Solid State Forms of Racemic Ilaprazole

Priority Statement

[0001] This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/877,608, filed December 29, 2006 and U.S. Provisional Application No. 60/887,499, filed January 31, 2007, both of which are herein incorporated by reference in their entirety.

Field of the Invention

[0002] This invention relates to ilaprazole, 2[[(4-methoxy-3-methyl-2-pyridinyl)-methyl]sulfinyl]-5-(1H-pyrrol-1-yl) 1H-Benzimidazole, a substituted benzimidazole having a chiral sulfur atom. More particularly, the invention relates to solid state forms of racemic ilaprazole. Ilaprazole is a proton pump inhibitor and is useful in the treatment of various acid-related gastrointestinal disorders.

Background of the Invention

[0003] Since their introduction in the late 1980s, proton pump inhibitors have improved the treatment of various acid-related gastrointestinal (GI) disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease, Zollinger-Ellison Syndrome (ZES), ulcers, and nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy. GERD encompasses three disease categories: non-erosive reflux disease (NERD), erosive esophagitis, and Barrett's esophagus. ZES is caused by a gastrin-secreting tumor of the pancreas that stimulates the acid-secreting cells of the stomach to maximal activity. Proton pump inhibitors have also be used to treat ulcers such as duodenal, gastric, and NSAID-associated gastric/duodenal ulcers.

[0004] As antisecretory drugs, proton pump inhibitors are currently the recommended first line therapy, being viewed as more effective than other treatments. In general, proton pump inhibitors offer superior gastric acid suppression over histamine H2-receptor blockers. The use of proton pump inhibitors by patients who suffer from gastric acid-related disorders is generally believed to have led to an increase in their quality of life, productivity, and overall well being.

[0005] Proton pump inhibitors are also used to treat extra-esophageal manifestations of GERD (asthma, hoarseness, chronic cough, non-cardiac chest pain), and with antibiotics for Helicobacter pylori eradication. The goals of GERD management are threefold: prompt and

sustained symptom control, healing of the injured esophageal mucosa and prevention of GERD-related complications (including stricture Formation, Barrett's esophagus, and/or adenocarcinoma). Pharmacological therapy with proton pump inhibitors Forms the basis of both acute and long-term management of GERD. Proton pump inhibitors provide effective relief of symptoms and healing of the esophagitis, as well as sustaining long-term remission.

[0006] Although therapeutic efficacy is the primary concern for a therapeutic agent, the solid-state form, as well as the salt form, and the properties unique to the particular form of a drug candidate are often equally important to its development. Each solid state form (crystalline or amorphous) of a drug candidate can have different physical and chemical properties, for example, solubility, stability, or the ability to be reproduced. These properties can impact the ultimate pharmaceutical dosage form, the optimization of manufacturing processes, and absorption in the body. Moreover, finding the most adequate form for further drug development can reduce the term and the cost of that development.

[0007] Obtaining substantially pure crystalline, amorphous or even other non-crystalline forms is extremely useful in drug development. It permits better characterization of the drug candidate's chemical and physical properties and thereby allows identification of the form or forms with the desired combination of therapeutic effect and comparative ease of manufacture. The solid state crystalline form may possess more favorable pharmacology than the amorphous form or may be easier to process. It may also possess more storage stability.

[0008] The solid state physical properties of a drug candidate may also influence its selection as a pharmaceutical active ingredient and the choice of form for its pharmaceutical composition. One such physical property, for example, is the flowability of the solid, before and after milling. Flowability affects the ease with which the material is handled during processing into a pharmaceutical composition. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate. Another important solid state property of a pharmaceutical compound is its dissolution rate in aqueous fluid. The rate of dissolution of an active ingredient in a patient's gastrointestinal fluid may have therapeutic consequences since it impacts the rate at which an orally-administered active ingredient may reach the patient's bloodstream.

[0009] These practical physical properties are influenced by the properties of the particular solid state form of the compound, for example, by the conformation and orientation of molecules in the unit cell of the crystalline compound. A crystalline form often has different thermal behavior characteristics from an amorphous, a non-crystalline form or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and may be used, for example, to distinguish some polymorphic forms from others. A particular solid state form generally possesses distinct crystallographic and spectroscopic properties detectable by powder X-ray diffraction (XRPD), single crystal X-ray crystallography, solid state NMR, and infrared spectrometry among other techniques.

Summary of the Invention

[0010] The invention relates to solid state forms of racemic ilaprazole, 2[[(4-methoxy-3-methyl-2-pyridinyl)-methyl]sulfinyl]-5-(1H-pyrrol-1-yl) 1H-Benzimidazole. The invention also relates to a pharmaceutical composition for inhibiting gastric acid secretion comprising a crystalline form of racemic ilaprazole according to the invention in an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier. The invention also provides methods of treatment for various acid-related gastrointestinal (GI) disorders such as those discussed above.

Brief Description of the Drawings

[0011] Fig. 1 is a comparison of the XRPD patterns of the crystalline forms of racemic ilaprazole.

[0012] Fig. 2 is a comparison of the solid state ^{13}C CP/MAS NMR spectra of crystalline Forms A, B, E, and F of racemic ilaprazole.

[0013] Fig. 3 is a comparison of the IR spectra of the crystalline forms of racemic ilaprazole.

[0014] Fig. 4 is a comparison of the Raman spectra of crystalline Forms A, B, and I of racemic ilaprazole.

[0015] Fig. 5 is the XRPD pattern of racemic ilaprazole, Form A.

[0016] Fig. 6 is the TGA thermogram of racemic ilaprazole, Form A.

[0017] Fig. 7 is the DSC thermogram of racemic ilaprazole, Form A.

[0018] Fig. 8 is the proton NMR spectrum of racemic ilaprazole, Form A.

[0019] Fig. 9 is the solid state ^{13}C CP/MAS ssNMR spectrum of racemic ilaprazole, Form A.

[0020] Fig. 10 is the IR spectrum of racemic ilaprazole, Form A.

[0021] Fig. 11 is the RAMAN spectrum of racemic ilaprazole, Form A.

[0022] Fig. 12 is the DVS isotherm of racemic ilaprazole, Form A.

[0023] Fig. 13 is an ORTEP drawing of racemic ilaprazole Form A. Atoms are represented by 50% probability anisotropic thermal ellipsoids

[0024] Fig. 14 is the packing diagram of racemic ilaprazole Form A viewed down the crystallographic *a* axis.

[0025] Fig. 15 is the packing diagram of racemic ilaprazole Form A viewed down the crystallographic *b* axis.

[0026] Fig. 16 is the packing diagram of racemic ilaprazole Form A viewed down the crystallographic *c* axis.

[0027] Fig. 17 is the calculated X-ray powder pattern of racemic ilaprazole Form A based on the single crystal X-ray data.

[0028] Fig. 18 is a comparison of the calculated XRPD pattern of racemic ilaprazole Form A to the experimental XRPD of racemic ilaprazole Form A.

[0029] Fig. 19 is the XRPD pattern of racemic ilaprazole, Form F.

[0030] Fig. 20 is the TGA thermogram of racemic ilaprazole, Form F.

[0031] Fig. 21 is the DSC thermogram of racemic ilaprazole, Form F.

[0032] Fig. 22 is the proton NMR spectrum of racemic ilaprazole, Form F.

[0033] Fig. 23 is the solid state ^{13}C CP/MAS ssNMR spectrum of racemic ilaprazole, Form F.

[0034] Fig. 24 is the IR spectrum of racemic ilaprazole, Form F.

[0035] Fig. 25 is the RAMAN spectrum of racemic ilaprazole, Form F.

[0036] Fig. 26 is the DVS isotherm of racemic ilaprazole, Form F.

[0037] Fig. 27 ORTEP drawing of racemic ilaprazole Form F. Atoms are represented by 50% probability anisotropic thermal ellipsoids

[0038] Fig. 28 is the packing diagram of racemic ilaprazole Form F viewed down the crystallographic *a* axis.

[0039] Fig. 29 is the packing diagram of racemic ilaprazole Form F viewed down the crystallographic *b* axis.

[0040] Fig. 30 is the packing diagram of racemic ilaprazole Form F viewed down the crystallographic *c* axis.

[0041] Fig. 31 Comparison of the packing along the crystallographic *b* axis for racemic ilaprazole Form F (top) and Form A (bottom). The layers are highlighted by arrows show the alternating arrangement of the layers for the Form F crystal structure.

[0042] Fig. 32 is the calculated X-ray powder pattern of racemic ilaprazole, Form F.

[0043] Fig. 33 is a comparison of the calculated XRPD of racemic ilaprazole, Form F (top) with the experimental XRPD of racemic ilaprazole, Form F (bottom).

[0044] Fig. 34 is the XRPD pattern of racemic ilaprazole, Form I.

[0045] Fig. 35 is the TGA thermogram of racemic ilaprazole, Form I.

[0046] Fig. 36 is the DSC thermogram of racemic ilaprazole, Form I.

[0047] Fig. 37 is the proton NMR spectrum of racemic ilaprazole, Form I.

[0048] Fig. 38 is the IR spectrum of racemic ilaprazole, Form I.

[0049] Fig. 39 is the RAMAN spectrum of racemic ilaprazole, Form I.

[0050] Fig. 40 is the DVS isotherm of racemic ilaprazole, Form I.

[0051] Fig. 41 is the XRPD pattern of racemic ilaprazole, Form B.

[0052] Fig. 42 is the TGA thermogram of racemic ilaprazole, Form B.

[0053] Fig. 43 is the DSC thermogram of racemic ilaprazole, Form B.

[0054] Fig. 44 is the proton NMR spectrum of racemic ilaprazole, Form B.

[0055] Fig. 45 is the solid state ^{13}C CP/MAS ssNMR spectrum of ilaprazole, Form B.

[0056] Fig. 46 is the IR spectrum of racemic ilaprazole, Form B.

[0057] Fig. 47 is the RAMAN spectrum of racemic ilaprazole, Form B.

[0058] Fig. 48 is the DVS isotherm of racemic ilaprazole, Form B.

[0059] Fig. 49 is the XRPD pattern of racemic ilaprazole, Form E.

[0060] Fig. 50 is the TGA thermogram of racemic ilaprazole, Form E.

[0061] Fig. 51 is the DSC thermogram of racemic ilaprazole, Form E.

[0062] Fig. 52 is the proton NMR spectrum of racemic ilaprazole, Form E.

[0063] Fig. 53 is the solid state ^{13}C CP/MAS ssNMR spectrum of racemic ilaprazole, Form E.

[0064] Fig. 54 is the IR spectrum of racemic ilaprazole, Form E.

[0065] Fig. 55 depicts the tableting process for preparing a delayed release pharmaceutical composition of the invention.

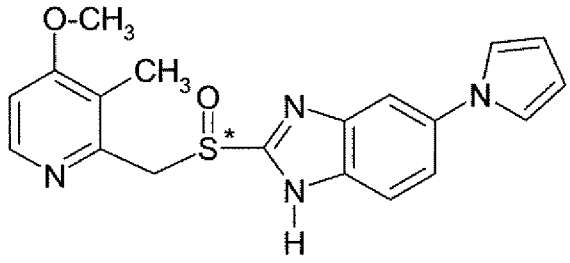
[0066] Fig. 56 shows mean plasma concentration versus time profiles of racemic ilaprazole following administration of a single 40 mg oral dose of ilaprazole as delayed-release tablets containing Forms A, B or F.

[0067] Fig. 57 shows the ^{13}C CP/MAS ssNMR spectra of delayed-release formulations containing 40 mg of racemic ilaprazole, Forms A, B, and F.

Detailed Description of the Invention

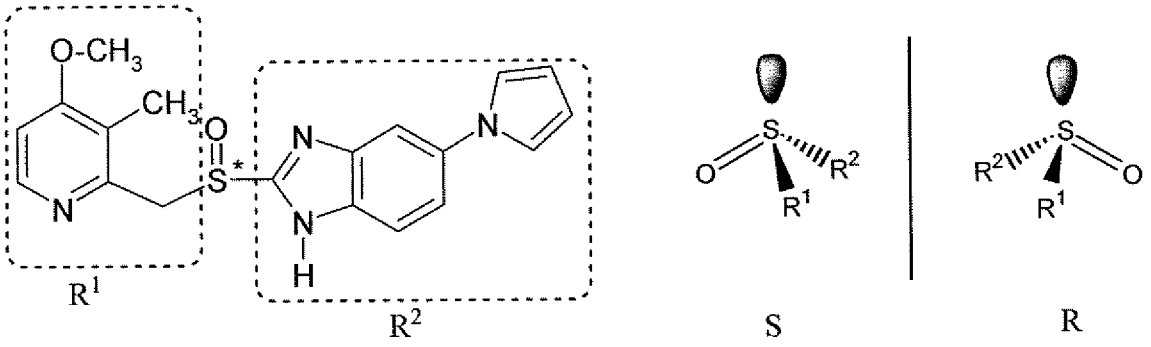
[0068] Ilaprazole, 2[[(4-methoxy-3-methyl-2-pyridinyl)-methyl]sulfinyl]-5-(1H-pyrrol-1-yl) 1H-Benzimidazole, is a substituted benzimidazole that acts as a proton pump inhibitor. Ilaprazole selectively and irreversibly inhibits gastric acid secretion through inhibition of the hydrogen-potassium adenosine triphosphatase (H+K+-ATPase) (proton pump) mechanism. Inhibition of the proton pump occurs by formation of disulfide covalent bonds with accessible cysteines on the enzyme. Ilaprazole has a prolonged duration of action that persists after their elimination from plasma. See, for example, U.S. Patent Nos. 5,703,097 and 6,280,773, which are incorporated herein by reference.

