Ifosfamide drug stability: A formulation challenge

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ABSTRACT

Although ifosfamide is usually formulated as a sterile solution and delivered as intravenous injection, major efforts in both academic and industrial laboratories have been directed toward developing effective oral formulations and increasing the oral absorption of ifosfamide through the use of formulations that protect the drug and/or enhance its uptake into the intestinal mucosa. However, in spite of these major attempts, relatively little progress has been made. For the efficient delivery of ifosfamide by non-parenteral route, in particular through the gastrointestinal tract, novel concepts are needed to overcome significant diffusion barriers. The properties of ifosfamide, which are of major interest in oral delivery, are highlighted in the article. This article reviews the various problems associated and novel approaches for formulation and development of oral ifosfamide delivery systems.

KEY WORDS: Formulation issues, Ifosfamide, Nanoparticles, Oral delivery

INTRODUCTION

Selecting the optimal route of administration and formulation for a drug is crucial to ensure its clinical and commercial success. As pharmaceutical companies face competitive challenges from generic-drug incursion and reduced R and D productivity from their pipelines, strategies for more efficiently bringing drugs to market and for managing the product life cycle of new and existing drug products are vital.

Pharmaceutical scientists are important participants in realizing these goals. To gain a better understanding of the technical challenges and solutions in drug delivery, this review was gained through a literature survey. The survey examined key issues in formulation development and drug delivery overall for ifosfamide specifically. The survey showed that the complex physiochemical properties were top technical concerns and that partnering strategies were important approaches for addressing technical challenges and concerns in resource allocation.

Ifosfamide is one of the widely used antineoplastic drugs belonging to the alkylating agent group. It is a small molecule with a molecular weight of 260 amu. Due to the isotopic distribution of chlorine, the molecular weight is sometimes calculated as 261 amu. It was first approved by the USFDA in 1988 as a third-line treatment for testicular cancer. Ifosfamide is chemically 3-(2-chloroethyl)-2-[(2-chloroethyl) amino]-tetrahydro-2H-1,3,2oxazaphosphorin-2-oxide and is represented by the formula [Figure 1].

Ifosfamide is a white crystalline hygroscopic powder having a melting point of 40°C belongs to BCS Class III drug. The powder has a water solubility of about 100 mg/ml. Ifosfamide is used in the treatment of a variety of solid tumors including those of the cervix, endometrium, lung, ovary, testes, and thymus as well as in sarcoma and in the treatment of Burkitts lymphoma. However, the treatment with ifosfamide is associated with serious side effects such as hemorrhagic cystitis, myelosuppression, cardiac arrhythmias, central nervous system (CNS) disturbances, nephrotoxicity, hematological, and gastrointestinal reactions. The LD50 in mouse on intravenous administration has been reported to be 338 mg/kg body weight. Combination with the uroprotective agent, mesna reduces the incidence of hemorrhagic cystitis. Thus, mesna is normally administered intravenously at a dose of 20% of the...
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Figure 1: Structure of ifosfamide

Ifosfamide dose, initially at the time of administration of ifosfamide and then at 4 and 8 h.[1]

FORMULATION CHALLENGES OF IFOSFAMIDE

The survey showed that decisions on the route of administration are made early in the drug development process. Once a route of administration has been decided, pharmaceutical scientists face a myriad of issues. The key findings from the survey are shown below. Chief among them are the overall safety of the drug product and developing the appropriate therapeutic and delivery profile.

