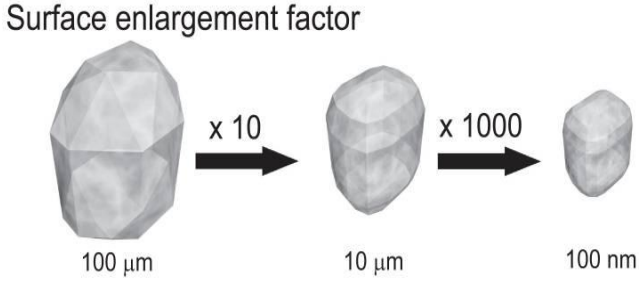

Figure 1.9: Surface enlargement and increase in number of crystals by particle size diminution (Jens - Uwe et al., 2008).

1.9.1 Increase in saturation solubility
The general textbook statement is that the saturation solubility Cs is a constant depending on the compound, the dissolution medium and the temperature. This is valid for powders of daily life with a size in the micrometer range or above. However, below a critical size of 1–2 µm, the saturation solubility is also a function of the particle size. It increases with decreasing particle size below 1000 nm. Therefore, drug nanocrystals possess increased saturation solubility. This has two advantages:

- According to Noyes and Whitney (1897), the dissolution velocity is further enhanced because dc/dt is proportional to the concentration gradient (Cs−Cx) /h (Cs - saturation solubility, Cx - bulk concentration, h - diffusional distance).
- Due to the increased saturation solubility the concentration gradient between gut lumen and blood is increased, consequently the absorption by passive diffusion (Jens - Uwe et al., 2008).

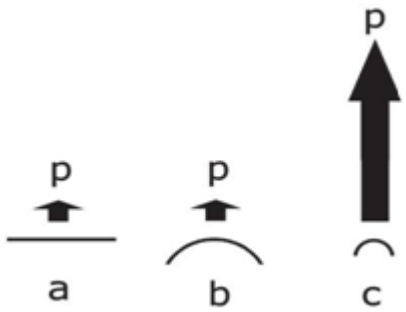

Figure 1.9.1: Increasing dissolution pressure over a flat surface, a microparticle, and a nanoparticle. p, dissolution pressure; a, flat surface; b, microparticle; c, nanoparticle. (Junghanns, 2006).

1.9.2 Advantages of an amorphous particle state:

It is well known that amorphous drugs possess a higher saturation solubility compared to crystalline drug material. A classic example from the literature is chloramphenicol palmitate. The polymorphic modification I has a solubility of 0.13, the high energy modification II a solubility of 0.43 and the amorphous material of 1.6 mg/ml. The same is valid for drug nanoparticles. Therefore, to reach the highest saturation solubility increase, a combination of nanometer size and amorphous state is ideal. However, a prerequisite for utilization in pharmaceutical products is that the amorphous state can be maintained for the shelf life of the product (Jens - Uwe et al., 2008).

1.10 Indications and Usages of Docetaxel:

Docetaxel is used in the treatment of various cancers, including breast, lung, prostate, gastric, head and neck, and ovarian cancer. Clinical data have shown docetaxel to have cytotoxic activity against breast, colorectal, lung, ovarian, prostate, liver, renal, gastric, and head and neck cancers and melanoma. In hormone - refractory prostate cancer docetaxel improves life expectancy and overall life quality. (Hettiarachchi SM, et al., July 2021). Docetaxel is also used to treat non - small cell lung cancer, head and neck cancer, stomach cancer and prostate cancer. The treatment is also used alone or as part of a combination regimen to treat secondary breast cancer, which is cancer that has spread from the breast to other parts of the body (Dr. Ananya Mandal., Feb 2019).

1.10.1 Breast Cancer

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node - positive breast cancer (John P. Cunha, et al., 2022).

1.10.2 Non - small Cell Lung Cancer

Docetaxel as a single agent is indicated for the treatment of patients with locally advanced or metastatic non - small cell lung cancer after failure of prior platinum - based chemotherapy. Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non - small cell lung cancer who have not previously received chemo - therapy for this condition (John P. Cunha, et al., 2022).

1.10.3 Prostate Cancer

Docetaxel in combination with prednisone is indicated for the treatment of patients with metastatic castration - resistant prostate cancer (John P. Cunha, et al., 2022).

1.10.4 Gastric Adenocarcinoma

Docetaxel in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease (John P. Cunha, et al., 2022).

