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Pharmacological and Preformulation Insights into Etoposide for Testicular Cancer Therapy

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ABSTRACT :

Etoposide, a semisynthetic derivative of podophyllotoxin, is widely used as an anticancer agent in the treatment of various malignancies, including testicular cancer, lung cancer, and malignant lymphoma. As a topoisomerase II inhibitor, etoposide disrupts DNA synthesis and promotes apoptosis in rapidly dividing cells. It can be administered orally, making it a convenient option in chemotherapeutic regimens. This review highlights the role of etoposide in the management of testicular cancer, one of the most prevalent cancers among men aged 14 to 45. Additionally, it presents comprehensive preformulation studies essential for developing effective oral dosage forms of etoposide. These include analyses of organoleptic properties, melting point, solubility, FTIR spectroscopy, UV-visible spectroscopy, partition coefficient, pH stability, dissociation constant, and polymorphism. This review aims to provide a concise yet informative overview of etoposide's pharmaceutical profile and its potential as an oral anticancer agent.

Key words: Etoposide, Testicular cancer, Topoisomerase II inhibitor, Preformulation studies

INTRODUCTION

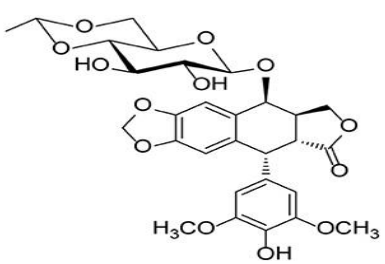
Cancer is one of the leading causes of mortality worldwide in the 21stcentury [1]. This illness is typified by the unchecked growth of altered cells that are subject to natural selection-driven evolution. The World Health Organization (WHO) reports that in 2015, cancer was the primary cause of death for most countries before the age of 70. The global cancer burden is predicted to increase by 2030, with an estimated 13.2 million cancer-related deaths and 21.4 million new cases each year. External factors including tobacco use, radiation exposure, dangerous chemicals, and infections can also cause it, in addition to internal causes include immunological dysfunction, hormone imbalances, inherited genetic abnormalities, and random genetic changes.[2]

1.Testicular cancer

One of the most prevalent cancers among men between the ages of 15 and 45 is testicular cancer. Numerous genetic and environmental factors contribute to the complex nature of etiology. A tumorigenic event in utero that results in intratubular germ-cell neoplasia is known to be the secondary cause of germ-cell malignancies. Gonocytes that have not developed into spermatogonia are the source of intratubular germ-cell neoplasia. It takes the hormonal changes that come with puberty for these cells to reach their invasive potential. Transformed germ cells that lack the ability to differentiate make up seminomas. Embryonic cancer cells resemble undifferentiated stem cells and have gene expression similar to stem cells and intratubular germ-cell neoplasms. Whereas choriocarcinomas and yolk-sac tumors have extraembryonic differentiation, teratomas have somatic differentiation.There are a number of known genetic loci that give a propensity to testicular cancer. The genes encoding the proteins involved in KITLG–KIT signaling, located at 12q21, had the most significant influence from the variation. Abnormally activated KITLG–KIT in utero may cause embryonic germ cells to be arrested at the gonocyte stage, which may lead to intratubular germ-cell neoplasia. Following this, there is an overexpression of embryonic transcription factors that suppress apoptosis and increase gonocyte proliferation and mutation accumulation, such as NANOG, sex-determining-region Y–box 17 (SOX17), and octamer-binding transcription factor 3–4 (OCT3/4, also known as POU domain, class 5, transcription factor 1 [POU5F1]).[3]

2. ETOPOSIDE

Fig 1: Structure of etoposide



2.1 Mechanism of action

One chemotherapy drug that is frequently used to treat testicular cancer is etoposide. It is a member of the topoisomerase II inhibitor class. Etoposide inhibits DNA topoisomerase II, which stops DNA from re-ligating. At the premitotic stage of cell division, this results in crucial mistakes in DNA synthesis and may cause the cancer cells to undergo apoptosis. Etoposide primarily affects the S and G2 phases of cell division and is phase-specific and reliant on the cell cycle. Inhibition of the topoisomerase II alpha isoform results in the antitumor activity of etoposide. The drug is also capable of inhibiting the beta isoform but inhibition of this target is not associated with the antitumor activity. It is instead associated with the carcinogenic effect.[4]

2.2 PHARMACOKINETICS

2.2.1 Absorption: In the initial clinical trials, the lipophilic capsules poor solubility was attributed to etoposide absorption. New hydrophilic gelatine capsules containing etoposide in solution quickly supplanted such formulations, which had unacceptable poor bioavailability. These capsules had higher absorption properties. Maximum concentration attained 0.5-4 hours after oral administration.
2.2.2 Distribution: For both oral and intravenous treatment, etoposide's steady-state volume of distribution varies between 3 and 21 L/m^2, with children exhibiting the lower values.
2.2.3 Metabolism: Liver metabolism of etoposide is important not only for the systemic excretion of the drug but also for the bioavailability of oral etoposide**.** Furthermore UGT1A1 and GSTT1/GTP1 catalyse the conjugation of etoposide with glutathione and glucuronides, respectively.
2.2.4 Excretion: Patients with creatinine levels above the normal range demonstrated a significant reduction in etoposide clearance and a prolonged terminal elimination half-life, suggesting that dose adjustments may be beneficial for patients with renal impairment, as the kidney plays a significant role in the elimination of etoposides. When administering oral etoposides to elderly people, more care must be used.[5]