Challenges with Sterile Crystallizate

Ifosfamide is available in the form of a sterile crystallizate which is dispensed in injection bottles in dosages from 200 mg to 2000 mg for parenteral use. Before administration, the sterile crystallizate must be dissolved in water for parenteral purpose, but it is required that the concentration not to exceed 4%. This solution is suitable for intravenous injection. For purposes of short intravenous infusion, the ifosfamide solution is dissolved in 500 ml Ringer’s solution or similar injection fluids. The duration of infusion is about 30 min, possibly 1–2 h. In the case of the 24 h infusion, the ifosfamide solution is, for example, dissolved in a total of 3 L of 5% dextrose-sodium chloride solution.[1]

Ifosfamide is very susceptible to hydrolytic degradation and accordingly prompt administration of such solutions is generally required. Therefore, commercially, it is predominantly available in dry form and is supplied as sterile packaged dry powder for dissolution in water for injection before administration. However, the low melting point and the hygroscopic nature of ifosfamide make it necessary to fill the powder with great care by accurately controlling both temperature and humidity to achieve a sterile product. Further, prolonged storage of the dry powder also results in sintering and yellowing, which in turn leads to a reduction in dissolution rate, thereby increasing the time required for reconstitution.[2]

To overcome the difficulties associated with thermal and hydrolytic susceptibility, previously, lyophilization of the drug was attempted. The lyophilized form of ifosfamide which is currently available is prone to stick together and form lumps and to become electrically charged. This makes it difficult or impossible to introduce it into injection vials and to achieve accurate dosage. In addition, the quality of ifosfamide varies from batch to batch.

Challenges with Ifosfamide Crystals Obtained by Recrystallization

An improved form of ifosfamide was obtained by means of the controlled recrystallization in a specific solvent mixture. This solvent consists either of (a) a mixture of diethyl ether and a C₃-C₅ alkanol, preferably diethyl ether/methanol or (b) a mixture of disopropyl ether and a C₃-C₅ alkanol, preferably disopropyl ether/methanol, diisopropyl ether/isopropanol, or disopropyl ether/n-propanol. Ifosfamide crystals obtained by this method were well developed and have no rounded edges or only slightly rounded edges. No electrostatic charging of crystals is observed. There are numerous problems associated with the preparation and processing of crystalline ifosfamide. During the preparation of sterile, crystallized ifosfamide a product is obtained having an unstable physical mixture. In particular, the fluctuating flow properties greatly impair accuracy of dosage during filling.[3]

Challenges with Lyophilized Preparation

US patent No. 4959215 described a lyophilized preparation consisting of ifosfamide, 0.05–1.0 parts by weight of mesna and 0.1–17 parts by weight of a mannitol. The lyophilizate of this method was found to have better heat stability than the dry-filled ifosfamide used in the past. The lyophilizate obtained by this method displays neither discoloration nor change in the consistency of the ifosfamide when stored at 40°C. Moreover, the lyophilization of ifosfamide in combination with mesna leads to an improvement in the product solubility and dissolution. However, there may be the possibility of incompatibility and bio-interference of the components and use of mannitol is restricted.[4]

However, the lyophilization process is quite time-consuming and requires specialized equipment. Personnel exposure to the strongly cytotoxic ifosfamide occurring during reconstitution of lyophilized powder is also very undesirable. To conquer, all these problems some attempts have been made worldwide to obtain clear liquid ifosfamide compositions, suitable for parenteral administration.

Challenges with Organic Solutions of Ifosfamide

An ethanolic solution of ifosfamide containing 96% and 100% ethanol was reported to reduce the degradation of ifosfamide. However, the use of ethanol in such high concentration leads to other problems.
such as volatility, handling during manufacturing, and miscibility with blood on administration. As such, ethanol is pharmacologically active, which may also affect the person on administration of alcoholic solution of ifosfamide.\(^5\)

Another US patent disclosed an ifosfamide formulation as a ready to dilute solution. The solution has organic polys, namely, propylene glycol and polyethylene glycol and their mixtures as a solvent also 0–50% water. The water may be partly replaced by 10%–30% of ethanol.\(^6\)

A clear solution comprising ifosfamide, solvent and optionally, conventional pharmaceutical carriers and excipients was reported for parenteral administration. The solvent comprises 35%–75% lower alcohol and 25%–65% polyol. While lower alcohol solvent is usually ethanol, the polyol solvent is propylene glycol, glycerol, and/or polyethylene glycol.\(^7\)

The parenteral administration of larger amounts of polys and alcohols may cause other problems such as pain or irritation on injection, hemolysis, otoxicity, cardiovascular effects, CNS effects, and seizures. It may also lead to hyperosmolarity and lactic acidosis in patients with renal impairment.

