SYNTHESIS

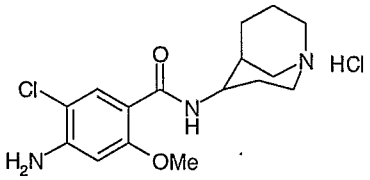
The present invention provides a process for the production of Form II renzapride hydrochloride hydrate. The invention further provides crystalline Form II renzapride hydrochloride hydrate at a level of 75% or above and its use as a medicament.

EP-A-94742 discloses the substituted azabicyclo compound, (±)-4-amino-5-chloro-2-methoxy-N-(1-azabicyclo[3.3.1]non-4-yl)benzamide known by the generic name renzapride (also known as renzapride free base). The substituted azabicyclo compounds are useful in the treatment of disorders relating to impaired gastro-intestinal motility, such as retarded gastric emptying, dyspepsia, flatulence, oesophageal reflux, and peptic ulcer, in the treatment of emesis and disorders of the central nervous system.

The inventors have found that renzapride hydrochloride hydrate is additionally effective in the treatment of irritable bowel syndrome (IBS), constipation, gastroparesis and abdominal pain and discomfort.

The hydrochloride salt of renzapride (renzapride hydrochloride) is preferred over the free base because of its improved stability.

EP-A-0239321 discloses the hydrate form of the hydrochloride salt of renzapride, which provides improved handling and stability characteristics over the anhydrous hydrochloride salt of renzapride.



Renzapride hydrochloride

EP-A-94742 discusses general procedures for the formation of the substituted azabicyclo compounds.

The 5-HT_4 receptor agonist and 5-HT_{2B} and 5-HT_3 receptor antagonist activities of renzapride hydrochloride hydrate make it an ideal candidate for use as a medicament. It will be appreciated that compounds used as medicaments require certain characteristics. In addition to their biological activity, such compounds must exhibit additional characteristics such as good solubility, stability and ease of formulation, etc.

The inventors have identified a new crystalline form of renzapride hydrochloride hydrate, which provides improved properties for its use as a medicament. This new crystalline form has been designated Form II.

Accordingly, the first aspect of the present invention provides a process for the production of Form II renzapride hydrochloride hydrate comprising incubating renzapride in a solution of water and a water miscible solvent, followed by the addition of concentrated hydrochloric acid to the renzapride solution and isolation of Form II renzapride hydrochloride hydrate by filtration. The water miscible solvents for the purposes of this invention can be one or more of tetrahydrofuran (THF), acetone and/or an alcohol. The alcohols are preferably one or more of methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, more preferably ethanol.

The water/water miscible solvent solution preferably contains from 3% to 15% water, more preferably 5% to 10% water, most preferably 8% water or above.

Incubation of renzapride in the water/water solvent solution is preferably carried out with agitation, more preferably with stirring. The renzapride solution can be incubated at 20-25°C. However, the renzapride solution can be heated to allow the dissolution of renzapride in the water/water miscible solvent solution. Preferably the renzapride solution is initially incubated at 20-25°C for example for 15 to 30 minutes followed by incubation with heat for example at reflux to allow dissolution.

After incubation of renzapride in the water/water miscible solvent solution, the solution can be filtered to remove any particulate material.

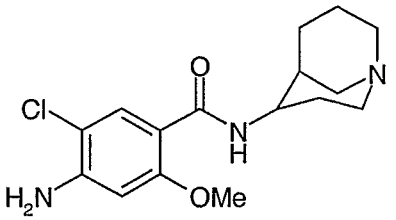
Addition of the hydrochloric acid to the renzapride solution is preferably carried out at 60-70°C. The temperature of the reaction mixture can then be reduced to room temperature, more preferably to 20-25°C and incubation carried out for one or more periods of 1 to 2 hours. The reaction mixture can additionally be incubated for one or more periods of 1 to 2 hours at 0-5°C.

If necessary, the isolated Form II renzapride hydrochloride hydrate can be dried *in vacuo* to reduce the solvent, e.g. ethanol, content to <3% and the resultant solid exposed to water, preferably purified water, in an enclosed area in order to modify the solvent content (for example the ethanol content) of the product to levels acceptable for commercial use whilst maintaining the final Form II product.

Preferably, the isolated Form II renzapride hydrochloride can be exposed to water without the need to dry *in vacuo*, preferably the Form II renzapride hydrochloride can be exposed to purified water in an enclosed area in order to modify the solvent, e.g. ethanol content of the product from about 3% (w/w) to levels acceptable for commercial use. For the purposes of this invention, the

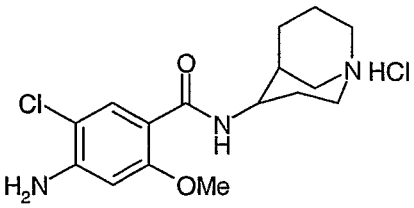
level acceptable for commercial use is a level of 1% (w/w) solvent or less, preferably 0.1% (w/w) solvent or less.

Renzapride can be prepared according to the protocols set out in EP-A-94742 and/or GB 0321091.1. For the purposes of this invention, the term renzapride relates to the free base as illustrated below



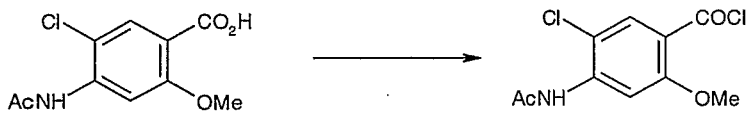
Renzapride (free base)

and renzapride hydrochloride relates to the hydrochloride salt of renzapride as illustrated below.



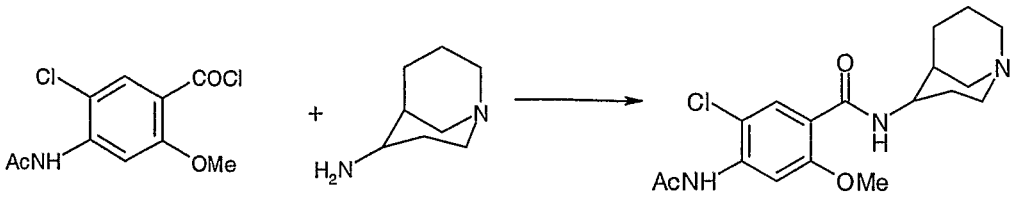
Renzapride hydrochloride

Renzapride is preferably produced by the condensation of a substituted phenyl (11) with an amine (14) to give the condensation product (8). In particular, the substituted phenyl (11) can be activated, for example to the acid chloride (13)



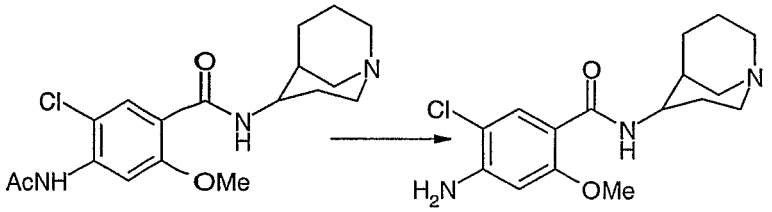
(11) (13)

and the acid chloride (13) of compound (11) can be condensed with an amine (14) to give the condensation product (8),



(13) (14) (8)

followed by deprotection of compound (8) to provide renzapride.



