

Repositioning of Non-Steroidal Anti Inflammatory Drug (NSAIDs) for Cancer Treatment: Promises and Challenges

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Introduction

Cancer, a disease is still the second most common cause of death in the U.S. According to the report of American Cancer Society, more than 1,500 people die every day because of cancer [1]. Current treatments for various cancers therapies have improved patients' survival rate but they suffer from several limitations [2]. For example, the non-specific distribution of drugs limits the therapeutic dose within cancer cells and thereby causing several adverse side effects including hair loss, weakness, and organ dysfunction, leading to a low quality of life for cancer patients [3].

Nanoparticles (NPs) have been of significant interest over the last decade as they offer great benefits for drug delivery to overcome limitations in conventional chemotherapy [3]. They can not only be formed in a range of sizes (1-1000 nm) but in addition, they can be tailored to simultaneously carry both drugs and imaging probes and designed to specifically target molecules of diseased tissues. Nanoparticles for anti-cancer drug delivery reached the first clinical trial in the mid 1980s [4], and the first nanoparticles (e.g. liposomal with encapsulated doxorubicin) entered the pharmaceutical market in 1995 [5]. Since then, numerous new nanoparticles for cancer drug delivery have been approved and or are currently under development due to their many advantages. Their advantages include enhancing solubility of hydrophobic drugs, prolonging circulation time, minimizing non-specific uptake, preventing undesirable off target and side effects, improving intracellular penetration, and allowing for specific cancer targeting [4].

NSAIDs-Anticancer Activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used medicines worldwide [6]. There have been several reports on the anticancer activities of NSAIDs. They were found to be effective against colorectal, colon, breast and pancreatic cancers [7-11]. However, their anticancer efficacy was poorer than the common anticancer drugs that are currently being used mainly due to poor water solubility and bioavailability. The anticancer activity can be enhanced by proper formulation or derivatisation [12]. Different researchers tried different formulations and have achieved enhancement in anticancer activity to some extent. Nanotechnology is a promising method to enhance the solubility and bioavailability by decreasing particle size to nanoscale level [13].

Promises

NSAIDs (aspirin [14], indomethacin [15], celecoxib [16], Ibuprofen (IBP) [17], Ketoprofen (KP) [18] and Naproxen [19] have significant anticancer activities. Different synthetic approaches have been

developed to enhance the anticancer activity of NSAIDs. For example, complex formation with metals (example Ru) and derivatisation (phospho-ibuprofen) was attempted to improve the solubility of IBP [20]. In one of the reports, delivery of IBP using micelles as carrier to breast cancer cells showed remarkable reduction in cancer cell viability [21]. Hydroxyapatite-chitosan nanocomposite was used for the delivery of celecoxib for the treatment of colon cancer [22]. KP loaded polymeric nanocapsules showed good anticancer activity against glioblastomamultiforme (GBM) [23]. The IBP loaded PLGA nanoparticles were prepared for the treatment of human gastric cancer (MKN45 cell) [24].

Challenges

The nanotechnology can be used to increase the bioavailability and the anticancer activity of NSAIDs by reducing the particle size without changing their chemical structure. Different techniques have been developed for nanoformulation of NSAIDs [25]. One such simple and easy method is antisolvent reprecipitation method. Kumar et al. recently developed this method at the advanced level by tuning the experimental parameters and controlling the rate of supersaturation to precipitate smaller and spherical nanoparticles of organic compounds with size well below 40 nm [26,27]. Using Evaporation Assisted Solvent Antisolvent Interaction (EASAI) method Kumar et al. enhanced the solubility of poor water soluble drugs carbamazepine and griseofulvin more than 10 times as compared to respective raw drugs [27,28].

This will open a new window to explore the research and development in nanomedicine for cancer with nano-NSAIDs which are less toxic, easy to synthesize, cheaper and widely available [29]. So the nanoformulation of NSAIDs through nanotechnology based techniques will be of great interest to understand the in depth mechanism of the anticancer activity of NSAIDs. Identifying and developing new uses of existing drug which is alternative method for traditional drug discovery is generally coined as drug repositioning [30]. Drug repositioning of NSAIDs in cancer treatment poses a big challenge in front of the researchers [30].

Traditional drug discovery is expensive. Thus, drug repositioning can offer a low cost alternative method of drug discovery and development for the treatment of number of diseases [31]. If a suitable pair of disease and existing drug molecule is found then, thorough understanding followed by clinical trials can lead to advancement in drug discovery and development [32]. If a drug has to enter the market, the traditional drug discovery takes nearly 15-20 years involving a huge amount of money (US\$ 500 million for a single drug molecule) with an overall success rate of below 10% [33,34]. On the other hand, drug repositioning methods could take nearly 3-7 years only and will not involve much money (US\$ 50-100 millions) with

escalated chances of success [31]. The major challenge is the effective screening of disease-drug pair.

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