

Dextran Microspheres as a Potential Carrier for Vincristine Sulphate Incorporated with Thermosensitive Gel offered Prolonged Release

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ABSTRACT

Vincristine sulphate (VCS) is a vinca alkaloid obtained from the periwinkle plant (*Catharanthus roseus*) is the most widely recognized chemotherapeutic medications utilized for the treatment of a few types of malignancies. Moreover, VCS is a potent anticancer agent and drug of choice for the treatment of childhood and adult acute lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma as well as solid tumors including sarcomas, neuroblastoma, breast cancer, etc. In any case, poor biopharmaceutical and pharmacokinetic characteristics of VCS like high dosing recurrence and broad protein binding limit the clinical capability of VCS in tumor treatment. This review focuses on progress in the encapsulation efficiency and sustained release pattern of the drug.

INTRODUCTION

Controlled and sustained release parenteral drug delivery vectors offer several advantages like reduced dose frequency, lesser side-effects, and mild local irritation as compared to conventional parental injections [1-2]. Consequently, modifications made parenteral dosage forms exhibit optimum drug plasma level within therapeutic range for longer period with enhanced therapeutic effect [3-5].

Vincristine sulphate (VCS) is a vinca alkaloid obtained from the plant *Catharanthus roseus* [6-7]. Moreover, VCS is a potent anticancer agent and drug of choice for the treatment of childhood and adult acute lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma as well as solid tumors including sarcomas, neuroblastoma, breast cancer, etc. [8]. VCS binds to tubulin in concentration dependent method and consequently results microtubule depolymerization, metaphase arrests and apoptosis [9]. Despite excellent anticancer efficacy, poor biopharmaceutical and pharmacokinetic traits of VCS impede the clinical efficacy and patient placate. The very short serum half-life (12 min), high dosing frequency (1.4 mg/m² per week for 4 weeks) and extensive protein binding (75%) limit the clinical potential of VCS in cancer therapy [10]. Notably, VCS is a cell specific anticancer agent and its therapeutic effect may be boosted by exposing VCS to tumor cells for longer period of time during sensitive stage of cell cycle [11]. Thus, there is a need for the development of long acting injectable drug delivery systems of VCS to regulate the frequency of drug administration and ultimately the quality of patient's life.

Previously, VCS was encapsulated in liposomes, microspheres, niosomes, nanoparticles, gold nanoparticles, and nanomicelles for augmenting the sustained release, pharmacokinetic profile and antitumor effect [12-13]. During the last two decades, injectable *in situ* gels have attracted considerable attention as polymeric drug carriers, and then great interest has arisen on the applications of *in situ* gels in injectable drug delivery systems [14-15]. These systems are *in situ* gel delivery systems, exposed to body temperature (37 °C), are capable of getting transformed to a very high viscous gel, though remaining fluid at room temperature [16-19]. The gel network

that remains insoluble in water and retains shape for a long period can become an appropriate carrier for therapeutic moieties [20-21]. For localized therapy, injection of *in situ* gel causes the formation of a depot at the site of drug administration, which continuously and slowly releases the drug to the target tissue [22-25]. Besides, the gel may deliver a drug throughout the tumor, thereby decreasing systemic toxicity, which is also an advantage over actively or other passive targeted therapies [26-28]. Chitosan/ β -glycerophosphate *in situ* gel has been proposed for diverse pharmaceutical applications including parenteral (intraperitoneal, intramuscular and subcutaneous injections), inhalation, oral, ophthalmic and topical administration [29-30]. Polymeric microspheres have gained enormous attention owing to wide range of applications [31-33]. Notably, microspheres pose enhanced physical and chemical stability in addition to high pay load and easy industrial scale up [34-35]. However, recent studies showed that dextran microspheres due to its well defined and desirable pharmaceutical attributes have been extensively studied for controlled and sustained drug delivery [36-39]. Moreover, biodegradable and biocompatible dextran microspheres do not influence the cell viability in biological system [40-44]. Meritoriously, it shows several advantages to integrate two distinct drug delivery systems for surmounting the biopharmaceutical and pharmacokinetic limitations of VCS with the aim of inducing the synergistic sustained release property through parenteral route of administration.

Therefore, in recent investigation, vincristine sulphate loaded dextran microspheres incorporated with chitosan/ β -glycerophosphate gel (VCS-Dextran MSs-Gel) were engineered by optimizing the processing conditions using central composite design (CCD) and response surface methodology (RSM) [6,45-48]. Furthermore, particle size, zeta potential, surface morphology, encapsulation efficiency, drug loading capacity, gelling temperature, viscosity, *in vitro* drug release, and standard cell proliferation assay using THP-1 (human leukemia cells) cell line were determined *in vitro* to analyze the therapeutic efficacy of VCS-Dextran MSs-Gel in comparison to VCS-Dextran MSs [20,49-50]. Additionally, pharmacokinetic elements of VCS-Dextran MSs-Gel and VCS-Dextran MSs were determined *in vivo* following subcutaneous route of administration and compared with VCS injected intravenously in Swiss albino male mice.

CONCLUSION

In recent years numerous studies focused on prolonged release of Vincristine sulphate. Recent studies showed that dextran microspheres due to its well defined and desirable pharmaceutical attributes have been extensively used for controlled and sustained drug delivery of drug. Dextran microspheres do not influence the cell viability in biological system because of its properties, such as biocompatibility and biodegradability. Meritoriously, it shows several advantages to integrate two distinct drug delivery systems for surmounting the biopharmaceutical and pharmacokinetic limitations of VCS.

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