2. The change and comparison of peripheral blood concentration of Sorafenib between group A and group C. The results show that there are statistical differences in drug release between the two groups. As shown in Table 2, compared with group A, the drug rise rate of group C (Solafenib lipiodol group) is significantly faster than that of the first two groups, and it is rapidly reduced. There are significant differences in Cmax (0.3 ± 0.06) and AUC (Area Under Curve, 1.82 ± 0.367 μg/mL min) between group A and group C (1.24 ± 0.109) and AUC (2.97 ± 0.267μg/mL min) (P = 0.002 < 0.05). In group C, the drug concentration cannot be measured until the 4th day, indicating the instability and uncontrollability of the release of Sorafenib with lipiodol as carrier.

**Table 2 plasma concentration of Sorafenib in group A and C after administration (μ g / ml, X ± s)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | **10min** | **30min** | **1h** | **4h** | **16h** | **1day** | **2days** | **4days** | **7days** | **10days** | **14days** |
|  **A****C** | **0.13±0.027****0.37±0.011** | **0.13±0.021****0.6±0.022** | **0.3±0.055****1.24±0.109** | **0.24±0.01****0.9±0.025** | **0.17±0.033****0.77±0.037** | **0.14±0.020****0.47±0.021** | **0.13±0.010****0.11±0.005** | **0.13±0.019****0** | **0.12±0.007****0** | **0.10±0.00****0** | **0****0** |



Group A: Curve of changes of peripheral blood drugs in different carriers with Sorafenib

Drug concentration Drug concentration (μg/ ml)

3. The change and comparison of the drug concentration of Sorafenib in group A and group C. The results show that the drug concentration in the tissues of group C is very low and cannot be measured at three days after the operation, while the drug concentration in group A is significantly increased, and the Sorafenib concentration in the tissues of group A can still be measured at one week after the operation, showing that DC-bead has better controllability in the release of Sorafenib as a carrier.

**Table 3 Plasma concentration of Sorafenib in liver tissue after administration in group A and C (μ g / ml, X ± s)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Group** | **3days** | **1week** | **2weeks** |
| **A****C** | **4.047±0.03****0.12±0.06** | **1.320±0.006****0** | **0.455±0.016****0** |

**Discussion**

1. Feasibility and mechanism of DC-bead carrying solafenib

The controllable and sustainably releasing drugs with local high concentration can not only act on the target site, but also avoid other non-target sites from being affected and reduce the occurrence of side effects of systemic medication, being one of the directions in the field of medical development. For instance, in the peripheral vascular interventional therapy, the technique of continuous drug infusion through indwelling catheter is often used to treat thrombotic diseases, continuous vasopressin infusion to treat bleeding cases, continuous infusion of chemotherapy drugs to treat malignant tumors, etc. The drug coated stent frequently used in cardiovascular interventional therapy constantly can release drugs through the drugs inside the stent (e.g. paclitaxel, rapamycin)[5] and along with the constant degradation of drug carrier multimers and play the pharmacological role. The anti-tumor drugs with biocompatible and biodegradable polymer materials as carriers can selectively release drugs in the focus, which can greatly improve the bioavailability of drugs and effectively reduce the toxic and side effects and dosage of drugs. With the development of modern technology, new technical means have been provided for the preparation of different carriers that meet the clinical requirements, and more carried DC-bead have been developed, such as gelatin beads, absorbable polymer beads, nano carried DC-bead, sodium alginate beads, polyvinyl alcohol acrylic beads that can carry Pingyangmycin [6-9].

 DC-bead is a hydrogel particle prepared by Biocompatibles, which is biocompatible, hydrophilic, non-absorbable and capable of carrying adriamycin. It is a new drug eluted embolization bead prepared by modern biological technology. It can simultaneously embolate tumor vessels and continuously release chemotherapeutic drugs to kill tumor cells [1 - 4].

