This invention relates to a method of treating an elastomeric seal for a pressurised dispenser device that dispenses a medicament in a carrier fluid, the method including the steps of: providing said elastomeric seal; and surface modifying the elastomeric seal by fluorinating the surface of same using a plasma which is formed using at least one fluorine containing precursor, wherein the fluorination converts hydrocarbon moieties on the surface of said seal into fluorocarbon moieties.
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ELASTOMERIC SEALS

This invention relates to elastomeric seals for use in a pressurised dispenser device that dispenses a medicament in a carrier fluid, and to methods of treating elastomeric seals.

It is well known to administer medicaments to a patient by inhalation using pressurised dispenser devices which dispense the medicament in a carrier fluid, commonly as an aerosol. Such devices are often referred to as pressurised metering dose inhalers (pMDIs), and are very commonly used for treating asthma and chronic obstructive pulmonary disease (COPD).

One problem associated with dispenser devices of this kind is absorption of the active medicament on the internal surfaces of the device. This in turn can lead to a loss of potency and/or erratic dosing during the shelf-life of the device. In some instances clustering of drug particles can occur if the active medicament is present as a suspension of particles. One approach that has been adopted in order to reduce the surface absorption of the active drug is to modify the surface properties of the device, and traditionally this has been done by spray coating with a low energy polymer. It is known also from EP0642992 and EP1066073 that various interior surfaces of pMDI devices can be provided with coatings deposited by plasma polymerisation, although only a limited range of polymer coatings are described.

Pressurised dispenser devices commonly include a can body containing the medicament which is in sealed contact with a metering valve system. Various elastomeric seals are provided to seal the can body against the
metering valve system and to seal internal components of the metering valve system. To date, most attention has been paid to methods of treating the can body to prevent loss of the medicament through absorption. However, it has been found that 10% of the medicament can be lost owing to absorption onto the elastomeric seals. It has been proposed in EP1066073 to deposit certain specific polymeric coatings onto the seals as a way of reducing absorption of the medicament thereon. The present inventors have realised that this proposal in itself does not represent an optimal way of dealing with the problem of medicament absorption onto the seals. The present inventors have realised that the nature of the elastomeric seals is such that it is difficult to successfully polymerise onto the surface of the seal. Furthermore, the present inventors have realised that it can be unnecessary and even undesirable to deposit a polymer coating on the seal, since the pressures that a seal is subjected to during the sealing process can cause cracking of the polymer coating.

The present invention, in at least some of its embodiments, addresses the above-described problems, needs and desires.

According to a first aspect of the invention there is provided a method of treating an elastomeric seal for a pressurised dispenser device that dispenses a medicament in a carrier fluid, the method including the steps of:

- providing said elastomeric seal; and
- surface modifying the elastomeric seal by fluorinating the surface of same using a plasma which is formed using at least one fluorine containing precursor, wherein the fluorination converts hydrocarbon moieties on the surface of said seal into fluorocarbon moieties.
The process is correctly described as a surface modification, because the effect is one of a chemical conversion of the surface of the seal. This can be contrasted with a polymer coating process, in which an entirely new polymeric layer is deposited on top of the surface. Typically, the surface modification treatment will penetrate into the seal to some depth. The modified surface can provide a good substrate for deposition of a polymer thereon. However, another advantage associated with the present invention is that the modified surface can itself inhibit the deposition of the medicament, and thus it is possible to use the surface modified seal in a pressurised dispenser device without requiring a subsequent polymer coating step.

Preferably the plasma is formed using CF$_4$ as a fluorine containing precursor. Most preferably, CF$_4$ is the only fluorine containing precursor used to form the plasma. Still more preferably, the plasma is a pure CF$_4$ plasma.

Advantageously, the plasma produces F$^-$ ions which react with the surface of the seal to perform the surface modification.

The seal may be subjected to one or more pre-treatment steps prior to the step of surface modifying the seal.

Advantageously, the seal is subjected to heating as a pre-treatment step.

