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Original Research Article

Polymeric drug carriers—Control of the daily dose and therapy duration

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ABSTRACT

This study evaluates the mass release of cyanocobalamin with various drug carriers. Monolithic structures with a liquid core covering a thick (>150 μm) porous, polymer membrane are recommended. Membrane pore size should ensure easy diffusion of the drug molecules. The selection of the carrier's parameters to fit a required daily dose and therapy duration must consider the following criteria: 1′ the determination of its size (geometric surface); 2′ the number of carriers, if more than one is necessary; 3′ the thickness of membrane covering the carrier; and 4′ the mass of the loading drug.

An algorithm to select these conjugated parameters to achieve the therapeutic threshold and duration of the drug effect was expanded upon.

A system to constantly deliver drugs over days/weeks/months can be maintained if the loaded mass of the drug significantly exceeds its solubility in the carrier's core.

1. Introduction

Reservoir delivery devices are an effective method for releasing a drug in a specific location at a specific rate. They have an inert membrane enclosing the solution with an active agent, which diffuses through the membrane at a finite, controllable rate. The main aim of this type of system is to facilitate the dosage and the duration of the drug effect, minimize harm to the patient and improve human health as they allow for the reduction of the dosage frequency [1]. Particularly, this type of treatment is of interest for highly toxic drugs and could be applied post-operatively in tumor resection sites and in external and internal inflammatory processes [2,3]. For reservoir delivery devices, biocompatibility and biodegradability (after a completely loaded drug release) are the fundamental requirements. Covering carrier with a non-immunogenic polymeric membrane protects against an inflammatory response [4]. Determining parameters for drug release rates is very important in the design of drug delivery system, specifically area and volume. The volume of a carrier determines the loaded mass of drug.

Unfortunately, the delivery rate of drugs decreases over time. At the beginning of therapy, the dose may be calculated to obtain a therapeutic effect. Often it is released in significant excess [5]. With a decrease of the concentration inside the carrier, the released mass stream also decreases. After a certain period of time, the daily dose does not reach the therapeutic value– Fig. 1. This moment is a clear indication of the end of the therapy. Additionally, the therapeutic threshold

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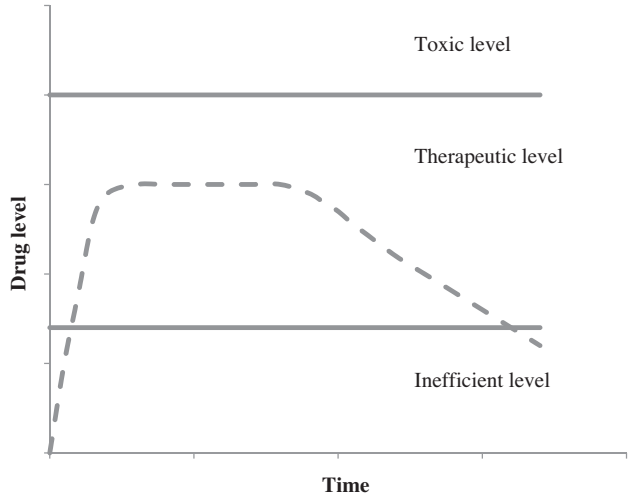

Fig. 1 – Schematic showing changes in time of the drug concentration on the outside of drug device.

and the toxic threshold of the drug must be known. Their detection is much more difficult than in classically (intravenously, orally) administered drugs.

Targeted drug delivery systems can be divided according to several criteria:

1. The geometry: planer (a thin film of polymer material), cylindrical and spherical;
2. The internal structure of a carrier: core-shelled structure, where a drug and a layer of material (typically a polymer) are physically separated; matrix system, also known as a monolithic system, where both a drug and release-controlling material (polymer or a lipid layer) comprise a homologous reservoir system;
3. The amount of drug in a carrier: drug concentration is above ($C_0 > C^*$) or below ($C_0 < C^*$) the substance solubility (C^*);
4. Release strategy: diffusion-controlled, solubility-controlled, osmotically-controlled, carrier biodegradation-controlled or carrier eruption-controlled, programmed systems (pulsed, feedback), and stimulus-sensitive (temperature, pH).