Drug carrying mechanism of DC-bead: DC-bead is formed by suspension polymerization of acrylic polyvinyl alcohol macromonomer and sulfonate monomer. The formation of covalent bonds transforms the dispersed droplets into insoluble particles. The polymerization starts at the surface of the droplet and forms free radicals. The monomer polymerizes from the outside to the inside, and then forms the cross-linking area on the particle surface. The ion exchange mechanism corresponding to sulfonic acid group is consistent with the charge of particles and drugs. The particles consist of sulfonated hydrogels, which are negatively charged. The carrying mechanism of DC-bead is that the amine matrix of drug (doxorubicin) in the form of hydrochloride is protonated, the whole is positively charged, and the electrostatic interaction between different charges.

According to the principle of ion exchange, foreign scholars have found that in addition to adriamycin, DC-bead can also be carried with other substances with positive charge such as mitoxantrone, irinotecan, topotecan [10-15]. All of the above drugs can achieve the goal of local high concentration and sustained release through in vitro and in vivo ion exchange mechanism, and have achieved good results in experimental and clinical application. Due to the differences of molecular structure and molecular weight, the maximum drug carrying quantity of the above substances is also different, among which adriamycin has the largest drug carrying capacity.

At present, there is no research and report on whether DC-bead can carry Solafenib at home and abroad. By studying the molecular structure of Sorafenib, we found that Sorafenib has the structural basis of exchange with DC-bead. The molecular structure of Sorafenib contains basic sorafenib and acid benzenesulfonic acid. In the solution state, both of them can form salts, i.e. sorafenib with positive charge (NH +) and benzenesulfonic acid (SO3 -) in a dynamic equilibrium state. In this state, benzenesulfonic acid (SO3 -) can exchange with DC-bead (SO3 -) to form ion exchange, and then make the sorafenib with positive charge (NH) + and negative DC-bead(SO3 -) to form salts, and make DC-bead carry Sorafenib successfully. Our in vitro and in vivo experiments further confirm this hypothesis. In vitro experiment, it is confirmed that DC-bead can adsorb Solafenib, while in vivo animal experiment, it is confirmed that Solafenib is controllable and slowly-releasable in the release of Solafenib, which is different from the simple adsorption and release of general substances. Therefore, we believe that the ion exchange mechanism may be the main role of DC-bead carrying Solafeni mechanism.

The solubility of drugs is the premise of ion exchange. Sorafenib is a non-water-soluble substance, which is in suspension state in the water for injection, so it is unable to exchange ions with DC-bead. According to the characteristics of its own substances, we found that Sorafenib can be dissolved in methanol and 75% ethanol. The former has higher solubility, but methanol is toxic to human body. Therefore, 75% ethanol with relatively lower solubility is selected to dissolve Sorafenib, so as to prepare conditions for ion exchange.

2. Characteristics and advantages of carrying Sorafenib with DC-bead as carrier

Kalayci et al. [15-16] found that there is no statistical difference between Cmax and AUC of chemotherapy drug carried with lipiodol and systemic chemotherapy, so the effect of traditional interventional therapy is limited by systemic toxicity of chemotherapy drug. The sponge embolization combined on the basis of lipiodol chemotherapeutic emulsion embolization can slow down the blood flow speed, but because many chemotherapeutic drugs are soluble in water, a large number of chemotherapeutic drugs have been rapidly released through the blood during the injection of sponge, and we also confirmed the deficiency of lipiodol as the carrier in the experiment. However, we found that the Cmax of sustained-release Sorafenib with lipiodol as the carrier is smaller than that of lipiodol carried chemotherapy drugs reported in literature, and the release time is hours after carrying, rather than minutes or tens of minutes. Our analysis may be related to the physical properties of Sorafenib. Sorafenib is insoluble in both water and lipiodol. Within 20 minutes after mixing, they can still form emulsion with certain stability, and can form stratification with water. With the passage of time and the impact of arterial blood flow, the clearance of lipiodol and the role of lipid soluble substances in the blood increase rapidly.

