Orally administrable pharmaceutical product and method of fabrication therefor

This invention relates to orally administrable pharmaceutical products and to methods of fabrication for such products. More particularly the invention relates to an orally administrable pharmaceutical product that comprises information about the product, the information being protected by a material that is resistant to the gastric environment.

Drugs are frequently taken orally by a patient, the drug being absorbed by the digestive system of the patient. Orally administered pharmaceutical products include tablets, pellets, capsules, powders, suspensions and solutions. Capsules comprise a shell that contains the drug; the size and shape of the capsule being such that the patient can swallow the capsule. Capsules can be used to deliver beneficial substances other than drugs, such as nutrients and minerals. Usually the shell comprises gelatine and is formed from two halves, the halves being bonded together. The gelatine is rapidly disfigured in the gastric tract permitting the gastric fluids to penetrate the shell and reach the drug.

Tablets and pellets comprise a sample of solid material having a shape and size that allows a patient to swallow the tablet or pellet. Prior art tablets and pellets are typically prepared by compression or moulding of the solid material; the material may comprise a beneficial substance combined with one or more of: a diluent, a coating, a colorant, and a disintegrant. Diluents are fillers used in preparing tablets or pellets of the appropriate size and consistency; disintegrants are used for the break up and separation of the tablet's or pellet's compressed ingredients.

There are several different types of tablet and pellet coating. Excipient coatings are used to make the beneficial substance, or other material from which the tablet or pellet is comprised, more palatable to the patient. For example the beneficial

substance may have an unpleasant or bitter taste which could be concealed by the coating.

There are a number of risks associated with drug administration. For example a patient may take a dosage that is in appropriate for her or his condition. A patient's condition may require the administration of a number of different pharmaceutical products at different times of the day; if the products are not clearly distinguished from each other then the patient may take the wrong product at the wrong time. Children may take a drug found in the home, mistaking it for candy or simply to emulate the patient for whom the drug has been prescribed. A patient or person associated with the patient may become depressed and deliberately take a large dose of a drug with the object of ending their life.

These risks can be reduced by appropriate packaging and labelling such as tamper-evident packaging, child-resistant safety containers, drug package inserts, and conspicuous labelling. Regulations continue to evolve so that even the drugs themselves often need individual labelling. According to FDA regulations effective from 1995 all solid dosage forms for human consumption must be imprinted with some form of product specific identification codes. Such imprints, together with the product's size shape and colour, enable the identification of a drug and its manufacturer prior to use.

Two established ways of enhancing tablet identification are: (a) polymer coating of intagliated tablet cores and (b) printing information relating to the tablet by offset or ink-jet technology. Typically orally administered drugs release their contents in the gastric tract of the patient. This means that a polymer coating will typically break up or becoming distorted in the gastric tract resulting in obliteration of information associated with the coating. Alternatively, if the information is printed onto the tablet, then the break up of the tablet in the gastric tract will also result in loss of the information.

When a patient has consumed a drug in a quantity or of a type that endangers the health of the patient, then such loss of information in the gastric environment may present a problem. It is essential that doctors treating such a patient be able to identify the drug as soon as possible so that remedial action can be taken. A rapid method of obtaining information about a pharmaceutical product would therefore be of great value in such an overdose situation.

The following prior art is of relevance to this application: WO 9909960 A, WO 9800107 A, US 5792048 A, US 5700998 A, and US 5079006 A. WO 9909960 relates to the use of sticking plaster as an information carrier. WO 9800107 relates to the use of microchips in the control of drug release. US 5792048 relates to the use of capsules that contains information relating to the identity of the person who has consumed the capsule. US 5,700,998 relates to the use of a code applied to the surface of capsules and tablets; the code is applied to ensure that the tablet or capsule is correctly administered. Finally, US 5079006 relates to the use of a magnetic material to detect whether a drug has entered the gastrointestinal environment.

It is an object of this invention to provide new pharmaceutical products that reduce the above mentioned problems. It is a further object of this invention to provide methods of fabricating such pharmaceutical products.

