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Hydrodynamically-driven drug release during interstitial flow through hollow fibers implanted near lymphatics

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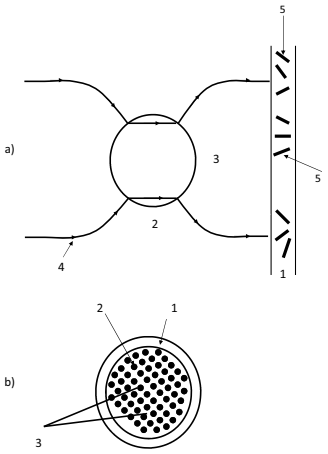
HIGHLIGHTS

- Invention of hydrodynamically-driven drug release (HDR).
- Advantage of hollow fiber with high hydrodynamic permeability of wall (HFHP).
- Hydrodynamics of HFHP, implanted near lymphatics.
- Unique strong release rate and simultaneously unique long release time for fabric of HFHP.
- Estimate for tiny contribution of diffusion release to predominating HDR.

GRAPHICAL ABSTRACT



a) Drug strip caused by hydrodynamically-driven drug release which encounters a small portion of disk-like lymphatic bed (LB). 1) Disk-like LB, 2) High hollow fiber with high permeability (HFHP), 3) Drug convective strip, 4)Streaming lines; b)1)membrane of hollow fiber, 2) drug powder, 3) lumen.

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ABSTRACT

Current drug delivery devices (DDD) are mainly based on the use of diffusion as the main transport process. Diffusion-driven processes can only achieve low release rate because diffusion is a slow process. This represents a serious obstacle in the realization of recent successes in the suppression of lymphatic metastasis and in the prevention of limb and organ transplant rejection. Surprisingly, it was overlooked that there is a more favorable drug release mode which can be achieved when a special DDD is implanted near lymphatics. This opportunity can be realized when the interstitial fluid flow penetrates a drug delivery device of proper design and allows such fluid to flow out of it. This design is based on hollow fibers loaded with drug and whose hydrodynamic permeability is much higher than that of the surrounding tissue. The latter is referred to as hollow fiber of high hydrodynamic permeability (HFHP). The interstitial flow easily penetrates the hollow fiber membrane as well as its lumen with a higher velocity than that in the adjacent tissue. The interstitial liquid stream entering the lumen becomes almost saturated with drug as it flows out of the HFHP. This is due to the drug powder dissolution in the lumens of HFHP which forms a strip of drug solution that crosses the interstitium and finally enters the lymphatics. This

Abbreviations: DDD, drug delivery device; DDR, diffusion-driven drug release; HDR, hydrodynamically-driven drug release; HFHP, hollow fiber of high hydrodynamic permeability; MIC, minimum inhibition concentration; MW, molecular weight; LB, lymphatic bed; LN, lymph node; ILC, initial lymph capillary; Pe, peclet number.

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hydrodynamically-driven release (HDR) may exceed the concomitant diffusion-driven release (DDR) by one or even two orders of magnitude. The hydrodynamics of the two-compartment media is sufficient for developing the HDR theory which is detailed in this paper. Convective diffusion theory for two compartments (membrane of hollow fiber and adjacent tissue) is required for exact quantification when a small contribution of DDR to predominating HDR is present. Hence, modeling is important for HDR which would lead to establishing a new branch in physico-chemical hydrodynamics. The release rate achieved with the use of HFHP increases proportional to the number of hollow fibers in the fabric employed in drug delivery. Based on this contribution, it is now possible to simultaneously provide high release rates and long release durations, thus overcoming a fundamental limitation in drug delivery. Perhaps this breakthrough in long-term drug delivery has potential applications in targeting lymphatics and in treating cancer and cancer metastasis without causing the serious side effects of systemic drugs.

1. Introduction

Drug release kinetics and related pharmaceutical drug delivery applications [1,2] are largely based on the principles of surface and colloid science, in particular, colloidal transport in porous adsorbing media, diffusion processes, lipophilic/hydrophilic balance and membrane wetting. The broad application of colloid and interface science has been successfully employed to describe lymphatic targeting with drugs [3,4]. The above principles have been further used to control the delivery of immunosuppressive drugs to prevent limb and organ transplant rejection, and to treat cancer or prevent cancer metastasis. There is evidence in the literature that when tacrolimus (FK-509) is injected subcutaneously in the form of a hydrogel, it could suppress limb rejection in rats for more than 100 days [3,4].