[0069] Ilaprazole has the empirical formula $C_{19}H_{18}N_4O_2S$ having a molecular weight of 366.44 daltons. Ilaprazole is a chiral molecule and has the following structural Formula (I):

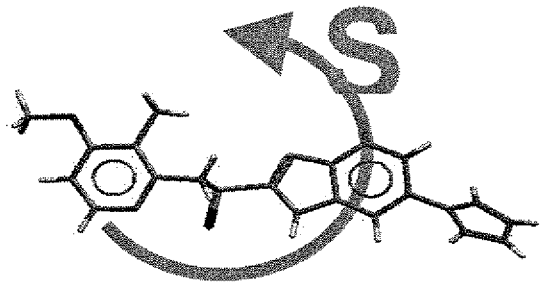


(I).

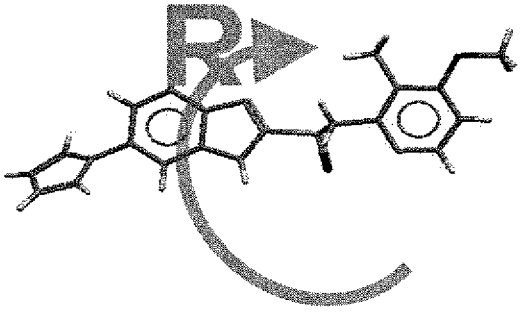
Ilaprazole, like all proton pump inhibitors, possesses the unique feature of a chiral sulfur atom, S*. This can be depicted as follows with the lone pair of electrons on the chiral sulfur atom occupying one position in each stereoisomer, as shown below:



The absolute structure and absolute confirmation of (-)-S-ilaprazole was made through single crystal structure determination and is shown below. See Example 7 of co-pending U.S. Application Ser. No. 11/966,808 of Brackett et al. entitled, "Solid State Forms of Enantiopure Ilaprazole" filed December 28, 2007, herein incorporated by reference in its entirety.



Thus, its complimentary enantiomer is (+)-R-ilaprazole, as shown below.



[0070] Chiral molecules are well known to chemists. Chiral molecules exist in two enantiomorphic forms that are mirror images of each other. In the same manner that left and right hands are mirror images of each other and cannot be superimposed over each other, enantiomers of chiral molecules cannot be superimposed over each other. The only difference in the molecules is the arrangement of groups connected to the chiral center in three dimensional space. The physical properties of enantiomers are identical to each other with the exception of the rotation of the plane of polarized light. It is this rotation of polarized light that allows one skilled in the art to determine if a chiral material is enantiomerically pure.

[0071] In the solid state, pure enantiomeric materials (also known as enantiopure materials) are, by definition, composed of a single enantiomer and can have very different properties compared to racemates. This is particularly true in the crystalline form. Racemates can crystallize as a conglomerate (where the two enantiomers form identical, mirror-image crystals that are the pure enantiomer), a racemic compound (where the two enantiomers coexist and are incorporated into specific locations of the crystal) or a solid solution (where the enantiomers can be located at random sites within the crystal). The solid state can be characterized by various physical properties such as solubility, melting point, x-ray powder diffraction, solid state NMR, Raman, and IR spectroscopy.

[0072] The solid state forms of racemic ilaprazole of the invention are designated as Forms A, B, E, F, and I. Each crystalline form of racemic ilaprazole of the invention is described in the Examples below. Figs. 1-4 are comparison figures showing the XRPD patterns, the solid state ^{13}C CP/MAS NMR spectra , the IR spectra, and the Raman spectra of the crystalline forms of racemic ilaprazole according to the invention. The different crystalline forms of racemic ilaprazole can be identified or characterized by comparing their respective spectra. Similarities may also be seen, such as the common XRPD peak at 15.8 °2θ ± 0.2 °2θ. The proton NMR spectra are useful in showing that each ilaprazole form is chemically the same as the starting material. Additional data for each crystalline form which may be used to identify each form is presented in the Examples below. Each form disclosed here possesses advantages vis-à-vis the other forms, for example, for a particular formulation or processing.

[0073] The term "racemic" or "racemate," is defined as a 1:1 mixture of the two enantiomers of ilaprazole regardless of their physical state. A racemic mixture of ilaprazole can be composed of individual crystals which may be the pure enantiomers or ratios of the R and S enantiomers,

such as 90/10, 10/90, 86/14, 14/86, 70/30, 30/70, 50/50, as well as other ratios in between these ratios, as long as the bulk enantiomeric composition remains 1:1.

[0074] The forms of racemic ilaprazole of the invention are each substantially pure or substantially free of the other crystalline forms or amorphous racemic ilaprazole and other impurities. In this context, "substantially pure" means that the particular form of racemic ilaprazole comprises less than 15% of another crystalline or amorphous form. The purity is preferably less than 10%, more preferably less than 5%, more preferably less than 2%, more preferably less than 1%, and even more preferably less than 0.5%. The term "substantially pure" also means that the form of racemic ilaprazole comprises less than 3% of other impurities, preferably less than 2%, more preferably less than 1%, and even more preferably less than 0.5%.

[0075] Racemic ilaprazole Form A is the most thermodynamically stable of these crystalline Forms. Form A is also the least soluble in aqueous solutions. It is not hygroscopic. A human bioavailability study of Forms A, B, and F, described in Example 9, showed Form A to be also the most bio-available form in humans. This is a surprising and unexpected combination of characteristics which causes racemic ilaprazole Form A to be a preferred form for solid dosage forms of the invention.

[0076] Racemic ilaprazole, Form A crystallizes with the monoclinic space group $P2_1$, which is not centrosymmetric (i.e. does not contain a center of symmetry). Surprisingly, unequal numbers of R and S isomers can coexist within this structure. Three Form A single crystal structures were determined. While not wishing to be bound by theory, it believed that an individual crystal of Form A contains an approximate 70/30 (or 30/70) mixture of the R and S isomers. The arrangement of isomers appears disordered and is manifest in the crystallographic data as two atomic positions for the single oxygen bound to the chiral sulfur of the sulfoxide group. It is believed that each oxygen position represents one isomer and is partially occupied (e.g. one position is 70% R(S) occupied and the other is 30% S(R) occupied).

[0077] Structures were determined for both enantiomeric compositions. Two of the predicted structures contained enantiomeric ratios of approximately 70-30 while another had a ratio of approximately 28-72, suggesting that such a ratio is preferred under these conditions. However, the bulk material is racemic, as demonstrated by a net 0° rotation of plane polarized light, indicating that the bulk material contains approximately equal numbers of crystals with ratios of 70% R/30% S and 30% R/70% S.

[0078] Chiral HPLC analysis was performed on a single crystal of Form A for which the structure had been determined. The result was consistent with enantiomeric enrichment of one isomer, whereas the analysis of bulk racemic ilaprazole, Form A material was consistent with a 50/50 racemic mixture. When crystallized from racemic solution at ambient temperature, Form A can be characterized as a solid solution in which individual crystals may contain mixture of the R and S isomers. This behavior is similar to that described by a conglomerate, except that a conglomerate is composed of equal numbers of pure S and pure R crystals.

[0079] Racemic ilaprazole Form F is believed to be a kinetically favored crystal form. Under certain conditions, e.g., temperatures, aqueous mixed solvent composition, and pH gradients, Form F is more soluble in aqueous solvents than Form A. Solubility studies are shown in Example 6. Like Form B, Form F is less bioavailable than Form A. It too may be used to prepare longer acting pharmaceutical compositions. Form F has the longest half-life of the crystalline Forms A, B, and F which were evaluated in the bioavailability study of Forms A, B, and F, Example 9. Form F is slightly hygroscopic.

[0080] Form F crystallizes with the centrosymmetric space group $P2_1/n$ which must contain a center of symmetry. Each crystal must contain an equal number of R and S isomers. Thus, Form F is a racemic crystal. The arrangement of isomers within this structure is disordered. There are two oxygen atom positions for the oxygen bound to the chiral sulfur of the sulfoxide group, each partially occupied in an 86/14 ratio. At first glance this seems similar to the Form A structure, but the presence of a center of symmetry in the space group of the Form F structure dictates it be racemic. Therefore, individual Form F crystals must contain an equal number of both enantiomers. In the disordered Form F structure, half of the crystallographic sites have an enantiomeric or occupancy ratio of approximately 86/14 and other half have the opposite ratio of approximately 14/86. Chiral HPLC and optical rotation analysis confirms that both the single crystals of Form F and the bulk material are racemic.

[0081] Racemic ilaprazole Form B crystallizes in pure form from aprotic solvents such as acetone or dichloromethane/ethyl acetate. This leads to a manufacturing advantage. For example, Form B may be used to purify ilaprazole. Form B is also a stable crystalline form having good long term stability or shelf life. Form B is more soluble in aqueous solvents than Form A. The bioavailability study of Forms A, B, and F, discussed in Example 9, showed that

Form B has a greater half-life than Form A which may be advantageously used to prepare longer acting pharmaceutical compositions. Form B is not hygroscopic.

[0082] Forms B, E, and I are racemic crystalline forms of ilaprazole whose individual crystal structures have not been determined. Although the enantiomeric composition of the individual crystal structure is not known, chiral HPLC confirms that the bulk composition of each of these forms is racemic, i.e. contains an equimolar mixture of each enantiomer. As mentioned above, the x-ray powder diffraction (XRPD) patterns the solid state ^{13}C CP/MAS NMR spectra , the IR spectra, and the Raman spectra obtained on these forms show characteristic peaks which identify each form. As shown in the Examples, the physical properties of Forms A, B, F, and I, such as melt onset temperature and moisture sorption/desorption profiles, also differ depending on the particular form.

Pharmaceutical Compositions and Methods

[0083] Ilaprazole is useful for inhibiting gastric acid secretion as well as for providing gastrointestinal cytoprotective effects in mammals, including humans. In a more general sense, ilaprazole may be used for prevention and treatment of gastrointestinal inflammatory diseases in mammals, including e.g. gastritis, gastric ulcer, and duodenal ulcer. As discussed above, such GI disorders include, for example, gastroesophageal reflux disease (GERD), peptic ulcer disease, Zollinger-Ellison Syndrome (ZES), ulcers, and nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy. Ilaprazole may also be used for prevention and treatment of other gastrointestinal disorders where cytoprotective and/or gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, in patients with acute upper gastrointestinal bleeding, and in patients with a history of chronic and excessive alcohol consumption.

[0084] The results of Phase 1 clinical studies conducted with ilaprazole results suggest that at the doses studied, suppression of gastric acid occurs over a 24-hour period. In Phase 2 clinical studies conducted with ilaprazole, the results indicated that ilaprazole at the doses studied provided symptomatic relief for patients with gastric-acid related disorders and promoted rapid healing of acid-related gastric and duodenal ulcers.

[0085] Accordingly, the invention relates to a pharmaceutical composition for inhibiting gastric acid secretion comprising a crystalline form of racemic ilaprazole according to the invention in

an amount effective to inhibit gastric acid secretion and a pharmaceutically acceptable carrier. Pharmaceutical compositions are discussed below.

[0086] The invention also relates to the treatment of various acid-related gastrointestinal (GI) inflammatory diseases and disorders such as those discussed above and providing gastrointestinal cytoprotection. The invention provides a method for inhibiting gastric acid secretion by administering to mammals a crystalline form of racemic ilaprazole according to the invention, or a pharmaceutical composition containing it, in an amount sufficient to inhibit gastric acid secretion. The invention also provides a method for the treatment of gastrointestinal inflammatory diseases in mammals by administering to mammals a crystalline form of racemic ilaprazole according to the invention, or a pharmaceutical composition containing it, in an amount sufficient to treat gastrointestinal inflammatory disease. The invention further provides a method for providing gastrointestinal cytoprotective effects in mammals by administering to mammals a crystalline form of racemic ilaprazole according to the invention, or a pharmaceutical composition containing it, in an amount sufficient to provide gastrointestinal cytoprotective effects.

[0087] The invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a crystalline form of racemic ilaprazole of the invention and a pharmaceutically acceptable carrier, (also known as a pharmaceutically acceptable excipient). The pharmaceutical composition may also contain a mixture of crystalline form of racemic ilaprazole. As discussed above, the crystalline forms of racemic ilaprazole are useful for the treatment of various acid-related gastrointestinal (GI) disorders. Pharmaceutical compositions for the treatment of those diseases and disorders contain a therapeutically effective amount of a crystalline form of racemic ilaprazole of the invention to inhibit gastric secretion as appropriate for treatment of a patient with the particular disease or disorder.