Advantageously, the seal is subjected to a plasma cleaning process as a pre-treatment step. The plasma cleaning process may use a plasma formed using oxygen, a noble gas, preferably argon, a fluorocarbon, preferably CF$_4$, or mixtures thereof. The plasma cleaning process may utilise an ozone producing plasma, which removes unreacted monomer by causing polymerisation of same.
The ozone producing plasma may also condition the surface by causing cross-linking of polymeric material at the surface.

It is possible to use both heating and a plasma cleaning process as pre-treatment steps.

In one embodiment of the invention, the surface modified seal is used in a pressurised dispenser device without further treatment (e.g., without coating same with a polymer coating).

In other embodiments, the method further includes the step of coating the fluorinated surface of the seal with a polymer coating. Advantageously, the polymer coating is preferably formed by plasma polymerisation. Preferably, the polymer coating is formed by plasma polymerisation of one or more monomers, wherein at least one monomer is selected from a per-fluorocarbon; a hydrocarbon, a silane, a silicone or a fluorosilicone. Most preferably, the polymer is polyperfluoropropylene or at least one monomer is selected from $C_nF_{2n+2}$ where $n$ is 1 to 5; a per-fluoroalkene of formula $C_mF_{2m}$ where $m$ is greater than 3; or a fluorohydrocarbon having more than two carbon atoms. At least one monomer may be selected from $CF_4$, $C_2F_6$, $C_3F_8$, $C_4F_8$, $CF_3CHFCF_3$, $CF_3CH_2F$, $C_5FioH_2$, $C_6F_{14}$, $C_8F_{18}$, $CH_4$, $C_2H_6$ and $C_2H_4$. Advantageously, the plasma polymerisation utilises at least two monomers, one of which is $CF_4$. Preferably, a $CF_4/ C_4F_8$ or $CF_4/ C_2H_4$ is plasma polymerised. The provision of a polymer coating can be advantageous when the surface of the seal is rough, with many cavities and pores. In such instances, the polymer can usefully fill these cavities and pores. As noted, the modified surface of the seal can itself inhibit deposition of the medicament, which is advantageous because it provides a second line of
defence against medicament loss on surfaces should the polymer coating fail, for example by cracking.

Advantageously, a plurality of elastomeric seals are introduced into a plasma device which causes the elastomeric seals to tumble whilst the step of surface modifying the seals using the plasma is performed.

The elastomeric seal may be formed from nitrile rubber, EPDM or other elastomer.

According to a second aspect of the invention there is provided an elastomeric seal treated by a method according to the first aspect of the invention.

According to a third aspect of the invention there is provided a surface modified elastomeric seal containing hydrocarbon moieties, in which the surface of the seal is modified so that substantially all of the hydrocarbon moieties originally present on the surface are converted into fluorocarbon moieties.

Whilst the invention has been described above, it extends to any inventive combination as set out or in the following description, drawings or claims.

Embodiments of methods and seals in accordance with the invention will now be described with reference to the accompanying drawings, in which:

Figure 1 is a cross sectional view of a pressurised dispenser device;

Figure 2 shows a first embodiment of a device for treating seals; and

Figure 3 shows a second embodiment of a device for treating seals.

Figure 1 depicts a pressurised dispenser device, shown generally at 10, which comprises a housing 12 which receives a pressurised medicament
containing arrangement 14. The housing 11 comprises an open ended cylindrical portion 12a in which the pressurised medicament containing arrangement 14 is disposed, and an open ended passage 12b which serves as a mouthpiece. The housing 12 further comprises an inner wall 12c which supports a socket 12d having a passageway 12e which receives the valve stem of the pressurised medicament container arrangement. The passageway 12e communicates with an opening 12f which in turn is in communication with the exit passage defined by open ended passage 12b. The inner wall 12c has a number of apertures 12g formed therein which permits air to flow from the upper area of the housing 12 into the open ended passage 12b.