1.10.5 Head and Neck Cancer

Docetaxel in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). (John P. Cunha, et al., 2022)

1.11 Dosage and Administration of Docetaxel:

For all indications, toxicities may warrant dosage adjustments Administer in a facility equipped to manage possible complications (e. g., anaphylaxis). Injection: One - vial Docetaxel: Single - dose vials 20 mg/mL, 80 mg/4 mL and 160 mg/8 mL. (John P. Cunha, et al., 2022). All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (e. g., 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. (John P. Cunha, et al., 2022).

1.12 Mechanism of action of Docetaxel:

DTX acts by binding reversibly to microtubules, promoting transitory structure stabilization, leading to cell cycle arrest. Therefore, docetaxel is a cytostatic drug for the control of tumor tissue growth (Cho H, 2014). Microtubules are building blocks of the cell's skeleton. During a cell's growth cycle, microtubules assemble and disassemble. The medication blocks this process and prevents a cell from dividing, and this eventually kills the cell cycles to interrupt the cell division cycle. (Michelle Llamas, Sep 2021).

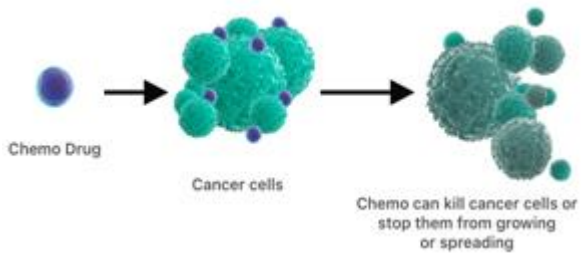

Figure 1.12: Chemotherapy drugs like Taxotere (Docetaxel) stop cancer cells from dividing. (Michelle Llamas, Sep 2021)

Docetaxel acts by disrupting the network of microtubules that controls the mitotic and interphase cellular functions essential for growth and division. Microtubules are polymers of α - and β - tubulin dimers. The primary mechanism of docetaxel action is direct bonding to the β - subunits of tubulin, promoting the stabilization of tubulin polymerization and inhibition of microtubule depolymerization. This action results in cell cycle arrest at the G2/M phase and inhibition of mitosis. Docetaxel has greater uptake into cells and more potent binding to tubulin subunits than paclitaxel. The other mechanism of antineoplastic action of docetaxel is BCL - 2 hyperphosphorylation, which induces apoptosis by disrupting the apoptosis - blocking BCL - 2 oncoprotein. Resistance of cancer cells to treatment has been correlated with overexpression of BCL - 2. Since BCL - 2 overexpression has been correlated with progression to advanced disease states and is associated with the

development of resistance, agents that interfere with BCL - 2 regulated pathways may improve outcomes. Docetaxel has approximately 100 - fold potency compared with paclitaxel in inhibiting antiapoptotic activity of BCL - 2 through phosphorylation (Supriya Gupta Mohile., et al., March 2008). In point, docetaxel is an appealing anticancer agent as it interferes with the cell cycle, producing both mitotic and antimitotic effects.

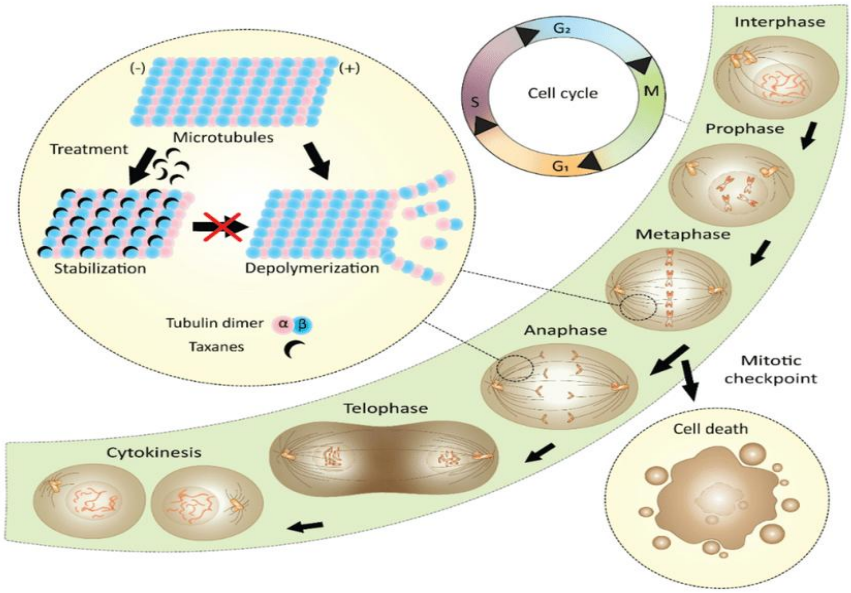

Figure 1.12.1: The mechanism of action of Docetaxel. (Jan Škubník, et al., March 2021)