(8) Renzapride (free base)

Processes for the formation of compounds (11) and (14) are disclosed in EP-A-94742 and GB0321091.1.

Renzapride can be used directly in the process of the first aspect of the invention to provide Form II renzapride hydrochloride hydrate. The first aspect of the invention therefore provides a convenient one-step process for the production of Form II renzapride hydrochloride hydrate from renzapride.

The second aspect of the invention provides a process for the formation of Form II renzapride hydrochloride hydrate from renzapride hydrochloride, said process comprising forming a saturated solution of renzapride hydrochloride in a solvent system comprising an organic solvent and from 3% to 30% water and isolating Form II renzapride hydrochloride hydrate therefrom.

In a preferred feature of the second aspect of the invention, the Form II renzapride hydrochloride hydrate can be isolated by crystallisation.

Crystallisation of the Form II renzapride hydrochloride hydrate can be initiated by methods known in the art. Preferably, Form II renzapride hydrochloride hydrate is crystallised from a solvent system by cooling the saturated solution of renzapride hydrochloride hydrate to 10°C or less, preferably 0°C or less, more preferably –5°C or less. The cooling of the saturated solution of renzapride hydrochloride hydrate may be accompanied by stirring until crystallisation of the renzapride hydrochloride hydrate is complete or has reached an appropriate stage.

It may be necessary to add a miscible organic solvent in which the renzapride hydrochloride hydrate is not soluble to facilitate crystallisation (referred to as the miscible non-solvent, for the purposes of this invention). Alternatively seed crystals of Form II renzapride hydrochloride hydrate may be added to the saturated solution of renzapride hydrochloride hydrate. The addition of such seed crystals can be used separately, simultaneously or sequentially with the use of cooling and/or stirring, and/or the addition of a miscible non-solvent.

In order to produce a saturated solution of renzapride hydrochloride, it may be necessary to warm the solution. Preferably, the renzapride hydrochloride solvent mixture is heated to reflux. The solution may be stirred or agitated to produce or aid production of the saturated solution.

For the purposes of this invention the solvent system may comprise one or more solvents which can solubilise renzapride hydrochloride and which are miscible with water. Preferably the solvents are one or more of ethanol,

acetone, isopropyl alcohol, tertiary-butyl methylether (TBME), or THF, more preferably ethanol.

Recrystallisation of renzapride hydrochloride hydrate to produce Form II renzapride hydrochloride hydrate is preferably carried out in an aqueous ethanol solution more preferably a 20% aqueous ethanol solution.

Isolation of the Form II renzapride hydrochloride hydrate can be achieved by filtration. Any solvent residue remaining in the isolated product can be removed by washing the crystalline solid in an organic solvent. Preferably, the washing solvent is more volatile than the solvent residue and can itself be easily removed from the product. Examples of such solvents for the purposes of this invention include THF, n-heptane or toluene. Alternatively, the isolated product can be washed in a cold organic solution comprising from 4 to 25% water more preferably 8% water or above, such as 8% aqueous ethanol.

The product can be dried to remove any remaining solvent. Preferably, the drying does not reduce the percentage water of the product. However should such reduction in the percentage of water occur, the product should be rehydrated to produce the Form II renzapride hydrochloride hydrate. Methods for drying the product include the use of fluidised bed drying and air drying in an oven in the presence or absence of a vacuum. Preferably, the drying is carried out in an inert atmosphere such as a nitrogen atmosphere.

Solvent residue can further be removed by slurrying the product in an organic solvent. Again, the slurry solvent should be more volatile than the solvent residue so that it can be easily removed from the product. Examples of suitable slurrying solvents include TBME.

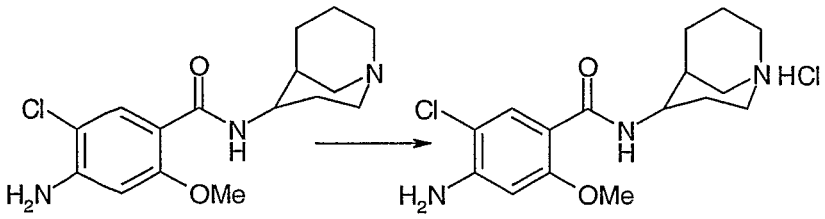
The third aspect of the invention provides a process for the formation of Form II renzapride hydrochloride hydrate comprising slurrying renzapride hydrochloride in an organic solvent comprising 4 to 25% water and isolating Form II renzapride hydrochloride hydrate therefrom.

Preferably the organic solvent is miscible with water and can be one or more of ethanol, acetone, isopropyl alcohol, TBME or THF. More preferably the solvent is ethanol.

The organic solvent is provided comprising preferably 6 to 10% water, more preferably 8% water or above. In a particularly preferred feature the organic solvent is ethanol containing 8% water.

Renzapride hydrochloride as discussed in the second and third aspects of the invention can be obtained according to the processes set out in EP 0239321. Renzapride hydrochloride may be provided in a hydrated or non-hydrated form for the second and third aspects of the invention.

In particular, renzapride (in its free base form) is dissolved in a suitable solvent, preferably ethanol, and a solution of hydrochloric acid in a suitable solvent, preferably ethanol, is added, allowing the product to precipitate.



renzapride renzapride hydrochloride

The fourth aspect of the invention provides crystalline Form II renzapride hydrochloride hydrate comprising two moles of water per mole of renzapride hydrochloride at a level of 75% Form II or above.

Preferably, Form II renzapride hydrochloride hydrate is provided at a level of 80% or above, more preferably 90% or above, most preferably 95% or above.

Form II renzapride hydrochloride hydrate is provided as the dihydrate form. It contains from 8.3 to 9.8% water, preferably 8.5 to 9.6% water, more preferably 9.0% water. Without being bound by scientific theory, it is proposed and studies indicate that the water is bound within the crystal structure of the renzapride molecules and is not loosely associated with the molecules.

