Chapter 2

Literature Review

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LITERATURE REVIEW

2.1 CANCER

Cancer represents a predominant cause of mortality globally, characterised by the unregulated proliferation of atypical cells within the organism. The global mortality rate is projected to increase from 7,600,000 deaths in 2008 to 13,200,000 million by 2030, according to World Health Organisation (WHO) [1]. The typical physiological process involves normal body cells growing, dividing into new cells, and undergoing apoptosis in a regulated fashion. In contrast, cancer cells evade this programmed cell death, leading to unchecked proliferation and the formation of tumours [1, 2].

Cancer cells frequently disseminate to various regions of the body, where they proliferate uncontrollably and establish new tumours that supplant normal tissue, a process known as metastasis. Cancer retains its nomenclature based on its origin, regardless of the sites to which it may metastasise. For instance, breast cancer that has metastasised to the liver retains its designation as breast cancer, rather than being classified as liver cancer [2-4]. The progress in cancer diagnosis and treatment options is hindered by several factors, including dose-related side effects, insufficient tumour specificity, challenges in effective intracellular delivery, inadequacies in predictive preclinical models, and the emergence of drug resistance. These issues contribute to a poor prognosis for patients suffering from prevalent metastatic tumours, including breast, prostate, lung, and gastrointestinal cancers [2-5].

2.2 BREAST CANCER

Breast cancer is malignancy wherein the cells of breast tissue show uncontrolled growth. It is the most common form of cancer widely reported in women and also scarcely reported in men. Breast cancer is the leading cause of cancer-related deaths in women across the globe. The epithelial cells of the mammary gland are the primarily the origin of breast cancer and the factors responsible for the development include genetic, environmental and hormonal. The transformation of normal cells into cancerous ones involves genetic mutations and alterations in cellular signaling pathways which can be traced back to various origins, including genetic predispositions, viral influences, and early life factors [6, 7].

2.2.1 Treatment for Breast Cancer

The management of breast cancer is liable upon various factors, including tumour's type, phase, size, and additional characteristics, alongside patient-specific considerations such as age, overall health status, and individual preferences [24]. The primary categories of treatments for breast cancer, along with representative examples for each, are outlined as follows:

[A] Surgery

The surgical procedure entails the excision of the tumour along with adjacent tissue to eradicate the malignancy from the breast.

Lumpectomy, commonly referred to as breast-conserving surgery, involves the excision of the malignant tumour along with a narrow margin of adjacent healthy tissue [24, 25].

Mastectomy involves the surgical excision of the complete breast tissue. Various surgical approaches exist, such as simple mastectomy, modified radical mastectomy, and skin-sparing mastectomy. In instances where there are substantial tumours or multiple tumours located in various regions of the breast, a mastectomy may be indicated [24, 25].

[B] Radiotherapy

Radiation therapy employs high-energy radiation to selectively target and eliminate malignant cells. This treatment is frequently administered post-operatively to eradicate any residual cancer cells [26, 27].

[C] Chemotherapy

Chemotherapy employs active pharmaceutical agents to eradicate neoplastic cells or inhibit their proliferation. The treatment may be administered prior to surgical intervention to reduce tumour size or post-operatively to eliminate residual cancerous cells [27-30].

Neoadjuvant chemotherapy is administered prior to surgical intervention to reduce the size of a significant tumour. It involves administering of agents such as doxorubicin and cyclophosphamide to decrease tumour volume for a more conservative surgical approach [28, 29].

Adjuvant chemotherapy is administered post-surgery to mitigate the risk of cancer recurrence. It utilises a synergistic approach with agents like paclitaxel and carboplatin for individuals exhibiting lymph node involvement [30, 31].

Systemic chemotherapy is delivered either intravenously or orally, resulting in effects throughout the entire body. For instance, agents such as Docetaxel (Taxotere) or Capecitabine (Xeloda) are utilised [32, 33].

[D] Hormonal Treatment

Hormone therapy, often referred to as endocrine therapy, is employed in the treatment of breast cancers characterised by hormone receptor positivity (ER+ or PR+). It inhibits the body's capacity to synthesise hormones or disrupts hormone functionality. Selective Oestrogen Receptor Modulators (SERMs) are compounds such as Tamoxifen, which function by inhibiting oestrogen receptors on breast cancer cells. This therapeutic agent is utilised in both premenopausal and postmenopausal women [34, 35].

Aromatase inhibitors, such as Anastrazole (Arimidex), Letrozole (Femara), and Exemestane (Aromasin), function by inhibiting the aromatase enzyme, thereby reducing oestrogen levels through the prevention of androgen conversion into oestrogen [34, 35]. These agents are primarily indicated for use in postmenopausal women. Ovarian suppression involves the reduction of oestrogen production by the ovaries, typically achieved through pharmacological agents such as Goserelin (Zoladex) or via surgical intervention, specifically oophorectomy [34, 35]. It is utilised in premenopausal females to lower hormone concentrations [34, 35].

[E]Targeted Therapy

Targeted therapy utilizes pharmacological agents that specifically engage with certain molecules involved in the growth and spread of cancerous cells. This agent is commonly employed in the management of HER2-positive breast cancer. HER2-Targeted Therapeutics For example, Trastuzumab (Herceptin) and Pertuzumab (Perjeta) are designed to specifically bind to the HER2 protein found on cancer cells, thereby effectively blocking growth signals [36, 37]. CDK4/6 inhibitors, including Palbociclib (Ibrance), Ribociclib (Kisqali), and Abemaciclib (Verzenio), specifically target proteins that are essential in the regulation of cell division [36-39]. These agents are employed specifically for the treatment of HR-positive,

HER2-negative breast cancer. PI3K inhibitors encompass compounds like Alpelisib (Piqray), which is indicated for individuals diagnosed with HR-positive, HER2-negative breast cancer that demonstrates a PIK3CA mutation [36-39].

[F] Immunotherapy

Immunotherapy improves the immune system's response, allowing for the accurate identification and targeting of malignant cells. This agent is frequently prescribed for particular subtypes of breast cancer, such as triple-negative breast cancer (TNBC). Immune checkpoint inhibitors, including Pembrolizumab (Keytruda), operate by engaging the PD-1/PD-L1 pathway, which subsequently boosts the immune system's capacity to recognize and attack cancer cells [40, 41].

2.2.2 Classification of Chemotherapeutics

Chemotherapy commonly referred to as "chemo," entails the administration of pharmacological agents/ pharmacologically active agents aimed at eradicating neoplastic cells. Chemotherapy agents are categorised according to their mode of action, molecular composition, and their impact on the cancerous cells. The following presents the types of chemotherapeutics, accompanied by illustrative examples for each classification:

1. Alkylating Agents

Alkylating agents function by introducing an alkyl group into the DNA of neoplastic cells, resulting in DNA damage that inhibits cellular division and proliferation [42]. These agents demonstrate efficacy across a spectrum of malignancies, encompassing breast cancer, leukaemia, lymphomas, and sarcomas [42].

Examples: Cyclophosphamide, Ifosfamide, Melphalan, Busulfan

2. Antimetabolites

Antimetabolites disrupt the synthesis of DNA and RNA by imitating the essential natural compounds necessary for cellular growth and division. Their primary activity occurs during the S-phase of the cell cycle, which is characterised by the replication of DNA [43, 44].

Examples: Methotrexate, 5-Fluorouracil, Capecitabine, Gemcitabine, Pemetrexed

3. Anthracyclines

Anthracyclines represent a class of chemotherapeutic agents that disrupt the function of enzymes critical to the process of DNA replication. The mechanism of action involves intercalation between DNA strands, leading to strand breaks, and inhibiting the replication processes of both DNA and RNA [45, 46].

Examples: Doxorubicin, Epirubicin, Daunorubicin, Idarubicin

4. Taxanes

Taxanes are derived from plant alkaloids and function by stabilising microtubules, thereby inhibiting their disassembly, a process essential for cell division. These agents are frequently utilised in the treatment of breast, lung, and ovarian malignancies [47, 48].

Examples: Paclitaxel, Docetaxel, Nab-paclitaxel

5. Topoisomerase Inhibitors

Topoisomerase inhibitors impede the function of topoisomerases, which are enzymes essential for the unwinding of DNA during the replication process. Inhibition of these enzymes results in the induction of DNA breaks, ultimately culminating in cellular apoptosis [49].