2.3 TOXICITY

Myelosuppression is the dose-limiting toxicity of etoposide. Twenty to thirty percent of individuals get stomatitis, nausea, vomiting, and alopecia. Additionally, it may have a role in drug-induced secondary cancers, including acute myeloid leukemia (t-AML). Chromosome 11q23 translocation is linked to etoposide-induced t-AML.[6]

2.4 ADVERSE EFFECT

Myelosuppression, primarily leucopenia, is the dose-limiting hazard of etoposide alone. Leucocyte nadir occurs 8–10 days after therapy, and recovery usually occurs by day 21. By days 21 to 28, thrombocytopenia is less frequent and healing is evident. In addition to being dose-limiting with high-dose regimens, bronchospasm has rarely happened, diarrhea is uncommon, and stomatitis is often only reported infrequently at conventional therapeutic dosages. But when using specific etoposide regimen, alopecia is common, if not universal. Although neurotoxicity has rarely been documented, more research is necessary to determine whether etoposide can exacerbate vincristine-induced neurotoxicity. Since bolus intravenous administration has been linked to hypotension, it is advised that etoposide be given gradually over 30 to 60 minutes.[6]

3. PREFORMULATION STUDIES OF ETOPOSIDE

Preformulation is a phase of research and development where a scientist characterizes a new drug substance's mechanical, chemical, biological, and physical properties in order to create a stable, safe, and effective dosage form.[7]

3.1 Organoleptic properties

The medication is a white to off-white crystalline powder.

3.2 Melting point

Melting point samples were stored in thin-walled capillary melting point tubes. The Bunsen flame must be used to seal one end of this tube. After that, a little sample of the crystalline minerals was gently forced into the open end. to transfer the crystals from the open end of the tube to the bottom. On the left was a mercury thermometer with a column of crystals that were closely spaced and about 3mm high. The capillary tube method in melting point determination device was used to estimate the melting point of etoposide.
Etoposide has a melting point of **236-252°C. [8]**

3.3 Solubility

Designing efficient formulations, such as tablets, capsules, or injections, is aided by solubility data. By dispersing a medicine in a solvent, its solubility can be evaluated. The suspension is agitated at a steady temperature. To determine a plateau concentration, samples of the suspension are taken out over time, centrifuged to clarify, and then analyzed.

Table 1: Solubility analysis of Etoposide

Solvent	Solubility
Methanol	Sparingly soluble
Ethanol	Slightly soluble
Dichloromethane	Slightly soluble
Water	Practically insoluble[9]

3.4 UV Visible spectroscopy

The standard stock solution having concentration 1000µg/ml (Stock-I) of etoposide is prepared by dissolving accurately weighed 5mg of etoposide in 5ml methanol. To get solutions with concentrations of 100µg/ml (Stock-II) and 10µg/ml (Stock-III), the stock-I solution of the bulk medication was further appropriately diluted with solvent system methanol. Similarly, standard stock solutions of the combination dosage form of etoposide were prepared at concentrations of 1000µg/ml, 100µg/ml, and 10µg/ml. The standard stock solution of etoposide was scanned in UV range from 200-400 nm using methanol as reference and spectrum were recorded.
When the λ_{max} was calculated, it was discovered to be 208 nm.[11]

3.5 Partition Coefficient

The n-octanol and water were mutually pre-saturated by shaking together in amber-colored bottles for 24 hours. 10 mg of etoposide were combined with 5ml of each of the two pre-saturated solvents in a screw-capped tube on a rotatory mixer set at 25 degrees Celsius. We collected samples at 6, 12, and 24 hours. The n-octanol and water layers of the samples were analysed separately for etoposide by HPLC. It took 12 hours to reach the equilibrium partition of etoposide between the n-octanol and water phases. When the temperature was 25°C, the partition coefficient (o/w) was 9.94 ± 0.095. [12]

3.6 pH Stability profile

Etoposide solutions of 100µg/ml prepared in the buffers were maintained at 25°C in a water bath. The samples were taken at various time intervals and analysed by HPLC until the remaining etoposide level was negligible. The degradation rate constants at all pH values were calculated by plotting the log concentration of etoposide against the time profile. The pH stability profile was generated by plotting the rate constant as a function of pH. First order degradation was indicated by the plots' linear curves at all pH values. The degradations were extremely rapid under highly acidic and alkaline conditions. The degradation half-lives were 2.88 and 3.83 hr at pH 1.30 and pH 10 respectively while pH 5-6.15 was the pH range of maximal stability, with degradation half-lives of 63 and 49.5 days respectively.[12]

3.7 Dissociation constant

The equilibrium constant for a compound's dissociation reaction is known as the dissociation constant. It is determined by performing potentiometric titration.
The dissociation constant pKa of etoposide was found to be 9.8.[13]

3.8 Polymorphism

Polymorphism is the capacity of a solid material to exist in different crystalline forms without altering its chemical makeup.

Etoposide has two polymorphs:
• Etoposide I (monohydrate): This the commercially used form ad is chemically stable at room temperature and normal humidity.
• Etoposide II (anhydrous): This is metastable form obtained by heating etoposide I above 200°C.
Although it crystalizes from the melt it tends to revert to more stable forms when exposed to moisture indicating it is less stable than the monohydrate under standard storage conditions.[14]

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