The structure and operation of the pressurised medicament container arrangement 14 will now be described in more detail. The arrangement 14 comprises a can body 16 on which is crimped a ferrule 18. Mounted on the ferrule 18 is a metering valve system, shown generally at 20. The metering valve system 20 comprises a valve stem 22, a portion of which is disposed in a valve member 24. The valve stem 22 and valve member 24 are both located in a valve housing 26, and the valve stem 22 is axially reciprocal therein against the action of a spring 28 which biases the valve stem 22 into a closed position as shown in Figure 1.

The metering valve system 20 further comprises a metering chamber 30 which is defined by the valve member 24 and a portion of the valve stem 22 together with inner and outer seals 32,34. The inner seal 32 acts to seal the valve member 24 against the valve housing 26, and separates the metering chamber 30 from the interior 36 of the valve housing 26. The outer seal 34 acts
to seal the valve member 24 and valve housing 26 against the ferrule 18, and also seals the metering chamber 30 from the outside of the pressurised medicament container arrangement 14.

Further sealing is provided by a can body seal 42 which acts to seal the can body 16 against the ferrule 18 upon crimping of same. The valve housing 26 has a plurality of slots 38 which enable the interior 36 of the valve housing 26 to communicate with the interior 40 of the can body 16. The valve stem 22 has two channels 44,46. Each channel, 44,46 comprises a longitudinal passageway and a transverse passageway. The transverse passageway of the valve stem channel 44 is disposed so that, when the pressurised medicament container arrangement 14 is in its closed position as shown in Figure 1, the metering chamber 30 is in communication with the interior 36 of the valve housing 26 and thus is also in communication with the interior 40 of the can body 16. As explained in more detail below, the volume of the metering chamber 30 corresponds to the volume of medicament containing fluid administered in a single dose. In the closed position shown in Figure 1, the dose is wholly contained in the metering chamber 30 and cannot escape to the outside of the pressurised medicament container arrangement 14 owing to the action of the outer seal 34.

To release a dose of medicament containing fluid, the valve stem 22 is pushed against the biasing action of the spring 28 into the interior 36 of the valve housing 26 to an extent that the valve stem channel 44 no longer communicates with the metering chamber 30. The valve stem 22 is designed so that, in this dispensing position, the valve stem channel 46 of the valve stem 22
communicates with the metering chamber 30, thereby allowing the dose of medicament containing fluid in the metering chamber 30 to be dispensed through the valve stem 22. The dose then passes through the passageway 12e, opening 12f and open ended passage 12b to exit the device.

When the valve stem 22 is subsequently released the biasing action of the spring 28 causes the valve stem 22 to move back towards the position shown in Figure 1. Thus, the valve stem channel 46 assumes a position whereby the metering chamber 30 is sealed against the outside, and the valve stem channel 44 assumes a position whereby the interior 36 of the valve housing 26 is in communication with the metering chamber 30. Owing to the pressure differential between the relatively high pressure interior 40 of the can body 16 and the relatively low pressure of the metering chamber 30, the metering chamber 30 is refilled with another dose of the medicament containing fluid.

The pressurised dispenser device 10 shown in Figure 1 is one example of such a device, and many other metering arrangements are known which differ to a greater or lesser degree in their precise mode of action. The present invention does not lay claim to the mode of action of the device shown in Figure 1 or of any other pressurised dispenser device. Rather, the present invention provides seals for such devices which inhibit losses of medicaments to their internal surfaces, and associated methods of production of such seals. The device shown in Figure 1 is provided in order to assist the reader's appreciation of how the present invention might be applied. The skilled reader will appreciate that the seals of the present invention can be used in other designs of pressurised
dispenser device than the one shown in Figure 1.

