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RESEARCH

Frontiers in Molecular Medicine and Therapeutics

A new method for determining drug half-life and evaluating stability

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Abstract

In the measurement system of 4-5 different types of anticancer drugs and commonly used drugs and corresponding solvents, the microcalorimetry was the main research method to determine the dissolving enthalpy of the drug in the corresponding solvent to study the dissolution behaviour of drugs in solvents. According to the established mathematical model of thermodynamics, the dissolution half-life of drugs in the corresponding solvents is calculated, the kinetic equation, kinetic parameters and thermodynamic parameters in the dissolution process are established, and the database of thermodynamic and kinetic parameters of the anticancer drugs and commonly used drugs is established, which provides a theoretical basis for the stability evaluation and clinical application of drugs..

Keywords: *drugs, half-life measurement, stability evaluation, thermodynamic and kinetic mathematical models, microcalorimetry*

Introduction

With the development of society and the progress of science and technology, people have realized that plant medicine and synthetic medicine in natural treasure have gradually become powerful weapons to fight diseases and prolong life. However, people's understanding and correct use of drugs still need to be improved. Obviously, research on drug properties has become one of the important topics for medical and chemical researchers. It is gratifying to note that this kind of research has been carried out in large numbers in recent years, and along with the deepening of research, drug research calls for new evaluation methods

Scientists are always concerned about the efficacy, half-life and stability of a drug. For this reason, people have used spectrophotometry or liquid chromatography to detect changes in the concentration of drugs in the blood of organisms. Since the 1970s, the half-life of drugs has been measured by blood samples to determine the time interval and dosage of drugs. This method is called plasma method, and it is effective and has been passed down for many years, but it is difficult to master and time-consuming. Therefore, it is imperative to use the microcalorimetry ingeniously to create a new way of drug evaluation.

Microcalorimetry is an important method in thermochemistry research. The thermodynamic process of the system is studied directly by calorimetric instruments. According to the exothermic (or endothermic) rate of the change process of the research object, the kinetic law of the system is explored. And some practical problems are solved by integrating thermodynamics and chemical kinetics, which sublimates the theory. This kind of research is more and more respected, especially with the appearance of various high-sensitivity microcalorimeters, the research of calorimetry has expanded from some typical chemical reactions in the past to various slow reactions, reactions with very small enthalpy change and even biological metabolic processes, which enables calorimetry to study the thermal properties of substances from a static point of view, as well as to track many reactions process dynamically in real time to obtain the relationship between the thermal power and the time in a process, and obtain the kinetic information related to the process, so we should explore the changing law of reaction process, and seek new methods to solve the urgent scientific and technological problems. Obviously, if microcalorimetry can be applied to the determination of drug half-life and drug stability assessment, the long-term cost-consuming and time-consuming biological circulation method will be modified and revised, and a new drug half-life and stability evaluation method will be created.

The drug half-life refers to the time required to halve the concentration of drugs in the blood, which is generally expressed in t 1/2. Half-life of drugs reflects the speed of elimination (excretion, biotransformation and storage) of drugs in vivo, and is an important basis for determining dosage and frequency of administration. Based on the fact that the half-life of the drug is a certain value at a certain temperature and the dissolution process is generally a simple reaction, important thermodynamic information is obtained by measuring the heat of dissolution, from which the dissolution half-life and dissolution entropy of the drug are calculated. Through these thermodynamic data, the stability of the drug can be evaluated and providing theoretical guidance for pharmaceutical enterprises. Interestingly, the half-life of the drug obtained by microcalorimetry is in good agreement with that determined by plasma spectroscopy. But the numerical coincidence is two different concepts, and these two theories and two methods can achieve the same goal, which provides another simple and scientific method for the determination of half-life of drugs.