[0088] A "therapeutically effective amount of a crystalline form of racemic ilaprazole to inhibit gastric secretion" (discussed here concerning the pharmaceutical compositions) refers to an amount sufficient to inhibit or reduce gastric secretion and thereby to treat, i.e. to reduce the effects, inhibit or prevent, various acid-related gastrointestinal (GI) disorders and/or provide gastrointestinal cytoprotection. The actual amount required for treatment of any particular patient will depend upon a variety of factors including the disorder being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex and

diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion of the crystalline form of racemic ilaprazole according to the invention; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics," Tenth Edition, A. Gilman, J.Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173 (2001), which is incorporated herein by reference.

[0089] The absorption of the crystalline forms of racemic ilaprazole can be altered depending on when the subject consumes food in relation to when the dosage is administered. The rate of absorption can also depend on the type of diet consumed, particularly if the diet has a high concentration of fats. These factors, as well as others known to those of skill in the art that can affect the absorption of proton pump inhibitors, can consequently influence the efficacy of the crystalline forms of racemic ilaprazole in inhibiting gastric acid secretion. It has been found that the absorption of the crystalline forms of racemic ilaprazole can be delayed and the bioavailability increased when administered in the fed state or approximately five minutes before a high-fat meal, compared to administration in the fasted state. Administration of the crystalline forms of racemic ilaprazole approximately one hour before a high-fat meal produces results similar to that observed during administration in the fasted state. These findings are consistent with similar studies performed with other tableted formulations of proton pump inhibitors.

[0090] A pharmaceutical composition of the invention may be any pharmaceutical form which contains and retains the crystalline form of racemic ilaprazole according to the invention. The pharmaceutical composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. A comprehensive disclosure of suitable formulations (including controlled-release formulations, e.g. delayed release, sustained/extended release, etc.) may be found in U.S. Published Application No. 2006/013868, herein incorporated by reference in its entirety. For injectables and liquid suspensions, those should be formulated such that the crystalline form of racemic ilaprazole is present in the formulated composition.

[0091] Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends upon the pharmaceutical form and the desired method of administration to be used. For a pharmaceutical composition of the invention, that is

one having a crystalline form of racemic ilaprazole of the invention, a carrier should be chosen that maintains the crystalline form of racemic ilaprazole of the invention. In other words, the carrier should not substantially alter the crystalline form of the racemic ilaprazole of the invention. Nor should the carrier be otherwise incompatible with a crystalline form of racemic ilaprazole according to the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

[0092] The pharmaceutical compositions of the invention are preferably formulated in unit dosage form for ease of administration and uniformity of dosage. A "unit dosage form" refers to a physically discrete unit of therapeutic agent appropriate for the patient to be treated. It will be understood, however, that the total daily dosage of a crystalline form of racemic ilaprazole of the invention and its pharmaceutical compositions according to the invention will be decided by the attending physician within the scope of sound medical judgment.

[0093] It may be desirable to administer the dosage in a composition where the crystalline form of racemic ilaprazole is released from the dosage form as a first and a second dose where each of the first and second dose contain a sufficient amount of the crystalline form of racemic ilaprazole to raise plasma levels to a desired concentration. Suitable formulations to achieve this are disclosed in PCT Published Application No. WO 2006/009602, herein incorporated by reference in its entirety.

[0094] Because the crystalline form of racemic ilaprazole of the invention is more easily maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of the invention. Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, are particularly preferred. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable carrier (also known as a pharmaceutically acceptable excipient). The solid dosage form may, for example, include one or more pharmaceutical carriers/excipients as known in the art, including: a) fillers or extenders such as starches, lactose, lactose monohydrate, sucrose, glucose, mannitol, sodium citrate, dicalcium phosphate, and silicic acid; b) binders such as, for example, carboxymethylcellulose, microcrystalline cellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch

glycolate, and sodium carbonate; e) dissolution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; i) lubricants such as talc, calcium stearate, magnesium stearate, magnesium hydroxide, solid polyethylene glycols, sodium lauryl sulfate; and j) glidants such as colloidal silicon dioxide. The solid dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, and/or optionally in a delayed manner Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), herein incorporated by reference in its entirety, discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Solid dosage forms of pharmaceutical compositions of the invention can also be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art, including formulations and coatings designed to provide for extended release of the active pharmaceutical ingredient (API). For example, U.S. Patent No. 6,605,303, incorporated herein by reference, describes oral extended release formulations for the proton pump inhibitor omeprazole. Accordingly, the solid dosage form may be an extended or delayed release formulation. An exemplary delayed-release tablet formulation is described in Example 8, below.

[0095] A crystalline form of racemic ilaprazole of the invention can also be in a solid micro-encapsulated form with one or more carriers as discussed above. Microencapsulated forms of a crystalline form of racemic ilaprazole of the invention may also be used in soft and hard-filled gelatin capsules with carriers such as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0096] The invention also provides methods for the treatment of the GI disorders discussed above. The solid forms of racemic ilaprazole and pharmaceutical compositions containing them may, according to the invention, be administered using any amount, any form of pharmaceutical composition and any route of administration effective for the treatment. After formulation with an appropriate pharmaceutically acceptable carrier in a desired dosage, as known by those of skill in the art, the pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intraveneously, intracisternally, intravaginally,

intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the location and severity of the condition being treated. As discussed above, when administering a pharmaceutical compositions of the invention via one of these routes, the pharmaceutical composition contains racemic ilaprazole in one of the crystalline forms of the invention. Oral administration using tablets or capsules is generally preferred.

[0097] In certain embodiments, the crystalline forms of racemic ilaprazole according to the invention may be administered at dosage levels of about 0.001 mg/kg to about 50 mg/kg, from about 0.01 mg/kg to about 25 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. It will also be appreciated that dosages smaller than 0.001 mg/kg or greater than 50 mg/kg (for example 50-100 mg/kg) can be administered to a subject. For extended release formulations, the dosage may range from about 5 mg to about 80 mg, preferably ranging from about 10 mg to about 50 mg ilaprazole, and more preferably ranging from about 20 mg to about 40 mg.

Examples

[0098] Example 1 describes the preparation of ilaprazole. Examples 2-4 describe the preparation and characterization of three crystalline forms of racemic ilaprazole, Forms A, F and I. These solid state forms were characterized by various techniques. Each technique is described below. Example 5 describes solubility studies of racemic ilaprazole Forms A and F.. Examples 6 and 7 describe the preparation and characterization of two additional crystalline forms of racemic ilaprazole, Forms B and E. Example 8 describes delayed release tablet formulations containing racemic ilaprazole Forms A, B, and F. Example 9 describes a human bioavailability study with those delayed release tablets.

[0099] Differential Scanning Calorimetry (DSC): Analyses were carried out on a TA Instruments differential scanning calorimeter 2920 or Q1000. The instrument was calibrated using indium as the reference material. The sample was placed into an aluminum DSC pan and the weight accurately recorded. The sample cell was equilibrated at 25 °C and heated under a nitrogen purge at a rate of 10 °C/min or 40 °C/min, up to a final temperature of 350 °C. Specific heating rates and pan configurations are identified in the comment section above each individual thermogram. Pan configurations are defined as follows: NC is non-crimped and HSP is hermetically sealed.

[00100] Dynamic Vapor Sorption/Desorption (DVS): Data were collected on a VTI SGA-100 moisture balance system. For sorption isotherms, a sorption range of 5 to 95% relative humidity (RH) and a desorption range of 95 to 5% RH in 10% RH increments were used for analysis. The samples were not dried prior to analysis. Equilibrium criteria used for analysis were less than 0.0100% weight change in 5 minutes with a maximum equilibration time of 3 hours if the weight criterion was not met. Data were not corrected for the initial moisture content of the samples.

[00101] IR Spectroscopy: Infrared spectra were acquired on a Magna-IR 860® Fourier transform infrared (FT-IR) spectrophotometer (Thermo Nicolet) equipped with an Ever-Glo mid/far IR source, an extended range potassium bromide (KBr) beamsplitter, and a deuterated triglycine sulfate (DTGS) detector. An attenuated total reflectance (ATR) accessory (Thunderdome™, Thermo Spectra-Tech), with a germanium (Ge) crystal was used for data acquisition. The spectra represent 256 co-added scans collected at a spectral resolution of 4 cm^{-1}. A background data set was acquired with a clean Ge crystal. Log 1/R (R = reflectance) spectra were acquired by taking a ratio of these two data sets against each other. Wavelength calibration was performed using polystyrene.

[00102] Solution State ^1H NMR Analyses: Samples were prepared for ^1H NMR spectroscopy as ~5-50 mg solutions in deuterated methylene chloride, CD_2Cl_2. The spectra were obtained on an INOVA-400 spectrometer. The spectra were obtained with the acquisition parameters in Table 1.

Table 1: ^1H NMR Acquisition Parameters

Solvent:	CD_2Cl_2, (internal reference at 5.32 ppm)
Temperature:	Ambient
Spin rate:	20 Hz
Pulse sequence:	s2pul
Relaxation delay:	5 seconds
Pulse width:	8.4 μseconds, (90.0 degree)
Acquisition time:	2.5 seconds
Spectral width:	6400.0 Hz, (16.008 ppm)
Scans:	40
Acquired points:	32000
Data processing:	
Line broadening:	0.2 Hz
FT size:	131072

[00103] Solid State ^{13}C CP/MAS NMR Analyses (ssNMR): Samples were prepared for solid-state NMR spectroscopy by packing them into 4 mm PENCIL type zirconia rotors. The spectra were acquired on an INOVA-400 spectrometer using ^{1}H cross-polarization (CP) and magic angle spinning, (MAS). The specific acquisition parameters are listed in Table 2, with exceptions noted for different examples:

Table 2: ^{13}C ssNMR Acquisition Parameters

Reference:	Glycine (external reference at 176.5 ppm)
Temperature:	Ambient
Pulse sequence:	xpolvtlrho1
Relaxation delay:	10 seconds
Pulse width:	2.2 μseconds, (90.0 degree, 76.2 degree for Form E (Example 7))
Acquisition time:	0.030 seconds
Spectral width:	44994.4 Hz, (447.517 ppm)
Scans:	100 for Forms A and F (Examples 2 and 3); 200 with 2 dummy scans for Form B (Example 6); 400 with 2 dummy scans for Form E (Example 7)
Acquired points:	27000
^{1}H Decoupling	400 MHz
SPINAL-64 decoupling	
Cross Polarization tangent RAMP-CP on C13	
Contact Time:	5.0 mseconds
Spin rate:	12000 Hz
Data processing:	
Backward linear prediction:	3 points
Line broadening:	10.0 Hz
FT size:	3278

[00104] Thermogravimetric Analysis (TGA): Thermogravimetric analyses were carried out on a TA Instruments 2950 thermogravimetric analyzer. The calibration standards were nickel and Alumel™. Each sample was placed in an aluminum sample pan and inserted into the TG furnace. Samples were started directly from ambient and then heated under a stream of nitrogen at a heating rate of 10 °C/min, up to a final temperature of 350 °C.

[00105] Raman Spectroscopy: Fourier Transfrom-Raman spectra were acquired on an FT-Raman 960 spectrometer (Thermo Nicolet). This spectrometer uses an excitation wavelength of 1064 nm. Approximately 0.5 W of Nd:YVO4 laser power was used to irradiate the sample. The Raman spectra were measured with an indium gallium arsenide (InGaAs) detector. The samples

were prepared for analysis by placing the sample into a capillary. A total of 256 sample scans were collected from 3600 – 100 cm^{-1} at a spectral resolution of 4 cm^{-1}, using Happ-Genzel apodization. Wavelength calibration was performed using sulfur and cyclohexane.

[00106] X-Ray Powder Diffraction (XRPD): XRPD patterns were obtained using the two diffractometers discussed below.

[00107] Shimadzu XRD-6000 Diffractometer: Analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer using Cu Kα radiation. The instrument is equipped with a long fine focus X-ray tube. The tube voltage and amperage were set at 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3 °/min (0.4 sec/0.02° step) from 2.5 to 40 °2θ was used. A silicon standard was analyzed to check the instrument alignment. Samples were prepared for analysis by placing them in an aluminum/silicon sample holder.

[00108] Inel XRG-3000 Diffractometer: Analyses were also performed on an Inel XRG-3000 diffractometer, equipped with a curved position-sensitive detector with a 2θ range of 120°. Real time data were collected using Cu Kα radiation starting at approximately 4 °2θ at a resolution of 0.03 °2θ. The tube voltage and amperage were set to 40 kV and 30 mA, respectively. Samples were run for 5 or 15 minutes. Patterns are displayed from 2.5 to 40 °2θ to facilitate direct pattern comparisons. Samples were prepared for analysis by packing them into thin-walled glass capillaries. Each capillary was mounted onto a goniometer head that is motorized to permit spinning of the capillary during data acquisition. Instrument calibration was performed daily using a silicon reference standard.

[00109] XRPD Peak Picking Methods: Any XRPD files generated from an Inel instrument were converted to Shimadzu .raw file using File Monkey version 3.0.4. The Shimadzu .raw file was processed by the Shimadzu XRD-6000 version 4.1 software to automatically find peak positions. The "peak position" means the maximum intensity of a peaked intensity profile. Parameters used in peak selection are shown with each parameter set of the data. The following processes were used with the Shimadzu XRD-6000 "Basic Process" version 2.6 algorithm: 1) smoothing was done on all patterns; 2) the background was subtracted to find the net, relative intensity of the peaks; and 3) the Cu K alpha2 (1.5444 Å wavelength)

peak was subtracted from the pattern at 50% of the Cu K alpha1 (1.5406Å) peak intensity for all patterns. This method was used when selecting all peaks, except Form E. For Form E, peaks were selected using Match v 2.3.6 with default parameters.