According to a first aspect, the invention provides an orally administrable pharmaceutical product comprising an information carrier having a form and composition such that information is recorded by the carrier; wherein the information carrier comprises a resistant material having a composition such that the resistant material is resistant to the gastric environment.

Preferably at least part of the resistant material is arranged such that, when the pharmaceutical product is located in a gastric tract, it forms a barrier that protects the recorded information from the gastric environment.

Advantageously the resistant material is shaped in such a manner that the information is recorded by the shape of the resistant material.

The information may be encoded, for example a colour code may be used in which a particular colour corresponds to a type of pharmaceutical product. Preferably the information comprises alphanumeric characters. Advantageously the orally administrable pharmaceutical product comprises at least one beneficial substance and the information relates at least partly to the or at least one of the beneficial substances, more advantageously the information comprises the identity of the or at least one of the beneficial substances. The identity of the beneficial substance may be encoded on the information carrier, for example the identity may be encoded in the form of a bar code.

The barrier may substantially surround the recorded information. Regardless of whether the resistant material surrounds the recorded information or is shaped to record the information, it forms a barrier to corrosion that tends to preserve the information.

Advantageously the information carrier comprises a semiconductor; more preferably the information carrier comprises silicon.

The information carrier may comprise a semiconductor chip or a silicon chip.

Advantageously the information is recorded by engraving the semiconductor chip to form characters on the chip. The characters may be engraved photolithographically.

By arranging the resistant material in such a way that it preserves the information in the stomach of the patient, the information remains intact. In the event that an overdose occurs, the patient's stomach may be pumped, and the contents of the stomach examined to locate the information carrier. Once located, the information present in the carrier will allow the most effective remedial action to be taken. The information, present on the carrier, may be read using a microscope.

Throughout this specification the term "patient" is to be taken to mean any animal or human to which a pharmaceutical product may be orally asdministered.

For the purposes of this specification the phrase: "resistant material that is resistant to the gastric environment" means that the resistant material is substantially uncorroded in simulated human gastric fluid when immersed for a period of less than 10 minutes. Preferably the resistant material has a composition such that it is substantially uncorroded when immersed in simulated human gastric fluid for a period of up to 1 hour. More preferably the resistant material has a composition such that it is substantially uncorroded when immersed in simulated human gastric fluid for a period of up to 10 hours.

It is advantageous to provide as much information about the composition of the pharmaceutical product as possible. If the product comprises a drug then information about the drug, the dosage of the drug, batch number, and its expiry date may be of value. It is also advantageous to provide this information in as compact a form as possible. For this reason the use of an information carrier comprising a semiconductor is advantageous since it is possible to engrave large quantities of information on small samples of semiconductor. Techniques that allow such compaction of information include electron beam lithography, laser ablation, photolithography, and other micromachining techniques. Silicon is a semiconductor that may be used to form at least part of the resistant material. Silicon has been shown to have high levels of resistance to gastric corrosion. Therefore information engraved onto silicon is resistant to gastric corrosion.

However, the information carrier need not comprise a semiconductor. The information carrier may comprise any material upon which information may be recorded, whether by printing, engraving, or by some other technique.

The largest dimension of the information carrier may be less than 10mm. Alternatively the largest dimension of the information carrier may be less than 2 mm. The dimensions of the information carrier may also be sufficiently small to have substantially no effect upon the delivery of the beneficial substance.

Advantageously the resistant material comprises a semiconductor. More advantageously the resistant material comprises silicon.

Preferably the information carrier comprises at least one micromachined component.

Advantageously the information is recorded onto the information carrier photolithographically. Preferably information is recorded onto the information carrier by electron beam lithography. The information may also be recorded onto the information carrier by laser ablation.

Advantageously the information carrier comprises a fluorescent or photoluminescent material; more advantageously the fluorescent or photoluminescent material comprises a fluorescent or photoluminescent semiconductor; yet more advantageously the semiconductor comprises porous silicon.