The provision of renzapride as the Form II renzapride hydrochloride hydrate provides a number of advantageous properties over those observed for amorphous renzapride hydrochloride hydrate. The advantageous properties of this crystalline form include improved stability to atmospheric water or moisture, improved filtering and improved drying. It will be appreciated by a person skilled in the art that the properties of Form II renzapride hydrochloride hydrate make this form of renzapride particularly preferred for use as a medicament. In particular, Form II renzapride hydrochloride hydrate shows good stability with respect to moisture and can therefore be stored on a long-term basis without deterioration. In particular, Form II renzapride hydrochloride hydrate can be stored on a long term basis without a significant change in the water content of the stored medicament.

It has been noted that Form II renzapride hydrochloride hydrate exhibits a narrow particle size distribution. This provides a form of renzapride hydrochloride hydrate, which allows the production of homogeneous

formulation blends, especially at low dosage strengths. The Form II renzapride hydrochloride hydrate may additionally not require screening during blending of the material thereby allowing more efficient formulation. Form II renzapride hydrochloride hydrate additionally exhibits improved filtering characteristics compared with the amorphous form.

Furthermore the provision of Form II renzapride hydrochloride hydrate allows the formation of a uniform blend without the need for size reduction, filtering etc. This allows more effective handling and formulation of renzapride. Furthermore, the improved water stability of Form II renzapride hydrochloride hydrate allows more efficient drying of the active ingredients, facilitating its formulation into for example a capsule or tablet form.

Form II is therefore particularly preferred for the production of a medicament comprising renzapride as its narrow particle size distribution allows Form II to be used for low strength capsules or tablets without the need for milling or micronisation.

Form II renzapride hydrochloride hydrate shows consistent behaviour when Form II is exposed to moisture. This form can therefore be stored on a long-term basis. Furthermore the material will behave in a predictable fashion during dispensing and manufacture.

The improved properties of Form II renzapride hydrochloride hydrate mean that the formulation of Form II renzapride hydrochloride hydrate into a dosage form such as a tablet is more time, energy and cost efficient that the formulation of amorphous renzapride hydrochloride hydrate. Furthermore, both Form II renzapride hydrochloride hydrate and formulations thereof can be

stored on a long-term basis due to the stability of Form II renzapride hydrochloride hydrate with respect to moisture.

Form II renzapride hydrochloride hydrate can be characterised by its Infra-Red spectrum, wherein Form II renzapride hydrochloride hydrate exhibits a diagnostic peak at 835±1.5 cm^{-1}.

The present invention therefore provides a method for the identification of Form II renzapride hydrochloride hydrate in a sample characterised by carrying out infra-red spectroscopy on a sample of renzapride hydrochloride hydrate and monitoring for the diagnostic peak at 835±1.5 cm^{-1} (as illustrated for example in figure 13).

The fifth aspect of the invention relates to a pharmaceutical composition comprising Form II renzapride hydrochloride hydrate as defined in the fourth aspect of the invention and a pharmaceutical excipient.

Suitable carriers and/or diluents are well known in the art and include pharmaceutical grade starch, mannitol, lactose, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose (or other sugar), magnesium carbonate, gelatin, oil, alcohol, detergents, emulsifiers or water (preferably sterile). The composition may be a mixed preparation of a composition or may be a combined preparation for simultaneous, separate or sequential use (including administration).

The compounds according to the invention for use in the aforementioned indications may be administered by any convenient method, for example by oral (including by inhalation), parenteral, mucosal (e.g. buccal, sublingual,

nasal), vaginal, rectal or transdermal administration and the compositions adapted accordingly.

Form II renzapride hydrochloride hydrate according to the present invention can be provided in a delayed release composition. This delayed release composition comprises Form II renzapride hydrochloride hydrate in combination with a delayed release component. This composition allows targeted release of Form II renzapride hydrochloride hydrate into the lower gastrointestinal tract for example into the small intestine, the large intestine, the colon and/or the rectum. The delayed release composition may comprise Form II renzapride hydrochloride hydrate and an enteric or pH dependent coating such as cellulose acetate phthalates and other phthalates (e.g. polyvinyl acetate phthalate, methacrylates (Eudragits)). Alternatively, the delayed release composition may provide controlled release to the small intestine and/or colon by the provision of pH sensitive methacrylate coatings, pH sensitive polymeric microspheres, or polymers which undergo degradation by hydrolysis. The delayed release composition can be formulated with hydrophobic or gelling excipients or coatings. Colonic delivery can further be provided by coatings which are digested by bacterial enzymes such as amylose or pectin, by pH dependent polymers, by hydrogel plugs swelling with time (Pulsincap), by time dependent hydrogel coatings and/or by acrylic acid linked to azoaromatic bonds coatings.

For oral administration, the compound can be formulated as liquids or solids, for example solutions, syrups, suspensions, emulsions, tablets, capsules, lozenges, dry powder and/or granules.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable aqueous or non-

aqueous liquid carrier(s) for example water, ethanol, glycerol, polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and microcrystalline cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, powders, granules or pellets containing the active ingredient can be prepared using standard carriers and then filled into a capsule, for example a hard gelatin capsule, a HPMC capsule, a soft gelatin capsule etc; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compositions for oral administration may be designed to protect the active ingredient against degradation as it passes through the alimentary tract, for example by an outer coating of the formulation on a tablet or capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or non-aqueous or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or oral administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a pharmaceutically acceptable propellant. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal or vaginal administration are conveniently in the form of suppositories (containing a conventional suppository base such as cocoa butter), pessaries, vaginal tabs, foams or enemas.

Compositions suitable for transdermal administration include ointments, gels and patches, and injections, including powder injections.

Conveniently the composition is in unit dose form such as a tablet, capsule or ampoule.

The composition may contain from 0.1% to 99% (w/w) preferably from 0.1-60% (w/w), more preferably 0.2-20% by weight and most preferably 0.25 to

12% (w/w) of the Form II renzapride hydrochloride hydrate, depending on the method of administration.

The sixth aspect of the invention relates to Form II renzapride hydrochloride hydrate as defined in the fourth aspect of the invention or a pharmaceutical composition thereof as defined in the fifth aspect of the invention for treating and/or preventing a disorder relating to impaired gastro-intestinal motility and/or abdominal pain.

For the purposes of the present invention, gastro-intestinal includes the oesophagus, the stomach, the small intestine and the large intestine (including the colon and the rectum). Form II renzapride hydrochloride hydrate may generally be used in the treatment of disorders relating to impaired gastro-intestinal motility. The disorders include one or more of irritable bowel syndrome, retarded or delayed gastric emptying, dyspepsia, oesophageal reflux, peptic ulcer, flatulence, impaired evacuation, constipation, diabetic neuropathy, functional abdominal bloating, gastroparesis or abdominal pain. Form II renzapride hydrochloride hydrate can also be used in the treatment of symptoms associated with such disorders including abdominal pain and/or discomfort, abdominal bloating, an abnormality in stool consistency, an abnormality in frequency of stool passage, a feeling of incomplete emptying, feelings of urgency and passage of mucus. It may also be used in the treatment of emesis and/or the treatment of disorders of the central nervous system such as psychosis. Preferably Form II renzapride hydrochloride hydrate is used for the treatment of irritable bowel syndrome, more preferably constipation-predominant, diarrhoea-predominant or alternating (mixed-symptom) irritable bowel syndrome.