Nowadays, with the rapid development of life science, biothermodynamics theory and microcalorimetry have been widely used in drug research. It has been proved that microcalorimetry plays a very good role in the modernization of medicine including the four characteristics of traditional Chinese medicine,

the processing of traditional Chinese medicine, the quality evaluation, the screening and testing of pharmacodynamics and the development of new drugs. The results of research indicates that microcalorimetric analysis can be used as one of the effective tools to characterize the four properties of traditional Chinese medicine. Combining with the kinetic parameters such as enthalpy change (ΔH) in the process of system reaction, microcalorimetric analysis can be used as an important objective index to measure the four properties of traditional Chinese medicine. A series of thermodynamic experiments have been carried out on the interaction between drugs and some biological macromolecules in human cells using a microcalorimeter. The experimental results show that microcalorimetry technology can be used as a new method for screening and testing medicine. Under the dual guidance of traditional Chinese medicine and thermodynamics theory, taking the traditional Chinese medicine radix isatidis with large clinical dose and exact curative effect but the basis of pharmacodynamic substance as the research object, the energy metabolism process of radix isatidis on the organism are concerned, and the research idea and method system for the quality evaluation and the screening of pharmacodynamic substances based on the expression of biothermodynamic are proposed and attempted to construct. Thermodynamic experiments on the interaction between drugs and some biological macromolecules in human cells by microcalorimetry have also made some progress. Some studies [1-5] have screened out reasonable solvents to ensure the complete dissolution of drugs. The dissolution behavior of drugs has been studied by microcalorimetry, and the integral heat of dissolution and differential heat of dissolution have been measured. The relationship between solute and heat has been established, and the kinetic equation, half-life, $\Delta_{sol}H_m$, $\Delta_{sol}G_m$ and $\Delta_{sol}S_m$ of drugs in solvents have been obtained. The half-life of drugs obtained is basically consistent with the data of the liquid chromatography method commonly used in the pharmaceutical industry. Microcalorimetry avoids the troubles caused by blood collection and the errors caused by individual differences, thus providing a reliable and systematic theoretical basis for drug stability research and clinical application, and accumulating thermodynamic and kinetic data for various drug development. Some scholars at home and abroad have done relevant research, but only related to thermodynamics, can not reflect the dynamic characteristics. The calculation methods used by researchers are basically similar. Most of the theoretical models of thermodynamics and various methods of chemical thermodynamics have been established based on Tian's equation, some possible mechanisms of known reactions have been proposed according to the experimental data. Many scholars at home and abroad have carried out a lot of research using this model, but seldom involved in the field of drugs, so it is a very useful work to apply it to drug research.

Scientific problems and research contents to be solved by microcalorimetry

Scientific problem to be solved

Microcalorimetry is in good agreement with the drug half-life values obtained by plasma spectroscopy, but it is two different conceptual interpretations. So microcalorimetry provides a simple and scientific method for the determination of drug half-life. The scientific problems to be solved here are as follows:

1. Relationship between dissolution half-life of drugs and plasma half-life: Usually called plasma method as in vivo circulation method, dissolution method as in vitro method, then why the same drug has a very similar half-life in the living and non-living body, and clarifying the reasons will be of great help to explain the mechanism of drug treatment.
2. What is the value of the drug's dissolved negative entropy($\Delta_{sol}S_m$) in application? Entropy is a measure of the degree of chaos of the system, which can be used to judge the stability of the system. How to evaluate the stability of drugs by using the function relationship of negative entropy will be one of the problems to be solved.
3. Explanation of Abnormal Phenomena: At a certain temperature, the dissolution half-life of fixed solvents is a certain value, but there are also some abnormal phenomena. Understanding their dissolution mechanism is conducive to the application of core technology.

Research content

Two major problems in the use of drug have attracted considerable attention. One is drug interval and half-life, and the other is drug stability. Especially, the storage stability of injections has brought many challenges and variables to the circulation time of drugs. Therefore, using a good microcalorimeter and titration calorimeter as a means to design the research route, and determine the dissolution enthalpy of different drugs in corresponding solvents (water, brine, glucose, etc.) to observe the dissolution behavior of drugs in solvents and the changes of entropy and free energy during dissolution. Based on this, a mathematical model was established to determine the kinetic equation of drug dissolution and calculate the kinetics parameters. The parameters can be used to obtain the half-life and dissolution entropy of the drug. The dissolution entropy can be used to judge the stability of the drug system. These provide a theoretical basis and a new method for drug research and application.