A stable and ready to use liquor of ifosfamide using sodium chloride as a stabilizing agent were reported. This work described a 10–500 mg/ml ifosfamide composition containing urea, sodium chloride, and sodium dihydrogen phosphate. These compositions were found to be stable. However, there is no mention about the safety and toxicity of the composition. The higher composition of urea in the formulation may lead to complications such as hemolysis, irritation, phlebitis and thrombosis at the site of injection, and elevated blood ammonia, and urea concentrations may lead to hepatic and renal function impairment.\(^8\)

A ready-to-use aqueous composition of ifosfamide having enhanced stability at elevated temperatures was reported. This aqueous composition comprises ifosfamide, a pharmaceutically acceptable buffer, and water. This composition was prepared by controlling the molar ratio of ifosfamide to buffer in the composition. However, such compositions may not be adequately stable at ambient temperatures. There is no report on the toxicity of ifosfamide compositions described in this work.\(^9\)

**Challenges with Ifosfamide Composition Comprising 2-hydroxypropyl-β-cyclodextrin**

An aqueous ifosfamide composition comprising 2-hydroxypropyl-β-cyclodextrin that provides reduced toxicity, as compared to conventional ifosfamide formulations was prepared. The use of HPβCD according to this work enables the production of aqueous concentrates of ifosfamide in concentrations above the saturation concentration of ifosfamide in water, that is, up to 1100 mg/ml. However, the complex of HPβCD-ifosfamide can be easily dissociated and may result in decreased stability at elevated temperatures.\(^10\)

All the attempts made to prepare a ready-to-use solution of ifosfamide were found to be tricky. The potential danger of the substance necessitates extensive protective measures for the staff during the manufacture of the sterile injection solution from the dry substance. Apart from the difficulties in manufacturing the sterile crystallize, there are also some serious disadvantages in use. Parenteral therapy is unpleasant for a patient since he has to submit to a painful puncture during application and is connected to an infusion apparatus for the duration of the infusion. Parenteral administration can only be performed by specialized medical personnel. The patient has to be admitted to hospital as an inpatient or must at least attend hospital every day for treatment. This involves a great deal of time on the part of staff and patient and added expense.

**Challenges with Solid Oral Dosage Form**

Oral delivery of ifosfamide could provide better means and its success is expected to revolutionize cancer chemotherapy. Oral delivery can maintain an optimum concentration of drug in circulation which can provide prolonged exposure to cancerous cells, which will in turn improve the efficacy and decrease the adverse effects. Recently, there has been a surge in the development of oral chemotherapeutic agents, and many molecules are undergoing clinical trials or already approved for their oral efficacy.\(^11\) Oral administration could permit ambulatory therapy. Oral administration of ifosfamide would be pleasant for the patient and would no longer constitute a risk for the medical personnel.

However, all the attempts to develop a solid oral dosage form of ifosfamide have been failed because of its complex physicochemical properties. In particular, it was not possible to prepare a medicinal form in soft-gelatin capsules. The active substance appears to react with the capsule wall, becomes tanned and the capsule no longer dissolves in the gastric juices. Similarly, many attempts to develop a tablet have hitherto failed. The substance adhered to the die of the punching machine, the tablets were too soft and the active substance sometimes spurted in liquefied form from the mold during compressing. An attempt has been made to fill the ifosfamide into hard-gelatin capsules in a mixture with microcrystalline cellulose. It was found that there was no deleterious interaction between ifosfamide and the capsule wall. Although the capsule wall contains 12–15% of water (weight/
Moreover, ifosfamide degrades in acidic media with its rate of degradation depending on the pH of the solution. Acid hydrolysis has shown to yield 2-DCEIF. The incidences of neurotoxic abnormalities were found to be higher with oral administration than with i.v. administration of ifosfamide. Hence, it is difficult to develop a conventional dosage form for the delivery of ifosfamide.