The amount of Form II renzapride hydrochloride hydrate effective to treat a disorder as set out above depends on the nature and severity of the disorder being treated and the weight of the patient in need thereof. However, a single unit dose for a 70kg adult will normally contain 0.01 to 100mg, for example 0.1 to 50mg, preferably 0.5 to 16mg of the compound of the invention per day. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, usually 1 to 3 times a day, more preferably 1 or 2 times per day. It will be appreciated that the dose ranges set out above provided guidance for the administration of Form II renzapride hydrochloride hydrate to an adult. The amount to be administered to for example, an infant or a baby can be determined by a medical practioner or person skilled in the art and can be lower or the same as that administered to an adult. The unit dose is preferably provided in the form of a capsule or a tablet.

The seventh aspect of the invention relates to a method of treating a disorder relating to impaired gastro-intestinal motility comprising and administering to a subject in need thereof Form II renzapride hydrochloride hydrate as defined in the fourth aspect of the invention or a pharmaceutical composition as defined in the fifth aspect of the invention.

All preferred features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

The invention may be put into practice in various ways and a number of specific embodiments will be described by way of example to illustrate the invention with reference to the accompanying drawings, in which:

Figure 1 shows the solid state ^{13}C-NMR of Form II renzapride hydrochloride hydrate;

Figure 2 shows the solid state ^{13}C-NMR of amorphous renzapride hydrochloride hydrate;

Figure 3 shows a DVS sorption plot of Form II renzapride hydrochloride hydrate;

Figure 4 shows a DVS sorption plot of Form II renzapride hydrochloride hydrate;

Figure 5 shows a DVS sorption plot of Form II renzapride hydrochloride hydrate;

Figure 6 shows an Isotherm map for Form II renzapride hydrochloride hydrate;

Figure 7 shows DVS sorption plots and isotherm maps for Form II renzapride hydrochloride hydrate;

Figure 8 shows DVS sorption plot of Form II renzapride hydrochloride hydrate;

Figure 9 shows an isotherm map for Form II renzapride hydrochloride hydrate;

Figure 10 shows DVS sorption plot of amorphous renzapride hydrochloride hydrate;

Figure 11 shows an isotherm map for amorphous renzapride hydrochloride hydrate;

Figure 12 shows the IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 13 shows an expanded region of the IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 14 shows an IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 15 shows an expanded region of the IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 16 shows an expanded region of the IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 17 shows an IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 18 shows an expanded region of the IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 19 shows an IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 20 shows an expanded region of the IR spectrum of Form II renzapride hydrochloride hydrate;

Figure 21 shows an X-ray powder diffraction pattern for Form II renzapride hydrochloride hydrate;

Figure 22 shows thermal analysis of Form II renzapride hydrochloride hydrate;

The present invention will now be illustrated by reference to one or more of the following non-limiting examples.

EXAMPLES

Manufacture of Form II and amorphous renzapride hydrochloride hydrate

Manufacture of Form II renzapride hydrochloride hydrate

Renzapride and renzapride hydrochloride can be obtained using the methods set out in EP-A-0094742, EP-A-0239321and GB 0321091.1.

Preferred Salt Formation Procedure

The free base of renzapride (1wt) is suspended in 8% aqueous ethanol (5 vol; made up from 0.4 vol. water and 4.6 vol. absolute ethanol) and stirred at 20-25°C for 15-30 minutes. The mixture is heated to reflux and held at reflux until dissolution is achieved (up to 70 minutes expected) and then cooled to 60-65°C and clarified through pre-heated lines and filter (1μm) to remove any particulate material. The lines and filter are rinsed with hot (60-65°) 8% aqueous ethanol (1 vol. made from 0.08 vol. water 0.92 vol. absolute ethanol). The solution of free base is then treated with concentrated hydrochloric acid (1.05 mol. equiv.) maintaining the internal temperature in the range 60-70°C. The resultant mixture is cooled to 20-25°C and aged in this range for 1-2 hours. The resultant slurry is further cooled to 0.5°C and aged for a further 1-2 hours. A sample of the slurry is removed, filtered and the solid checked by IR to ensure it is Form II. The slurry may be aged for further 1-2 hours periods as necessary to ensure the material is Form II ahead of isolation.

The product is isolated by filtration and the filter cake washed by displacement with cool (0-5°C) 8% aqueous ethanol (1 vol., made from 0.08 vol. water and 0.92 vol. absolute ethanol) and then pulled down on the filter for 3-4 hours. The solid is transferred to trays and stood in an enclosed area in the presence of purified water until the ethanol content is 1% (w/w) or less.

Recrystallisation Procedure

Renzapride hydrochloride (1wt) is treated with 20% aqueous ethanol (3 vol., made from 0.6 vol. water and 2.4 vol. absolute ethanol). The stirred mixture is heated to reflux and held at reflux until dissolution is achieved (up to 70 minutes expected) and then cooled to 60-65°C and clarified through pre-heated lines and filter (1μm) to remove any particulate material. The lines and filter are rinsed with hot (60-65°C) ethanol (4.5 vol.), maintaining the temperature of the renzapride hydrochloride solution at 60-65°C throughout.

The resultant mixture is cooled to 20-25°C and aged in this range for 1-2 hours. The resultant slurry is further cooled to 0-5°C and aged for a further 1-2 hours. A sample of the slurry is removed, filtered and the solid checked by IR to ensure it is Form II. The slurry may be aged for further 1-2 hours periods as necessary to ensure the material is Form II ahead of isolation.

The product is isolated by filtration and the filter cake washed by displacement with cool (0-5°C) 8% aqueous ethanol (1 vol., made from 0.08 vol. water and 0.92 vol. absolute ethanol) and then pulled down on the filter for 3-4 hours. The solid is transferred to trays and stood in an enclosed area in the presence of purified water until the ethanol content is 1% (w/w) or less.

Slurry Procedure

The renzapride hydrochloride (1 wt) is treated with 8% aqueous ethanol (5 vol.) and the suspension stirred and cooled to 0-5°C and once in range, stirred at 0-5°C for 2-3 hours. A sample of the slurry is removed, filtered and the solid checked by IR to ensure it is Form II. The slurry may be aged for further 1-2 hour periods as necessary to ensure the material is Form II ahead of isolation.