Previous studies have confirmed that the dissolution of resveratrol [6], bacillus thuringiensis [7-8], oxymatrine [9], matrine [10], paclitaxel, sophocarpine, oridonin, sesamin, genistein, astragaloside, salicylin, aloe emodin, chickpea sprouts and other ten drugs conforms to the conclusion that drug dissolution is a simple reaction, but the stability of the same drug in different solvents varies greatly. In order to explore the dissolution law between drugs and solvents, reveal the dissolution nature of different types of drugs, summarize the rules, and facilitate their application, microcalorimetry method can be used to carry out research work:

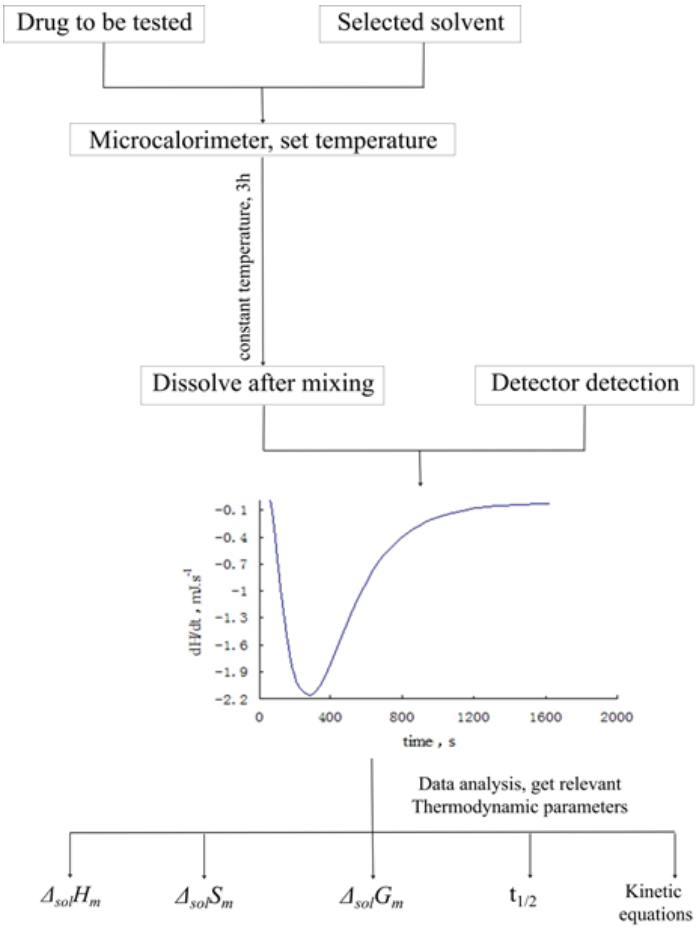
1. Designing drug systems with high clinical applicability and defined half-life.
2. Design some new anticancer drugs as a system.
3. Simulating human environment, use microcalorimetry to find ideal solvents to determine enthalpy of dissolution, calculate half-life and entropy of dissolution.

Obviously, it is necessary to find the most suitable solvent to represent in vivo circulation method and in vitro method in order to meet the needs of microcalorimetry, while ensuring the accuracy of data obtained and the reproducibility of experimental results. However, the most critical problem is that most drugs do not necessarily maintain good solvability in ideal solvents. How to solve this problem will become another difficult problem to be solved.

Research methods

For a chemical reaction, the change of enthalpy is proportional to the reaction rate and the change rate of enthalpy is proportional

to the reaction rate under isothermal and isobaric conditions. If the calorimetric curve of the next change process can be recorded continuously and accurately in microcalorimetry, the thermodynamic and dynamic information of the process can be provided simultaneously. Thermal conductivity microcalorimeter reads out the exothermic spectrum curve (the endothermic spectrum curve is downward), and the total thermal effect of the change process is the integrated area under the curve: $\int_0^t \frac{dH}{dt}, \frac{dH}{dt}$ is the rate of enthalpy change, which is related to time. Therefore, this curve is also called "thermodynamic curve". On the microcalorimeter, the thermal signal can be converted into electrical signal by AD conversion and the detailed thermodynamic data can be recorded on the interface by computer program "restoration".



