POROUS CARBON PARTICLES FOR USE IN THE TREATMENT OR PREVENTION OF LIVER DISEASE

Field of the invention

The invention relates to the treatment or prevention of liver disease using porous carbon particles comprising micropores of diameter 2 nm or less and meso pores/small macropores of diameter 30 nm to 500 nm, but substantially no mesopores of diameter greater than 2 nm and less than 30nm, and substantially no large macropores of diameter greater than 500 nm. Also disclosed herein is the treatment or prevention of liver disease using porous carbon particles wherein at least 20% of the total pore volume is made up of pores having a mean diameter of from 2 to 200 nm. The invention also relates to methods for the treatment or prevention of liver disease, using such porous carbon particles.

Background to the invention

In the United States alone it is estimated that 60,000 people die each year of liver failure, whereas the donor pool remains constant at approximately 4000 with 16-18,000 on the waiting list. The odds of receiving a donor liver for subjects waiting on the list are only 1 in 8, yet there is no effective treatment or prevention available to extend the lifetime of this group of patients.

Liver failure results in multiple organ dysfunction and mortality rates are in the order of 80%. Bacterial-derived toxin and toxic metabolites such as acetaldehyde play key roles in disease pathogenesis. For example, gut-derived endotoxaemia and bacterial translocation play a central role in the pathogenesis of cirrhosis and its complications. However therapeutic options to target these factors are currently limited to long-term antibiotics with the attendant problem of infection with resistant organisms.

Orally administered adsorbent porous carbon particles have been used for centuries for the treatment or prevention of various disorders without any major side effects. Activated carbons are widely used to treat poisoning. A microporous carbon, AST-120 (available under the trade name KREMEZIN® from Kureha Corp., Japan) is used to treat patients with renal failure. However clinical trials evaluating the efficacy of AST-120 in the management of hepatic encephalopathy have proven negative.

Summary ~~of the invention~~

The ~~invention~~ present disclosure relates to the treatment or prevention of liver disease.

In a first aspect of the present disclosure, there is provided a use of porous carbon particles in the manufacture of a medicament for the treatment or prevention of liver disease wherein 20% to 90% of the total pore volume of the particles is made up of pores having a mean diameter of 2 nm or less and 75% or more of the remainder of the total pore volume is made up of pores having a mean diameter of from 30 nm to 500 nm, and the particles are formulated for oral or rectal administration.

In a second aspect of the present disclosure, there is provided a use of porous carbon particles as defined herein in the manufacture of a medicament for modulation of the gut-liver axis.

~~Accordingly t~~The present disclosure ~~invention~~ also provides porous carbon particles for use in the treatment or prevention of liver disease wherein 20% to 90% of the total pore volume is made up of pores having a mean diameter of 2 nm or less and 75% or more of the remainder of the total pore volume is made up of pores having a mean diameter of from 30 nm to 500 nm.

The present disclosure ~~invention~~ also provides a method of treating or preventing liver disease, comprising administering an effective amount of such porous carbon particles.

The present disclosure ~~invention~~ also provides use of such porous carbon particles in the manufacture of a medicament for the treatment or prevention of liver disease.

Brief description of the drawings

Figure 1: Pore distribution for phenolic resin derived carbons as measured by nitrogen adsorption and determined using BJH method for TE9 carbons unactivated to activated to 29 and 47% burn off. Activation primarily increases the pores in the micropore (<2nm diameter). The small macropores (50-500nm) are largely unaltered with no introduction of pores in the 2-50nm range (mesopores).

Figure 2: Representative pore size distribution of porous carbon particles of the invention, measured by Mercury porosimetry (A: TE7 test carbon; B: TE8 test carbon). The larger peak at above 30,000 is due to the voids between the carbon particles and not to porosity.

Figure 3: Increase in the macropore volume (50-500nm) with the increase in the pore former concentration from TE3 to TE7 for carbon activated to approximately 50% burn

off along. No significant introduction of pores in the mesopore range (2-50nm) or change in the pores in the micropore domain.

Figure 4: A Effect of degree of activation on the pore structure as determined by mercury porosimetry, evolution of pore volume on a cm3/gm basis and reduction in bulk density caused by activation; B Effect of degree of activation on pore structure as determined by mercury Porosimetry, change in the mercury pore volume in cm3/cm3 as a function of activation extent.

CLAIMS

1. Use of ~~P~~porous carbon particles in the manufacture of a medicament for ~~use in~~ the treatment or prevention of liver disease wherein 20% to 90% of the total pore volume of the particles is made up of pores having a mean diameter of 2 nm or less and 75% or more of the remainder of the total pore volume is made up of pores having a mean diameter of from 30 nm to 500 nm, and the particles are formulated for oral or rectal administration.