The product is isolated by filtration and the filter cake washed by displacement with cool (0-5°C) 8% aqueous ethanol (1 vol., made from 0.08 vol. water and 0.92 vol. absolute ethanol) and then pulled down on the filter for 3-4 hours. The solid is transferred to trays and stood in an enclosed area in the presence of purified water until the ethanol content is 1% (w/w) or less.

Manufacture of amorphous renzapride hydrochloride hydrate

Amorphous renzapride hydrochloride hydrate is prepared according to EP-A-0094742 and EP-A-0239321. For the purposes of this invention, the term "amorphous" encompasses a sample of renzapride hydrochloride hydrate comprising non-crystalline and crystalline material, wherein said crystalline material may be present in a mixture of one or more forms.

Comparison of Form II renzapride hydrochloride hydrate and amorphous renzapride hydrochloride hydrate

Solid state ^{13}C-NMR

Solid state ^{13}C-NMR spectra were collected for Form II and amorphous

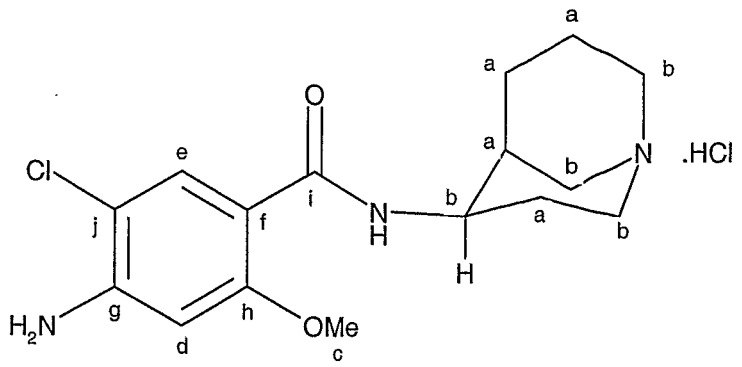
renzapride hydrochloride hydrate and are illustrated in figures 1 and 2 respectively.

The sample of Form II renzapride hydrochloride hydrate gave a different spectrum to that obtained for amorphous renzapride hydrochloride hydrate. The relaxation properties of Form II renzapride hydrochloride hydrate (which determine the acquisition conditions) also differed to those of amorphous renzapride hydrochloride hydrate. The experimental parameters were therefore optimised for each sample.

Table 1 below sets out the observed signals for Form II renzapride hydrochloride. In addition a proposed assignment of these peaks is provided.

Table 1: Solid state ^{13}C-NMR data for Form II renzapride hydrochloride hydrate

Signals (ppm)	Proposed Atom assignment
19.233, 21.856, 28.413, 30.307	a
46.141, 51.823, 53.329	b
55.855	c
99.373	d
109.184	e
130.992	f
149.352	g
158.483	h
164.700	i
Not resolved from baseline	j



$.2H_2O$

The molecule should give seven high-frequency (90+ ppm) signals (neglecting any fine structure) but only six were detected. The missing signal is from the carbon attached to the chlorine. Coupling between these nuclei results in a broadened signal (and possibly a multiplet) which probably accounts for the signals in the baseline between 100 and 130 ppm. A similar coupling slightly broadens the signals from the carbons attached to nitrogen (for example, the signal at ~149 ppm is presumably the aromatic C-NH_2).

A proposed assignment of the other signals is as follows: the three -CH_2-s + CH in the group between 15 and 30 ppm, the three -CH_2-N's + >CH-N in the group between 43 and 53 ppm, OMe at 55-58 ppm, amide carbon at 164-168 ppm, aromatic C-O at 156-159 ppm, aromatic C-C at ~131 ppm and the CH ortho to the OMe is probably the 99 ppm line with the other CH at 109-112 ppm. The remaining unlabelled, low-intensity signals are spinning sidebands and can be ignored.

Comparison of solid state NMR spectra of Form II renzapride hydrochloride hydrate and amorphous renzapride hydrochloride hydrate.

Variation is observed in the pattern of signals observed from 60 to 15 ppm in the spectra obtained for Form II renzapride hydrochloride hydrate and

amorphous renzapride hydrochloride hydrate. In addition the spectrum obtained for amorphous renzapride hydrochloride hydrate contains a signal at 131.8ppm for the OMe signal which is split. The signal at 131.8 ppm appears to be an unresolved pair. Furthermore the lack of resolution in the low-frequency signals in the amorphous renzapride hydrochloride hydrate spectrum appear to be caused by the presence of additional lines.

Dynamic Vapour Sorption

Methodology

Each sample is placed into a sample pan and loaded into the DVS system. An initial weight reading is taken. The sample is then exposed to an atmosphere with a relative humidity (RH) of 0% to dry the sample and a dry weight reading taken. The sample is exposed to an adsorption/desorption cycle between 0 and 90 % RH in 10 % RH intervals. The change in weight data is fitted to an exponential expression that is used to automatically determine the end point of each stage, which then triggers the next increase/decrease in relative humidity.

For the DVS traces, the stepped lines represent the relative humidity (RH) level in the Chamber. The curved line represents the weight change in the sample. The RH is controlled automatically and changes once the rate of change in weight of the sample is small.

Form II renzapride hydrochloride hydrate

The sorption isotherm plot for Form II show a rapid initial uptake in moisture (to ca. 9% w/w) at 10 % RH, after which there is very little change in the

sample mass, indicating that Form II is a very stable material which is consistent in its properties with respect to moisture.

The DVS and isotherm plots for Form II are shown in figures 3 to 9.

Samples of Form II renzapride hydrochloride hydrate show behaviour that implies a very stable material that is consistent in its properties with respect to moisture.

The DVS data provides no evidence of equilibration of Form II renzapride hydrochloride hydrate between different forms. There was very little change in mass when the three cycles are compared with each other (*i.e.* they are very similar as indicated by the isotherm plots).

In addition there was very little change in the mass of the sample when the chamber had reached 90% RH conditions and the sample had taken up *ca* 9.5% (w/w) moisture, indicating that the material was stable with respect to moisture content, and consistent across the three cycles. The weight gain observed for Form II renzapride hydrochloride hydrate is consistent with the formation of a dihydrate. The batches analysed all show a very stable profile with respect to exposure to humidity, once above 10% RH. Above 10% RH there is very little variation in the mass of the dihydrate material.

Amorphous renzapride hydrochloride hydrate

The DVS plot and isotherm map for amorphous renzapride hydrochloride hydrate are shown in figures 10 and 11.

The DVS plot for amorphous renzapride hydrochloride hydrate (figure 10) shows approximately 6 % (w/w) uptake upon exposure to a 10% RH environment which is followed by a more gradual uptake up to 50% RH. Above this there is a lower uptake of moisture as the RH increases. There is a gradual decrease in mass as the RH decreases from 90 to 10% RH.

