are those used for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer's disease patients and animal models for Parkinson's disease, as described by Harbaugh, *J. Neural Transm. Suppl.* 24:271, 1987; and DeYebenes *et. al*., *Mov. Disord*. 2:143, 1987.

[0005] The limitation to these systems is that they allow only bolus administration of therapeutic agents and this bolus injection approach may be less than ideal. For example, the Ommaya reservoir includes an injectable reservoir and catheter that accesses the ventricles of the brain. It has been used to sample CSF and administer therapeutic agents directly into the ventricle. With a bolus injection of a therapeutic agent, the concentration of the agent in the patient's ventricle may peak greater than the required therapeutic dose and decrease to below the therapeutic dose before the next administration.

SUMMARY OF INVENTION

[0005A] According to an aspect of the present invention, there is provided a device for delivery of a drug into cerebrospinal fluid of a brain, the device comprising:

a hollow container having a reservoir volume and an outlet, the container comprising an upper surface and a lower surface;

a porous structure comprising a sintered rigid material that passively regulates diffusion of a drug from the container at a controlled release rate; and

a catheter coupled to a lower end of the container, the catheter having a lumen, a proximal end region, and a distal end region, the lumen configured to communicate with the reservoir volume of the container through the porous structure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] These and other aspects will now be described in detail with reference to the following drawings. Generally speaking the figures are not to scale in absolute terms or comparatively but are intended to be illustrative. Also, relative placement of features and elements may be modified for the purpose of illustrative clarity.

[0007] FIG. 1A is a cross-sectional exploded view of an implementation of a drug delivery device;

[0008] FIG. 1B shows the drug delivery device of FIG. 1A implanted within the brain;

[0009] FIG. 1C shows the drug delivery device of FIG. 1A implanted within the brain and the reservoir positioned between the skin and skull;

[0010] FIG. 1D is a detailed view of the barbed connector of the device of FIG. 1A;

[0011] FIG. 2 shows an interrelated implementation of the drug delivery device of FIG. 1A having a smaller reservoir volume;

[0012] FIG. 3 shows high molecular weight monoclonal antibody (mAb) released (%) over time using the device having a reservoir volume of 4.5 mL with no release control element (RCE) or with a high porosity RCE;

[0013] FIG. 4 shows mAb released (%) over time using the device having a reservoir

CLAIMS

WHAT IS CLAIMED IS:

1. A device for delivery of a drug into cerebrospinal fluid of a brain, the device comprising:

a hollow container having a reservoir volume and an outlet, the container comprising an upper surface and a lower surface;

a porous structure comprising a sintered rigid material that passively regulates diffusion of a drug from the container at a controlled release rate; and

a catheter coupled to a lower end of the container, the catheter having a lumen, a proximal end region, and a distal end region, the lumen configured to communicate with the reservoir volume of the container through the porous structure.

2. The device of claim 1, wherein the container is sized for implantation between a region of the skull and overlying skin.

3. The device of claim 2, wherein, when implanted, the lower surface of the container is positioned against the skull and the overlying skin covers the upper surface of the container.

4. The device of claim 3, wherein the lower surface of the container is flat or has a curved profile that conforms substantially to a shape of the skull at the region.

5. The device of claim 1, wherein the container is about 10 mm to about 45 mm in diameter.

6. The device of claim 1, wherein a maximum height of the container between the lower surface and the upper surface is about 3 mm to about 15 mm.

7. The device of claim 1, wherein the container is oval, elliptical or circular in perimetrical shape.

8. The device of claim 1, wherein the reservoir volume is about 0.5 mL to about 5.0 mL.

9. The device of claim 1, wherein the container comprises a lower base having the lower surface and an upper cap having the upper surface, the base and cap together defining the reservoir volume.

10. The device of claim 9, wherein at least a portion of the cap is formed of a material configured to be penetrated by a needle for injection of the drug.

11. The device of claim 9, wherein the base defines the outlet from the container.

12. The device of claim 9, wherein the base has an internal surface that includes a seat configured to seal with the porous structure.

13. The device of claim 12, further comprising a diffusion chamber located distal to the porous structure within the seat, the diffusion chamber comprising an upper region and a lower region.