[00110] Each figure listing XRPD peaks for each Form shows peaks selected by the peak picking method described above. Tables listing peaks for each Form shows peaks that are visually present in the diffractogram. Peaks which characteristically define the particular form are identified. I/Io is relative intensity.

[00111] Example 1: **Preparation of Racemic Ilaprazole, Form A**

[00112] 3% NH_4OH/Acetonitrile (MeCN) (6.00 kg, 15.0 parts) was charged to a flask. After adjusting the temperature to 5°C (2-8°C), Ilaprazole (0.400 kg) was charged and the contents were agitated for 1 hour. The slurry was filtered off and the filter cake rinsed with 3% NH_4OH/MeCN (2 x 0.400 kg, 2 x 1.00 part).

[00113] The filter cake was charged into the flask, followed by 0.5% NH_4OH/EtOH (0.200 kg, 0.500 part) and concentrated at 20-25°C under reduced pressure, until distillation stopped. 0.5% NH_4OH/EtOH (1.00 kg, 2.50 parts) was charged to the flask, followed by methylene chloride (2.40 kg, 6.00 parts). The resulting solution was concentrated at 20-25°C under reduced pressure to ca. 1.0 L (2.50 volumes). 0.5% NH_4OH/EtOH (1.20 kg, 3.00 parts) was charged and the mixture was concentrated at maximum 20-25°C under reduced pressure to ca. 1.2 L (3.00 volumes). 0.5% NH_4OH/EtOH (0.200 kg, 0.500 part) was charged and the contents were adjusted to 5°C (2-8°C) and agitated for 45 minutes. The slurry was filtered off and rinsed with 0.5% NH_4OH/EtOH (0.200 kg, 0.500 part), EtOH (0.200 kg, 0.500 part) and MTBE (2 x 0.200 kg, 2 x 0.500 part). The filter cake was pull-dried for 2 hours, and further dried under vacuum at maximum temperature of 53°C for 92 hours. Yield of racemic ilaprazole, Form A: 0.338 kg (85%). Particle size: 206

[00114] **Example 2:** Preparation and Characterization of Racemic Ilaprazole Form A

[00115] A saturated solution of ilaprazole in acetone and triethylamine was filtered through a nylon filter into a glass vial. The open vial was then exposed to hexanes vapor within a closed chamber. The sample was allowed to equilibrate at ambient temperature and humidity.

The crystals, recovered by decantation, were found to have a morphology of clustered needles and plates with birefringence and identified as racemic ilaprazole Form A.

[00116] The XRPD pattern of racemic ilaprazole Form A was obtained using a Shimadzu XRD-6000 X-ray powder diffractometer, as described above. The measurement conditions are reported in Table 3. Fig. 5 shows the XRPD pattern for racemic ilaprazole Form A. Table 4 reports the peaks identified in the XRPD pattern. In its XRPD racemic ilaprazole Form A may be characterized by peaks at 8.0 °2θ ± 0.2 °2θ; 13.2 °2θ ± 0.2 °2θ; and 24.1 °2θ ± 0.2 °2θ. Another characteristic grouping includes peaks at 8.0 °2θ ± 0.2 °2θ; 31.6 °2θ ± 0.2 °2θ; 32.0 °2θ ± 0.2 °2θ; 35.5 °2θ ± 0.2 °2θ; 36.1 °2θ ± 0.2 °2θ; 36.3 °2θ ± 0.2 °2θ; 37.8 °2θ ± 0.2 °2θ; and 38.9 °2θ ± 0.2 °2θ.

Table 3: Measurement Conditions for XRPD Pattern of Racemic Ilaprazole Form A.

Measurement Condition:		Data Process Condition:	
X-ray tube		Smoothing	[AUTO]
target	= Cu	smoothing points	= 13
voltage	= 40.0 (kV)		
current	= 40.0 (mA)	B.G. Subtraction	[AUTO]
		sampling points	= 13
Slits		repeat times	= 30
divergence slit	= 1.00000 (deg)		
scatter slit	= 1.00000 (deg)	Ka1-a2 Separate	[MANUAL]
receiving slit	= 0.15000 (mm)	Ka1 a2 ratio	= 50.0 (%)
Scanning		Peak Search	[AUTO]
drive axis	= 2Theta/Theta	differential points	= 13
scan range	= 2.500 - 40.000	FWHM threshold	= 0.050 (deg)
scan mode	= Continuous Scan	intensity threshold	= 30 (par mil)
scan speed	= 3.0000 (deg/min)	FWHM ratio (n-1)/n	= 2
sampling pitch	= 0.0200 (deg)		
preset time	= 0.40 (sec)	System Error Correction: [NO]	
		Precise Peak Correction: [NO]	

Table 3: Peak Positions of Ilaprazole Form A XRPD Pattern

Peak No.	Position (°2θ ± 0.2 °2θ)	d-spacing	Intensity	I/I$_o$
1	7.5	11.7	39	5
2	8.0	11.1	426	51
3	8.5	10.4	354	42
4	9.4	9.4	28	3
5	13.2	6.7	96	12
6	15.4	5.7	143	17
7	15.7	5.6	833	100
8	16.0	5.5	74	9
9	16.6	5.3	53	6
10	17.8	5.0	159	19
11	18.9	4.7	27	3
12	19.7	4.5	218	26
13	20.0	4.4	592	71
14	20.9	4.3	631	76
15	21.2	4.2	35	4
16	22.5	3.9	36	4
17	23.0	3.9	43	5
18	23.5	3.8	659	79
19	24.1	3.7	272	33
20	25.1	3.5	54	6
21	25.6	3.5	34	4
22	25.8	3.5	41	5
23	26.0	3.4	57	7
24	26.8	3.3	81	10
25	27.4	3.3	35	4
26	27.7	3.2	89	11
27	28.9	3.1	48	6
28	29.2	3.1	62	7
29	29.6	3.0	93	11
30	30.3	2.9	42	5
31	31.6	2.8	81	10
32	32.0	2.8	115	14
33	35.5	2.5	52	6
34	35.8	2.5	35	4
35	36.1	2.5	49	6
36	36.3	2.5	46	6
37	37.8	2.4	44	5
38	38.9	2.3	30	4

[00117] Fig. 6 is the TGA thermogram of racemic ilaprazole, Form A. The sample showed 0.3% weight loss up to 160 °C.

[00118] Fig. 7 is the DSC thermogram of racemic ilaprazole, Form A. The endotherm onset was at 167 °C (max 170 °C).

[00119] Fig. 8 is the proton NMR Spectrum of racemic ilaprazole, Form A. Peaks near 5.32 are due to solvent – not to ilaprazole. Peaks near 1.0 and 2.5 are due to triethylamine (TEA), which is used to stabilize ilaprazole in solution, and not to ilaprazole.

[00120] Fig. 9 is the solid state ^{13}C CP/MAS NMR spectrum of racemic ilaprazole, Form A. The spectrum is externally referenced against glycine at 176.5 ppm. The peaks in the solid state ^{13}C NMR spectrum are reported in Table 5. A minor amount of Form F was observed in the solid state ^{13}C NMR spectrum. The peaks associated with Form F are not reported in Table 5, although the peak at 148.4 ppm is coincident between the forms.

Table 5: Solid State ^{13}C NMR Peaks for Racemic Ilaprazole, Form A.

PPM	HEIGHT
163.9	89.8
154.6	71.1
148.4	104.2
141.8	94.2
139.1	92.8
137.2	105.2
123.9	66.1
122.1	88.6
120.1	141.8
111.6	83.2
108.2	80.9
61.0	63.8
56.1	135.6
12.6	104.2

[00121] Fig. 10 is the IR spectrum of racemic ilaprazole, Form A. Table 6 reports the absorbance peaks in the IR spectrum.

Table 6: Peaks in IR Spectrum of Racemic Ilaprazole, Form A

Position:	689.7	Intensity:	0.0164
Position:	730.9	Intensity:	0.131
Position:	775.0	Intensity:	0.0079
Position:	822.1	Intensity:	0.0673
Position:	832.5	Intensity:	0.0444
Position:	849.1	Intensity:	0.0220
Position:	869.5	Intensity:	0.0303
Position:	895.0	Intensity:	0.0155
Position:	961.0	Intensity:	0.0124
Position:	1018.5	Intensity:	0.0269
Position:	1050.7	Intensity:	0.0507
Position:	1067.0	Intensity:	0.0475
Position:	1079.2	Intensity:	0.0572
Position:	1096.6	Intensity:	0.0507
Position:	1116.4	Intensity:	0.0125
Position:	1147.6	Intensity:	0.0330
Position:	1178.7	Intensity:	0.0124
Position:	1186.6	Intensity:	0.0121
Position:	1222.2	Intensity:	0.0104
Position:	1255.1	Intensity:	0.0392
Position:	1296.0	Intensity:	0.0642
Position:	1337.9	Intensity:	0.0111
Position:	1358.2	Intensity:	0.0196
Position:	1378.5	Intensity:	0.0118
Position:	1386.5	Intensity:	0.0117
Position:	1428.4	Intensity:	0.0350
Position:	1457.1	Intensity:	0.0198
Position:	1480.7	Intensity:	0.0543
Position:	1510.6	Intensity:	0.0257
Position:	1539.9	Intensity:	0.0085
Position:	1559.4	Intensity:	0.0119
Position:	1581.7	Intensity:	0.0501
Position:	1623.0	Intensity:	0.0215
Position:	1652.8	Intensity:	0.0077
Position:	1684.2	Intensity:	0.0064
Position:	1733.8	Intensity:	0.0063
Position:	2360.9	Intensity:	0.0063
Position:	2586.3	Intensity:	0.0081
Position:	2791.8	Intensity:	0.0091
Position:	2838.4	Intensity:	0.0081
Position:	2879.0	Intensity:	0.0088
Position:	2935.3	Intensity:	0.0091
Position:	2966.2	Intensity:	0.0097
Position:	3074.6	Intensity:	0.0083
Position:	3098.3	Intensity:	0.0079

Position: 3853.2 Intensity: 0.0067

[00122] Fig. 11 is the RAMAN spectrum of racemic ilaprazole, Form A. Table 7 reports the absorbance peaks in the Raman spectrum.

Table 7: Peaks in the Raman Spectrum of Racemic Ilaprazole, Form A.

Position:	419.0	Intensity:	0.382
Position:	448.1	Intensity:	0.489
Position:	468.3	Intensity:	0.274
Position:	495.9	Intensity:	0.861
Position:	513.6	Intensity:	1.139
Position:	537.3	Intensity:	1.416
Position:	570.9	Intensity:	0.499
Position:	609.0	Intensity:	8.471
Position:	626.0	Intensity:	1.247
Position:	647.6	Intensity:	0.750
Position:	665.0	Intensity:	1.347
Position:	693.7	Intensity:	6.328
Position:	713.2	Intensity:	3.418
Position:	733.4	Intensity:	0.611
Position:	749.8	Intensity:	0.518
Position:	762.0	Intensity:	0.587
Position:	776.3	Intensity:	1.559
Position:	815.9	Intensity:	3.102
Position:	836.1	Intensity:	1.731
Position:	876.5	Intensity:	1.778
Position:	900.1	Intensity:	1.031
Position:	938.8	Intensity:	0.483
Position:	962.8	Intensity:	1.847
Position:	1019.7	Intensity:	2.473
Position:	1056.0	Intensity:	0.873
Position:	1076.7	Intensity:	1.525
Position:	1104.2	Intensity:	2.107
Position:	1119.9	Intensity:	3.057
Position:	1149.1	Intensity:	0.500
Position:	1179.9	Intensity:	11.380
Position:	1222.7	Intensity:	3.826
Position:	1251.2	Intensity:	4.911
Position:	1266.1	Intensity:	12.991
Position:	1296.3	Intensity:	3.051
Position:	1306.7	Intensity:	5.460
Position:	1337.8	Intensity:	24.178
Position:	1358.5	Intensity:	2.454
Position:	1386.7	Intensity:	3.014

Position:	1429.9	Intensity:	10.411
Position:	1457.9	Intensity:	4.703
Position:	1483.8	Intensity:	2.072
Position:	1512.5	Intensity:	8.978
Position:	1583.4	Intensity:	4.749
Position:	1623.7	Intensity:	9.033
Position:	2839.0	Intensity:	1.219
Position:	2859.6	Intensity:	1.659
Position:	2883.9	Intensity:	0.722
Position:	2935.4	Intensity:	4.143
Position:	2966.2	Intensity:	1.164
Position:	2992.6	Intensity:	1.344
Position:	3021.9	Intensity:	2.174
Position:	3063.9	Intensity:	2.400
Position:	3075.3	Intensity:	3.810
Position:	3098.6	Intensity:	2.686
Position:	3110.2	Intensity:	1.922
Position:	3130.6	Intensity:	3.377

[00123] Fig. 12 is the DVS isotherm of racemic ilaprazole, Form A. The DVS isotherm shows a 0.06% weight loss at 5% RH, a 0.10% weight gain from 5 to 95% RH and a 0.13% weight loss from 95 to 5% RH.

