Pharmacokinetics of EF24

Subjects: Oncology

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EF24, a synthetic monocarbonyl analog of curcumin, shows significant potential as an anticancer agent with both chemopreventive and chemotherapeutic properties. It exhibits rapid absorption, extensive tissue distribution, and efficient metabolism, ensuring optimal bioavailability and sustained exposure of the target tissues. The ability of EF24 to penetrate biological barriers and accumulate at tumor sites makes it advantageous for effective cancer treatment. Studies have demonstrated EF24's remarkable efficacy against various cancers, including breast, lung, prostate, colon, and pancreatic cancer. The unique mechanism of action of EF24 involves modulation of the nuclear factor-kappa B (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways, disrupting cancer-promoting inflammation and oxidative stress. EF24 inhibits tumor growth by inducing cell cycle arrest and apoptosis, mainly through inhibiting the NF-κB pathway and by regulating key genes by modulating microRNA (miRNA) expression or the proteasomal pathway.

anticancer agent curcumin EF24 pharmacokinetics

1. Absorption of EF24

The pharmacokinetics of EF24 encompass its processes of absorption, distribution, metabolism, and excretion within the human body. Despite the limited availability of comprehensive pharmacokinetic data for EF24, its profile can be influenced by various conditions. The specific absorption properties of EF24 may display variability depending on its method of administration. EF24 is commonly administered orally, utilizing capsules or tablets as the preferred delivery form. Determining EF24's oral bioavailability relies on multiple factors, including its solubility, stability, and gastrointestinal absorption [1][2].

The lipophilicity of EF24 could facilitate its absorption through the intestinal epithelium due to the ability of lipophilic substances to easily traverse cell membranes [2][3]. However, several factors might limit EF24's oral bioavailability, such as poor solubility in water, potential metabolism in the gastrointestinal tract or liver, and the presence of efflux transporters that actively expel EF24 from intestinal cells [2][4].

EF24 can also be administered parenterally, including via intravenous (IV) or intraperitoneal (IP) injection [5]. IV injection directly introduces EF24 into the systemic circulation, resulting in rapid and thorough absorption [2][5][6]. The process of IP administration entails the introduction of EF24 into the peritoneal cavity, facilitating its absorption into the circulation through the blood vessels present in the peritoneum [1][5].

A study on the topical administration of EF24, particularly in dermatological applications, remains limited. The transdermal absorption of EF24 may be influenced by factors such as lipophilicity, molecular size, formulation, and skin barrier integrity. Enhancers or specific formulation techniques might augment the transdermal absorption of EF24.

Further research and specific pharmacokinetic studies are necessary to provide detailed information on the absorption of EF24, including its oral bioavailability, absorption rates, and the factors influencing its absorption profile.

2. Distribution of EF24

Once absorbed into the bloodstream, EF24 is transported to different tissues and organs throughout the body, guided by blood perfusion patterns [1]. Tissues with high blood flow rates, such as the heart, liver, kidneys, and brain, may exhibit comparatively elevated concentrations of EF24 [2]. However, the specific distribution pattern depends on several factors, including tissue perfusion rates, the presence of efflux transporters, and EF24's affinity for different tissues [2]. EF24 can also bind to plasma proteins, particularly albumin, which affects its distribution [2]. The extent of protein binding influences the availability of EF24 for distribution and the equilibrium between plasma and tissues.

When considering potential therapeutic applications of EF24 for neurological disorders, its lipophilic properties, compact size, and ability to cross the blood–brain barrier (BBB) are significant considerations [7]. These factors play a crucial role in evaluating its suitability for treating neurological conditions.

To provide a more comprehensive understanding of EF24's distribution patterns, further investigation is essential. Parameters such as tissue-to-plasma concentration ratios, volume of distribution, and extent of absorption in specific tissues should be examined. The combination of pharmacokinetic research and modern imaging techniques can enhance comprehension of how EF24's distribution profile varies across different physiological and pathological scenarios.

3. Metabolism of EF24

EF24 undergoes significant metabolic transformations through enzymatic pathways, primarily in the liver [1][3][8]. However, the specific metabolic pathways and associated enzymes involved in EF24's metabolism have not been elucidated yet. There is potential for EF24 to undergo a phase I metabolism, followed by subsequent phase II conjugation events [2].

Phase I metabolism encompasses a series of enzymatic processes, mainly involving oxidation, reduction, and hydrolysis, which introduce or unmask functional groups in the molecule [2]. The same study conducted by Reid et al. (2014) revealed that EF24 exhibited a higher metabolic rate in human liver microsomes compared to mice, both tested under similar protein concentrations [2]. This group demonstrated that the similarity in metabolic activity

between microsomes from untreated mice and those treated with phenobarbital suggests that the inducible mouse P450s and their human orthologs, specifically CYP3A and CYP2B, do not significantly contribute to EF24 metabolism. However, microsomes obtained from mice treated with 3MC demonstrated a higher metabolic rate, indicating that CYP1A isoforms are responsible for catalyzing EF24 hydroxylation in both mice and humans [2].