Hence, it was sought to develop an oral delivery system that could stabilize ifosfamide in acidic environment and reduce the formation of the toxic metabolites by preventing its exposure to the acidic medium. A sustained release oral formulation of ifosfamide can sustain its release over a longer period and with better stability could prove helpful in decreasing the dosing frequency.

Advanced drug delivery strategies can offer alternatives which can circumvent the issues associated with drug’s toxicity and on the other hand can lead to enhanced therapeutic performance by increasing the bioavailability of the drug. In recent years, new strategies for cancer treatment-based drug-loaded nanoparticulate formulations have emerged. Nanoparticles represent promising drug carriers, especially for the specific transport of anticancer drugs to the tumor site, which can improve therapeutic efficacy and reduce systemic toxicity. Nanoparticles have high drug-loading efficiency, with minor drug leakage and good storage stability, and may circumvent multidrug resistance in cancer cells. Moreover, the loaded drug can be released from the nanoparticles in a controlled fashion at a desired rate over a sufficiently long duration, thereby increasing the overall payload of drug to cancerous cells.

Preparation of nanoparticles for hydrophilic drugs remains a challenge for formulation scientists due to rapid diffusion of the drug to the external aqueous phase and its low entrapment efficiency. In this study, to overcome the limitations of the current therapy strategies of ifosfamide, a novel lipid drug delivery system containing chitosan was proposed.

**FORMULATING LONGEVITY: NANOPARTICLES**

To circumvent above-mentioned limitations, a practical approach could be developed for the formation of a novel lipid carrier, termed as “lipid nanoparticles,” in selected nanoscale size dimensions. Lipid nanoparticles have been evolved as alternative drug carrier systems. Lipids and lipid nanoparticles are extensively employed as oral-delivery systems for drugs and other active ingredients. Lipid nanoparticle matrix is composed of a mixture of spatially different lipid molecules, normally mixture of solid and liquid lipid, which makes more imperfections in the matrix to accommodate more drug molecules than solid lipid nanoparticles. Despite the presence of liquid lipid, nanostructured lipid carriers matrix is solid at room/body temperature. It is expected that the drug loading capacity will be enhanced, drug expulsion during storage will be minimized due to the imperfect crystal lattice and drug release profile can be easily modulated by varying the lipid matrix composition. These have been exploited for many features in the field of pharmaceutical technology. Lipids usually enhance drug absorption in the gastrointestinal tract (GIT), and when formulated as nanoparticles, these molecules improve mucosal adhesion due to small particle size and increasing their GIT residence time. In addition, lipid nanoparticles may also protect the loaded drugs from chemical and enzymatic degradation and gradually release drug molecules from the lipid matrix into blood, resulting in improved therapeutic profiles compared to free drug. Therefore, due to their physiological and biodegradable properties, lipid molecules may decrease adverse side effects and chronic toxicity of the drug-delivery systems when compared to other of polymeric nature.

**CONCLUSIONS**

The successful development of a challenging medicine depends on an intimate understanding of its physicochemical and biological characteristics, including chemical and physical stability, and their efficacy and safety profile. The scientific community has reached a new stage in the understanding of the physicochemical properties of ifosfamide and in the manufacturing of these therapeutic agents. In the past, administration of ifosfamide through oral route was believed to be impossible, while nowadays it is expected that the obstacles for effective delivery of ifosfamide will be overcome and delivery systems with better compliance would be made available to the patients. To get available, a new, safe therapeutic medicine to be delivered orally, it is important to obtain a detailed understanding of what kind of surface modification might be acceptable from a safety and efficacy point of view early in the development process. This includes strategies to reduce or prevent chemical degradation and other structural changes that could prove to be prohibitive for successful development of the drug. It is the joint responsibility of academia, the pharmaceutical industry, and the regulatory authorities to establish the scientific
background for the safe, fast testing, and assessment of promising new biopharmaceuticals to the benefit of patients and society.

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