[00124] A single crystal X-ray diffraction study of the structure of racemic ilaprazole, Form A was done. The data was collected using colorless plate of racemic ilaprazole, Form A having approximate dimensions of 0.44 x 0.35 x 0.13 mm, which was mounted on a glass fiber in random orientation. Preliminary examination and data collection were performed with Mo K_α radiation (λ = 0.71073 Å) on a Nonius KappaCCD diffractometer. Refinements were performed on an LINUX PC using SHELX97. Sheldrick, G. M. *SHELX97, A Program for Crystal Structure Refinement*, University of Gottingen, Germany, 1997. The crystallographic drawings were obtained using the programs ORTEP (Johnson, C. K. ORTEPIII, Report ORNL-6895, Oak Ridge National Laboratory, TN, U.S.A. 1996; OPTEP-3 for Windows V1.05 ,. Farrugia, L.J., *J. Appl. Cryst.* **1997**, *30*, 565); CAMERON (Watkin, D. J.; Prout, C .K.; Pearce, L. J. CAMERON, Chemical Crystallography Laboratory, University of Oxford, Oxford, 1996), and Mercury (Bruno, I. J. Cole, J. C. Edgington, P. R. Kessler, M. K. Macrae, C. F. McCabe, P. Pearson, J. and Taylor, R. *Acta Crystallogr.*, **2002** *B58*, 389).

[00125] Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 8027 reflections in the range $2° < \theta < 27°$.

The refined mosaicity from DENZO/SCALEPACK (Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307) is 0.54° indicating moderate crystal quality. The space group was determined by the program XPREP. Bruker, XPREP in SHELXTL v. 6.12., Bruker AXS Inc., Madison, WI, USE, **2002**. From the systematic presence of the following conditions: $0k0$ $k=2n$, and from subsequent least-squares refinement, the space group was determined to be $P2_1$ (no. 4). The data were collected to a maximum 2θ value of 54.9°, at a temperature of 150 ± 1 K.

[00126] The data reduction was done as follows: Frames were integrated with DENZO-SMN. Otwinoski et al., supra. A total of 8027 reflections were collected, of which 3676 were unique. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient was 2.0 cm^{-1} for Mo K_α radiation. An empirical absorption correction using SCALEPACK (Otwinoski et al., supra) was applied. Transmission coefficients ranged from 0.94 to 0.98. Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 4.3% based on intensity.

[00127] The structure was solved by direct methods using SIR2004. Burla, M.C., Caliandro, R., Camalli, M,. Carrozzini, B., Cascarano, G.L., De Caro, L., Giacovazzo, C., Polidori, G., and Spagna, R., *J. Appl. Cryst.* **2005**, *38*, 381. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least-squares by minimizing the function:

$$\sum w\left(|F_o|^2 - |F_c|^2\right)^2$$

The weight w is defined as $1/[\sigma^2(F_o^2) + (0.0507P)^2 + (0.0000P)]$, where $P = (F_o^2 + 2F_c^2)/3$.

[00128] Scattering factors were taken from the "International Tables for Crystallography." International Tables for Crystallography, Vol. C, Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992, Tables 4.2.6.8 and 6.1.1.4. Of the 3676 reflections used in the refinements, only the reflections with $F_o^2 > 2\sigma(F_o^2)$ were used in calculating R. A total of 2844 reflections were used in the calculation. The final cycle of refinement included 252 variable parameters and converged (largest parameter shift was approximately equal to its estimated standard deviation) with unweighted and weighted agreement factors of:

$$R = \sum |F_o - F_c| / \sum F_o = 0.041$$

$$R_w = \sqrt{\left(\sum w\left(F_o^2 - F_c^2\right)^2 / \sum w\left(F_o^2\right)^2 \right)} = 0.091$$

[00129] The standard deviation of an observation of unit weight was 1.014. The highest peak in the final difference Fourier had a height of 0.22 e/Å^3. The minimum negative peak had a height of -0.30 e/Å^3. The factor for the determination of the absolute structure (Flack, H. D. *Acta Cryst.* **1983,** *A39*, 876) refined to -0.04(8).

[00130] A calculated XRPD pattern was generated for Cu radiation using Mercury 1.3 and the atomic coordinates, space group, and unit cell parameters from the single crystal data.

[00131] A summary of the crystal data and crystallographic data collection parameters for racemic ilaprazole Form A are provided in Table 8. The monoclinic cell parameters and calculated volume are: a = 10.8006(9) Å, b = 7.3333(3) Å, c = 11.5247(10) Å, α = 90.00°, β = 107.261(4)°, γ = 90.00°, V = 871.69(11) Å^3. The formula weight of ilaprazole Form A is 366.44 g/mol, with Z = 2 and a calculated density of 1.396 g cm^{-3}. The space group was determined to be $P2_1$. The quality of the structure obtained is high, as indicated by the R-value of 0.041 (4.1%). Usually R-values in the range of 0.02 to 0.06 are quoted for the most reliably determined structures.

Table 8 Single Crystal Data and Data Collection Parameters for Racemic Ilaprazole, Form A.

formula	$C_{19}H_{18}N_4O_2S$
formula weight	366.44
space group	$P2_1$ (No. 4)
a, Å	10.8006(9)
b, Å	7.3333(3)
c, Å	11.5247(10)
b, deg	107.261(4)
V, Å^3	871.69(11)
Z	2
d_{calc}, g cm^{-3}	1.396
crystal dimensions, mm	0.44x0.35x0.13
temperature, K	150
radiation (wavelength, Å)	Mo K_a (0.71073)
monochromator	graphite
linear abs coef, mm^{-1}	0.198
absorption correction applied	empirical[a]
transmission factors: min, max	0.94, 0.98
diffractometer	Nonius KappaCCD
h, k, l range	-13 to 14 -8 to 8 -14 to 14

2θ range, deg	4.54-54.94
mosaicity, deg	0.54
programs used	SHELXTL
F_{000}	384.0
weighting $1/[\sigma^2(F_o^2)+(0.0507P)^2+0.0000P]$ where $P=(F_o^2+2F_c^2)/3$	
data collected	8027
unique data	3676
R_{int}	0.043
data used in refinement	3676
cutoff used in R-factor calculations	$F_o^2>2.0\sigma(F_o^2)$
data with $I>2.0\sigma(I)$	2844
refined extinction coef	0.0300
number of variables	252
largest shift/esd in final cycle	0.01
$R(F_o)$	0.041
$R_w(F_o^2)$	0.091
goodness of fit	1.014
absolute structure determination	*F*lack parameter[b] (-0.04(8))

[a] Otwinowski Z. & Minor, W. *Methods Enzymol.*, **1997**, *276*, 307.
[b].Flack,H. D. *Acta Cryst.*, **1983** *A39*, 876.

[00132] An ORTEP drawing of racemic ilaprazole form A is shown in Fig. 13. Atoms are represented by 50% probability anisotropic thermal ellipsoids. Note that the appearance of the second oxygen affixed to the sulfinyl group is a representation of the disorder most likely caused by the presence of both enantiomers in the unit cell. The occupancy of the enantiomers was refined to approximately a 75:25 ratio. The major enantiomer is represented with a solid bond between S2 and O2a and the minor enantiomer with a hollow bond between S2 and O2b, respectively. The material appears to be a member of a rare class of racemic compounds where the stoichiometry of the two enantiomers is not a 1:1 ratio. This class of compounds is sometimes referred to "anomalous" racemates. The asymmetric unit shown in Fig. 14 contains a single ilaprazole molecule exhibiting a packing arrangement where every fourth molecule is the minor enantiomer.

[00133] Packing diagrams viewed along the *a*, *b*, and *c* crystallographic axes are shown in Figs. 14–16 respectively. The packing arrangement in the Form A crystal structure can be described as sheets of ilaprazole molecules running perpendicular to the crystallographic *b* axis (Fig. 15). The calculated density of the Form A crystal structure (1.396 g cm^{-3}) is slightly higher that the Form F crystal structure (1.391 g cm^{-3}), suggesting Form A would be the more stable form at 150 K.

[00134] Hydrogen bonds are observed between the secondary amine (N3) of the benzimidazole ring of one ilaprazole molecule to the pyridine nitrogen (N26) of an adjacent ilaprazole molecule. This hydrogen-bonding network forms sheets of ilaprazole molecules that are rotated approximately 90° from each other, resulting in a one-dimensional hydrogen bonding network. Closer examination of the structure reveals two close contacts between the two oxygen sites of the sulfinyl group. There is a close contact of approximately 3.4 Å between the oxygen atom of the major enantiomer (O2a) and the nitrogen atom secondary amine (N3) of the benzimidazole group. This is not a hydrogen bonding interaction because the hydrogen atom in not in a position to interact with the sulfinyl oxygen. The second close contact of approximately 3.3 Å between the oxygen atom of the minor enantiomer (O2b) and the ether linkage might actually be a slightly repulsive interaction due to the lone pairs. No other potential interactions were observed in the crystal structure.

[00135] Fig. 17 shows a calculated XRPD pattern of ilaprazole, generated from the single crystal data. The experimental XRPD pattern of ilaprazole Form A is shown in Fig. 5. Fig. 18 shows a comparison of the calculated XRPD pattern to the experimental pattern of racemic ilaprazole Form A. All peaks in the experimental patterns are represented in the calculated XRPD pattern, indicating the bulk material is likely a single phase. The slight shifts in peak location are likely due to the fact that the experimental powder pattern was collected at ambient temperature, and the single crystal data was collected at 150 K. Low temperatures are used in single crystal analysis to improve the quality of the structure.

[00136] If the material was a single enantiomer, the absolute configuration of the molecule would be determined by analysis of anomalous X-ray scattering by the crystal. The differences in intensities of the anomalous scattering are then compared with calculated scattering intensities for each enantiomer. These measured and calculated intensities can then be fit to a parameter, the Flack factor. Because each crystal contains a mixture of enantiomers and therefore is not enantiopure, the absolute configuration of the model in Fig. 13 cannot be uniquely determined with the current data set.

[00137] **Example 3**: Preparation and Characterization of Racemic Ilaprazole, Form F

[00138] Approximately 153.4 mg racemic ilaprazole Form A was added to a solution containing 3 mL dichloromethane (DCM) and 10 μL triethylamine (TEA). The solid was

dissolved using sonication. The solution was filtered through a 0.2 micron nylon filter into a glass vial and left to evaporate at ambient room temperature. A lightly colored solid resulted approximately 1 day later, which was identified as Form F.

[00139] Racemic ilaprazole, Form F was also prepared by the following procedure. Racemic ilaprazole (0.5 g, Form A) was slurried in EtOH/10% water (5 mL, 10 volumes) and was stirred at 0 °C for 24 h. The resulting solids were isolated by filtration and dried under vacuum at 40 °C to afford 0.44 g of Form K; 87.8 % recovery. Racemic ilaprazole (40 mg, Form K) was then slurried in anhydrous EtOH (2 mL, 50 vol) and stirred at temperatures ranging from 5 to 20 °C for 24 h. The obtained solids were isolated by filtration and dried under vacuum at 40 °C to afford Form F. A slurry temperature of 6 °C is preferred.

[00140] The XRPD pattern of racemic ilaprazole, Form F was obtained using an Inel XRG-3000 diffractometer, as described above. The measurement conditions are reported in Table 9. Fig. 19 shows the XRPD pattern for racemic ilaprazole, Form F. Table 10 reports the peaks identified in the XRPD pattern. In its XRPD racemic ilaprazole, Form F may be characterized by peaks at 9.4 °2θ ± 0.2 °2θ; 17.5 °2θ ± 0.2 °2θ; 18.8 °2θ ± 0.2 °2θ and 32.8 °2θ ± 0.2 °2θ. Another characteristic grouping includes peaks at 7.9 °2θ ± 0.2 °2θ; 28.8 °2θ ± 0.2 °2θ; 30.5 °2θ ± 0.2 °2θ; 31.9 °2θ ± 0.2 °2θ and 35.8 °2θ ± 0.2 °2θ.