Figure 2 shows a first embodiment of a device, shown generally at 70, for performing a method of the invention. The device 70 comprises a gas inlet 72 for conducting gasses into a chamber 74. The chamber 74 has located therein a rotating barrel 76 and water cooled RF electrode 78. Gases are evacuated from the chamber 74 through a vacuum port 80 using a suitable pump (not shown). The wall of the chamber 74 is earthed, and the rotating barrel 76 may be at RF, earth, or - most preferably - floating potential. The rotating barrel 76 is fabricated from a perforated sheet. The surface area of the RF electrode 78 is designed to ensure a self DC bias of between 5 and 500 volts. In the arrangement shown in Figure 2, the rotating barrel 76 causes seals disposed therein to tumble during treatment. This is a preferred arrangement, since it enables a plurality of seals to be treated at the same time whilst ensuring homogenous treatment conditions.

In use, then, a plurality of elastomeric seals are disposed in the barrel 76 of the device 10. Surface modification of the elastomeric seals is performed by subjecting the seals to a CF₄ plasma. Pure CF₄ gas is introduced into the chamber 74 through the gas inlet 72 and a plasma is struck using techniques well known in the art. Typically a 13.56 MHz RF power is applied to the RF electrode 78, although other RF frequencies might be used, and it is anticipated that frequencies within the range 4 kHz to 20 MHz might be utilised. It has been found that gas pressures in the range 5 x 10⁻² mbar to 1 x 10⁻¹ mbar give rise to particularly good results, although gas pressures in the range 5 x 10⁻² mbar to 9 x 10⁻¹ mbar can be used. Power densities between 0.1 and 1.5 watts cm⁻² of
electrode are employed. Without wishing to be limited by any particular theory, it is believed that the plasma that dissociates the CF$_4$ to form reactive F$^-$ ions which react with the surfaces of the seals to form a highly hydrophobic species. The process is not a coating process, but rather is a surface modification wherein hydrocarbon moieties on the surfaces of the seals are converted into hydrophobic fluorocarbon moieties.

It has been found that seals which have been surface modified in accordance with the invention can be highly resistant to deposition of the medicament, and thus may be used directly in a pressurised dispenser device. Alternatively, it may be appropriate to provide a discrete coating of a polymer on top of the modified surfaces of the seals. This is particularly useful when the surface of the seal is rough, for example having any cavities, since pores, cavities, and other features associated with surface roughness can be filled by a polymer coating. It is particularly preferred to deposit a polymer coating by plasma polymerisation. Plasma polymerisation of a coating can be effected by turning off the flow of CF$_4$ into the chamber whilst introducing a second, monomeric, gas to the chamber. Alternatively, it is possible to maintain a flow of CF$_4$ and to bleed a second gas into the CF$_4$ gas flow to produce a gas blend which is used to perform the plasma polymerisation. Suitable monomeric gases include C$_4$F$_8$, C$_2$H$_6$, C$_8$F$_{18}$ and CF$_3$CHFCF$_3$. These gases can also be used to form a blend with the CF$_4$ for polymerisation purposes. Similar pressures and power densities to those used during the surface modification step can be used during the polymerisation step.

It can be desirable to stabilise the surfaces of the seals using one or more
pre-treatment steps prior to the surface modification step. Such pre-treatment steps are particularly important with seals formed from nitrile materials, since the outer layer of the rubber can be semi-porous, and typically contains material such as fillers, plasticisers, and unreacted monomers. These methods can react with or absorb the medicament and/or dissociate a subsequent polymer coating. Other forms of elastomeric seals, such as those formed from EPDM, can also be usefully pre-treated prior to surface modification. The pre-treatment can comprise a heat treatment, a plasma treatment, or a combination of the two. The heat treatment drives off some of the lower molecular weight volatile contaminants and/or can promote cross-linking. A further advantage of the heating step is that the seals are relatively hot at the commencement of the surface modification step, which results in better efficiency and fluorination during the surface modification step. The heat treatment is advantageously performed at greater than 90°C, most preferably in the range 90-120°C. A subsequent plasma treatment can sputter away any residual surface contaminants and can cause cross-linking of monomers present on the surface. The plasma cleaning/cross-linking step can be performed using the apparatus which is used to perform the subsequent surface modification, and similar gas pressures and power densities may be used. The plasma pre-treatment step may be performed using an argon, oxygen, or argon/oxygen plasma. Oxygen containing plasmas have the advantage of producing ozone which enables the cross-linking of unreacted material to take place.