The adsorption / desorption profiles for the 2nd and 3rd cycles are identical, with the desorption cycle being identical to that of the 1st cycle. The uptake at 10 to 40% RH is greater than that observed for the 1st cycle and again shows the majority of moisture loss on going from 10 to 0% RH.

The isotherm map (figure 11) shows quite clearly the difference between the first and subsequent adsorption cycles. The desorption cycles are identical on all 3 cycles.

The data set out in figures 10 and 11 show that there is a clear difference between the sample before and after the first adsorption cycle. There is a significant difference between the first adsorption and desorption cycle. As this cycle is not reproducible, it indicates that a change in the form of the material has occurred, rather than the hysteresis being related to other physical attributes. The overall moisture gain from 0% RH to 90% RH is approximately 12% (w/w), which is higher than the amount required for a stoichiometric dihydrate.

After completion of the first cycle the absorption / desorption profile is reproducible indicating that the material is then stable with respect to its interaction with moisture.

The behaviour of the amorphous renzapride hydrochloride hydrate does not appear to be consistent with that of a dihydrate material.

Intrinsic Dissolution Rate

Methodology

The samples were prepared as discs. Each disc was prepared by compressing the sample for 5 minutes at 2 tons of pressure. Each disc was transferred to a static dissolution system, whereby one surface of the disc is exposed to the dissolution medium. Six discs were prepared from each batch of material for duplicate intrinsic dissolution rate (IDR) determinations at pHs 2.2, 4.0 and 7.0. Dissolution samples (0.8ml) were withdrawn at 5 minute intervals up to 60 minutes and samples were analysed.

The amount of drug released (mg) is divided by the surface area of the disc ($0.5cm^2$) to obtain an amount per unit area (mg cm^{-2}). The average of the duplicate determinations is plotted as a function of time (minutes). The IDR (mg cm^{-2} $minutes^{-1}$) is given by the gradient (determined by linear regression) over the linear range of the release profile. When the dissolution into solution is deemed independent of pH, a pH independent IDR is calculated. The pH independent IDR is calculated by averaging the data for each time point at all of the pHs studied and calculating the linear regression on at least the first 5 data points. All IDR values are reported with the error encompassing the upper and lower 95% confidence limits of the linear regression.

Linear regression analysis of the IDR data used all of the data points, as the release profiles are linear.

Table 2: IDR for Form II and amorphous renzapride hydrochloride hydrate (mg/min/cm^2)

Sample	pH 2.2	pH 4.0	pH 7.0	independent
Form II	5.5±0.2	5.7±0.2	5.9±0.3	5.7±0.3
Amorphous	6.6±0.2	6.7±0.1	6.9±0.1	6.8±0.3

The Form II material exhibits a different intrinsic dissolution rate characteristic to that of the amorphous material.

Characterisation of Form II renzapride hydrochloride hydrate

Analysis of moisture content of Form II renzapride hydrochloride hydrate.

The water content of 11 different samples of Form II renzapride hydrochloride hydrate was determined by Karl Fischer analysis and was reproducibly found to be ca. 9.0% (w/w) water, corresponding to 2 molecules of water being present within the crystalline structure. This reproducibility in the water content of Form II renzapride hydrochloride has been found to be independent of both the method used to produce Form II and the scale of the synthesis. The present invention provides the ability to reproducibly control the amount of water present in Form II renzapride hydrochloride hydrate, which is highly advantageous for controlling the quality of the approved pharmaceutical ingredient during storage, handling, formulation and product manufacture.

Moisture Content (by Karl Fischer)

Form II	9.0% (w/w) ±0.31 (SD; n=11)

Infra red (IR) analysis

IR spectra were recorded on a number of samples of Form II manufactured according to the processes of the present invention. Figures 12 to 20 illustrate the IR spectra of Form II renzapride hydrochloride hydrate. Table 3 below sets out the IR peaks observed.

Table 3: Representative IR data for a sample of Form II renzapride hydrochloride hydrate.

Form II *
3434.0 (br, m)
3358.5 (s, st)
2951.2 (br, w)
2591.5 (s, w)
2585.4 (br, m)
2511.7 (br, w)
1592.9 (s, st)
1540.8 (s, st)
1463.9 (s, st)
1454.9 (s, st)
1419.6 (s, w)
1316.4 (s, m)
1249.8 (s, m)
1209.9 (s, st)
1143.8 (s, w)
1130.0 (s, w)
1086.1 (s, m)
992.5 (s, m)
950.6 (s, w)
891.4 (s, w)
834.1 (s, m)
771.2 (s, w)
671.8 (s, m)
650.5 (s, w)

*Key: values in wavenumbers (cm^{-1}). Peak descriptors are s = sharp, br = broad with relative intensities assigned as st = strong, m = medium and w = weak

All observed samples of Form II renzapride hydrochloride hydrate exhibit a characteristic peak at 835 ± 1.5 cm^{-1}. This peak can be used to distinguish the presence of Form II renzapride hydrochloride hydrate. It will be appreciated that the exact value of this characteristic peak will vary depending on the sample preparation, apparatus used, etc. To this end, Table 4 sets out a number of values for this characteristic peak as observed for different samples of Form II renzapride hydrochloride hydrate.

The range for the signature peak in the IR spectrum for Form II is taken from the values tabulated below:

Table 4: Values observed for characteristic peak at 835±1.5 cm^{-1}

Form II Sample	Signature peak (cm^{-1})
1	834.11
2	834.11
3	835.06
4	834.31
5	834.31
6	834.91
7	834.01, 835.29 and 834.12 on repeat runs
8	834.31
9	835.28
10	835.28
11	835.28
12	836.28

The presence of a characteristic peak at 835 ± 1.5cm^{-1} in the IR spectra of Form II renzapride hydrochloride hydrate permits confirmation that Form II renzapride hydrochloride hydrate has been manufactured.

XRPD analysis of Form II renzapride hydrochloride

Form II renzapride hydrochloride hydrate has been analysed by X-ray Powder Diffraction:

The X-ray powder diffraction (XRPD) pattern of Form II renzapride hydrochloride hydrate is shown in figure 21. The presence of defined peaks in the XRPD pattern indicates that Form II has a crystalline character.

Stability of Form II renzapride hydrochloride hydrate

Samples of Form II renzapride hydrochloride hydrate were placed in storage under conditions of 25°C/60% relative humidity.

Table 5: Stability of Form II renzapride hydrochloride hydrate

	t = 0 months	**t = 6 months**	**t = 12 months**	**t = 18 months**	**t = 24 months**
Stability test					
1. Description	White uniform solid	White uniform solid	White uniform solid	White uniform solid	White uniform solid
2.Water content (by Karl Fisher)	8.9%(w/w)	8.6%(w/w)	8.8%(w/w)	8.8%(w/w)	8.8% (w/w)

Form II renzapride hydrochloride hydrate shows good stability to moisture on storage.