Examples: Topoisomerase I inhibitors: Irinotecan, Topotecan

Topoisomerase II inhibitors: Etoposide, Teniposide, Mitoxantrone

6. Mitotic Inhibitors

Mitotic inhibitors commonly referred to as spindle poisons or mitosis poisons, function by interfering with the microtubule structures that are crucial for the process of cell division. These compounds are obtained from natural botanical sources, including periwinkle and yew trees [50, 51].

Examples: Vincristine, Vinblastine, Vinorelbine, Eribulin

7. Corticosteroids

Corticosteroids are a class of steroid hormones frequently utilised alongside various chemotherapy agents to mitigate nausea and allergic responses, as well as to directly address certain malignancies [52].

Examples: Prednisone, Dexamethasone, Methylprednisolone

8. Platinum-Based Compounds (Alkylating-Like Agents)

Platinum-based compounds, known as platinum analogues, exhibit mechanisms akin to alkylating agents by inducing cross-linking in DNA. This interaction inhibits both replication and transcription processes, ultimately resulting in cellular apoptosis [53].

Examples: Cisplatin, Carboplatin, Oxaliplatin

9. Miscellaneous Agents

These agents represent a class of chemotherapy drugs that do not conform strictly to the established categories, exhibiting distinct mechanisms of action [54].

Examples:

- Bleomycin - causes DNA strand breaks.

- L-asparaginase - depletes asparagine, an amino acid essential for leukemia cells.

- Hydroxyurea - inhibits DNA synthesis by acting on ribonucleotide reductase.

10. Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates represent an innovative category of targeted chemotherapy, integrating monoclonal antibodies that are specific to neoplastic cells with cytotoxic chemotherapeutic agents. The antibody directs the therapeutic agent specifically to neoplastic cells, thereby reducing the adverse effects on healthy tissues [55, 56].

Examples: Trastuzumab Emtansine, Sacituzumabgovitecan

Chemotherapy regimens typically incorporate a combination of these drug classes to enhance their efficacy, target cancer cells at various stages of proliferation, and minimise the potential for resistance development. The selection of chemotherapeutic agents and their combinations is contingent upon the specific cancer type and its stage, the patient's general health status, and the therapeutic objectives established for treatment [57].

2.2.3 Drug Resistance – A challenge in Breast Cancer

Effective drug delivery has been a major contributor to the improvement of cancer treatment. Ineffective drug delivery has resulted in inadequate tumour response, severe adverse effects, and the emergence of infamous cancer drug resistance [58].

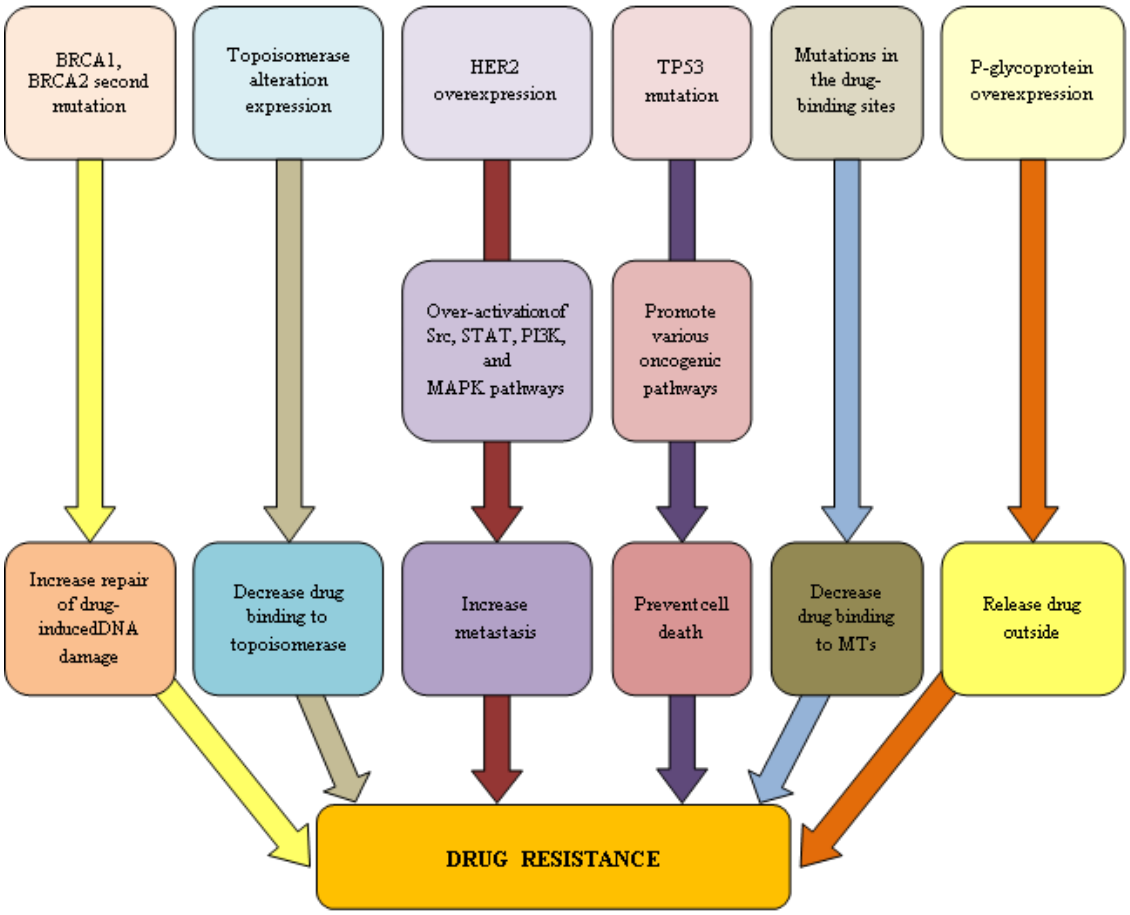


Figure 2.1: Key mechanisms of drug resistance in breast cancer

Anticancer drugs are not specific to cancer cell only but are also toxic to healthy proliferating cells and therefore restriction in dose is inevitable to avoid potentially fatal adverse effects [59, 60]. Such factors as limited systemic circulation lifetime, undesirable biodistribution, non-specific cellular uptake, and inadequate tumour vascularisation can further reduce the therapeutic efficacy of such a low drug dose [61-63]. Consequently, each course of chemotherapy has typically resulted in partial treatment, which has led to a selective pressure that favours mutations and drug resistance among the surviving cancer cells [64-66]. Drugs with a favourable initial response are frequently rendered ineffective after repeated administrations, making the treatment of recurrent tumours more challenging [67, 68]. Various mechanisms of drug resistance in breast cancer are presented in Figure 2.1.

The occurrence of mutations has been associated with an increase in resistance to chemotherapeutic drugs. These mutant types include altered drug targets, higher drug metabolism, improved damage repair mechanisms, compromised apoptotic signaling, and up-regulation of drug efflux pumps [59-63]. Therefore, an effective method for enhancing the

treatment of cancer cells would involve activating multiple pathways to prevent tumour cells from acquiring mutations. In addition, the majority of malignancies have been linked to multiple genetic alterations or abnormalities that result in tumour heterogeneity [59-68].

2.2.4 Review of Drug Combinations used in Cancers

The need for drug combinations in cancer treatment arises from the complex nature of cancer, which often involves multiple genetic mutations and signalling pathways. Single-agent therapies frequently fall short due to drug resistance and limited efficacy [69-71]. Drug combinations offer a strategic approach to enhance treatment outcomes by targeting multiple pathways simultaneously, reducing resistance, and improving patient tolerance [69-71]. This multifaceted approach is crucial for addressing the diverse and adaptive nature of cancer cells. Combination therapies can improve treatment effectiveness by utilizing synergistic effects, resulting in a combined impact of drugs that exceeds the total of their separate effects. [69]. Machine learning frameworks have been employed to predict synergistic drug combinations, identifying effective pairs such as kinase inhibitors with mTOR inhibitors for various cancers [69].