Table 9: Measurement Conditions for XRPD Pattern of Racemic Ilaprazole, Form F

Measurement Condition:		Data Process Condition:	
X-ray tube		Smoothing	[AUTO]
target	= Cu	smoothing points	= 11
voltage	= 40.0 (kV)		
current	= 30.0 (mA)	B.G. Subtraction	[AUTO]
		sampling points	= 13
Slits		repeat times	= 30
divergence slit	= 1.00000 (deg)		
scatter slit	= 1.00000 (deg)	Ka1-a2 Separate	[MANUAL]
receiving slit	= 0.15000 (mm)	Ka1 a2 ratio	= 50.0 (%)
Scanning		Peak Search	[AUTO]
drive axis	= 2Theta/Theta	differential points	= 11
scan range	= 2.507 - 39.987	FWHM threshold	= 0.050 (deg)
scan mode	= Continuous Scan	intensity threshold	= 30 (par mil)
scan speed	= 0.0040 (deg/min)	FWHM ratio (n-1)/n	= 2

sampling pitch = 0.0200 (deg) preset time = 300.00 (sec)	System Error Correction: [NO] Precise Peak Correction: [NO]

Table 10: Peak Positions of Racemic Ilaprazole, Form F XRPD Pattern

Peak No.	Position (°2θ ± 0.2 °2θ)	d-spacing	Intensity	I/I_o
1	7.9	11.2	614	22
2	8.5	10.4	1619	59
3	9.4	9.4	784	29
4	14.6	6.1	184	7
5	14.9	5.9	142	5
6	15.1	5.8	90	3
7	15.4	5.7	135	5
8	15.8	5.6	2600	95
9	17.5	5.1	505	18
10	18.8	4.7	752	27
11	19.2	4.6	114	4
12	19.5	4.5	89	3
13	20.0	4.4	757	28
14	20.3	4.4	616	22
15	20.6	4.3	166	6
16	21.0	4.2	2742	100
17	22.5	3.9	1327	48
18	23.5	3.8	763	28
19	23.7	3.7	242	9
20	24.6	3.6	339	12
21	25.0	3.6	124	5
22	25.9	3.4	102	4
23	26.8	3.3	170	6
24	27.1	3.3	465	17
25	27.8	3.2	196	7
26	28.5	3.1	118	4
27	28.8	3.1	114	4
28	29.5	3.0	184	7
29	29.8	3.0	212	8
30	30.1	3.0	157	6
31	30.5	2.9	135	5
32	31.9	2.8	229	8
33	32.8	2.7	278	10

34	33.1	2.7	198	7
35	35.8	2.5	85	3

[00141] Fig. 20 is the TGA thermogram of racemic ilaprazole, Form F. The sample showed a 2.4% weight loss up to 150 °C.

[00142] Fig. 21 is the DSC thermogram of racemic ilaprazole, Form F. The endotherm onset was at 170 °C (max 173 °C).

[00143] Fig. 22 is the proton NMR Spectrum of racemic ilaprazole, Form F. Any peaks near 5.32 ppm are due to solvent – not to ilaprazole. Peaks near 1.0 and 2.5 ppm are due to TEA, which is used to stabilize ilaprazole in solution, and not to ilaprazole.

[00144] Fig. 23 is the solid state ^{13}C CP/MAS NMR spectrum of racemic ilaprazole, Form F. The spectrum is externally referenced against glycine at 176.5 ppm. The peaks in the solid state ^{13}C NMR spectrum are reported in Table 11.

Table 11: Solid State ^{13}C NMR Peaks for Racemic Ilaprazole, Form F.

PPM	HEIGHT
164.2	72.4
156.2	64.0
148.4	104.2
143.2	75.7
137.4	141.8
121.2	137.2
110.4	79.1
107.7	55.2
60.3	54.1
56.3	103.3
10.5	95.9

[00145] Fig. 24 is the IR spectrum of racemic ilaprazole, Form F. Table 12 reports the absorbance peaks in the IR spectrum.

Table 12: Peaks in IR Spectrum of Racemic Ilaprazole, Form F.

Position:	721.3	Intensity:	0.0746
Position:	817.9	Intensity:	0.0384
Position:	833.0	Intensity:	0.0296
Position:	876.1	Intensity:	0.0125

Position:	895.1	Intensity:	0.0074
Position:	962.0	Intensity:	0.0038
Position:	1015.9	Intensity:	0.0209
Position:	1052.9	Intensity:	0.0308
Position:	1064.8	Intensity:	0.0289
Position:	1080.3	Intensity:	0.0402
Position:	1096.5	Intensity:	0.0355
Position:	1148.8	Intensity:	0.0160
Position:	1187.3	Intensity:	0.0042
Position:	1221.1	Intensity:	0.0034
Position:	1255.0	Intensity:	0.0246
Position:	1295.2	Intensity:	0.0398
Position:	1337.4	Intensity:	0.0022
Position:	1358.8	Intensity:	0.0081
Position:	1379.3	Intensity:	0.0050
Position:	1434.2	Intensity:	0.0183
Position:	1454.8	Intensity:	0.0053
Position:	1478.4	Intensity:	0.0278
Position:	1509.7	Intensity:	0.0124
Position:	1580.8	Intensity:	0.0293
Position:	1623.1	Intensity:	0.0073
Position:	1723.7	Intensity:	0.00054
Position:	1903.9	Intensity:	0.00058
Position:	2587.5	Intensity:	0.0022
Position:	2794.3	Intensity:	0.0028
Position:	2841.0	Intensity:	0.0022
Position:	2881.5	Intensity:	0.0026
Position:	2971.7	Intensity:	0.0038
Position:	3011.4	Intensity:	0.0030
Position:	3072.9	Intensity:	0.0032
Position:	3100.8	Intensity:	0.0027
Position:	3735.3	Intensity:	0.0010

[00146] Fig. 25 is the RAMAN spectrum of racemic ilaprazole, Form F. Table 13 reports the absorbance peaks in the Raman spectrum.

Table 13: Peaks in the Raman Spectrum of Racemic Ilaprazole, Form F

Position:	100.2	Intensity:	2.257
Position:	122.9	Intensity:	2.700
Position:	171.0	Intensity:	1.653
Position:	238.3	Intensity:	1.247
Position:	311.8	Intensity:	1.028
Position:	441.9	Intensity:	1.048
Position:	511.4	Intensity:	1.464

Position:	533.6	Intensity:	1.198
Position:	610.5	Intensity:	6.403
Position:	694.6	Intensity:	4.080
Position:	715.5	Intensity:	2.084
Position:	778.0	Intensity:	1.180
Position:	816.8	Intensity:	2.217
Position:	877.2	Intensity:	1.112
Position:	898.2	Intensity:	0.895
Position:	970.7	Intensity:	1.336
Position:	1020.8	Intensity:	1.520
Position:	1081.5	Intensity:	1.116
Position:	1101.4	Intensity:	1.434
Position:	1122.2	Intensity:	1.769
Position:	1182.2	Intensity:	5.141
Position:	1222.7	Intensity:	2.099
Position:	1269.0	Intensity:	6.256
Position:	1298.6	Intensity:	2.538
Position:	1312.2	Intensity:	2.544
Position:	1338.4	Intensity:	15.434
Position:	1360.2	Intensity:	1.596
Position:	1383.9	Intensity:	1.700
Position:	1432.8	Intensity:	5.905
Position:	1460.3	Intensity:	2.586
Position:	1511.7	Intensity:	5.232
Position:	1582.7	Intensity:	2.970
Position:	1624.4	Intensity:	4.880
Position:	2842.4	Intensity:	1.136
Position:	2934.0	Intensity:	3.251
Position:	3014.8	Intensity:	2.247
Position:	3073.7	Intensity:	4.180
Position:	3103.0	Intensity:	2.744
Position:	3131.0	Intensity:	1.871
Position:	3150.4	Intensity:	1.583

[00147] Fig. 26 is the DVS isotherm of racemic ilaprazole, Form F. The DVS isotherm shows a 0.04% weight loss at 5% RH, a 1.05% weight gain from 5 to 95% RH, and a 1.33% weight loss from 95 to 5% RH.

[00148] A single crystal X-ray diffraction study of racemic ilaprazole, Form F was done using crystals obtained from a acetone/methylene chloride solution. A solution of ilaprazole (~35.8 mg) and piperazine (~10.4 mg) was prepared in a solvent mixture of acetone (2.0 mL) and methylene chloride (0.5 mL) at room temperature. Hexanes (5.0 mL) were added to provide a turbid solution. The vial was sealed and the solution was left, undisturbed, at ambient

conditions. Racemic ilaprazole, Form F crystals were observed after six days were subsampled from the parent sample.

[00149] The data was collected using a colorless needle of racemic ilaprazole, Form F having approximate dimensions of 0.44 x 0.13 x 0.10 mm, which was mounted on a glass fiber in random orientation. Preliminary examination and data collection were performed with Mo K_α radiation (λ = 0.71073 Å) on a Nonius KappaCCD diffractometer. Refinements were performed on an LINUX PC using SHELX97. Sheldrick, G. M. *SHELX97, A Program for Crystal Structure Refinement*, University of Gottingen, Germany, 1997.

[00150] Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 22729 reflections in the range $2° < \theta < 27°$. The refined mosaicity from DENZO/SCALEPACK (Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307) is 0.85° indicating moderate to poor crystal quality. The space group was determined by the program XPREP. Bruker, XPREP in SHELXTL v. 6.12., Bruker AXS Inc., Madison, WI, USE, **2002**. From the systematic presence of the following conditions: *h0l h+l=2n , 0k0 k=2n* and from subsequent least-squares refinement, the space group was determined to be $P2_1/n$ (no. 14). The data were collected to a maximum 2θ value of 54.94°, at a temperature of 150 ± 1 K.

[00151] The data reduction was accomplished as follows. The frames were integrated with DENZO-SMN. Otwinowski, et al. supra. A total of 22729 reflections were collected, of which 2277 were unique. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 2.0 cm^{-1} for Mo K_α radiation. An empirical absorption correction using SCALEPACK (Otwinowski, et al. supra). was applied. Transmission coefficients ranged from 0.912 to 0.981. Intensities of equivalent reflections were averaged. A secondary extinction correction was applied. The final coefficient, refined in least-squares, was 0.0010000 (in absolute units). The agreement factor for the averaging was 5.4% based on intensity.

[00152] The structure was solved by direct methods using PATTY in DIRDIF99. P. T. Beurskens, G. Beurskens, R. deGelderS. Garcia-Granda, R. O. Gould, R. Israel and J. M. M. Smits, The DIRDIF-99 Program System. Crystallography Laboratory, Univ. of Nijmegen, The Netherlands, **1999**. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to

which they are bonded. The structure was refined in full-matrix least-squares by minimizing the function:

$$\sum w\left(|F_o|^2 - |F_c|^2\right)^2$$

The weight w is defined as $1/[\sigma^2(F_o^2) + (0.1403P)^2 + (0.5425P)]$, where $P = (F_o^2 + 2F_c^2)/3$.

[00153] Scattering factors were taken from the "International Tables for Crystallography." International Tables for Crystallography, Vol. C, Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992, Tables 4.2.6.8 and 6.1.1.4. Of the 2277 reflections used in the refinements, only the reflections with $F_o^2 > 2\sigma(F_o^2)$ were used in calculating R. A total of 1706 reflections were used in the calculation. The final cycle of refinement included 252 variable parameters and converged (largest parameter shift was essentially equal to its estimated standard deviation) with unweighted and weighted agreement factors of:

$$R = \sum |F_o - F_c| / \sum F_o = 0.066$$

$$R_w = \sqrt{\left(\sum w\left(F_o^2 - F_c^2\right)^2 / \sum w\left(F_o^2\right)^2\right)} = 0.174$$

The standard deviation of an observation of unit weight was 1.07. The highest peak in the final difference Fourier had a height of 0.63 e/Å^3. The minimum negative peak had a height of -0.46 e/Å^3.

[00154] A calculated XRPD pattern was generated for Cu K_α radiation using Mercury v 1.3 (Bruno, I. J. Cole, J. C. Edgington, P. R. Kessler, M. K. Macrae, C. F. McCabe, P. Pearson, J. and Taylor, R. *Acta Crystallogr.*, **2002** *B58*, 389) and the atomic coordinates, space group, and unit cell parameters from the single crystal data.

[00155] The ORTEP diagram was prepared using ORTEP III. Johnson, C. K. ORTEPIII, Report ORNL-6895, Oak Ridge National Laboratory, TN, U.S.A. 1996. OPTEP-3 for Windows V1.05, Farrugia, L.J., J. Appl. Cryst. **1997**, 30, 565. Atoms are represented by 50% probability anisotropic thermal ellipsoids. Packing diagrams were prepared using CAMERON (Watkin, D. J.; Prout, C .K.; Pearce, L. J. CAMERON, Chemical Crystallography Laboratory, University of Oxford, Oxford, 1996) modeling software. Hydrogen bonding is represented as dashed lines. Additional figures were generated using Mercury 1.3 modeling software.

[00156] A summary of the crystal data and crystallographic data collection parameters for racemic ilaprazole Form F are provided in Table 14. The monoclinic cell parameters and calculated volume are: a = 11.8469(8) Å, b = 7.2242(3) Å, c = 20.9109(16) Å, α = 90.00°, β = 102.224(3)°, γ = 90.00°, V = 1749.07(19) Å^3. The formula weight of ilaprazole, Form F is 366.44 g/mol and with Z = 4 gives a calculated density of 1.391 g cm^{-3}. The space group was determined to be $P2_1/n$. The quality of the structure obtained is moderate, as indicated by the R-value of 0.066 (6.6%). Usually R-values in the range of 0.02 to 0.06 are quoted for the most reliably determined structures. Glusker, Jenny Pickworth; Trueblood, Kenneth N. *Crystal Structure Analysis: A Primer*, 2nd ed.; Oxford University press: New York, 1985; p.87.