Clinical experience has demonstrated that long-term drug delivery by means of daily injection is not convenient for patients. A cardinally new development to achieve long-term drug delivery without daily injection can be based on the implantation of a drug delivery device (DDD) near the initial lymphatics, mainly near the ensembles of initial lymph capillaries (ILCs). This new device could provide a permanent drug stream along the initial lymphatics to lymph nodes (LNs) which are located downstream of the interstitial fluid flow. Since LNs are the main site where leukocytes/lymphocytes reside and where circulating/released cancer cells are transported, their targeting with drug will suppress the local immune system, kill cancer cells or provide other forms of therapy.

A similar strategy in drug delivery may be suitable to suppress cancer metastasis when the tumor is close to and draining into local lymphatics. Currently, there is central recognition that lymphatic targeting with immunosuppressant and cytotoxic drugs can be used to prevent or decrease cancer metastasis [5]. In this particular application, similar to tacrolimus (KF-509) [3,4], long-term drug release can be employed to suppress tumors. To achieve this goal, simultaneously a high-release rate is required to provide drug concentration within LNs (C_{ln}) above the minimum inhibitory concentration (MIC) of the drug. MIC is the minimal drug concentration needed to achieve effective therapy. Simultaneously providing high release rates, dictated by the MIC value of the drug, and a long release duration will be possible if a rather large amount of drug is stored in a DDD in the form of solid particles or powder. This DDD may be a hollow fiber with a porous wall having a sufficiently large pore radius and where a large amount of drug can be stored in the lumen of the fiber to provide for long-term release. In this DDD, the wall of the hollow fiber functions as a membrane to transport the drug loaded in the fiber lumen to the surrounding tissue.

If pore wetting of the hollow fiber wall membrane of the DDD is provided, significant flow of interstitial fluid flow in the pores takes place. This process leads to the filling of fiber lumen with interstitial liquid and to the gradual dissolution of the drug. After a short relaxation time, the onset of steady drug diffusion from the fiber lumen through the membrane (fiber wall) into adjacent tissue occurs.

This mechanism corresponds to the accepted understanding of drug release when the walls of the device are porous. We will define this mechanism as diffusion-driven drug release (DDR). There is a serious constraint in this mechanism caused by the low diffusivity of drug molecules in adjacent tissue D_{ti}. D_{ti} is only 6.10^{-8} cm^2/s, as for example in the Tenofovir (HIV drug) case [6].

The drug delivery from the DDD to the lymphatics is a two-stage process: (i) short-range transport from DDD to adjacent tissue (drug release), and (ii) further long-range transport along the tissue to the lymphatics. Although the characteristic distance for the second stage of transport may be orders of magnitude larger than the first, its duration may be orders of magnitude shorter. This occurs because there is interstitial fluid flow to the lymphatics and this involves the released drug during this movement (convective transport).

In spite of the very low velocity of interstitial flow [7], about 1 μm/s, the second stage of transport takes less than 20 min (time required to cover a distance of about 1 mm between the hollow fiber of the DDD and the lymphatics at a velocity of 1 μm/s).

According to this much faster transport mechanism, the convection affects drug diffusion transport from the hollow fiber into the interstitial flow. At a much smaller distance than fiber radius R_f, diffusion predominates in the thin diffusion layer δ. At a distance larger than δ, convective flow predominates. Nevertheless, we accounted for diffusion enhancement due to convection in this work and found that the diffusion-controlled drug release rate is too slow to provide drug concentration in the lymph node (C_{ln}) higher than MIC. Hence, the inevitable weakness of the diffusion-controlled drug release mechanism represents a serious constraint for lymphatic targeting by means of a DDD implanted near the lymphatics.

Fortunately, DDD in the form of hollow fibers with a porous wall offers an opportunity to realize a cardinally different and surprisingly stronger mechanism for drug release. As there is no relevant information available in the literature, we call this new and promising mechanism of drug release “hydrodynamically-driven drug release (HDR)”.

Two conditions are needed to realize the HDR mode. The first condition for the onset of HDR is the placement of the DDD near initial lymphatics in order to provide a stable and a not weak interstitial flow in the fiber vicinity. The second condition for the onset of HDR relates to the property of the hollow fiber membrane, namely: its pore diameter and porosity need to be sufficiently large to provide hydraulic permeability of the membrane (and fiber) much higher than that of the tissue. Correspondingly, this kind of hollow fiber may be called hollow fiber of high permeability (HFHP). Although increasing the pore size leads to an increase in drug

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