14. The device of claim 13, wherein the diffusion chamber is located within a projection that projects from the lower surface of the base.

15. The device of claim 13, wherein the porous structure has an upper surface facing the reservoir volume of the container and a lower surface facing the diffusion chamber.

16. The device of claim 13, wherein the upper region of the diffusion chamber has an inner diameter that is less than an inner diameter of the container.

17. The device of claim 16, wherein an outlet channel is located below the lower region of the diffusion chamber, the outlet channel having an inner diameter that is less than an inner diameter of the lower region.

18. The device of claim 17, wherein the lower region of the diffusion chamber tapers from the inner diameter of the upper region to the inner diameter of the outlet channel.

19. The device of claim 17, wherein the outlet channel is positioned within a barbed connector of the container, the barbed connector configured to couple the catheter to the container.

20. The device of claim 19, wherein a barb of the barbed connector mitigates unintentional dislodgement between the catheter and the container.

21. The device of claim 20, wherein the barb of the barbed connector has an outer diameter that is larger than an inner diameter of the lumen of the catheter.

22. The device of claim 19, wherein the barbed connector and base are formed of a material that is more rigid than the proximal end region of the catheter.

23. The device of claim 21, wherein when the device is implanted in a patient, the barbed connector positioned within the lumen of the catheter is positioned internal to the skull and the container is positioned external to the skull.

24. The device of claim 1, wherein the catheter is straight between proximal and distal ends upon implantation so that the container is positioned above the distal end of the catheter when the distal end is positioned within a target site.

25. The device of claim 1, wherein the catheter has a length sufficient to extend to a target location in the brain.

26. The device of claim 25, wherein the length is about 3 cm to about 15 cm.

27. The device of claim 25, wherein the length of the catheter is no greater than 11 cm.

28. The device of claim 25, wherein the target location is a dural sinus or a ventricle of the brain.

29. The device of claim 25, wherein the length of the catheter is longer than a distance between the skull and the target location.

30. The device of claim 29, wherein the proximal end region of the catheter is configured to be cut to size prior to implantation of the container.

31. The device of claim 30, wherein the length of the catheter is between 30 cm and 50 cm and the distance is about 3 cm to about 15 cm.

32. The device of claim 30, wherein an outer surface of the catheter at the proximal end region comprises one or more marks indicating a length of the catheter to a distal-most end of the catheter.

33. The device of claim 1, wherein the distal end region of the catheter has at least one opening from the lumen.

34. The device of claim 33, wherein the at least one opening of the distal end region of the catheter includes a plurality of outlets positioned through a wall of the catheter.

35. The device of claim 34, wherein the plurality of outlets are about 0.02 mm to about 2 mm in diameter.

36. The device of claim 34, wherein each outlet of the plurality of outlets are spaced angularly at about 90 degrees from each other so as to occur circumferentially around the distal end region of the catheter.

37. The device of claim 34, wherein each outlet of the plurality of outlets are spaced apart by about 45, 90, 120, or 180 degrees.

38. The device of claim 1, wherein the catheter has a cross-sectional outer diameter that is no more than 5 mm.

39. The device of claim 38, wherein the cross-sectional outer diameter of the catheter is about 1/8” (3.175 mm) and an inner diameter of the catheter is about 1/16” (1.5875 mm).

40. The device of claim 1, wherein the porous structure is made of titanium or stainless steel.

41. The device of claim 1, wherein the porous structure has a porosity that is about 1% to about 70%.

42. The device of claim 1, wherein the drug is released from the container for at least 1 month up to about 36 months.

43. The device of claim 1, wherein the drug has a molecular weight of at least about 100 Daltons up to about 200,000 Daltons.

44. The device of claim 1, wherein the drug is a peptide, a protein, an antisense oligonucleotide, or antigen-binding fragment.

45. The device of claim 1, wherein the drug is useful for treating a neurodegenerative disease of the brain.

46. The device of claim 1, wherein the drug is useful for treating Alzheimer’s disease, stroke, Huntington’s disease, amyotrophic lateral sclerosis (ALS), Angelman syndrome, Parkinson’s disease, motor neuron disease, brain cancer, neuronal ceroid lipofuscinosis, tripeptidyl peptidase 1 (TPP1) deficiency, or central nervous system trauma.