Phase II metabolism involves a series of conjugation processes, where the metabolite generated during phase I is combined with endogenous molecules to enhance water solubility and facilitate its elimination from the body. Common conjugation processes in phase II metabolism include glucuronidation, sulfation, and glutathione (GST) conjugation [2]. The exact phase II metabolic pathways involved in EF24's metabolism remain incompletely defined, necessitating further investigation to identify the specific conjugation processes undergone by EF24.

The clearance of EF24 from the body can affect its overall pharmacokinetics and therapeutic efficacy. Nonetheless, more research is imperative to gain a comprehensive understanding of the precise metabolic pathways, relevant enzymes, and pharmacokinetic implications of EF24 metabolism.

4. Elimination of EF24

The elimination half-life of EF24 exhibits variability and is influenced by parameters such as dosage and method of administration [2]. Elimination from the human body primarily takes place via renal excretion, predominantly through the urinary system. Metabolites resulting from phase II conjugation processes, such as glucuronides or sulfates, are water soluble and can be excreted as they are or further processed through renal transporters [2]. Reid et al. determined the terminal elimination half-life of EF24 in mice to be 73.6 min. with a plasma clearance value of 0.482 L/min/kg [2]. Biliary excretion is another potential route for EF24 and its metabolites. This process eliminates lipophilic substances like EF24 from the gastrointestinal tract. Subsequently, these substances could be excreted through feces or undergo enterohepatic circulation, wherein they are reabsorbed into the bloodstream, undergo additional metabolism, and are then excreted once again [2]. In liver microsomal preparations, EF24 metabolism generates multiple metabolites aligned with EF24 hydroxylation and reduction processes [2]. EF24 might undergo further metabolic transformations in various tissues before excretion, potentially within organs like the liver or specific target tissues [2].

Further investigation is necessary to gain a comprehensive understanding of EF24's precise pharmacokinetic properties. Specifically, detailed exploration is required regarding its bioavailability, volume of distribution, elimination pathways, extent of renal and biliary excretion, potential involvement of alternative routes, and the role of specific transporters and enzymes in its elimination process. Additionally, the pharmacokinetics of EF24 could be influenced by various variables, such as drug interactions, individual patient characteristics, and underlying medical conditions. Understanding the pharmacokinetics of EF24 is essential for optimizing dosage regimens, assessing therapeutic efficacy, and evaluating potential drug interactions.

5. Cytotoxicity of EF24

Understanding the toxicity profile of EF24 is essential to ensure safe and effective cancer treatment [9]. EF24 has shown promise as a cytotoxic agent, with the ability to reduce cancer cell viability, primarily through mechanisms involving caspases and modulation of ROS production [9][10]. However, its effects vary across different cancer cell lines, suggesting a complex interplay of signaling pathways [9]. Notably, the study of Monroe et al. (2011) pointed out that combining EF24 with cisplatin does not mitigate its effects on noncancerous cells but, rather, amplifies them, emphasizing the intricate and sometimes unexpected nature of drug interactions [9]. In addition, recent studies have uncovered diverse ROS responses in different cell lines, adding to the complexity of EF24's mechanisms [9][10][11]. Furthermore, the ability of EF24 to induce apoptosis in cancer cells represents an important aspect of its toxicity [10]. EF24's pro-apoptotic effects are thought to be mediated through multiple mechanisms. One key mechanism involves the modulation of various signaling pathways, including those related to cell survival and proliferation [10]. Hence, EF24 holds significant promise as a cytotoxic agent for cancer treatment, but its application is marked by the complex interplay of signaling pathways and diverse effects on various cell lines. A deeper understanding of its impact on both cancer and noncancer cells is essential to ensure its safe and effective use in cancer therapy. When it comes to systemic toxicity, the robust bioavailability of EF24 following intraperitoneal administration facilitates its efficient attainment of the necessary therapeutic concentration, essential for both animal models and clinical applications [12]. Also, the high clearance, surpassing the liver blood flow rate, and the substantial volume of distribution imply rapid metabolism and widespread tissue distribution following intravenous administration of EF24. According to Mosley et al. (2007), EF24 demonstrated no toxicity at doses up to 100 mg/kg, well below the established maximum tolerated dose (MTD) of 400 mg/kg [12]. This finding highlights the superior safety profile of this curcuminoid derivative compared to cisplatin, which has an MTD of 10 mg/kg. Furthermore, post-mortem examinations of EF24-treated animals revealed no signs of damage to the liver, kidney, or spleen in the sacrificed animals [12]. In the same direction, the study of Reid et al. (2014) suggests that EF24 metabolism involves cytochrome P450 enzymes, with species-dependent differences in the predominant metabolic routes, pointing out that reduction is a predominant route of EF24 metabolism [2]. Hence, EF24 emerges as a promising lead compound, demonstrating increased antitumor efficacy in both in vitro and in vivo settings compared to CUR, with preliminary assessments indicating minimal to no observable toxicity [2][12].

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