By using lower doses of multiple drugs, combination therapies can reduce toxicity and side effects, improving patient tolerance and quality of life [70]. This approach allows for more personalized treatment regimens, potentially leading to better patient outcomes [71]. Cancer's polygenic nature and complex signalling networks necessitate a multifaceted treatment approach. Combinatory treatments can effectively target these intricate networks [71]. Drug repurposing within combination therapies offers a cost-effective and efficient strategy to address these complexities, utilizing existing drugs for new therapeutic purposes [71]. The review of drug combinations used in treatment of cancer is presented in Table 2.1.

Table 2.1: Review of Drug Combinations used in treatment of Cancer

Sr. No.	Drug Combination	Application in type of cancer	Outcomes	Ref.
1	Doxorubicin + Cyclophosphamide + Carboplatin + Paclitaxel + Pembrolizumab	Neoadjuvant treatment of triple negative breast cancer	The study reported an overall pathologic complete response (pCR) rate of 56 % among patients treated with modified regimen, which included dose-dense doxorubicin plus cyclophosphamide (ddAC). A pCR indicates that there was no evidence of cancer in tissue samples after treatment, suggesting a significant response to drug combination.	72
2	Docetaxel + Doxorubicin + Cyclophosphamide	Adjuvant therapy for metastatic breast cancer and ovarian cancer	The provided context does not specify whether drug combination of Docetaxel, doxorubicin, and cyclophosphamide was able to cure cancer. It mentions that combination has a marked therapeutic effect compared to other adjuvant therapies, but does not confirm a cure.	73
3	Doxorubicin + Cyclophosphamide	Treatment of cancer	The combination treatment of doxorubicin and cyclophosphamide in C57BL/6J mice was found to be clinically relevant and did not induce hepatotoxicity, indicating a favourable safety profile for this treatment regimen. The study suggests that combination therapy may be effective in cancer treatment without associated risk of liver damage, which is a common concern with many chemotherapeutic agents.	74
4	Paclitaxel + Cisplatin + Cyclophosphamide	Advanced ovarian carcinoma	The study presents preliminary results from a phase I/II trial evaluating combination of paclitaxel, cisplatin, and cyclophosphamide in patients with advanced ovarian carcinoma, indicating a potential therapeutic benefit of this regimen. The findings suggest that treatment is feasible and may lead to improved outcomes in terms of tumor response, although further analysis and longer follow-up are necessary to confirm these results.	75
5	Epirubicin + Paclitaxel or Epirubicin + Docetaxel	Breast cancer	The combination of Epirubicin plus paclitaxel showed greater efficacy compared to Epirubicin plus Docetaxel, with a higher overall remission rate of 94.87% in study group versus 74.36% in control group. The study indicated that Epirubicin plus paclitaxel resulted in more cases of complete remission and partial remission. However, study does not explicitly state that drug combination was able to cure cancer, as it primarily focuses on treatment efficacy and remission rates rather than definitive cures.	76

Sr. No.	Drug Combination	Application in type of cancer	Outcomes	Ref.
6	Bevacizumab + Liposomal Doxorubicin + Cyclophosphamide + Paclitaxel	Advanced breast cancer	The drug combination of bevacizumab, liposomal doxorubicin, cyclophosphamide, and paclitaxel (PLAC-B) demonstrated efficacy in treating locally advanced breast cancer in studied population. The complete clinical response (cCR) rate was 25.8%, and pathologic complete response (pCR) rate was 38.7%. The pCR rate was 42.9% for triple-negative breast cancer (TNBC) patients and 30% for estrogen receptor/ progesterone receptor-positive (ER/PR+) patients. Over a 3-year follow-up, all patients were alive, indicating a favourable outcome. Disease-free survival (DFS) was reported at 87.1%, suggesting that drug combination was effective in managing cancer in this patient population.	77
7	Paclitaxel + Carboplatin	Small cell lung cancer	The combination of carboplatin and paclitaxel was not reported to cure small cell lung cancer (SCLC). The response rate observed was 33.3%, indicating some level of effectiveness. Median progression-free survival was 4.1 months, and overall survival was 8.7 months. The study concluded that combination therapy is effective and feasible, particularly for patients with interstitial lung disease (ILD), but it does not imply a cure for the cancer.	78
8	Paclitaxel + Oxaliplatin	Advanced gastric cancer	The combination chemotherapy with Paclitaxel and Oxaliplatin did not cure the cancer in patients with advanced gastric cancer. The overall objective response rate was 42.9%, with two complete responses and 40 partial responses, indicating some level of effectiveness but not a cure. The median overall survival was 11.5 months, and 1-year survival rate was 48.0%, suggesting that while treatment improved survival, it did not eliminate cancer.	79
9	Paclitaxel + Cyclosporine A	Lung cancer	The combination of cyclosporine A (CsA) and Paclitaxel (PTX) aerosol showed more favourable effects on tumor growth compared to untreated and PTX-only groups. However, study does not indicate that drug combination was able to cure the cancer. The findings suggest that while combination may improve treatment outcomes, further toxicity control is necessary for effective aerosol treatment.	80

Sr. No.	Drug Combination	Application in type of cancer	Outcomes	Ref.
10	Vandetanib + Fulvestrant	Advanced breast cancer	Vandetanib and Fulvestrant combination did not improve progression-free survival (PFS) in patients with aromatase inhibitor-resistant advanced breast cancer. The median PFS was 5.5 months for both the combination treatment (Fulvestrant plus Vandetanib) and the placebo (Fulvestrant plus placebo). High total RET expression was associated with improved PFS, suggesting a potential prognostic role, but the drug combination itself did not cure the cancer.	81
11	Fulvestrant and Doxorubicin	In breast cancer	Fulvestrant reinstated the intracellular accumulation of Doxorubicin and additionally repositioned it to the nuclei in Bats-72 and Bads-200 cells, which could represent another potential mechanism for reversing P-gp mediated doxorubicin resistance.	82
12	Fulvestrant and Docetaxel/ Fulvestrant and Paclitaxel	In breast cancer	Regarding chemoresistant factors, Bcl2 and microtubule-associated protein tau were downregulated by Fulvestrant and Docetaxel and synergistic effect on tumour growth observed	83
13	Doxorubicin + Cyclophosphamide versus Docetaxel + Cyclophosphamide	Breast cancer	It was found that there were no significant differences in Progression Free Survival between the two regimens. However, the TC regimen (Docetaxel and Cyclophosphamide) showed better Overall Survival compared to the AC regimen (Doxorubicin and Cyclophosphamide). Both treatment regimens were well tolerated, but the TC regimen was better tolerated regarding adverse effects and overall survival. The study does not explicitly state that either drug combination was able to cure the cancer, but it suggests that the TC regimen is a recommended adjuvant chemotherapy option due to its better overall survival outcomes.	84
14	Adriamycin + Paclitaxel + Cyclophosphamide	High risk breast cancer	The study indicates that the adjuvant sequential chemotherapy regimen is efficient in treating high-risk breast cancer. The results suggest that while the drug combination did not guarantee a cure for all patients, it significantly improved survival outcomes for many.	85

Sr. No.	Drug Combination	Application in type of cancer	Outcomes	Ref.
15	Paclitaxel + Cyclophosphamide	Metastatic urothelial bladder cancer	The combination of paclitaxel and oral cyclophosphamide was well tolerated and showed promising efficacy in patients with metastatic urothelial bladder cancer. However, the study does not report a complete cure for cancer, as the primary endpoints focused on maximum tolerated doses and objective response rates rather than complete remission.	86
16	Paclitaxel + Cyclophosphamide	Advanced or recurrent breast cancer	The provided contexts do not specify whether the combination therapy of weekly paclitaxel and cyclophosphamide was able to cure cancer in patients with advanced or recurrent breast cancer. The focus of the study was on determining the maximum tolerated dose and recommended dose of the combination therapy, rather than on definitive outcomes related to cancer cure. Therefore, there is no information available regarding the effectiveness of the drug combination in curing cancer.	87
17	Topotecan + Docetaxel	In ovarian cancer and endometrial cancer	Has clinical benefit and is well tolerated in patients with platinum-resistant tumours	88
18	Paclitaxel + Cyclophosphamide	Recurrent breast cancer	The provided context does not indicate whether the drug combination of nanoparticle albumin-bound paclitaxel and cyclophosphamide was able to cure the cancer. The study focused on determining the maximum tolerated dose and recommended dose of the combination therapy in patients with metastatic or recurrent breast cancer, rather than assessing its curative effects.	89

Paclitaxel and Cyclophosphamide are used in the treatment of various cancers. However, the synergism between the two drugs is not established due to lack of systematic and focused research. Phase I studies, including those conducted by Kutomi et al., investigated the simultaneous administration of nanoparticle albumin-bound paclitaxel (nab-PTX) and cyclophosphamide (CYC) to establish the maximum tolerated dose and the recommended dose for this combination therapy in patients with metastatic or recurrent breast cancer [89]. The study primarily reported on dose-limiting toxicities and patient enrolment rather than exploring the mechanisms or efficacy of the drug combination's synergistic effects [89]. Current research evaluated the synergism between the two drugs and evaluated the effect of drug combination when loaded in the advanced carrier systems for drug delivery.