The mechanism of docetaxel action is strongly dose - dependent. While at lower nanomolar concentrations (5–10 nM) mitosis is delayed, cells are still able to exit this state, even often with misaligned chromosomes. Treatment with higher paclitaxel concentrations (ca. to 10–500 nM) leads to prolonged mitotic arrest, the formation of altered mitotic spindles, and specific microtubule asters. These structures, which are not always nucleatedby a centrosome, prevent normal mitosis and cells undergo apoptosis. (Risinger A. L, et al., 2014). Microtubule asters are in some characteristics like spindles, at least by the presence of centrosomal material and calmodulin. Interestingly, asters do not grow from some organizing centers, but they are formed by the reorganization of microtubules, in which dyneins play a key role because microtubules slide along each other during this process. The mechanism of paclitaxel action is more complex since the effect of the drug might be influenced by differences in the cell structure composition, for example, the microtubules (Jan Škubník, et al., March 2021).

1.13 Active targeting a cancer cell by Docetaxel drug:

Active targeting specifically targets cancer cells through direct interactions between ligands and receptors. The ligands on the surface of NPs are selected to target the molecules that are over expressed on the surface of cancer cells, which allows them to distinguish targeted cells from healthy cells (Shi et al., 2011; Kamaly et al., 2012). The interaction between ligands on NPs and the receptors on the surface of cancer cells induces receptor - mediated endocytosis, which allows internalized NPs to successfully release therapeutic drugs (Farokhzad and Langer, 2009).

1.13.1 Targeting to Cancer Cells

Transferrin, a type of serum glycoprotein, functions to transport iron into cells. Transferrin receptors are overexpressed in most solid tumor cells and are expressed at low levels in normal cells. Thus, transferrin - conjugated NPs are used as an active targeting method to deliver drugs for cancer treatment (Santi et al., 2017). Compared to unmodified NPs, transferrin - modified NPs have been shown to exhibit higher cellular uptake efficiency and enhanced intracellular delivery of drugs. Moreover, evidence indicates that transferrin - conjugated polymeric NPs play a significant role in overcoming drug - resistant chemotherapy (Soe et al., 2019).

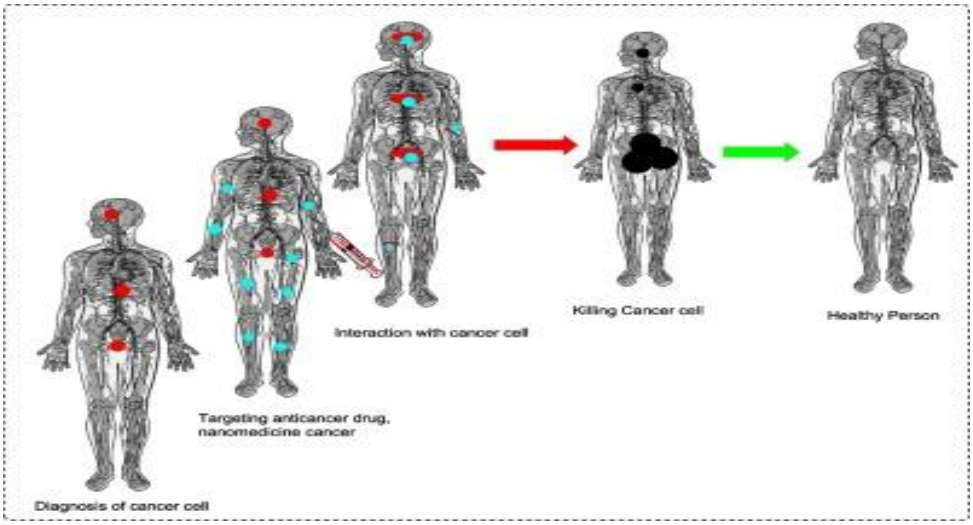

Figure 1.13.1: Diagnosis and targeting of cancer cells using emerging nanoparticle. (Anand Maurya, et al., 2019).

1.13.2 Mechanisms of NPs in overcoming Drug Resistance

Drug resistance is still a major problem in cancer treatment, despite the fact that methods of cancer therapy are increasing. The mechanisms of tumor drug resistance include cellular and physiological factors, such as overexpression of ATP binding cassette (ABC) transporters (e. g., efflux transporter), defective apoptotic machineries, interstitial fluid pressure, and acidic and hypoxic tumor microenvironment (Litman et al., 2000).