Technology roadmap

Dissolution Behavior of Drugs in Solvents

Thermodynamics Research: The dissolution heat spectrum curves of 4-5 groups of drugs with different mass in a certain volume of corresponding solvents were determined, and the average value of molar enthalpy of drugs with different mass was calculated. This value can be considered as the molar enthalpy of drugs dissolved in infinitely diluted solvents, also known as integral dissolution enthalpy. The differential enthalpy of dissolution of drugs in corresponding solvents can be obtained from the linear equation between mass and heat effect of dissolution.

Dynamic process: Based on the experimental data, the dissolution rate of drugs in the corresponding solvents was calculated by kinetic equation. According to the following (1)(2) dynamic equations:

$$\frac{d\alpha}{dt} = kf(\alpha) \quad \text{.....(1)}$$

$$f(\alpha) = (1-\alpha)^n \quad \text{.....(2)}$$

And substitutes logarithm to get the following formula (3)

$$\ln[\frac{1}{H_0}(\frac{dH}{dt})_i] = \ln k + n\ln[1-(\frac{H_t}{H_0})_i] i = 1,2,\cdots,L \quad \text{.....(3)}$$

Among them, α: the amount consumed by the reactant; *f(α)* the kinetic equation; *t*: the reaction time; H_t: the heat change at time *t*; H_0: the heat change during the whole dissolution process; *k:* the reaction rate constant; n: the reaction order. Taking $\ln\left[\frac{1}{H_0}\left(\frac{dH}{dt}\right)\right] \sim \ln\left[1-\left(\frac{H_t}{H_0}\right)\right]$ as a graph, where the slope of the straight line is the reaction order n and the intercept is ln*k*, and then the specific form of the kinetic equation of the dissolution reaction is determined. It is approximated that the dissolution process is a quasi-first-order reaction, and the half-life of the first-order reaction is Formula (4)

$$t_{1/2} = ln2 / k \quad \text{.....(4)}$$

Thermodynamic calculation of the dissolution process of drugs in solvents: From thermodynamic relations(5),(6),(7), we get (8) and (9):

$$\Delta G_{\neq} = -RTlnk^{\neq} \quad \text{.....(5)}$$

$$\Delta G_{\neq}^{o} = \Delta H_{\neq}^{e} - T\Delta S_{\neq}^{o} \quad \text{.....(6)}$$

$$k = \frac{RT}{Nh}k^{\neq} \quad \text{.....(7)}$$

$$\Delta G_{\neq}^{o} = RT\ln[\frac{RT}{Nhk}] \quad \text{.....(8)}$$

$$k = \frac{RT}{Nh}e^{-\Delta G_{\neq}^{\theta}/RT} = \frac{RT}{Nh}e^{(T\Delta S_{\neq}^{\theta} - \Delta H_{\neq}^{\theta})/RT} = \frac{RT}{Nh}e^{\Delta S_{\neq}^{\theta}/R}e^{-\Delta H_{\neq}^{\theta}/RT} \quad \text{.....(9)}$$

Finishing (9) The formula is:

$$ln\frac{k}{T} = (\frac{\Delta S_{\neq}^{\theta}}{R} + ln\frac{k_B}{h}) - \frac{\Delta H_{\neq}^{\theta}}{RT} \quad \text{.....(10)}$$

$$ln\frac{kh}{k_B T} = \frac{\Delta_{sol}S_m}{R} - \frac{\Delta_{sol}H_m}{RT} \quad \text{.....(11)}$$

The correlation data is substituted into the above formula to obtain $\Delta_{sol}S_m$, and then the kinetic formula a under isothermal conditions is used to obtain $\Delta_{sol}G_m$.

Calculation of partial molar enthalpy and dilution enthalpy: Based on the ΔsolHm of the different concentrations of the drug solution obtained in 3.2.2, plotting b to $\Delta_{sol}H_m$ to obtain the equation (12) of the following form:

$$\Delta_{diss}H_m = A + Bb + Cb^{1/2} \quad \text{.....(12)}$$

The corresponding concentrations were substituted for the formulas $\Delta_{diss}H_m$(b = b) and $\Delta_{diss}H_m^{\theta}$ (b = 0), and then $\Delta_{sol}H_m$(app) was calculated by formula (13).

$$\Delta_{diss}H_m(app) = \Delta_{diss}H_m(b=b) - \Delta_{diss}H_m^{\theta}(b=0) \quad \text{.....(13)}$$