It is advantageous that the information carrier comprises a fluorescent or photoluminescent material because this assists location of the carrier in the contents of the gastrointestinal tract. Once the stomach of a patient has been

pumped its contents may be illuminated with light of an appropriate wavelength, causing the information carrier to fluoresce, and facilitating identification.

Preferably the orally administrable product comprises a beneficial substance.

Throughout this specification the term "beneficial substance" means a substance that has an overall beneficial effect upon the patient when administered in an appropriate dose. The term "beneficial substance" includes drugs and minerals. The term "beneficial substance" also includes substances that may be, to some extent, toxic to the patient provided the overall effect upon the patient was beneficial. For example anti-cancer drugs are often, to some degree, toxic to the patient. For the avoidance of doubt the term "beneficial substance" further includes substances that are harmful to the patient when administered at an inappropriate dose.

Advantageously the orally administrable pharmaceutical product may comprise at least one moulded plastic component.

Preferably the recorded information comprises at least one character, the or at least one of the characters having a largest dimension less than 100μm; more preferably the largest dimension is less than 50μm; yet more preferably the largest dimension is less than 20μm.

Advantageously the information carrier may comprise a beneficial substance; more advantageously the information carrier comprises a beneficial substance together with porous and/or polycrystalline silicon, the arrangement of the beneficial substance being such that corrosion of the porous and or polycrystalline silicon in the gastrointestinal tract of the patient results in release of the beneficial substance.

The arrangement of a beneficial substance and a sample of porous and/or polycrystalline silicon in this manner is disclosed in GB 9924334.7.

Preferably the pharmaceutical product is a capsule and comprises a shell, the beneficial substance being disposed within the shell. More preferably the information carrier is disposed within the capsule shell.

Advantageously the information carrier is not located at the surface of the pharmaceutical product. More preferably the information carrier does not form part of the surface of the pharmaceutical product.

The information carrier may be located in the interior of the pharmaceutical product The information carrier may be obscured by the material (not including the material that comprises the information carrier) comprising the pharmaceutical product.

According to a second aspect the invention provides a method of fabricating a pharmaceutical product comprising the step of recording information onto an information carrier; wherein the method further comprises the step of at least partly forming the information carrier from a resistant material that is resistant to the gastric environment.

Preferably the method of fabricating the pharmaceutical product further comprises the step of arranging the resistant material in such a manner that, when the information carrier is located in the gastric environment, the resistant material forms a barrier that protects the recorded information from the gastric environment.

Advantageously the recording step comprises the step of shaping at least part of the resistant material; more advantageously the step of shaping the resistant material comprises the step of engraving the resistant material.

Preferably the method of fabricating the pharmaceutical product comprises the further step of micromachining at least part of the material from which the information carrier if formed.

Advantageously the method of fabricating the pharmaceutical product comprises the step of photolithographically engraving at least part of the material from which the information carrier is formed.

Preferably method of fabricating the pharmaceutical product comprises the step of engraving, by electron beam lithography, at least part of the material from which the information carrier is formed.

Alternatively the method of fabricating the pharmaceutical product comprises the step of engraving, by laser ablation, at least part of the material from which the information carrier is formed.

Advantageously the information carrier comprises a plastic material and the step of recording information onto an information carrier comprises the step of moulding the plastic material; more advantageously the step of moulding the plastic material comprises the step of at least partly filling a semiconductor mould with the plastic material; yet more advantageously the semiconductor mould comprises silicon.

Preferably the semiconductor is micromachined to form the mould.

Advantageously the method of fabricating a pharmaceutical product further comprises the step of combining a beneficial substance with the information carrier; more advantageously the recording step is performed in such a manner that the recorded information relates at least partly to the beneficial substance.

According to a third aspect, the invention provides an information carrier comprising a bulk crystalline semiconductor region and porous semiconductor region wherein the information carrier is shaped in such a manner that information is recorded by the shape of the information carrier.

The largest dimension of the bulk crystalline region may be less than 10mm. Alternatively the largest dimension of the bulk crystalline region may be less than 2 mm.