2.3 NANOSTRUCTURED LIPID CARRIERS (NLCS)

Nanostructured lipid carriers (NLCs) are an advanced form of lipid-based nanocarriers designed to improve drug delivery systems. They are composed of a blend of solid and liquid lipids, which creates a less ordered lipid matrix, enhancing their drug loading capacity and stability compared to earlier lipid-based carriers like solid lipid nanoparticles (SLNs) [90]. The particle size of NLCs typically ranges from 20 to 1000 nm, which is optimal for drug delivery as it allows for enhanced permeability and retention in target tissues [91].

The inclusion of liquid lipids in NLCs leads to a less ordered crystalline structure, which increases the available space within the lipid matrix for drug accommodation. This disordered structure prevents the expulsion of drugs during storage, a common issue with solid lipid nanoparticles (SLNs) [90-92]. The presence of liquid lipids enhances the entrapment efficiency of drugs within the NLCs, allowing for higher drug loading compared to traditional solid lipid systems [92, 93]. Lipid-based carriers are composed of natural or synthetic lipids that are biocompatible and biodegradable, reducing the risk of toxicity and immunogenicity compared to other delivery systems [94, 95]. These carriers mimic cell membranes, facilitating enhanced cellular uptake and controlled release of drugs, which optimizes therapeutic efficacy while minimizing side effects [94].

2.3.1 Classification of NLCs

Nanostructured lipid carriers (NLCs) are a type of lipid-based nanocarrier that has been developed to improve drug delivery systems. They are classified into three types based on their composition and structure: Type 1 (Low Oil), Type 2 (High Oil), and Type 3 (Amorphous). Each type has distinct characteristics that influence their application and effectiveness in drug delivery. The classification is primarily based on the ratio of solid to liquid lipids and the resulting structural organization within the lipid matrix.

Type 1: Low Oil Content NLCs: These NLCs have a low content of liquid oil mixed with solid lipids. The solid lipid matrix is predominant, providing a more structured and stable form. The low oil content results in a more ordered crystalline structure, which can lead to lower drug loading capacity but higher physical stability. Due to their stability, Type 1 NLCs are suitable for applications where long-term storage and controlled release are critical. They are often used in formulations where the stability of the active ingredient is a priority.

Type 2: High Oil Content NLCs: These carriers contain a higher proportion of liquid oil compared to solid lipids, leading to a less ordered structure. The increased oil content allows for higher drug loading capacity and improved release profiles. However, this can also result in reduced physical stability compared to Type 1 NLCs. Type 2 NLCs are ideal for applications requiring high drug loading and rapid release, such as in the delivery of hydrophobic drugs where enhanced bioavailability is needed.

Type 3: Amorphous NLCs: These NLCs are characterized by an amorphous structure, resulting from a balanced mixture of solid and liquid lipids that prevents crystallization. The amorphous nature of these carriers provides a high degree of flexibility in drug loading and release. They offer a compromise between stability and drug loading capacity. Amorphous NLCs are used in applications where a balance between stability and drug release is required, such as in dermal applications where penetration and sustained release are important.

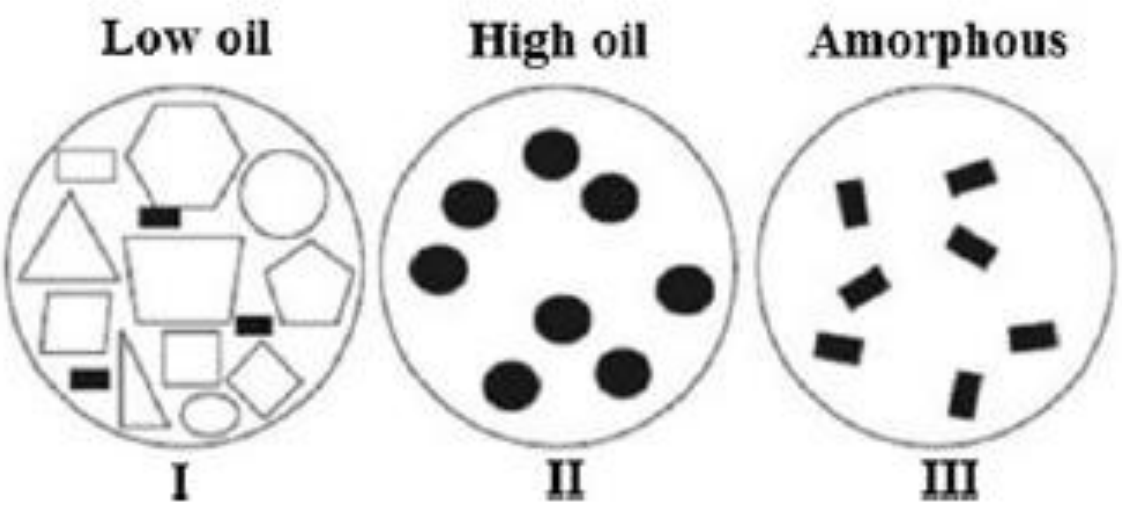


Figure No. 2.2: Classification of NLCs

Advantages of NLCs [95-97]

- Enhanced physical stability,
- Simplified preparation and scalability,
- Improved dispersability in an aqueous medium,
- Significant drug entrapment efficiency,
- Regulated particle dimensions,
- A sophisticated and effective delivery system specifically designed for lipophilic compounds,

- Prolonged drug release profiles,
- Enhanced benefit-to-risk ratio,
- These delivery systems exhibit high efficacy owing to their solid lipid matrices, which are typically acknowledged as safe or possess regulatory acceptance.
- A three to five-fold increase in drug plasma concentrations
- Reduced clearance rate and diminished volume of distribution
- Minimal adverse effects
- Extended circulation duration of the drug
- Reduced cytotoxic effects
- Enhanced bioavailability of the drug
- Improved permeability and retention of the drug within tumor tissues

2.3.2 Methods of Preparation

Nanostructured lipid carriers (NLCs) are advanced drug delivery systems that can be prepared using various techniques, each with unique mechanisms and applications. These methods include hot and cold high-pressure homogenization, solvent emulsification/evaporation, microemulsion formation, ultrasonic solvent emulsification, phase inversion temperature, and melting dispersion technique. Each technique offers distinct advantages and challenges, making them suitable for different types of drugs and delivery routes. [91-97].

1. High pressure homogenization technique

[A] ***Hot high pressure homogenization***

This method involves melting the lipid phase and mixing it with an aqueous surfactant solution at the same temperature. The mixture is then subjected to high pressure, which reduces particle size and forms NLCs. This technique is suitable for heat-stable drugs and allows for large-scale production [91-97].

[B] ***Cold high pressure homogenization***

In contrast, this method involves solidifying the lipid phase by cooling it before homogenization. The solid lipid is then ground into microparticles and dispersed in a cold aqueous surfactant solution. This method is beneficial for heat-sensitive drugs as it avoids thermal degradation [91-97].

2. Solvent emulsification/evaporation technique

This technique involves dissolving the lipid in a water-immiscible organic solvent, followed by emulsification in an aqueous phase containing surfactants. The organic solvent is then evaporated, leading to the formation of NLCs. This method is advantageous for drugs that are soluble in organic solvents and allows for precise control over particle size [91-97].

