IN VITRO-IN VIVO CORRELATIONSHIP APPROACH OF THE PREPARED MAGNETIC MICROSPHERES OF CYTARABINE

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ABSTRACT

Objective: The objective of this study was to study the in vitro-in vivo correlationship between the magnetic microspheres prepared by continuous solvent evaporation (CSE) method by 3\(^2\) factorial designs.

Methods: CSE technique was used in the preparation of magnetic microspheres. Drug used was cytarabine and mice were the animal model used to check the correlationship.

Results: The profiles are nearly identical and reveal that drug absorption is rapid. The in vivo drug absorbed was found to be in concordance with the in vitro release as seen in the superimposable curves.

Conclusion: Cytarabine effectively reduces the amount of drug released and consequently absorbed in vivo in the initial phase.

Keywords: Cytarabine, Microspheres, Magnetic, in vivo, in vitro.

INTRODUCTION

Magnetic microspheres are the particles that are targeted to the desired site of action by the application of the magnetic field. These are mainly used for targeting in case of tumor sites; cytarabine is mainly used for leukemia. Leukemia is a cancer of the white blood cells and bone marrow. Magnetic microspheres were formulated by 3\(^2\) factorial designs [1]. Thus, a formulation, that is, magnetic microspheres was prepared for cytarabine. In vitro-in vivo correlation (IVIVC) approach involves the comparison of the behavior of drug absorbed in vivo and its comparison for the profile in vitro. Thus, leukemia cases can be minimized by having an idea about IVIVC. Mice were the animal model used.

MATERIALS AND METHODS

Dosing and blood sample collection

Wistar strain of rats was used for the study. The protocol for performing experiment was approved by the Institutional Animal Ethical Committee as per the rules of Committee for the Purpose of Control and Supervision of Experiments on Animals, India. Animals were euthanized after accomplishment of the study and the carcasses were disposed as per the guidelines of the institute.

Blood samples (1 ml) were withdrawn from animals and collected directly in tubes containing 300 ml of sodium citrate solution (2% w/v). Blood samples were collected at predetermined time intervals that are 0, 1, 2, 3, 4, 8, 9, and 10 h (seven time points).

The blood samples were centrifuged at 4000 revolutions/min (for 10 min at 4°C); separated plasma samples were stored in clean screw capped polypropylene plasma tubes until further analysis.

Extraction of drug from plasma

About 0.5 ml plasma sample was taken in a centrifuge tube, and extraction was later on done with chloroform. After shaking for 1 min and then subjecting to centrifugation at 2000 rpm, all the three layers were separated. The separated layers were again mixed with chloroform 0.5 ml and further subjected to centrifugation. The organic layer from all the three vials was collected. The collected organic layer was later on subjected to dryness on water bath. The residue was dissolved in methanol, 0.20 ml of aliquot was applied for HPLC (Kromasil C18 column, 1.5 ml/min, ambient 50°C, retention time 8.5±0.03 min) [2,3].

Pharmacokinetic parameters and their statically evaluation

The highest observed plasma cytarabine concentration C\(_{\text{max}}\) and the time to reach C\(_{\text{max}}\) relative to the time of dosing (t\(_{\text{max}}\)) were noted from the plasma concentration versus time profile.

Plasma concentration of cytarabine and cytarabine magnetic microspheres at different time intervals was determined [4-8].

RESULTS AND DISCUSSION

Comparison of plasma concentration (ng/ml) obtained for cytarabine magnetic microspheres and cytarabine is shown in Fig. 1.

The relationship of observed drug concentration-time profiles following administration of microsphere with drug dissolution and pharmacokinetics can be described graphically (Fig. 2).

It is presumed that absorption and dissolution have a linear relationship; thus, absorption and dissolution features of a drug can be used interchangeably. Profiles of drugs can be established with dissolution profiles in combination with the pharmacokinetic characteristics of the drug. This method of attaining a drug profile from dissolution results is convolution. Extracting a dissolution profile from blood profile is deconvolution.

The mean peak plasma concentration of the drug was 103±10.14 ng/ml, while that of cytarabine magnetic microspheres were 110±21.13 ng/ml. This showed that magnetic microspheres of cytarabine effectively reduce the amount of drug released and consequently absorbed in vivo in the initial phase.

The relation between percentage drug released in vitro and the percent absorbed for magnetic microspheres was assessed using Wagner-Nelson...
The fraction absorbed (\(\text{\textit{F}}_{\text{abs}}\)) was determined from the plasma concentration-time data by deconvolution using the Nelson-Wagner method.

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\text{\textit{F}}_{\text{abs}} (\text{\textit{t}}) = \frac{C(t)e^{-kt}\text{AUC}(0-\text{\textit{t}})}{k\text{e}^{-k\text{AUC}(0-\text{\infty})}}
\]

With the Nelson-Wagner equation, the pharmacokinetic profile is deconvoluted to obtain the \textit{in vivo} absorption as a function of time and is plotted alongside the \textit{in vitro} release data to assess the superimposability of the two profiles. If the two curves are superimposable and a linear relationship is obtained, it suggests a strong correlation between \textit{in vivo} and \textit{in vitro} drug release.

Once deconvoluted, the \textit{in vivo} curve is plotted alongside the \textit{in vitro} release data to assess the superimposability of the two profiles. Thus, the deconvolution approach allows comparison of \textit{in vivo} release profile with \textit{in vitro} behavior. The profiles are nearly identical and reveal that drug absorption is rapid. The \textit{in vivo} drug absorbed was found to be in concordance with the \textit{in vitro} release as seen in the superimposable curves.

Percentage release \textit{in vivo} curves, using the Nelson-Wagner method, are nearly superimposable for the formulations. Nearly likely findings were reported by Chu \textit{et al.} in a study on PLGA microspheres containing the alkaloid, Huperzine A.

**AUTHORS’ CONTRIBUTIONS**

The first author contributed in the conceptualization of the article and preparation of manuscript. The corresponding author provided expertise and feedback without which it was not possible to publish it.

**CONFLICTS OF INTEREST**

There are no conflicts of interest.

**REFERENCES**