2. Materials and methods

The equipment used in the study complies with the requirements governing the access to pharmaceuticals in vivo conditions, as defined in the Pharmacopeia [5].

Drug release tests were conducted in an acceptor liquid – 0.1 M solution of phosphate buffered saline (PBS) at pH 7.4 and 37 °C, conditions similar to those in the human body. The drug employed was cyanocobalamin. The concentration of cyanocobalamin was measured by high-performance liquid chromatography (HPLC) on WatersTM LC Module I plus C18 Waters column, using a method developed by Heudi et al. [6].

Microcapsules were formed by cross-linking a sodium alginate liquid solution with Ca^{2+} ions [7]. The following process conditions of cross-linking were established: 1.5% (w/v) sodium alginate and 2% (w/v) concentration of calcium ions in the cross-linking bath for 2 h. After cross-linking, the capsules were washed twice with distilled water, dried from outside and transferred to the acceptor liquid (100 mL) shaking in an incubator (IKA KS 4000). There were 50 capsules with a diameter of $d = 3.2$ mm and a total mass transfer area of 16.08 cm^2.

Asymmetric cellulose acetate membranes (wall thickness of 30 μm, inner tube diameter of 10 mm) produced by Spectra/Por® Biotech and supplied by Sigma–Aldrich were used in the investigations. Due to the size of the cyanocobalamin molecules (1355 Da), membranes with 0.5–1 kDa and 8–10 kDa cut-offs were selected to determine the effect of pore size on mass flux. The core of the membrane was filled with an aqueous solution or liquid sol with sodium alginate (1.5%, w/v) containing cyanocobalamin at a given concentration. Additionally, an experiment with membranes filled with cross-linked capsules containing an encapsulated substance was carried out. The capsules were very tightly packed inside a tube and the voids between them were filled with water. Water (1 mL) constituted approximately 50% of the whole volume of the lumen of the tube. In all experiments, the ratio of the whole carrier volume (1.96 mL) to the acceptor liquid (100 mL) was 1:51. The total surface area of the carrier was 7.85 cm^2 (without taking porosity into account) and the length of the membrane tube was 2.50 cm.

The rate of substance transport by diffusion through thick polymer membranes was analyzed using capillary membranes made of polyethersulfone (150 μm wall thickness, 550 μm inner diameter) or polysulfone (250 μm wall thickness, 530 μm inner diameter). Membranes, classified as nanofiltration membranes, were produced by IBIB-PAN, Warsaw, Poland. For the purpose of the tests, the membranes were in the form of capillaries through which a solution could circulate; however, using the same polymers it was possible to form capsules of any diameter with encapsulated water solution, liquid gel or cross-linked alginate containing a model substance [8]. Before starting the experiment, the membranes were hydrophilyzed for 1 h with a 60% ethanol solution. Next, they were rinsed several times with a 0.1 M solution of PBS at pH = 7.4, dried and subjected to proper testing.

Modules containing a bundle of 10 capillaries 7.1 cm long were used in the experiments. The capillaries (15.7 mL for polysulfone membranes and 16.9 mL for polyethersulfone membranes) were filled with a solution of cyanocobalamin at a given concentration. The ratio of the carrier volume to the acceptor liquid was 1:178 for polyethersulfone membranes and 1:192 for polysulfone membranes. The total geometric surface area of the capillaries was 23.0 cm^2 for polysulfone membranes and 18.9 cm^2 for polyethersulfone membranes. The acceptor liquid (0.1 M PBS at pH = 7.4) circulated on the shell side of the module at a constant flow, Re_{ext}, of 155.

A drug delivery system where the drug was dispersed in a liquid sodium alginate was tested with a carrier covered with the 8.0–10.0 kDa cellulose acetate membrane. The mass of cyanocobalamin loaded into the liquid core was 30 mg. The surface area of the carrier containing 1 mL liquid gel inside was 4.08 cm^2, while the volume of the acceptor liquid was 200 mL. The flow rate of dosing and receiving stream was 276 mL/h.