3. Microemulsion formation technique

Microemulsions are thermodynamically stable mixtures of oil, water, and surfactant. In this method, a microemulsion is formed and then dispersed in cold water, leading to the precipitation of NLCs. This technique is simple and does not require high energy input, making it suitable for sensitive drugs [91-97].

4. Ultrasonic solvent emulsification technique

This method uses ultrasonic waves to create emulsions of the lipid and aqueous phases. The high energy from the ultrasound reduces particle size and helps in forming stable NLCs. It is particularly useful for small-scale production and for drugs that require gentle processing conditions [91-97].

5. Phase inversion temperature (PIT) method

This technique involves heating the emulsion to a specific temperature where the phase inversion occurs, leading to the formation of NLCs. The method is based on the principle that the solubility of surfactants changes with temperature, which can be exploited to control the formation of NLCs [91-97].

6. Melting dispersion method

In this method, the lipid is melted and dispersed in an aqueous phase containing surfactants. The mixture is then cooled to form NLCs. This technique is straightforward and does not require complex equipment, making it suitable for various applications [91-97].

7. Solvent injection (or solvent displacement) technique

This involves injecting a lipid solution in a water-miscible organic solvent into an aqueous phase under stirring. The rapid diffusion of the solvent into the aqueous phase leads to the

precipitation of lipids as NLCs. This method is advantageous for its simplicity and ability to produce small particles [91-97].

Table 2.2: Review of NLCs formulations for treatment of Cancer

Sr. No.	Drugs used	Type of Formulation	Results	Applications	Ref.
1	Doxorubicin	NLCs by solvent emulsification/ evaporation method	Size: 134.0 ± 2.3 nm; Zeta potential: −19.0 ± 3.9 mV; EE: 75%	Increased cytotoxicity on MCF-7 lines	98
2	Doxorubicin and Cisplatin	NLCs	Size: 108.3 ± 2.3 nm; Zeta potential: +16.4 ± 1.6 mV; EE: 89.5 ± 3.7%	Breast cancer combination therapy	99
3	Doxorubicin and Docosahexaenoic Acid	NLCs by hot melting homogenization and emulsification – ultrasound	Size: 64.4 ± 3.6nm; Zeta potential: − 31.6 ± 1.4 mV; EE: 96.9 ± 0.7 %	Evaluation of Biodistribution and Antitumor Activity in Experimental Model	100
4	Doxorubicin and Imatinib	Pegylated NLCs by emulsification and ultrasonication	Size:~ 120 nm; Zeta potential: -30mV EE: ~ 100 %	To Overcome Drug Resistance in Metastatic Tumours	101
5	Lapachone and Doxorubicin	NLCs by melted ultrasonic dispersion method	Size: 100.2 ± 6.8nm; Zeta potential: - 23.5 ± 3.6 mV; EE: ~ 92 %	Overcoming multidrug resistance in breast cancer therapy	102
6	Paclitaxel and Doxorubicin	NLCs by melted ultrasonic dispersion method	Size: 129.3±4.2 nm; Zeta potential: +26.6±3.2mV; EE: 81 to 83 %	Synergistic effect in Lung cancer combination therapy	103
7	Doxorubicin and Bombesin	Peptide modified carriers	Size: 135.2±2.1 nm; Zeta potential: +41.3±3.6 mV; EE: 72.7 ± 2.8 %	Breast cancer targeted chemotherapy	104
8	Doxorubicin and Lonidamine	Nanoparticles by Solvent exchange	Not applicable	Synergistic chemotherapy to conquer drug resistance	105
9	Paclitaxel	NLCs by emulsion solvent evaporation method	Size: 154.6nm; Zeta potential: -16.5mv; EE: 79.1 %	Folic acid and PEG modified NLCs for breast cancer	106
10	Paclitaxel	NLCs by homogenization ultra-Sonication method	Particle size ranged between 172.8 ± 0.8 to 378.2 ± 1.8 nm and zeta potential between -18.6 ± 0.4 to -28.1 ± 1.2 mV	Improved efficacy and enhanced delivery	107

Sr. No.	Drugs used	Type of Formulation	Results	Applications	Ref.
11	Paclitaxel	SLNs and NLCs by hot melt high pressure homogenization	For SLNs, Particle size: 239.1 ± 32.6nm, Zeta potential: -9.82 ± 2.16mV; EE: 82 ± 5.2 % For NLCs, Particle size: 183.6 ± 36.2nm; Zeta potential: -11.4 ± 2.75 mV; EE: 73 ± 7.5 %	Effective drug delivery in cancer and Multidrug resistance	108
12	Paclitaxel	NLCs by Melt Emulsion technology	Before Lyophilization, Particle size: 102.63±7.36 nm, Zeta potential: 70.57±5.17 mV; EE: 91.99±0.7 % After Lyophilization, Particle size: 140.9 ± 7.51 nm, Zeta potential: 68.83 ± 1.81 mV; EE: 90.11±0.68 %	Effective drug delivery for targeting tumours	109
13	Paclitaxel and Indocyanine	NLCs by Solvent Injection method	Particle size: 92.6nm	Synergistic anti-cancer action	110
14	Paclitaxel and Tocopherol succinate Cisplatin prodrug	SLNs by emulsification and solvent evaporation method	Particle size: 108.6±3.1 nm, Zeta potential: −31.2±2.7 mV; Entrapment efficiency: 91.1±3.2 %	Enhanced permeability and retention effects in tumour	111
15	Paclitaxel and Gemcitabine	NLCs by emulsification and solvent evaporation method	Particle size: 120.3±1.3 nm, Zeta potential: approx. -27mV	Beneficial combination effect on tumours	112
16	Fulvestrant	Polymer based nanoparticles by salting out and emulsion evaporation technique	Particle size: 113.3 ± 9.93 nm, Zeta potential: -5.7 ± 1.05 mV; Entrapment efficiency: 79.74 ± 3.25 %	Novel modified matrix-forming polymeric materials are superior to traditional forms in terms of side effects	113
17	Docetaxel and Trastuzumab	NLCs by Solvent diffusion method	Particle size: 147±8 nm Entrapment efficiency: 68.1±2.0 %	Trastuzumab conjugated NLCs seem promising in oriented delivery of DTX to HER2 positive breast cancer cells	114

Sr. No.	Drugs used	Type of Formulation	Results	Applications	Ref.
18	Docetaxel	Oral NLCs by emulsification and ultrasonication technique	Particle size: 85.8 ± 4.7 nm, Zeta potential: -8.88 ± 0.37 mV Entrapment efficiency: 99.89 ± 0.01%	promising method for enhancing the oral absorption of anticancer drugs	115
19	Docetaxel	NLCs by modified film ultrasonication dispersion method.	Particle size: 193.47 ± 5.69 nm, zeta potential: −33.17 ± 1.20 mV Entrapment efficiency: 88.9 ± 1.02%	Higher cytotoxicity in malignant melanoma	116
20	Docetaxel	Cysteine functionalized NLCs for oral delivery	Particle size: 96.6 ± 8.0 nm; Zeta potential: -13.72 ± 0.07 mV Entrapment efficiency: 99.34 ± 0.33 %	Great potential for improving oral absorption of anticancer drugs.	117
21	Docetaxel	NLCs by Hot high pressure homogenization method	Particle Size: 60.5 ± 5.0 nm, Zeta potential: −43.19 ± 3.6 mV; Entrapment efficiency: 60.0 ± 5.0 %	More efficient targeting of tumours	118
22	Topotecan	SLNs and NLCs by microemulsion technique	Particle size: approx. 150 nm Entrapment efficiency: approx. 90 to 95 %	Improved chemical stability and cytotoxicity	119

2.4 MICROEMULSIONS (ME)

Microemulsions are thermodynamically stable, isotropic liquid mixtures composed of oil, water, surfactant, and often a co-surfactant. These systems are characterized by their ability to form spontaneously and their unique properties, such as ultralow interfacial tension and high solubilization capacity for both hydrophilic and lipophilic compounds [120, 121]. Microemulsions form spontaneously due to the thermodynamic stability provided by the surfactant and co-surfactant, which facilitate the mixing of oil and water phases. The spontaneity of microemulsion droplet formation is primarily attributed to the negative free energy changes associated with the process [120, 121]. This negative free energy is a result of various factors, including the reduction in interfacial tension, the dynamic equilibrium of forces, and the thermodynamic stability of the system. These factors collectively contribute to the spontaneous formation and stability of microemulsions [120, 121].