Particle Size Distribution

The Particle Size Distribution (PDS) of renzapride is measured according to the method detailed below.

Material Parameters:	renzapride: R.I. = 1.5 Absorption = 0.1
	Model: General purpose (fine)-enhanced sensitivity
Measurement Parameters:	Measurement time: 4 secs
	Background time: 8 secs
	Obscuration limits: 3 <Obscuration <20 (filter on)
Sampling Parameters:	Scirocco 2000
	Vibration feed rate: 40%
	Air pressure: 3.5 Bar
	Single measurement of each batch performed in triplicate.

Table 6: Particle Size Distribution of Form II renzapride hydrochloride hydrate manufactured as a 5 kg batch.

	d (0.1)/μm	d(0.5)/μm	d(0.9)/μm	Span*
Form II	11.5	47.1	109.0	2.1

* Span = (d(0.9)-d(0.1))/d(0.5)

Form II shows a narrow particle size distribution, with a span of 2.1.

Photomicroscopy

A small amount of sample was dispersed in silicon oil (on a microscope slide) and a cover slip place over it. Images of the sample were captured (minimum of two magnifications) using calibrated image capture software.

Form II renzapride hydrochloride hydrate is composed of regular shaped cubic/rhombohedra crystals that are preferred for the manufacture of a solid dosage form.

Thermochemical analysis

A TGA trace of the Form II is illustrated in figure 22.

The TGA trace for Form II renzapride hydrochloride hydrate contains an endotherm at 150-180°C. This endotherm appears to be associated with a phase change of the dehydrated material, following loss of water during analysis.

The thermogram illustrates a large endothermic peak (with T_{max} at approximately 100°C) due to the loss of two moles of water. The endothermic peak is followed by two exothermic peaks at T_{max} 170°C and 240°C. The Form II material therefore undergoes loss of water to a dehydrated hydrate, which at around 150-170°C undergoes a phase change that then proceeds to melt around 270°C and finally decomposes at elevated temperatures.

Solubility studies

Solubility studies on Form II renzapride hydrochloride hydrate in various water/solvent mixtures were carried out using the following standard procedure:

Approximately 50-100mg of Form II renzapride hydrochloride hydrate was added to a $10cm^3$ glass vial and $5cm^3$ of the appropriate solvent was added. The suspensions were stirred at 20°C for 24 hours. After this time the suspensions were filtered and the clear solutions were analysed by HPLC.

The results are summarised below.

Table 7: Solubility studies of Form II renzapride hydrochloride hydrate

Water/Solvent Mixtures	Solubility (mg/mL)
1% water in ethanol	9.0
5% water in ethanol	17.5
10% water in ethanol	21.2
1% water in IPA	1.1
5% water in IPA	2.8
10% water in IPA	4.6
1% water in acetone	0
5% water in acetone	0.9
10% water in acetone	6.7
1% water in THF	0
5% water in THF	0.4
10% water in THF	8.9

Removal of Ethanol by Solvent Slurry

Residual solvent can be removed from Form II by solvent slurry. A series of slurries were performed in water-wet acetone, THF, TBME and toluene to investigate the effect on the level of ethanol. The following standard procedure was used:

100mg of Form II was stirred at room temperature in 1cm^3 (10vol) of solvent for 24 hours. After this time the solid was isolated by filtration and analysed for solvent content and physical form.

The results are summarised in tables 8 and 9:

Table 8: Removal of ethanol by solvent slurry

Solvent	Solvent content	Ethanol content
5% water in THF	Not detected	Not detected
Wet TBME	Trace (0.1% w/w)	Not detected
Wet Toluene	Not detected	Not detected

The results show that ethanol can be removed by solvent slurries in acetone, tetrahydrofuran (THF), toluene and TBME to a level not detected by NMR (estimated to be <0.1% detection). The form of the material isolated from the slurries was determined by IR and found to be Form II in all cases.

Table 9: Isolated form after solvent slurry

Solvent	Isolated form
5% water in acetone	Form II
5% water in THF	Form II
Wet TBME	Form II
Wet Toluene	Form II

Crystallisation and Drying Studies with Form II

In order to remove any residual ethanol, the material is dried under vacuum at up to 80°C. The 'ethanol-free' solid is then rehydrated to provide the final material.

To investigate the drying of different forms of renzapride hydrochloride hydrate, 1g samples were prepared from crystallisations in 1% water in ethanol, 5% water in ethanol, 1% water in IPA and 5% water in IPA. It will be appreciated that the recrystallisation procedure set out below allows the reworking of renzapride hydrochloride hydrate to Form II renzapride hydrochloride hydrate. The following procedure was used:

1g of renzapride hydrochloride hydrate was dissolved in the minimum amount of refluxing solvent and then allowed to cool for ca.1 hour at room temperature and then placed at 5°C for a further 18 hours. Solid was isolated by filtration and analysed by NMR, IR and KF. The data obtained is summarised in the tables 10 and 11 below.

Table 10: Initial Analysis

Solvent	Water content	Recovery* (mg)	Solvent content# % (w/w)	Water (KF)# % (w/w)	Form (by IR)#
Ethanol	1%	599	5.37	1.73 ± 0.29	Other
	5%	714	0.16	9.21 ± 0.42	Form II
IPA	1%	565	9.07	0.99 ± 0.05	Other
	5%	698	0.65	8.96 ± 0.34	Form II

*Crude weight – not corrected for solvent or water

#after drying under vacuum (17mbar) at 30°C for 4 hours

Table 11: After Further Drying

Solvent	Water content	Solvent content# % (w/w)	Water (KF)# % (w/w)
Ethanol	1%	0.16[a]	1.08 ± 0.5
	5%	0.02	0.99 ± 0.4
IPA	1%	1.20	0.61 ± 0.02
	5%	0.15	0.57 ± 0.1

[a]the solvent was apparently IPA, presumably due to drying the samples in the oven with the IPA derived material

#after drying under vacuum (17mbar) at 30°C for 4 hours + 15 hours at 60°C.

Initial analysis of the samples shows that Form II (containing ca. 9% water) is produced by crystallisation in either 5% water in ethanol or 5% water in IPA.

The isolated material initially contains relatively low solvent residues, 0.16% ethanol and 0.65% IPA, respectively. These solvent levels are much lower than those found for the material isolated from either 1% water in ethanol or 1% water in IPA, which contain 5.4% and 9.1%, respectively. This suggests that Form II dihydrate material does not hold onto excess solvent readily and as a consequence will be easier to dry than the material isolated from solvents containing low water levels (<4%).