Figure 3 shows a second embodiment of a device, depicted generally at 90, which may be used in place of the device shown in Figure 2 to perform the
surface modification step. The device 90 comprises a gas inlet 92 leading into a chamber having an earthed wall 94. The chamber houses a rotating barrel 96 formed from a perforated sheet, and has an exhaust outlet 98. In contrast to the embodiment shown in Figure 2, the second embodiment has an RF electrode 100 formed from a perforated sheet which is concentric with and lies in between the chamber wall 94 and the rotating barrel 96. Again, the rotating barrel 96 enables a plurality of seals to be tumbled during the surface modification procedure.
1. A method of treating an elastomeric seal for a pressurised dispenser device that dispenses a medicament in a carrier fluid, the method including the steps of:

   - providing said elastomeric seal; and
   - surface modifying the elastomeric seal by fluorinating the surface of same using a plasma which is formed using at least one fluorine containing precursor, wherein the fluorination converts hydrocarbon moieties on the surface of said seal into fluorocarbon moieties.

2. A method according to claim 1 in which the plasma is formed using CF$_4$ as a fluorine containing precursor.

3. A method according to claim 2 in which CF$_4$ is the only fluorine containing precursor used to form the plasma.

4. A method according to claim 3 in which the plasma is a pure CF$_4$ plasma.

5. A method according to any previous claim in which the plasma produces F$^-$ ions which react with the surface of the seal to perform the surface modification.

6. A method according to any previous claim in which the seal is subjected to one or more pre-treatment steps prior to the step of surface modifying the seal.

7. A method according to claim 6 in which the seal is subjected to heating as a pre-treatment step.

8. A method according to claim 6 or claim 7 in which the seal is subjected to
a plasma cleaning process as a pre-treatment step.

9. A method according to claim 8 in which the plasma cleaning process uses a plasma formed using oxygen, a noble gas, preferably argon, a fluorocarbon, preferably CF₄, or mixtures thereof.

10. A method according to any previous claim further including the step of coating the fluorinated surface of the seal with a polymer coating.

11. A method according to claim 10 in which the polymer coating is formed by plasma polymerisation.

12. A method according to claim 11 in which the polymer coating is formed by plasma polymerisation of one or more monomers, wherein the polymer is polyperfluoropropylene or at least one monomer selected from CₙF₂ₙ₊₂ where n is 1 to 5; a per-fluoroalkene of formula CₘF₂ₘ where m is greater than 3; a fluorohydrocarbon having more than two carbon atoms; a hydrocarbon; a silane; or a fluorosilicone.

13. A method according to claim 12 in which at least one monomer is selected from CF₄, C₂F₆, C₃F₆, C₄F₈, CF₃CHFCF₃, CF₃CH₂F, C₅F₁₀H₂, C₆F₁₂, C₈F₁₈, CH₄, C₂H₆ and C₂H₄.

14. A method according to claim 13 in which the plasma polymerisation utilises at least two monomers, one of which is CF₄.

15. A method according to claim 14 in which a CF₄/ C₄F₈ or CF₄/ C₂H₄ blend is plasma polymerised.

16. A method according to any previous claim in which a plurality of elastomeric seals are introduced into a plasma device which causes the elastomeric seals to tumble whilst the step of surface modifying to seals using
the plasma is performed.

17. A method according to any previous claim in which the elastomeric seal is formed from nitrile rubber.

18. A method according to any one of claim 1 to 16 in which the elastomeric seal is formed from EPDM.

19. An elastomeric seal treated by a method according to any one of claims 1 to 18.

20. A surface modified elastomeric seal containing hydrocarbon moieties, in which the surface of the seal is modified so that substantially all of the hydrocarbon moieties originally present on the surface are converted into fluorocarbon moieties.
Fig. 2