2.4.1 Classification of Microemulsions

Microemulsions represent thermodynamically stable colloidal dispersions comprising two immiscible liquids, typically oil, and water, which are stabilized by an interfacial film formed by surfactant molecules [120-122]. Microemulsions can be categorized into three primary types:

1. Oil-in-water (O/W) microemulsions:

In oil-in-water microemulsions, oil droplets are uniformly dispersed throughout a continuous aqueous phase. Surfactant molecules encapsulate the oil droplets, positioning their hydrophilic heads towards the aqueous phase while their hydrophobic tails are directed towards the oil droplets. This particular microemulsion is frequently utilized across various sectors, including pharmaceuticals, cosmetics, and the food industry, owing to its stability and straightforward formulation process [120, 122].

2. Water-in-oil (W/O) microemulsions: In W/O microemulsions, aqueous droplets are uniformly dispersed within a continuous lipid phase. Surfactant molecules encapsulate the water droplets, aligning their hydrophobic tails towards the oil phase while positioning their hydrophilic heads in proximity to the water droplets. Water-in-oil microemulsions are less prevalent compared to oil-in-water microemulsions; however, they serve important roles in applications such as enhanced oil recovery and controlled release formulations [120, 122].

3. Bi-continuous microemulsions: Bi-continuous microemulsions often referred to as middle-phase microemulsions, exhibit an absence of a distinct separation between the oil and water phases. The system is characterized by interconnected domains of oil and water, with surfactant molecules localized at the interfaces between these distinct phases. Bi-continuous microemulsions exhibit distinctive characteristics and are utilized in various domains, including drug delivery systems, emulsion polymerization processes, and soil remediation techniques. Different microemulsion types present unique benefits tailored to specific applications, including improved solubilization, regulated release, or increased stability. The selection of surfactants and co-surfactants, along with the formulation of the oil and water phases, can be optimized to attain targeted properties and functionalities in microemulsion formulations [120, 122].

Advantages of Microemulsions [120-125]

Microemulsions present numerous benefits across a range of applications:

1. *Improved Solubility Profile:* Microemulsions exhibit the capability to solubilise a diverse range of both polar and non-polar compounds, thereby rendering them advantageous for formulations that necessitate an increased solubility of active pharmaceutical ingredients [123-125].

2. *Enhanced Stability:* These compounds exhibit a thermodynamically stable configuration, effectively inhibiting phase separation over extended periods. The enhanced stability contributes to an extended shelf life for various products, including pharmaceuticals and cosmetics [123-125].

3. *Optimized Delivery:* Microemulsions facilitate the precise and directed administration of active compounds, resulting in enhanced bioavailability and therapeutic effectiveness. This renders them significant in medicinal and topical applications [121-125].

4. *Enhanced Absorption:* The reduced droplet size increases the surface area available for interaction with biological membranes, thereby promoting improved absorption of pharmaceuticals or nutrients [120-125].

5. *Ease of Manufacture:* Microemulsions can be synthesized with relative simplicity and can be produced using standard methodologies, which contributes to a reduction in both production costs and time [120-125].

6. *Versatility:* Microemulsions can be customized for particular applications through the modification of surfactant, co-surfactant, and oil compositions. This versatility renders them suitable for a range of sectors, encompassing pharmaceuticals, cosmetics, and agriculture [123-125].

7. *Transparency:* Numerous microemulsions exhibit transparency or translucency, rendering them visually appealing for incorporation into clear formulations, including skincare products and oral solutions [120-125].

8. *Environmental Considerations:* Microemulsions have the potential to minimize the reliance on organic solvents, resulting in formulations that are more environmentally sustainable, with reduced toxicity and flammability hazards [120-125].

Disadvantages of microemulsions [120-125]

1. *Phase separation:* Micro emulsions may exhibit a tendency for phase separation as time progresses, especially if they are not adequately formulated or are stored in suboptimal conditions.

2. *Restricted loading capacity:* The diminutive droplet size of micro emulsions may result in a constrained ability to accommodate elevated concentrations of active ingredients, potentially diminishing their efficacy in specific applications.

3. *Potential toxicity:* Certain surfactants and co-surfactants incorporated in microemulsion formulations may present toxicity issues, particularly if they are not adequately eliminated during the manufacturing process of the product.

2.4.2 Methods of Preparation

1. Phase titration method

The phase titration method involves the gradual addition of one phase to another while monitoring the system's properties to achieve the desired microemulsion state. This method typically starts with a mixture of oil, water, and surfactant. The titration involves adding either the oil or water phase slowly to the mixture while stirring continuously. The system makes transition through different phases until a clear, isotropic microemulsion is formed [120, 123].

The phase titration method allows for precise control over the composition and properties of the microemulsion. It is particularly useful for determining the phase behaviour and stability of the system, which is essential for applications requiring specific droplet sizes and distributions [120, 123]. This method is widely used in the pharmaceutical industry to optimize drug delivery systems by enhancing the solubility and bioavailability of drugs. It is also employed in the cosmetic and food industries to improve the stability and penetration properties of active ingredients [120, 123].

2. Phase Inversion Method

The phase inversion method involves changing the system's conditions, such as temperature or composition, to invert the phases and form a microemulsion. Phase inversion can be achieved by altering the temperature (Phase Inversion Temperature, PIT) or by changing the composition of the system. For instance, increasing the temperature can lead to the inversion of oil-in-water (O/W) emulsion to water-in-oil (W/O) emulsion, or vice versa [126-128].

This method is advantageous for producing microemulsions with specific characteristics, such as droplet size and stability, without the need for high shear forces. It is also beneficial for systems that require a precise balance of hydrophilic and lipophilic components [126-128]. The phase inversion method is particularly useful in the formulation of microemulsions for drug delivery, where the control of droplet size and stability is crucial for effective delivery and release of active compounds. It is also used in the food industry to create stable emulsions with high oil content [126-128].

Table 2.3: Review of Microemulsions formulations for treatment of Cancer

Sr. No.	Drugs used	Composition	Results	Remarks	Ref.
1	Docetaxel + Brucea javanica oil	The microemulsion containing *Brucea javanica* oil, medium-chain triglyceride, soybean lecithin, Solutol® HS 15, PEG 400, and water was developed for Docetaxel intravenous administration.	Droplet size = 13.5nm, Zeta potential = -41.3 mV	Combination provided synergistic effect with CI = 0.58 (< 1 required for synergistic effect).	129
2	Doxorubicin	Lignin, fatty acid (sodium Caprylate), and finally, ethyl butyrate in PBS (pH 7.4) via vigorous stirring at an oil-to-Lignin molar ratio of 1.	Droplet size = 7.5mm, % EE = 82 %, % release = 68% in 24 hours	Novel synthesized LGN/ DOX microemulsions exert cytotoxic effects on oral and breast carcinoma cells while inducing unfavourable toxic effects on normal human cells.	130
3	Paclitaxel	To prepare PTX microemulsion concentrated solution, PTX was dissolved in dehydrated alcohol and then mixed with Lipoid E 80, CrEL and soybean oil.	Particle size = 142.4 ± 1.2 nm, PDI = 0.267 ± 0.07,	Paclitaxel has lower solubility in Soybean oil which may cause instability of microemulsion during long term stability.	131
4	Methotrexate	Tween-60 (41%), 1-butanol (41%), Castor oil (8%) and water (10%)	Particle size = 72.0 ± 3.0nm, Zeta potential = -36.8 ± 0.5mV	Use of high levels of organic solvents like 1-butanol is not recommended for i.v. administration	132
5	Tamoxifen citrate	F1=sesame oil, Tween 80 and Glycerine F2=sesame oil, Tween 80 and Span 80	Particle size F1= 26.60±0.2 nm and F2=67.11±0.3nm, Zeta Potential = F1=12.6 and F2=19.8mv	Formulated for oral administration only	133
6	Doxorubicin	36 wt% paraffin oil, 54 wt% PGPR–Tween 80 mixture with 3 : 1 weight ratio and 10 wt% aqueous phase	Particle size = 200±20 nm, IC_{50} of DOX solution = 1.4µg/mL, DOX Microemulsion = 5.1µg/mL	Controlled release oral microemulsion was formulated, however % viability was higher in DOX microemulsion	134
7	5-Fluorouracil	Isopropyl myristate (oil phase), Aerosol OT (surfactant), Tween 80 (surfactant)	Particle size = 178nm	Optimised formulation was effective in treating squamous cell carcinoma	135