Preferably the recorded information comprises at least one character, the or at least one of the characters having a largest dimension less than 100μm; more preferably the largest dimension is less than 50μm; yet more preferably the largest dimension is less than 20μm.

The bulk and porous semiconductor regions may comprise different semiconductors; more preferably both the bulk and porous regions comprise silicon.

The bulk semiconductor region may be shaped in such a manner that the information is recorded by the bulk region. Alternatively the porous region may be shaped in such a manner that the information is recorded by the porous region.

According to a fourth aspect the invention provides a product comprising an information carrier, the information carrier comprising a bulk crystalline semiconductor region and a porous semiconductor region; wherein the information carrier is shaped in such a manner that information is recorded by the shape of the information carrier.

The product may be a pharmaceutical product or it may be some other product. The information carrier may be used as a covert marker to identify the product. For example the information carrier may be used to identify the product as originating from a particular manufacturer.

According to a fifth aspect the invention provides a method of fabricating an information carrier comprising a bulk semiconductor region and a porous semiconductor region, the method comprising the steps of micromachining the bulk

semiconductor and/or the porous semiconductor in such a manner that information is recorded by the micromachined bulk and/or porous semiconductor.

Preferably the method of fabricating the information carrier further comprises the step of taking a sample bulk silicon and anodising it to form porous silicon.

In order that the invention might be more fully understood, embodiments thereof will now be described, by way of example only, with reference to accompanying drawings, in which:

Figure 1 is an illustration of a pharmaceutical product, comprising an information carrier, according to the invention;

Figure 2 is a schematic diagram of processing steps, according to the invention, required to fabricate the information carrier shown in figure 1;

Figure 3 shows the results of an experiment showing the effect of immersing a sample of bulk crystalline silicon in simulated human gastric fluid; and

Figure 4 shows the pharmaceutical product of figure 1, located in a gastric environment.

Figure 1 shows a schematic cross section of an orally administrable pharmaceutical product, according to the invention, in the form of a capsule 110. The capsule 110 comprises an information carrier in the form of a silicon chip 120, a beneficial substance 130, and a gelatin shell 140. The silicon chip 120 has a bulk crystalline silicon region 150 and a porous silicon region 160. Recorded information in the form of a number of alphanumeric characters 170 are engraved into the bulk crystalline silicon region 150. The characters 170 may relate to the identity of the

beneficial substance 130, to the manufacturer of the beneficial substance 130, and to the dose of the beneficial substance 130 contained in the capsule 110.

When the capsule 110 is consumed by a patient the shell 140 becomes distorted in the patient's stomach releasing the beneficial substance 130. In the event that the patient has taken an overdose, in other words a number of capsules 110, the stomach may be pumped to empty it of its contents. The stomach contents, containing the silicon chips 120, are then illuminated with light having a wavelength between 300 and 500 nm. The porous silicon 160, associated with each pharmaceutical product, fluoresces at wavelengths between 400 and 900 nm. T. fluorescence of the porous silicon 160 allows the silicon chips 120 to be located in the stomach contents. Once a silicon chip 120 has been located it is removed from the stomach contents, cleaned and placed under a microscope. The characters 170 are read and appropriate remedial action is taken once the identity and dose of the beneficial substance 130 have been identified. The dose may easily be determined by counting the number of fluorescing silicon chips 120 and combining this information with information contained on each chip 120.

Figures 2 shows the processing steps involved in fabricating a number of silicon chips 120, from a silicon wafer 210 that comprises bulk crystalline silicon. A 1 μm thick silicon nitride layer 230 is deposited onto one of the surfaces 240 of the silicon wafer 210. The silicon nitride, once patterned, provides a stencil for isotropic etching of characters 170 into the wafer 210. An organic photosensitive resist is deposited or spun onto the silicon nitride layer 230, photolithographically exposed and developed. The wafer 210 is then reactively ion etched to provide etch windows such as 250 through the silicon nitride layer 230. The organic resist is then stripped off using oxygen plasma ashing or acetone. The wafer 210 is then immersed in a mixture of potassium hydroxide solution and ethanol to isotropically etch a first set of characters 170 into the wafer 210. The potassium hydroxide etched wafer 210 is then exposed to ion milling to remove remnants of the silicon nitride layer 230. The wafer 210 is then anodised in aqueous HF, as described in