Then, based on the equations (12)and (13), the dilution enthalpy (15) is calculated by formula (14):

$$\Delta_{diss} H_m\ (partial) = b(\frac{\partial \Delta_{diss} H_m\ )}{\partial b} - \Delta_{diss} H_m\ (app).....(14)$$

$$\Delta_{dil} H_{1,2} = \sum_{2}^{1} A_i [(b_2^{1/2})^i - (b_1^{1/2})^i].....(15)$$

Conclusion

Microcalorimetry was used to study the dissolution systems of paclitaxel, genistein, matrine, Sophora alkaloids, genistein, resveratrum, cytidine, cytarabine and cyclophosphamide. The half-lives of the drugs obtained by thermodynamic and kinetic analysis were in agreement with those obtained by traditional methods. It is important to use the obtained ΔsolSm to guide pharmaceutical enterprises to select the appropriate solvent, so as to maximize the drug shelf life and pharmacodynamics.

Microcalorimetry aims at the problems existing in the application of drugs, and the thermographic curves of drug dissolution in solvents are obtained by using calorimetric techniques with simple operation and high measurement accuracy. Considering the characteristics of multi-component and multi-factor in the dissolution system and the effects of interaction among components, the effect of the interaction between the points is to minimize these interactions with low concentrations, aimed to simplifying complex problems and scientificizing empirical problems.

The innovations of this method are mainly embodied in the following two points: (1) idea innovation: microcalorimeter simulates different dissolution systems to study the determination of heat of dissolution and calculation of thermodynamic and kinetic parameters, thus realizing the breakthrough of research concept; and (2) application innovation: applying the theoretical results of chemical research to the study of half-life and stability of drugs, the method is simple, the precision is high and easy to realize. It is believed that this method has a profound theoretical basis and advanced experimental means to rely on, and its application and development prospects are objective.

References

1. Peng L, Yi L, Zhixiong X, Anxin H, Ping S, et al. Microcalorimetric studies of the action of Er^{3+} on Halobacterium halobium R_1 growth. *Biol Trace Elem Res*. 2005; 104: 275-284.
2. Li ZX, Zhao WW, Pu XH. Study on the oscillation dissolved behavior of oxysophocarpine in water. *Thermochimica Acta*. 2012; 537: 76-79.
3. Moosavi-Movahedi AA, Golchin AR, Nazari K, et al. Microcalorimetry. energetics and binding studies of DNA-dimethyltin dichloride complexes. *Thermochimica Acta*. 2004; 414: 233-241.
4. Liang XUE, Feng-Qi ZHAO, Xiao-Ling XING, et al. Dissolution properties of 1,3,3-trinitroazetidine in ethyl acetate and N,N-Dimethylformamide. *Acta Phy-Chim Sin*. 2009; 25: 2413-2416.
5. Li ZX, Zhao WW, Pu XH. Thermodynamic Properties of Matrine in Ethanol. *International Journal of Thermophysics*. 2011; 32: 1202-1209.
6. Li ZX, Zhao WW, Pu XH. Thermodynamic properties of resveratrol in dimethyl sulfoxide. *Journal of Thermal Analysis and Calorimetry.* 2012; 110: 1249-1252.
7. WU Dan, Zhou-xiang JIN, Xiao-wu XU, et al. Effects of resveratrol on platelet function in rats with severe acute pancreatitis. *Journal of Hepatopancreatobiliary Surgery*. 2011; 23: 26-28.
8. Yao J, Liu Y, Tuo Y, et al. Studies on the growth metabolism of bacillus thuringiensis and its vegetative insecticidal protein engineered strains by microcalorimetry. *Applied Biochemistry and Microbiology*. 2006; 42: 274-277.
9. Li ZX, Pu XH, Zhao WW. Dissolution properties of oxymatrine in citric acid solution. *Journal of Thermal Analysis and Calorimetry*. 2011; 104: 1191-1194.
10. Sun X, Xu X, Liu M, et al. Enthalpic Interactions of anti-tumor drug matrine in aqueous sodium chlorice solutions. *Journal of Thermal Analysis and Calorimetry*. 2010; 100: 1073-1077.

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