Sr. No.	Drugs used	Composition	Results	Remarks	Ref.
8	Fenretinide	Phosphatidylcholine: 45% Tricaprylin: 5% Propylene glycol: 50%	Droplet diameter of 175.3 ± 8.9 nm. Upon water uptake, it transformed into various phases, releasing 30% of Fenretinide over 9 days.	Fenretinide demonstrated significant efficacy in reducing breast cancer incidence in a preclinical model, with a 4.7-fold decrease in tumor occurrence. Sustained release of Fenretinide over 30 days without local irritation.	136
9	Vitamin D3 and tamoxifen	10 % V/V Oil, 60 % V/V Smix [TPGS: Transcutol® HP, (2:1)], 30 % V/V of water. Combination ME (1 mL) was prepared by dissolving TMX (10 mg) and vitamin D3 ME (1.5 mg) in 0.1 mL oil and 0.6 mL Smix and 0.3mL of water	Size: 76 ± 2.68 nm, PDI 0.218, Zeta potential: -20 to -25mV, EE: 98.92%	The combination microemulsion of vitamin D3 and tamoxifen (TMX-VD3 ME) demonstrated a synergistic effect on the MCF-7 breast cancer cell line, resulting in enhanced anticancer efficacy compared to individual treatments of vitamin D3 ME or tamoxifen ME alone.	137
10	Doxorubicin	O/W microemulsion was prepared as 1% w/w solutions of ethyl butyrate by the vigorous stirring of a suitable amount of sodium caprylate, PBS (pH = 7.4), and at a fixed oil-to-surfactant molar ratio (Ow = [ethyl butyrate]/[F127] = 1)	Toxicity evaluations indicated that the microemulsions exhibited reduced cytotoxicity compared to free Doxorubicin, suggesting a safer profile for drug delivery in cancer treatment.	The study successfully developed Pluronic F127/Doxorubicin microemulsions, demonstrating their potential as a drug delivery system that enhances the solubility and bioavailability of Doxorubicin, a commonly used chemotherapeutic agent.	138
11	Sorafenib	Isopropyl Myristate 9%, Smix ratio: 2.7:1, T80: (Phospholipon 90G: ethanol) (45%)	Size: 58.8 ± 0.02, PDI: 0.19 ± 0.14, Zeta potential: 0.05 ± 0.03mV, Drug content: 99.83%	The study demonstrated that the Sorafenib-loaded microemulsion (SFB-loaded ME) significantly improved the IC50 value compared to naïve Sorafenib, indicating enhanced efficacy against 4T1 cell lines.	139

2.5 DRUG PROFILE

2.5.1 PACLITAXEL

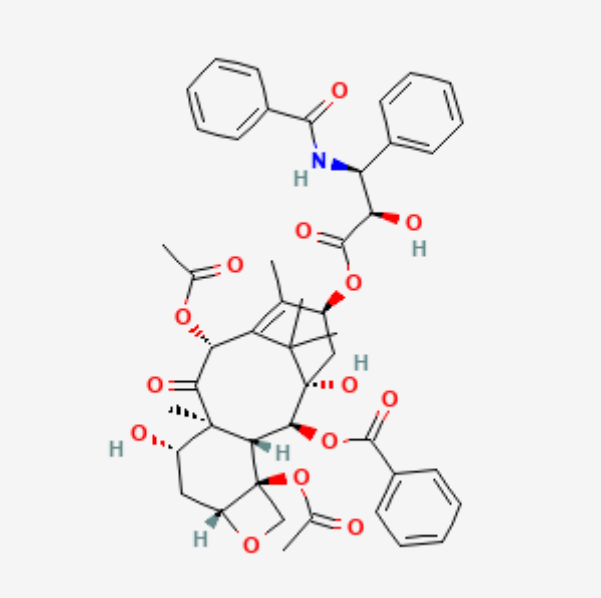
Name: Paclitaxel

Molecular formula: $C_{47}H_{51}NO_{14}$

Molecular weight: 853.9 g/mol

IUPAC Name: [(1S,2S,3R,4S,7R,9S,10S,12R,15S)-4,12-diacetyloxy-15-[(2R,3S)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl] benzoate

Structure:



CAS No.: 33069-62-4

Formal Charge: 0

Physical Description: fine white powder

Melting point: 216-217 °C

Indication: Used to treat lung, ovarian, and breast cancers as well as Kaposi's sarcoma.

Pharmacodynamics: A taxoid antineoplastic drug, Paclitaxel is used as a first-line and subsequent treatment option for advanced ovarian cancer and other cancers like breast cancer. By blocking depolymerization, the novel drug paclitaxel promotes stability and facilitates microtubule assembly from tubulin dimers. Important interphase and mitotic cellular processes depend on the microtubule network's regular dynamic reorganization, which is prevented by this stability. Additionally, Paclitaxel stimulates the production of numerous

microtubule asters during mitosis and the development of aberrant arrays or "bundles" of microtubules throughout the cell cycle.

Mechanism of action: Paclitaxel disrupts the standard processes involved in microtubule assembly and dynamics. Colchicine induces the depolymerisation of microtubules in vivo, while paclitaxel exerts its effects by hyper-stabilizing their structure, thereby arresting their function. This impairs the cell's capacity to utilise its cytoskeleton with flexibility. Paclitaxel exhibits a specific binding affinity for the β subunit of tubulin. Tubulin serves as the fundamental unit of microtubules, and the interaction with paclitaxel stabilises these units in a fixed configuration. The resultant microtubule/paclitaxel complex exhibits an inability to undergo disassembly. The impairment of cell function occurs due to the critical role of microtubule dynamics, specifically the processes of shortening and lengthening, which are essential for their operation as a transportation system within the cell. During mitosis, chromosomes depend on the characteristics of microtubules. Subsequent investigations have demonstrated that paclitaxel promotes programmed cell death (apoptosis) in neoplastic cells through its interaction with an apoptosis-inhibiting protein known as Bcl-2 (B-cell leukaemia 2), thereby inhibiting its activity.

Pharmacokinetics:

Absorption: After the intravenous administration of paclitaxel, the plasma concentrations of paclitaxel exhibited a biphasic decline. The initial swift decrease indicates the distribution of the drug to the peripheral compartment and its subsequent elimination. The subsequent phase can be attributed, in part, to a comparatively gradual efflux of paclitaxel from the peripheral compartment. A 24-hour infusion of 135 mg/m^2 administered to ovarian cancer patients results in a maximum plasma concentration (Cmax) of 195 ng/mL, with an area under the curve (AUC) of 6300 ng•h/mL.

Metabolism: About 90% of paclitaxel undergoes primary metabolism in the liver through the cytochrome P450 enzyme system, with significant involvement from the CYP2C8 and CYP3A4 isoenzymes. The primary metabolic pathway encompasses the hydroxylation of the side chain at the C13 position, resulting in the formation of various metabolites, such as 6α-hydroxy paclitaxel and 3'-p-hydroxy paclitaxel. The pharmacological activity of these metabolites is inferior to that of the parent drug.

Elimination: The principal pathway for the elimination of paclitaxel involves hepatic metabolism followed by biliary excretion. A small percentage of the drug, generally under 10%, is eliminated in its unchanged form through urine. Paclitaxel and its metabolites are

eliminated from the body through a biphasic decline in plasma concentration. The initial rapid elimination phase exhibits a half-life ranging from approximately 3 to 14 minutes, succeeded by a slower terminal phase characterized by a half-life of about 13 to 52 hours.

Route of Elimination: In five patients who received a 225 or 250 mg/m^2 dose of radio-labeled paclitaxel via a 3-hour infusion, an average of 71% of the radioactivity was eliminated in the faeces over a period of 120 hours, while 14% was found in the urine.