US Patent No. 5,348,618, to form a layer 160 of porous silicon. The porosity of the layer may be in the range 50% to 90%, and the thickness of the layer may be in the range 100 nm to 100μm. Finally the patterned wafer is diced to yield a number of chips 120 on which characters 170 have been etched. Only one porous layer 160 is shown in figure 2. However, it is possible to anodise both surfaces of the wafer 210 so that chips 120 having porous silicon on two surfaces result. It may be advantageous to have two such layers of porous silicon since this may assist in differentiating the chip from the stomach contents. In other words the existence of two porous surfaces reduces the chances of the fluorescent porous silicon being concealed from the ultraviolet radiation used to detect the chip 120.

Bulk crystalline samples of silicon were tested in both simulated gastric fluid following the formulations of Cooper et al (Hydrodysis Studies on oleamide in simulated GI fluids, Food Additives + Contaminants 12(6) p769-777 (1995)). The simulated gastric fluid (SGF) was prepared by first diluting 1M HCl to 0.07M and volume 500cm^3. 1.6g of pepsin and 1g of NaCl was then added and the solution incubated at 37°C. References to simulated gastric fluid, made in any part of this specification, refer to SGF having this composition and prepared in this manner. A silicon wafer were immersed in SGF for a period of 67 hours. Figure 3 shows the surface of a silicon wafer after (figure 3a) and before (figure 3b) 67 hours of immersion in SGF; as can be seen there is no appreciable corrosion of the wafer surface (the slight differences between the two images are due to organic deposition. It therefore follows that bulk crystalline silicon is resistant to the gastric environment.

Figure 4 shows the chip 120, comprising a bulk crystalline region 150, located in a gastric environment 410. Part of the bulk crystalline region 150 forms a barrier 420 that protects characters 170 from the gastric environment; the barrier comprising the same material and being integral with the rest of the region 150. The characters 170 are recorded by the shape of the resistant material, in this case bulk crystalline silicon.

An orally administrable pharmaceutical product according to the invention need not comprise an information carrier in which the information is recorded in a material that is resistant to the gastric environment. The information may be protected from the gastric environment, once the pharmaceutical product is located in the stomach, by a barrier formed from a resistant material. Such a barrier may surround the recorded information and, if the information is to be viewed, it may also be transparent.

Claims

1. An orally administrable pharmaceutical product comprising an information carrier having a form and composition such that information is recorded by the carrier; wherein the information carrier comprises a resistant material that is resistant to the gastric environment.

2. A pharmaceutical product according to Claim 1 wherein the at least part of the resistant material is arranged such that, when the pharmaceutical product is located in a gastric tract, it forms a barrier that protects the recorded information from the gastric environment.

3. A pharmaceutical product according to Claim 1 wherein the resistant material is shaped in such a manner that the information is recorded by the shape of the resistant material.

4. A pharmaceutical product according to Claim 1 wherein the largest dimension of the information carrier is less than 10 mm.

5. A pharmaceutical product according to Claim 3 wherein the information is engraved into the resistant material.

6. A pharmaceutical product according to Claim 1 wherein the information carrier comprises a semiconductor.

7. A pharmaceutical product according to Claim 1 wherein the resistant material comprises a semiconductor.

8. A pharmaceutical product according to either Claim 6 or Claim 7 wherein the semiconductor comprises silicon.

9. A pharmaceutical product according to Claim 1 wherein the information carrier comprises a fluorescent or photoluminescent material.

10. A pharmaceutical product according to Claim 9 wherein the fluorescent or photoluminescent material comprises porous silicon.

11. A pharmaceutical product according to Claim 1 wherein the information carrier comprises at least one micromachined component.

12. A pharmaceutical product according to Claim 1 wherein the product comprises at least one moulded plastic component.

13. A pharmaceutical product according to Claim 1 wherein the product further comprises a beneficial substance and wherein the recorded information relates at least partly to the beneficial substance.