Table 14. Single Crystal Data and Data Collection Parameters for Ilaprazole, Form F

formula	$C_{19}H_{18}N_4O_2S$
formula weight	366.44
space group	$P2_1/n$ (No. 14)
a, Å	11.8469(8)
b, Å	7.2242(3)
c, Å	20.9109(16)
β, deg	102.224(3)
V, Å^3	1749.07(19)
Z	4
d_{calc}, g cm^{-3}	1.391
crystal dimensions, mm	0.44 x 0.13 x 0.10
temperature, K	150.
radiation (wavelength, Å)	Mo K_a (0.71073)
monochromator	graphite
linear abs coef, mm^{-1}	0.197
absorption correction applied	empirical[a]
transmission factors: min, max	0.912, 0.981
diffractometer	Nonius KappaCCD
h, k, l range	0 to 15 0 to 9 -27 to 26
2θ range, deg	4.73-54.95
mosaicity, deg	0.85
programs used	SHELXTL
F_{000}	768.0
weighting $1/[\sigma^2(F_o^2)+(0.1403P)^2+0.5425P]$ where $P=(F_o^2+2F_c^2)/3$	
data collected	22729
unique data	2277
R_{int}	0.054
data used in refinement	2277
cutoff used in R-factor calculations	$F_o^2>2.0\sigma(F_o^2)$
data with $I>2.0\sigma(I)$	1706
refined extinction coef	0.0010
number of variables	252
largest shift/esd in final cycle	0.00
$R(F_o)$	0.066

$R_w(F_o^2)$	0.174
goodness of fit	1.072

[a] Otwinowski Z. & Minor, W. *Methods Enzymol.*, **1997**, *276*, 307.

[00157] An ORTEP drawing of racemic ilaprazole, Form F is shown in Fig. 27. Atoms are represented by 50% probability anisotropic thermal ellipsoids. The oxygen atom of the sulfinyl group is disordered due to the presence of both enantiomers in the unit cell. The occupancy of the enantiomers was refined to a ratio of approximately 86:14. The ORTEP diagram (Fig. 27) highlights the major enantiomer with a solid bond between S2 and O10a and the minor enantiomer with a hollow bond between S2 and O10b, respectively. The material appears to be an example of a rare class of compounds called "anomalous" racemates, where the stoichiometry of the two enantiomers is not a 1:1 ratio.

[00158] Packing diagrams viewed along the *a, b,* and *c* crystallographic axes are shown in Figs. 28-30 respectively. The packing arrangement of ilaprazole molecules in the Form F crystal structure can be described as sheets of ilaprazole molecules running perpendicular to the crystallographic *b* axis (Fig.29). Overlaying the ilaprazole molecule from this crystal structure (Fig. 27) and the ilaprazole molecule from the Form A crystal structure (Fig. 13) showed significant conformational similarity of the ilaprazole molecule in the two crystal structures. The Form F crystal structure consists of layers of ilaprazole molecules packing in a alternating ABAB arrangement.

[00159] Hydrogen bonds were observed between the secondary amine (N3) of the benzimidazole ring of one ilaprazole molecule to the pyridine nitrogen (N16) of an adjacent molecule, resulting in a similar hydrogen bonding pattern observed for racemic ilaprazole, Form A. Closer examination of the structure reveals two close contacts between the two oxygen sites of the sulfinyl group. There is a close contact of approximately 3.2 Å between the oxygen atom of the major enantiomer (O10a) and the nitrogen atom secondary amine (N3) of the benzimidazole group. This is not a potential hydrogen bonding interaction because the hydrogen atom is not in a position to interact with the sulfinyl oxygen. The second close contact of approximately 3.0 Å between the oxygen atom of the minor enantiomer (O10b) and the oxygen atom of the ether linkage (O131). This close contact is probably a slightly repulsive interaction since the shorter distance (3.0 Å for Form F and 3.4 Å for Form A) appears to be related to the occupancy of the minor enantiomer (~14 % for Form F and ~25% for Form A).

[00160] While the molecular conformations are very similar, the packing between the two forms is different. The packing along the crystallographic *b* axis for racemic ilaprazole, Form A and Form F is shown in Fig. 31. In the Form A crystal structure, the layers run parallel to the crystallographic *c* axis, while in Form F, the layers run perpendicular to the *c* axis. The layers propagate in an alternating fashion for the Form F crystal structure, accounting for the doubling of the *c* axis parameter. The calculated density of the Form A crystal structure (1.396 g cm^{-3}) is slightly higher that the Form F crystal structure (1.391 g cm^{-3}), suggesting Form A would be more stable at 0 K.

[00161] Fig. 31 shows a calculated XRPD pattern of ilaprazole, From F, generated from the single crystal data. The experimental XRPD pattern of ilaprazole, Form F is shown in Fig. 32 and a comparison of the calculated and experimental powder diffraction patterns is shown in Fig. 33. All peaks in the experimental patterns are represented in the calculated XRPD pattern, indicating the bulk material is likely a single phase. The slight shifts in peak location are likely due to the fact that the experimental powder pattern was collected at ambient temperature, and the single crystal data was collected at 150 K. Low temperatures are used in single crystal analysis to improve the quality of the structure.

[00162] **Example 4:** Preparation and Characterization of Racemic Ilaprazole, Form I

[00163] A solution containing 3 mL of methanol (MeOH) and 10 μL triethylamine (TEA) was saturated with racemic ilaprazole, Form A by sonicating with excess solids for approximately 3 minutes. The resulting slurry was filtered through a 0.2 micron nylon filter into a glass vial. The vial was capped and placed into the freezer. The resulting white solid was collected by vacuum filtration approximately 2 days later as the methanol solvate, Form G, which is believed to be a variable solvate. A small spatula full of Form G (e.g. >30 mg) was placed in a 1 dram glass vial. The open vial was exposed to ambient temperature under vacuum. A white solid resulted approximately 1 day later as Form I.

[00164] The XRPD pattern of racemic ilaprazole, Form I was obtained using an Inel XRG-3000 diffractometer, as described above. The measurement conditions are reported in Table 15. Fig. 34 shows the XRPD pattern for racemic ilaprazole, Form I. Table 16 reports the peaks identified in the XRPD pattern. In its XRPD racemic ilaprazole, Form I may be characterized by peaks at 11.9 °2θ ± 0.2 °2θ; 17.1 °2θ ± 0.2 °2θ; 21.5 °2θ ± 0.2 °2θ and 25.1

°2θ ± 0.2 °2θ. Another characteristic grouping includes peaks at 5.9 2θ ± 0.2 °2θ; 12.2 2θ ± 0.2 °2θ, and 35.6 2θ ± 0.2 °2θ.

Table 15: Measurement Conditions for XRPD Pattern of Racemic Ilaprazole, Form I.

Measurement Condition:	Data Process Condition:
X-ray tube target = Cu voltage = 40.0 (kV) current = 30.0 (mA) Slits divergence slit = 1.00000 (deg) scatter slit = 1.00000 (deg) receiving slit = 0.15000 (mm) Scanning drive axis = 2Theta/Theta scan range = 2.507 - 39.987 scan mode = Continuous Scan scan speed = 0.0040 (deg/min) sampling pitch = 0.0200 (deg) preset time = 300.00 (sec)	Smoothing [AUTO] smoothing points = 11 B.G. Subtraction [AUTO] sampling points = 13 repeat times = 30 Ka1-a2 Separate [MANUAL] Ka1 a2 ratio = 50.0 (%) Peak Search [AUTO] differential points = 11 FWHM threshold = 0.050 (deg) intensity threshold = 30 (par mil) FWHM ratio (n-1)/n = 2 System Error Correction: [NO] Precise Peak Correction: [NO]

Table 16: Peak Positions of Ilaprazole, Form I XRPD Pattern

Peak No.	Position (°2θ± 0.2 °2θ)	d-spacing	Intensity	I/I_0
1	5.9	15.0	3236	100
2	6.5	13.7	182	6
3	11.4	7.8	254	8
4	11.9	7.5	1453	45
5	12.2	7.2	100	3
6	13.0	6.8	101	3
7	15.1	5.8	174	5
8	15.8	5.6	142	4
9	16.2	5.5	198	6
10	17.1	5.2	283	9
11	17.5	5.1	391	12
12	17.8	5.0	125	4
13	18.1	4.9	167	5

14	20.6	4.3	402	12
15	21.5	4.1	458	14
16	21.7	4.1	183	6
17	24.6	3.6	180	6
18	25.1	3.5	618	19
19	25.3	3.5	207	6
20	25.7	3.5	219	7
21	35.6	2.5	98	3

[00165] Fig. 35 is the TGA thermogram of racemic ilaprazole, Form I. The sample showed a 0.9% weight loss up to 30 °C and 0.4% weight loss between 30 and 120 °C.

[00166] Fig. 36 is the DSC thermogram of racemic ilaprazole, Form I. The endotherm onset occurred at 113 °C (max 134 °C).

[00167] Fig. 37 is the proton NMR Spectrum of racemic ilaprazole, Form I. Any peaks near 5.32 ppm are due to solvent – not to ilaprazole. Peaks near 1.0 and 2.5 ppm are due to TEA, which is used to stabilize ilaprazole in solution, and not to ilaprazole.

[00168] Fig. 38 is the IR spectrum of racemic ilaprazole, Form I. Table 17 reports the absorbance peaks in the IR spectrum.

Table 17: Peaks in IR Spectrum of Racemic Ilaprazole, Form I.

Position:	716.8	Intensity:	0.0196
Position:	729.6	Intensity:	0.0262
Position:	744.1	Intensity:	0.0620
Position:	780.3	Intensity:	0.0037
Position:	810.6	Intensity:	0.0407
Position:	825.0	Intensity:	0.0488
Position:	838.3	Intensity:	0.0278
Position:	857.0	Intensity:	0.0163
Position:	880.8	Intensity:	0.0124
Position:	890.5	Intensity:	0.0160
Position:	906.6	Intensity:	0.0124
Position:	951.5	Intensity:	0.0108
Position:	960.8	Intensity:	0.0138
Position:	1015.6	Intensity:	0.0133
Position:	1021.5	Intensity:	0.0128
Position:	1057.0	Intensity:	0.115
Position:	1077.1	Intensity:	0.0548
Position:	1101.0	Intensity:	0.0396
Position:	1151.4	Intensity:	0.0111
Position:	1193.5	Intensity:	0.0082

Position:	1220.1	Intensity:	0.0099
Position:	1248.7	Intensity:	0.0217
Position:	1259.9	Intensity:	0.0222
Position:	1267.8	Intensity:	0.0227
Position:	1296.6	Intensity:	0.0558
Position:	1338.8	Intensity:	0.0042
Position:	1359.1	Intensity:	0.0112
Position:	1375.5	Intensity:	0.0032
Position:	1390.2	Intensity:	0.0072
Position:	1421.3	Intensity:	0.0266
Position:	1462.3	Intensity:	0.0146
Position:	1482.5	Intensity:	0.0436
Position:	1521.2	Intensity:	0.0148
Position:	1585.4	Intensity:	0.0487
Position:	1627.3	Intensity:	0.0103
Position:	1774.6	Intensity:	0.00059
Position:	1869.5	Intensity:	0.00049
Position:	2589.6	Intensity:	0.0052
Position:	2658.0	Intensity:	0.0045
Position:	2751.5	Intensity:	0.0046
Position:	2841.8	Intensity:	0.0040
Position:	2876.7	Intensity:	0.0039
Position:	2937.2	Intensity:	0.0079
Position:	2980.8	Intensity:	0.0079
Position:	3006.7	Intensity:	0.0040
Position:	3095.2	Intensity:	0.0030
Position:	3481.1	Intensity:	0.00066

[00169] Fig. 39 is the RAMAN spectrum of racemic ilaprazole, Form I. Table 18 reports the absorbance peaks in the Raman spectrum.

Table 18: Peaks in the Raman Spectrum of Racemic Ilaprazole, Form I.

Position:	402.5	Intensity:	6.251
Position:	423.4	Intensity:	4.046
Position:	439.3	Intensity:	6.695
Position:	467.2	Intensity:	1.280
Position:	508.9	Intensity:	6.226
Position:	537.0	Intensity:	7.294
Position:	575.9	Intensity:	2.058
Position:	602.1	Intensity:	14.741
Position:	608.4	Intensity:	19.813
Position:	625.0	Intensity:	3.686
Position:	641.3	Intensity:	0.343

Position:	671.9	Intensity:	6.680
Position:	687.4	Intensity:	10.109
Position:	705.1	Intensity:	18.324
Position:	715.2	Intensity:	40.085
Position:	746.3	Intensity:	0.223
Position:	757.2	Intensity:	0.657
Position:	779.3	Intensity:	13.833
Position:	814.4	Intensity:	7.625
Position:	824.3	Intensity:	3.724
Position:	839.5	Intensity:	3.268
Position:	858.2	Intensity:	0.596
Position:	872.3	Intensity:	2.936
Position:	883.2	Intensity:	3.271
Position:	892.6	Intensity:	2.679
Position:	906.6	Intensity:	3.272
Position:	937.9	Intensity:	0.628
Position:	964.6	Intensity:	12.167
Position:	1022.4	Intensity:	5.498
Position:	1058.4	Intensity:	8.147
Position:	1078.3	Intensity:	11.286
Position:	1105.5	Intensity:	12.333
Position:	1122.2	Intensity:	13.568
Position:	1153.0	Intensity:	1.822
Position:	1195.6	Intensity:	18.478
Position:	1218.6	Intensity:	11.741
Position:	1248.5	Intensity:	17.145
Position:	1271.0	Intensity:	66.038
Position:	1298.3	Intensity:	19.951
Position:	1312.9	Intensity:	12.236
Position:	1338.2	Intensity:	115.936
Position:	1390.7	Intensity:	14.399
Position:	1430.2	Intensity:	33.921
Position:	1463.4	Intensity:	22.573
Position:	1486.0	Intensity:	7.195
Position:	1520.5	Intensity:	33.708
Position:	1585.5	Intensity:	21.258
Position:	1628.5	Intensity:	27.280
Position:	2537.6	Intensity:	0.355
Position:	2738.6	Intensity:	1.268
Position:	2842.7	Intensity:	10.481
Position:	2938.7	Intensity:	35.252
Position:	2980.1	Intensity:	25.665
Position:	3007.6	Intensity:	10.180
Position:	3065.6	Intensity:	19.538
Position:	3095.0	Intensity:	20.168
Position:	3106.6	Intensity:	13.334

Position: 3127.2 Intensity: 14.441

[00170] Fig. 40 is the DVS isotherm of racemic ilaprazole, Form I. The DVS isotherm shows a 0.1% weight loss at 5% RH, a 4.2% weight gain from 5 to 95% RH, and a 4.2% weight loss from 95 to 5% RH.