Volume of Distribution: 227 to 688 L/m^2 [apparent volume of distribution at steady-state, 24 hour infusion]

Clearance: 21.7 L/h/m2 [Dose 135 mg/m2, infusion duration 24 h], 23.8 L/h/m2 [Dose 175 mg/m2, infusion duration 24 h], 7 L/h/m2 [Dose 135 mg/m2, infusion duration 3 h], 12.2 L/h/m2 [Dose 175 mg/m2, infusion duration 3 h]

Table 2.4: Review of Paclitaxel in treatment of Cancer

Sr. No.	Type of Formulation	Results	Applications	Ref.
1	NLCs	Size: 154.6nm; ZP: -16.5mv; EE: 79.1 %	Folic acid and PEG modified NLCs for breast cancer	106
2	NLCs	Particle size ranged between 172.8± 0.8to 378.2±1.8 nm and ZP between -18.6±0.4 to -28.1 ±1.2mV	Improved efficacy and enhanced delivery	107
3	SLNs and NLCs	For SLNs, Size: 239.1±32.6nm, ZP: -9.82±2.16mV; EE: 82±5.2% For NLCs, Size: 183.6±36.2nm; ZP: -11.4±2.75 mV; EE: 73±7.5%	Effective drug delivery in cancer and Multidrug resistance	108
4	NLCs	Before Lyophilization, Size: 102.63±7.36nm, ZP: 70.57±5.17mV; EE: 91.99±0.7% After Lyophilization, Size: 140.9±7.51nm, ZP: 68.83±1.81mV; EE: 90.11±0.68%	Effective drug delivery for targeting tumours	109
5	Microemulsion	Globule size = 142.4 ± 1.2 nm, PDI = 0.267 ± 0.07	Paclitaxel has lower solubility in Soybean oil which may cause instability of microemulsion during long term stability.	131
6	Liposomes	Palmitic acid was conjugated to Paclitaxel to form highly lipophilic prodrug.	Showed the longest circulation and highest tumor accumulation of PTX and exert the most potent anti-tumor capacities in vivo, owing to its moderate drug release and enzymatic conversion rate.	140

Sr. No.	Type of Formulation	Results	Applications	Ref.
7	Micelles	Size: 67.73±0.43nm, PDI: 0.293 ± 0.055, EE: 92.75 ± 2.25%	Polycaprolactone–vitamin E TPGS micelles (PCL-TPGS) improved solubility of Paclitaxel and demonstrated enhanced permeability and rapid absorption of drug orally in comparison to the marketed formulation Ebetaxel®	141
8	Polymeric micelles	Average diameter ranging from 18 nm to 21 nm, along with a low PDI of <0.020	Paclitaxel-induced toxicity was reduced by micelles	142
9	Prodrug-encapsulated polypeptide micelles	Size: 170nm, drug-loading rate of 22.84%	Highest level of tumor growth inhibition and the lowest systemic toxicity in comparison with ELP/PSH micelles and commercialized Taxol®.	143
10	Paclitaxel/hydroxy propyl-β-cyclodextrin complex-loaded liposomes	Size: 75 to 90nm, PDI: 0.2 to 0.3, Zeta potential: +3 to +7mV	Exhibited pH-sensitive PTX release, potent cytotoxicity, and enhanced intracellular accumulation	144

2.5.2 CYCLOPHOSPHAMIDE

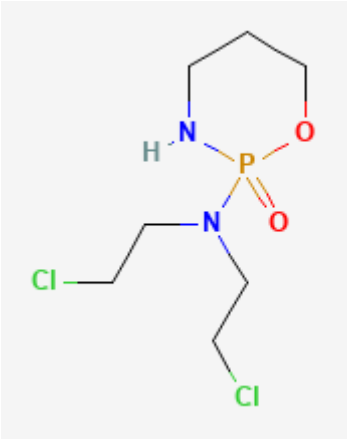
Name: Cyclophosphamide

Molecular formula: $C_7H_{15}Cl_2N_2O_2P$

Molecular weight: 261.08 g/mol

IUPAC Name: 2-[bis(2-chloroethyl)amino]-1,3,2lambda5-oxazaphosphinan-2-one

Structure:



CAS No.: 50-18-0

Formal Charge: 0

Physical Description: fine white crystalline powder

Melting point: 41-45 °C

Indication: Indicated for the therapeutic management of malignant lymphomas, multiple myeloma, leukemias, advanced mycosis fungoides, disseminated neuroblastoma, ovarian adenocarcinoma, retinoblastoma, and breast carcinoma. This medication is indicated for the treatment of biopsy-confirmed minimal change nephrotic syndrome in pediatric patients.

Pharmacodynamics: Cyclophosphamide is categorized as an antineoplastic agent within the class of alkylating agents and is employed in the management of various cancer types. Alkylating agents are named for their ability to add alkyl groups to different electronegative entities within cellular environments. The process entails the suppression of tumor growth via the cross-linking of guanine bases in the DNA double-helix configuration, thereby directly affecting the DNA molecule. This leads to the inability of the strands to uncoil and separate. The critical importance of this process in DNA replication renders cellular division unfeasible. Moreover, these compounds incorporate methyl or other alkyl groups onto molecules in a manner that disrupts their correct functionality through base pairing, resulting in DNA miscoding. Alkylating agents demonstrate a non-specific interaction with the cell cycle. Alkylating agents function via three separate mechanisms, all of which culminate in a common result: the interference with DNA activity and the ensuing demise of the cell.

Mechanism of action: Alkylating agents function via three separate mechanisms: 1) The covalent attachment of alkyl groups to DNA bases results in fragmentation of the DNA by repair enzymes as they endeavour to replace the alkylated bases, consequently inhibiting DNA synthesis and RNA transcription from the damaged DNA. 2) The generation of cross-links (bonds between atoms within the DNA) obstructs the separation of DNA strands essential for synthesis or transcription. 3) The promotion of nucleotide mispairing leads to mutations.

Pharmacokinetics:

Absorption: Following intravenous administration, the pharmaceutical agent is swiftly assimilated into the bloodstream. In subjects administered 6.7-80 mg/kg body weight per day of ring labelled cyclophosphamide, radioactivity exhibited rapid distribution across all tissues, with a plasma half-life of 6.5 hours.

Metabolism: The liver is the site of metabolism and activation processes. Seventy-five percent of the pharmaceutical compound is metabolized by cytochrome P450 isoforms, specifically CYP2A6, CYP2B6, CYP3A4, CYP3A5, CYP2C9, CYP2C18, and CYP2C19.

The CYP2B6 isoform exhibits the most significant activity as a 4-hydroxylase enzyme. Cyclophosphamide is activated to produce active metabolites, specifically phosphoramide mustard and acrolein. Cyclophosphamide seems to stimulate its own metabolic processes, leading to a general enhancement in clearance, heightened production of 4-hydroxyl metabolites, and reduced half-life values after multiple doses.

Elimination: Cyclophosphamide is eliminated primarily in the form of metabolites. 10-20% is excreted unchanged in the urine and 4% is excreted in the bile following IV administration.

Volume of Distribution: 30-50 L

Clearance: Total body clearance = 63 ± 7.6 L/kg.

Table 2.5: Review of Cyclophosphamide in treatment of Cancer

Sr. No.	Type of Formulation	Results	Applications	Ref.
1	Folic Acid-Decorated Nanoniosomes	Size: 213.9±3.2nm, PDI: 0.143±0.007, EE: 94.10±1.85	Led to the highest level of drug internalization observed. The expression levels of caspase-3 and caspase-9 are upregulated, indicating their role as pro-apoptotic genes, while there is a downregulation of cyclin-D, cyclin-E, MMP-2, and MMP-9, which are associated with cancer development and progression.	145
2	MIL-100(Fe)	The drug loading and release behaviour of the carriers is assessed through UV-visible spectrophotometry. The MTT assay is utilized to assess the biocompatibility and anticancer efficacy of MIL-100(Fe)/CP on the MCF-7 cell line.	In vivo antitumor experiments and histological observation demonstrate the inhibitory properties of MIL-100(Fe)/CP on tumor cells. MIL-100(Fe)/CP, exhibiting a drug payload of 37.41%, demonstrates significant antitumor efficacy.	146

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