1.13.3 The Role of NPs in Cancer Immunotherapy

The development of immunotherapy has brought cancer treatment into a new era. NPs not only play an important role in delivery chemotherapy but have also shown great potential for applications in immunotherapy. Cancer immunotherapy is mainly achieved by activating the anti - tumor immune response. NP - associated immunotherapy includes nanovaccines, artificial antigen - presenting cells (aAPCs), and targeting of the immunosuppressed tumor microenvironment (TME) (Zang et al., 2017). Nanovaccines deliver tumor - associated antigens (TAAs) and adjuvants to APCs, such as dendritic cells (DCs) (Paulis et al., 2013). Additionally, NPs can be used as adjuvants themselves to increase APC antigen presentation and promote DC maturation, leading to the activation of the anti - tumor function of cytotoxic T cells (Shao et al., 2015; Yang et al., 2018). NPs, such as liposomes, gold NPs, PLGA NPs, micelles, and dendrimers all have the capability of cytoplasmic delivery of TAAs into DCs, thus enhancing the immune response against tumor cells (Guo et al., 2015). Targeting the immunosuppressive TME is mainly achieved by targeting tumorassociated macrophages (TAMs), myeloid derived suppressor cells (MDSCs), and regulatory T cells (Tregs), all of which are important cell types in the TME (Shao et al., 2015). Furthermore, in order to minimize interactions with the reticuloendothelial system, NPs are usually modified with PEG (Zang et al., 2017).

1.14 Side effects of Docetaxel:

Some of the side effects docetaxel treatment can cause include:

Anemia (low red blood cell count), Alopecia (hair loss), Peripheral neuropathy (tingling and numbness in the hands and feet), Nausea and vomiting, Diarrhea, Muscle and joint pain, Water retention and weight gain, Dry skin, Fatigue (Dr. Ananya Mandal., Feb 2019). Myelosuppression and fatigue are the most common side effects of docetaxel. (Supriya G M, et al., 2008)

1.15 Adverse Reaction:

Most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia (John P. Cunha, et al., 2022)

1.16 Warnings and Precautions:

- Acute myeloid leukemia: In patients who received docetaxel, doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia.
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment.
- Neurologic reactions: Reactions including paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent.
- Asthenia: Severe asthenia may occur and may require treatment discontinuation.
- Pregnancy: Fetal harm can occur when administered to a pregnant woman (John P. Cunha, et al., 2022).

2. Methodology

The present study in based on the intensive field of the area during the period of 2000 to 2022. The data was collected from online journals, research papers, and books, all of which were published in different search engine websites such as Google, Google Scholar, Science Direct, Research gate and other online collections were utilized in this review to obtain information. This review provides a clear data of nanocrystal formulation of the anticancer drug with pharmacological activitiesand encourages further investigations for more effective result. This review also provides a lucid data of the achievements in improving the

bioavailability of poorly soluble drugs according to their administration route, and in particular observations different stabilizers and surface agents that are able to modify the drug delivery, penetrate target cells, and enhance the pharmacological action of docetaxel.

3. Result

Docetaxelmainly act by inducing microtubular stability and disrupting the dynamics of the microtubular network. The drug has shown a broad spectrum of antitumour activity in preclinical models as well as clinically, with responses observed in various disease types, including advanced breast cancer and non - small cell lung cancer. Nanotechnology will affect our lives tremendously over the next decade in very different fields, including medicine and pharmacy. Transfer of materials into the nanodimension changes their physical properties which were used in pharmaceutics to develop a new innovative formulation principle for poorly soluble drugs: the drug nanocrystals. Nanocrystals of Docetaxel anticancer drug have the great advantage of being intravenously injectable, reaching 100% bioavailability. Nanocrystals efficacy is more than 98%. Nearly 40% of drugs coming to the market nowadays are having poor solvency related issues and 70% molecules in the discovery pipeline are in effect fundamentally insoluble in water.