The release of Sorafenib with DC-bead as the carrier has more obvious advantages. By analyzing the metabolism trend of peripheral blood and histological drugs in group A (DC-bead, 500-700um-sorafenib group), group B (DC-bead, 300-500um, - sorafenib group), and group D (lipiodol sorafenib group), we found that the Cmax and AUC in group A/B are significantly lower than those in group D, with significant statistical difference. The research of histological concentration further found that the Sorafenib concentration in group A/B could still be measured 3 weeks after the intervention, while the Sorafenib concentration in group D could hardly be measured in the tissues from 1 week after the intervention. The results show that the carrier of Sorafenib with DC-bead has better controllability and slow release. DC-bead is capable of carrying and controllable release of Sorafenib. This feature has important clinical significance [17-25]: (1) With DC-bead as the carrier, the release of targeted drugs has the ability to continuously release Sorafenib in local high concentration and slowly, and continuously act on tumor cells and tumor blood vessels. Finally, it can inhibit tumor cells and tumor angiogenesis. (2) When Sorafenib is released by DC-bead as the carrier, combined with traditional TACE treatment, the target is more clear and the effect is stronger in inhibiting tumor blood vessels and tumor growth. Clinical researches have confirmed that TACE combined with molecular targeted drugs (e.g. ENDU) can significantly inhibit tumor growth, improve tumor inactivation level, and prolong the generation time of patients. However, compared with other targeted drugs, Sorafenib has more advantages: (1) it is a multi-target molecular targeted drug, which can inhibit tumor growth and angiogenesis. (2) it has a good synergistic antitumor effect with TACE common chemotherapy drugs (e.g. epirubicin, gemcitabine, cisplatin). (3) compared with oral Sorafenib, the advantage of local medication is more obvious. Clinical research found that TACE combined with sorafenib can control tumor progression and prolong the survival time of patients. However, the high cost of long-term oral medication, the low bioavailability of drugs, the large side effects, and the low objective effective rate have brought serious physiological and psychological burden to patients, making only a few patients can afford it. Local continuous drug use not only has a sustainable effect on the target, but also can improve the drug concentration and enhance the anti-tumor effect within a certain range without causing major side effects. In addition, local medication is expected to greatly reduce the clinical cost of systemic medication. Finally, because of the small toxicity of local drugs, it is possible to improve the efficacy of multiple interventional therapy.

However, the release of Sorafenib from different sizes of DC-bead is different, and is affected by the concentration of Sorafenib ethanol solution. We found that the amount, release rate and duration of Sorafenib carried by beads with small particles are shorter than those with large particles, while Cmax is higher than those with large particles. This phenomenon is not only related to the lower dosage of Sorafenib, but also related to the larger surface area, more negative charges and strong adsorption capacity of the beads. It is suggested that different doses of Sorafenib shall be selected for different sizes of DC-bead beads, and the effect of drug concentration in ethanol solution on drug carrying shall be considered. In addition, different drug carrying methods also have an impact on the drug's look-around performance. The research shows that compared with the traditional iodized oil drug, the new drug carried particles have longer sustained-release time in peripheral blood and tissue, and have better sustained-release performance.

3. Deficiencies of the research

There are certain deficiencies in this research: 1. In this research, ethanol is used as the solvent to dissolve Solafenib, and the maximum drug carrying quantity is only 82.5 mg, while the solvent used is 40ml, which is not conducive to full contact with the drug carrying. To increase the dissolution of Solafenib in ethanol is one of the directions of future research. 2. This research is based on the normal liver tissue instead of blood rich liver tumor model, so how to inhibit the liver tumor still needs to be further researched. We will improve the detection of VEGF, MVD and image in the tumor model of tumor bearing rabbits in the next step, so as to further evaluate the effect of DC-bead drug Sorafenib on malignant tumors (e.g. VX2 tumors).

**Conclusion**

The new Sorafenibcarried DC-bead is feasible in preparation technology, exact in the sustained-release effect, and superior to the carrying effect of lipiodol.

The safety and effectiveness need further research.

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