2. ~~Porous carbon particles for u~~Use according to claim 1 wherein 85% or more of the remainder of the total pore volume of the particles is made up of pores having a mean diameter of from 30 nm to 500 nm.

3. ~~Porous carbon particles for u~~Use according to claim 2 wherein 90% or more of the remainder of the total pore volume of the particles is made up of pores having a mean diameter of from 30 nm to 500 nm.

4. ~~Porous carbon particles for u~~Use according to any preceding claim wherein the 75% or more, 85% or more or 90% or more of the remainder of the total pore volume of the particles is made up of pores having a mean diameter of from 50 nm to 300 nm.

5. ~~Porous carbon particles for u~~Use according to any preceding claim wherein the 75% or more, 85% or more or 90% or more of the remainder of the total pore volume of the particles is made up of pores having a mean diameter of from 50 nm to 200 nm.

6. ~~Porous carbon particles for u~~Use according to any preceding claim wherein 35% to 60% of the total pore volume of the particles is made up of pores having a mean diameter of 2 nm or less.

7. ~~Porous carbon particles for u~~Use according to any preceding claim wherein 45% to 55% of the total pore volume of the particles is made up of pores having a mean diameter of 2 nm or less.

8. ~~Porous carbon particles for u~~Use according to any preceding claim wherein the total pore volume of the particles is from 0.5 to 2.5 cm^3g^{-1}.

9. ~~Porous carbon particles for u~~Use according to any preceding claim wherein the total pore volume of the particles is from 1.0 to 2.0 cm^3g^{-1}.

10. ~~Porous carbon particles for u~~Use according to any preceding claim wherein bulk density of the porous carbon particles is 0.10 gcm^{-3} to 0.30 gcm^{-3}.

11. ~~Porous carbon particles for u~~Use according to any preceding claim wherein bulk density of the porous carbon particles is 0.15 gcm^{-3} to 0.25 gcm^{-3}.

12. ~~Porous carbon particles for u~~Use according to any preceding claim wherein the specific surface area of the particles is from 700 m^2/g to 2000 m^2/g.

13. ~~Porous carbon particles for u~~Use according to any preceding claim wherein the specific surface area of the particles is from 900 m^2/g to 1400 m^2/g.

14. ~~Porous carbon particles for u~~Use according to any one of the preceding claims, wherein the particles are in the form of spherical particles.

~~15. Porous carbon particles for use according to any one of the preceding claims, wherein the particles are administered orally or rectally.~~

~~16.~~15. ~~Porous carbon particles for u~~Use according to any one of the preceding claims~~elaim 15~~, wherein the particles are formulated for administration~~ered~~ orally in free-flowing form or in tablet form.

~~17.~~16. ~~Porous carbon particles for u~~Use according to any one of the preceding claims, wherein the liver disease is selected from alcoholic liver disease (ALD), non-alcoholic liver disease, non-alcoholic steatohepatitis (NASH), cirrhosis and/or complications of cirrhosis.

~~18.~~17. ~~Porous carbon particles for u~~Use according to claim ~~17~~16, wherein the non-alcoholic liver disease is non-alcoholic fatty liver disease (NAFLD).

~~19.~~18. ~~Porous carbon particles for u~~Use according to any one of claims 1 to ~~16~~15, for use in treatment or prevention of inflammation and fibrosis in chronic liver disease, such as ALD, NAFLD or viral hepatitis.

~~20.~~19. ~~Porous carbon particles for u~~Use according to claim ~~17~~16, wherein the complication of cirrhosis is selected from portal hypertension, ascites, renal failure, hepatic encephalopathy and acute-on-chronic liver failure.

~~21. A method of treating or preventing liver disease, comprising administering an effective amount of porous carbon particles as defined in any one of claims 1 to 16.~~

~~22. Use of porous carbon particles as defined in any one of claims 1 to 16 in the manufacture of a medicament for the treatment or prevention of liver disease.~~

~~23.~~20. Use of ~~P~~porous carbon particles as defined in any one of claims 1 to ~~16~~ 15 ~~for use~~ in the manufacture of a medicament for modulation of the gut-liver axis.

~~24.~~21. ~~Porous carbon particles for u~~Use according to claim ~~23~~ 20 wherein the modulation of the gut liver axis is by modulation of gut dysbiosis or obesity, or increased gut permeability.

~~25.~~22. ~~Porous carbon particles for u~~Use according to claim ~~24~~21, for use in the treatment or prevention of a disease or condition selected from coronary artery disease, inflammatory bowel disease, irritable bowel syndrome, pouchitis, hypertension, stroke, obesity or complications of obesity.

~~26.~~23. ~~Porous carbon particles for u~~Use according to claim ~~25~~22, wherein the disease or condition is associated with gut dysbiosis and/or alterations in gut permeability.