Table 3.1: Comparative study on efficacy between nanocrystal formulation and conventional dosage form of tablet of Docetaxel anticancer drug

S. NO.	Distinction on efficacy between nanocrystal formulation and conventional dosage form of tablet of Docetaxel anticancer drug.	Range	Efficacy	Effectiveness
01	Nanocrystal formulation particle of Docetaxel	1- 100 nm	98%	More effectivethan conventional dosage form of tablet of Docetaxel anticancer drug.
02	Conventional dosage form of tablet of Docetaxel anticancer drug.	125-180 µm	40%	Less effectivethan nanocrystalformulation particle of Docetaxel

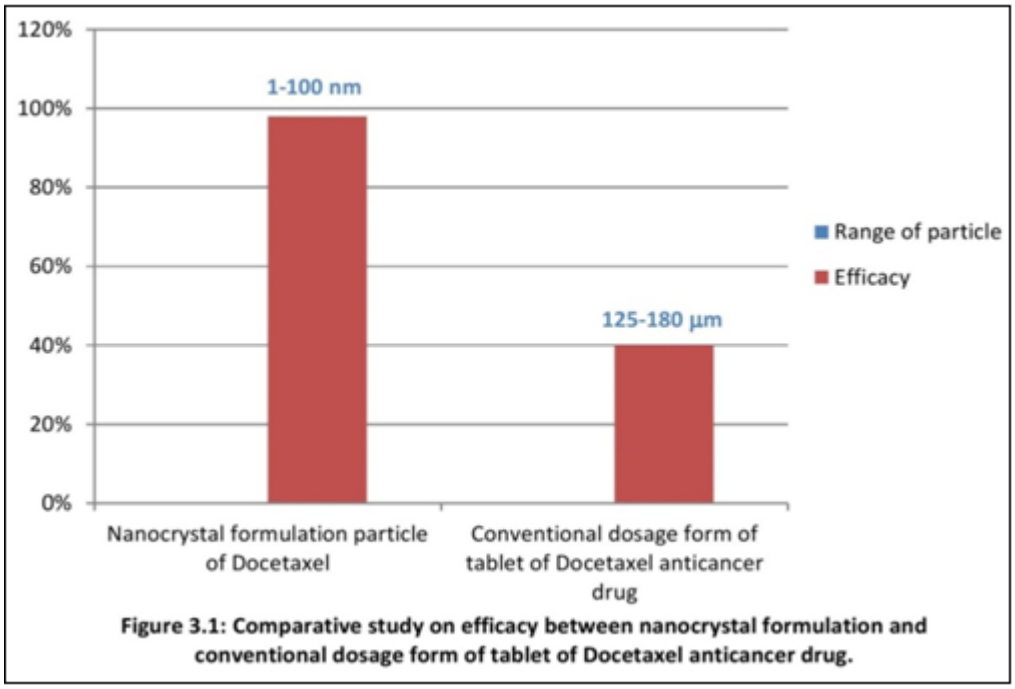

Figure 3.1: Comparative study on efficacy between nanocrystal formulation and conventional dosage form of tablet of Docetaxel anticancer drug.

4. Discussion

Poorly - water - soluble compounds are difficult to develop as drug products using conventional formulation techniques and are frequently abandoned early in discovery. In addition, aqueous dispersions of nanoparticles can be post - processed into tablets, capsules, fast - melts and lyophilized for sterile product applications. The technology has been successfully incorporated into all phases of the drug development cycle from identification of new chemical entities to refurbishing marketed products for improving their performance and value. The pharmacokinetics and metabolism of docetaxel are extremely complex and has been the subject of intensive investigation in recent years. The drug has shown a broad spectrum of antitumour activity in preclinical models as well as clinically, with responses observed in various disease types, including advanced breast cancer and non - small cell lung cancer that act by inducing microtubular stability and disrupting the dynamics of the microtubular network. Moreover, in a mouse model with pre - established tumors, the new DCX - Nanocrystal were significantly more effective than DCX solubilized in a Tween 80/ethanol solution in inhibiting tumor growth without toxicity, likely because the DCX - Nanocrystal increased the concentration of DCX in tumor tissues. Thus, chemotherapeutic drugs, including Docetaxel, are administered via an intravenous route, which poses many disadvantages of its own. Recent advances in pharmaceutical research have focused on designing new and efficient drug delivery systems for site - specific targeting, thus, chemotherapeutic drugs, including Docetaxel, leading to improved bioavailability and pharmacokinetics.

5. Conclusion

The present study recapitulates various nanoformulations used in drug delivery, their toxicological effects, and significance of nanotechnology in delivering natural bioactives. However, there is an essential need to develop rapid whole animal - based testing methods to assess the potential toxicity of nanomaterials in biomedical science. In this study, poorly - water – soluble conventional formulation of docetaxel compounds that are able to modify the drug delivery and enhance the bioavailability of antitumor drug docetaxel through the nanocrystal formulation. Overall, nanotechnology is a new path in the development of effective carrier systems for site - specific delivery of bioactive. This will introduce new vistas in clinically considering their various merits like maximum efficacy, targeted effects, and improved patient compliance.

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