14. A pharmaceutical product according to Claim 1 wherein the recorded information comprises at least one character, the or at least one of the characters having a largest dimension less than 100μm.

15. A method of fabricating a pharmaceutical product comprising the step of recording information onto an information carrier; wherein the method further comprises the step of at least partly forming the information carrier from a resistant material that is resistant to the gastric environment.

16. A method according to Claim 15 wherein the method further comprises the step of arranging the resistant material in such a manner that, when the information carrier is located in the gastric environment, the resistant material forms a barrier that protects the recorded information from the gastric environment.

17. A method according to Claim 15 wherein the recording step comprises the step of shaping at least part of the resistant material.

18. A method according to Claim 17 wherein the step of shaping the resistant material comprises the step of engraving the resistant material.

19. A method according to Claim 15 wherein the method comprises the further step of micromachining at least part of the material from which the information carrier if formed.

20. A method according to Claim 15 wherein the method comprises the step of photolithographically engraving at least part of the material from which the information carrier is formed.

21. A method according to Claim 15 wherein the method comprises the step of engraving, by electron beam lithography, at least part of the material from which the information carrier is formed.

22. A method according to Claim 15 wherein the information carrier comprises a plastic material and wherein the step of recording information onto an information carrier comprises the step of moulding the plastic material.

23. A method according to Claim 22 wherein the step of moulding the plastic material comprises the step of at least partly filling a semiconductor mould with the plastic material.

24. A method according to Claim 23 wherein the semiconductor mould comprises silicon.

25. A method according to Claim 23 wherein the method further comprises the step of micromachining the semiconductor to form the mould.

26. A method according to Claim 15 wherein the method further comprises the step of combining a beneficial substance with the information carrier and wherein the recording step is performed in such a manner that the recorded information relates at least partly to the beneficial substance.

27. An information carrier for use in a pharmaceutical product comprising a bulk crystalline semiconductor region and porous semiconductor region wherein the information carrier is shaped in such a manner that information is recorded by the shape of the information carrier and wherein the information relates to a beneficial substance.

28. An information carrier according to Claim 27 wherein the bulk and porous regions comprise different semiconductors.

29. An information carrier according to Claim 27 wherein both the bulk and porous regions comprise silicon.

30. An information carrier according to Claim 27 wherein the bulk region is shaped in such a manner that the information is recorded by the bulk region.

31. An information carrier according to Claim 27 wherein the porous region is shaped in such a manner that the information is recorded by the porous region.

32. An information carrier according to Claim 27 wherein the largest dimension of the information carrier is less than 10 mm.

33. An information carrier according to Claim 27 wherein the recorded information comprises at least one character, the or at least one of the characters having a largest dimension less than 100μm.

34. A method of fabricating an information carrier comprising a bulk semiconductor region and a porous semiconductor region, the method comprising the steps of micromachining the bulk semiconductor and/or the porous semiconductor in such a manner that information is recorded by the shape of the bulk semiconductor and/or porous semiconductor.

35. A method according to Claim 34 wherein the method further comprises the step of taking a sample bulk silicon and anodising it to form porous silicon.

36. A method according to Claim 34 wherein the micromachining step is performed in such a manner that the largest dimension of the information carrier is less than 10 mm.

37. A method according to Claim 36 wherein the largest dimension of the information carrier is less than 2 mm.

38. An method of fabricating an information carrier according to Claim 34 wherein the information comprises at least one character and wherein the micromachining step is performed in such a manner that the or at least one of the characters has a largest dimension less than 100μm.

39. A method according to Claim 38 wherein the largest dimension of the character is less than 50μm.

40. A method of fabricating a product comprising an information carrier the method comprising the step of fabricating an information carrier by the method of Claim 34 wherein the micromachining is performed in such a manner that information relates to the properties of the product.

41. The use of an information carrier as defined in any one of Claims 27 to 33 in the preparation of a medicament for use in any surgical, therapeutic or diagnostic method practised on a human or animal patient.