Further drying of the samples shows that after heating for 60°C under vacuum (17mbar) solvent and water have been removed from all the samples.

Summary of Characterisation of Form II

The characterisation data for Form II renzapride hydrochloride hydrate indicates that it is a crystalline material that gives a sharp X-ray diffraction pattern and IR spectrum and has a well-defined water content. The water content does not change over a wide range of humidity as indicated by DVS experiments. This allows long term storage of the material. Form II has a particle size distribution with a consistently narrow span, with satisfactory blend homogeneities. Microscopy has shown the batches to have consistent regular shaped crystals that are ideal for solid dosage form manufacture. Form II will behave in a predictable fashion during dispensing and manufacture. Form II has a diagnostic peak in the IR at 835 ± 1.5 cm^{-1} (sharp) that can be used to identify the presence of the form.

CLAIMS

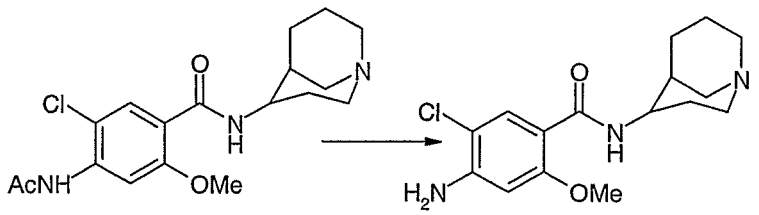
1. A process for the production of Form II renzapride hydrochloride hydrate comprising incubating renzapride in a solution of water and a water miscible solvent, followed by the addition of concentrated hydrochloric acid to the renzapride solution and isolation of Form II renzapride hydrochloride hydrate by filtration.

2. A process as claimed in claim 1 wherein the water miscible solvent is one or more of THF, acetone and/or an alcohol.

3. A process as claimed in claim 2 wherein the alcohol is one or more of methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol.

4. A process as claimed in any one of claims 1 to 3 wherein the water/water miscible solvent solution contains from 3% to 15% water.

5. A process as claimed in any one of claims 1 to 4 wherein renzapride is produced by the deprotection of compound (8);



(8) Renzapride (free base)

6. A process for the formation of Form II renzapride hydrochloride hydrate from renzapride hydrochloride, said process comprising forming a saturated solution of renzapride hydrochloride in a solvent system comprising an organic

solvent and from 3% to 30% water and isolating Form II renzapride hydrochloride hydrate therefrom.

7. A process as claimed in claim 6 wherein the Form II renzapride hydrochloride hydrate is isolated by crystallisation.

8. A process as claimed in claims 6 or 7 wherein the solvent system comprises one or more solvents, which can solubilise renzapride hydrochloride and which are miscible with water.

9. A process as claimed in claim 8 wherein the solvent is one or more of ethanol, acetone, isopropyl alcohol, TBME, or THF.

10. A process as claimed in claim 7 wherein the crystallisation of renzapride hydrochloride hydrate is carried out in an aqueous ethanol solution.

11. A process for the formation of Form II renzapride hydrochloride hydrate comprising slurrying renzapride hydrochloride in an organic solvent comprising 4 to 25% water and isolating Form II renzapride hydrochloride hydrate therefrom.

12. A process as claimed in claim 11 wherein the organic solvent is one or more of ethanol, acetone, isopropyl alcohol, TBME or THF.

13. A process as claimed in claim 11 or claim 12 wherein the organic solvent comprises preferably 6 to 10% water.

14. A process as claimed in any one of claims 1 to 13 wherein the Form II renzapride hydrochloride hydrate produced by said process has one or more features selected from the group consisting of:

a) a characteristic peak in its Infra red spectrum at $835\pm1.5cm^{-1}$;

b) an X-ray powder diffraction pattern substantially as depicted in Figure 21; and

c) 8.3 to 9.8% water content.

15. Form II renzapride hydrochloride hydrate as produced by any one of claims 1 to 14.

16. Crystalline Form II renzapride hydrochloride hydrate comprising two moles of water per mole of renzapride hydrochloride at a level of 75% Form II or above.

17. Crystalline Form II renzapride hydrochloride hydrate as claimed in claim 16 containing from 8.3 to 9.8% water.

18. Crystalline Form II renzapride hydrochloride hydrate as claimed in claim 16 or claim 17 having a diagnostic peak in its Infra-Red spectrum at $835\pm1.5cm^{-1}$.

19. Crystalline Form II renzapride hydrochloride hydrate as claimed in any one of claims 16 to 18 wherein said Form II has one or more features selected from the group consisting of:

a) a characteristic peak in its Infra red spectrum at $835\pm1.5cm^{-1}$;

b) an X-ray powder diffraction pattern substantially as depicted in Figure 21; and

c) 8.3 to 9.8% water content.

20. A method for the identification of Form II renzapride hydrochloride hydrate in a sample characterised by carrying out infra-red spectroscopy on a sample of renzapride hydrochloride hydrate and monitoring for the presence of a diagnostic peak at $835 \pm 1.5 cm^{-1}$.

21. A pharmaceutical composition comprising Form II renzapride hydrochloride hydrate as defined in claims 16 to 19 and a pharmaceutical excipient.

22. Crystalline Form II renzapride hydrochloride hydrate as defined in claims 16 to 19 or a pharmaceutical composition as defined in claim 21 for treating and/or preventing one or more of irritable bowel syndrome, retarded or delayed gastric emptying, dyspepsia, oesophageal reflux, peptic ulcer, flatulence, impaired evacuation, constipation, diabetic neuropathy, functional abdominal bloating, abdominal pain and/or discomfort, abdominal bloating, an abnormality in stool consistency, an abnormality in frequency of stool passage, a feeling of incomplete emptying, feelings of urgency, passage of mucus, emesis, gastroparesis and/or the treatment of disorders of the central nervous system.

23. Crystalline Form II renzapride hydrochloride hydrate as defined in claims 16 to 19 or a pharmaceutical composition as claimed in claim 21 for the treatment of constipation-predominant, diarrhoea-predominant or alternating (mixed-symptom) irritable bowel syndrome.

24. A method of treating a disorder relating to impaired gastro-intestinal motility comprising and administering to a subject in need thereof crystalline

Form II renzapride hydrochloride hydrate as defined in claims 16 to 19 or a pharmaceutical composition as defined in claim 21.

25. A process as substantially described herein with reference to one or more of the examples.

26. Crystalline form II renzapride hydrochloride hydrate as substantially described herein with reference to one or more of the examples.

27. A method as substantially described herein with reference to one or more of the examples.

28. A pharmaceutical composition as substantially described herein with reference to one or more of the examples.