[00171] **Example 5**: Preparation of Characterization of Racemic Ilaprazole, Form B

[00172] A solution containing 10 mL of acetone was saturated with ilaprazole, Form A by sonicating with excess solids for approximately 5 minutes at ambient temperature. The resulting slurry was filtered through a 0.2 micron nylon filter into a glass vial. The vial was capped and placed into a refrigerator. The resulting white solid was collected by vacuum filtration 11 days later as Form B.

[00173] The XRPD pattern of racemic ilaprazole, Form B was obtained using an Inel XRG-3000 diffractometer, as described above. The measurement conditions are reported in Table 19. Fig. 41 shows the XRPD pattern for racemic ilaprazole, Form B. Table 20 reports the peaks identified in the XRPD pattern. In its XRPD racemic ilaprazole Form B may be characterized by peaks at 6.8 °2θ ± 0.2 °2θ; 9.1 °2θ ± 0.2 °2θ; 22.0 °2θ ± 0.2 °2θ and 25.5 °2θ ± 0.2 °2θ. Another characteristic grouping includes peaks at 3.7 2θ ± 0.2 °2θ; 6.0 °2θ ± 0.2 °2θ; 6.8 2θ ± 0.2 °2θ; 9.1 2θ ± 0.2 °2θ; 12.1 2θ ± 0.2 °2θ; and 31.4 2θ ± 0.2 °2θ.

Table 19: Measurement Conditions for XRPD Pattern of Racemic Ilaprazole, Form B.

Measurement Condition:		Data Process Condition:	
X-ray tube		Smoothing	[AUTO]
target	= Cu	smoothing points	= 23
voltage	= 40.0 (kV)		
current	= 30.0 (mA)	B.G. Subtraction	[AUTO]
		sampling points	= 27
Slits		repeat times	= 30
divergence slit	= 1.00000 (deg)		
scatter slit	= 1.00000 (deg)	Ka1-a2 Separate	[MANUAL]
receiving slit	= 0.15000 (mm)	Ka1 a2 ratio	= 50.0 (%)
Scanning		Peak Search	[AUTO]
drive axis	= 2Theta/Theta	differential points	= 21
scan range	= 2.519 - 39.979	FWHM threshold	= 0.050 (deg)

scan mode = Continuous Scan scan speed = 0.0040 (deg/min) sampling pitch = 0.0200 (deg) preset time = 300.00 (sec)	intensity threshold = 30 (par mil) FWHM ratio (n-1)/n = 2 System Error Correction: [NO] Precise Peak Correction: [NO]

Table 20: Peak Positions of Ilaprazole, Form B XRPD Pattern

Peak No.	Position (°2θ ± 0.2 °2θ)	d-spacing	Intensity	I/I_o[c]
1	3.7	23.9	44	4
2	6.0	14.8	48	4
3	6.8	12.9	1227	100
4	9.1	9.7	114	9
5	11.8	7.5	73	6
6	12.1	7.3	56	5
7	12.6	7.0	315	26
8	14.8	6.0	114	9
9	15.8	5.6	537	44
10	18.1	4.9	258	21
11	19.4	5.6	156	13
12	20.2	4.4	148	12
13	20.7	4.3	70	6
14	21.2	4.2	413	34
15	22.0	4.0	357	29
16	22.7	3.9	124	10
17	23.2	3.8	133	11
18	23.6	3.8	362	30
19	24.1	3.7	317	26
20	24.4	3.6	177	14
21	25.5	3.5	417	34
22	26.7	3.3	67	5
23	27.2	3.3	101	8
24	27.8	3.2	87	7
25	29.1	3.1	84	7
26	31.4	2.8	66	5

[00174] Fig. 42 is the TGA thermogram of racemic ilaprazole, Form B. The sample showed a 0.2% weight loss up to 150 °C and 5.8% weight loss between 150 and 175 °C.

[00175] Fig. 43 is the DSC thermogram of racemic ilaprazole, Form B. The endotherm onset occurred at 159 °C (max 163 °C).

[00176] Fig. 44 is the proton NMR Spectrum of racemic ilaprazole, Form B. Any peaks near 5.32 ppm are due to solvent – not to ilaprazole. Peaks near 1.0 and 2.5 ppm are due to TEA, which is used to stabilize ilaprazole in solution, and not to ilaprazole.

[00177] Fig. 45 is the solid state ^{13}C CP/MAS NMR spectrum of racemic ilaprazole, Form B. The spectrum is externally referenced against glycine at 176.5 ppm. The peaks in the solid state ^{13}C NMR spectrum are reported in Table 21.

Table 21: Solid State ^{13}C NMR Peaks for Racemic Ilaprazole, Form B.

PPM	HEIGHT
163.5	99.8
155.0	62.2
152.2	77.5
149.5	58.7
142.2	80.6
135.7	104.3
121.5	65.4
118.3	141.8
116.2	88.5
110.3	53.5
107.8	44.0
104.5	94.3
55.7	117.1
11.5	85.4

[00178] Fig. 46 is the IR spectrum of racemic ilaprazole, Form B. Table 22 reports the absorbance peaks in the IR spectrum.

Table 22: Peaks in IR Spectrum of Racemic Ilaprazole Form B.

Position:	715.4	Intensity:	0.0125
Position:	732.2	Intensity:	0.0730
Position:	758.2	Intensity:	0.0131
Position:	810.3	Intensity:	0.0464
Position:	829.0	Intensity:	0.0126
Position:	864.1	Intensity:	0.0100
Position:	892.2	Intensity:	0.0101
Position:	953.4	Intensity:	0.0053
Position:	971.1	Intensity:	0.0089
Position:	1014.2	Intensity:	0.0154
Position:	1043.6	Intensity:	0.0534

Position:	1058.1	Intensity:	0.0339
Position:	1069.6	Intensity:	0.0229
Position:	1088.9	Intensity:	0.0406
Position:	1112.4	Intensity:	0.0120
Position:	1128.3	Intensity:	0.0029
Position:	1162.3	Intensity:	0.0051
Position:	1192.0	Intensity:	0.0026
Position:	1216.2	Intensity:	0.0077
Position:	1256.1	Intensity:	0.0173
Position:	1270.0	Intensity:	0.0283
Position:	1292.8	Intensity:	0.0366
Position:	1339.6	Intensity:	0.0051
Position:	1357.2	Intensity:	0.0073
Position:	1382.1	Intensity:	0.0107
Position:	1389.9	Intensity:	0.0161
Position:	1410.2	Intensity:	0.0205
Position:	1431.3	Intensity:	0.0194
Position:	1454.8	Intensity:	0.0124
Position:	1476.5	Intensity:	0.0258
Position:	1519.9	Intensity:	0.0179
Position:	1580.4	Intensity:	0.0368
Position:	1632.2	Intensity:	0.0088
Position:	1651.4	Intensity:	0.00090
Position:	1695.3	Intensity:	0.0011
Position:	1717.0	Intensity:	0.00097
Position:	2561.9	Intensity:	0.00043
Position:	2835.2	Intensity:	0.0018
Position:	2888.8	Intensity:	0.0028
Position:	2937.5	Intensity:	0.0035
Position:	2964.4	Intensity:	0.0028
Position:	3062.7	Intensity:	0.0031
Position:	3103.4	Intensity:	0.0047
Position:	3197.1	Intensity:	0.0090

[00179] Fig. 47 is the RAMAN spectrum of racemic ilaprazole, Form B. Table 23 reports the absorbance peaks in the Raman spectrum.

Table 23: Peaks in the Raman Spectrum of Racemic Ilaprazole, Form B.

Position:	402.3	Intensity:	3.360
Position:	419.7	Intensity:	3.450
Position:	437.4	Intensity:	4.555
Position:	469.0	Intensity:	3.223
Position:	492.9	Intensity:	2.746

Position:	510.3	Intensity:	3.524
Position:	536.4	Intensity:	2.993
Position:	593.1	Intensity:	3.826
Position:	612.8	Intensity:	3.449
Position:	623.2	Intensity:	2.192
Position:	638.2	Intensity:	1.651
Position:	669.8	Intensity:	2.705
Position:	694.0	Intensity:	11.100
Position:	704.1	Intensity:	9.112
Position:	732.1	Intensity:	10.557
Position:	754.1	Intensity:	20.453
Position:	816.5	Intensity:	9.149
Position:	828.4	Intensity:	4.623
Position:	874.1	Intensity:	4.017
Position:	893.0	Intensity:	6.371
Position:	954.1	Intensity:	10.071
Position:	969.7	Intensity:	18.993
Position:	1015.6	Intensity:	12.072
Position:	1045.9	Intensity:	4.196
Position:	1055.6	Intensity:	5.091
Position:	1068.8	Intensity:	6.913
Position:	1094.8	Intensity:	9.593
Position:	1110.4	Intensity:	7.641
Position:	1128.3	Intensity:	23.427
Position:	1166.2	Intensity:	13.097
Position:	1192.1	Intensity:	5.552
Position:	1216.8	Intensity:	15.624
Position:	1271.3	Intensity:	59.718
Position:	1292.5	Intensity:	13.415
Position:	1306.1	Intensity:	27.370
Position:	1340.8	Intensity:	93.661
Position:	1390.2	Intensity:	46.334
Position:	1406.0	Intensity:	24.397
Position:	1436.3	Intensity:	30.633
Position:	1460.1	Intensity:	16.408
Position:	1482.5	Intensity:	10.635
Position:	1518.8	Intensity:	35.366
Position:	1579.7	Intensity:	12.771
Position:	1590.8	Intensity:	17.002
Position:	1633.4	Intensity:	34.488
Position:	2737.0	Intensity:	1.265
Position:	2835.7	Intensity:	8.761
Position:	2890.1	Intensity:	15.700
Position:	2907.8	Intensity:	16.669
Position:	2936.8	Intensity:	15.868
Position:	2964.3	Intensity:	6.875

Position:	3006.0	Intensity:	6.752
Position:	3019.8	Intensity:	9.329
Position:	3065.1	Intensity:	24.167
Position:	3093.7	Intensity:	10.661
Position:	3101.4	Intensity:	11.283
Position:	3130.5	Intensity:	15.490

[00180] Fig. 48 is the DVS isotherm of racemic ilaprazole, Form B. The DVS isotherm shows a 0.03% weight loss at 5% RH, a 0.04% weight gain from 5 to 95% RH, and a 0.00% weight loss from 95 to 5% RH.

[00181] **Example 6:** Ilaprazole Solubility Studies

[00182] The solubility of racemic ilaprazole, Forms A, B, and F, were analyzed by exposing them to various ethanol solutions having various pHs for 1 hour. Duplicate analysis was performed for each sample on a second day. The solubility in 100% ethanol (with no pH adjustment) is shown in the first column. Various other aqueous solutions (87.5%, 75%, 62.5%, and 50% ethanol) with varying apparent pHs (7, 8, 9, 10, and 11) were also evaluated. All of the values below are the average of two duplicate preparations analyzed on different days. The results are shown in Table 24.

Table 24 Solubility of racemic ilaprazole Forms A, B, and F in various ethanol solutions

Form	Solubility (mg/mL)	Ethanol				
		100%	87.50%	75%	62.50	50%
A	pH 7	6.47		13.13		2.80
	pH 8	6.47	15.18		7.18	
	pH 9	6.47		14.94		3.99
	pH 10	6.47	18.15		9.48	
	pH 11	6.47		16.25		6.21
B	pH 7	8.38		18.86		3.62
	pH 8	8.38	21.65		9.56	
	pH 9	8.38		20.61		4.73
	pH 10	8.38	24.35		11.86	

	pH 11	8.38		22.34		7.27
F	pH 7	7.04		14.82		2.73
	pH 8	7.04	17.83		7.43	
	pH 9	7.04		16.11		3.54
	pH 10	7.04	20.25		9.51	
	pH 11	7.04		18.01		5.79

[00183] The solubility of ilaprazole, Forms A, B, and F, were analyzed by exposing them to 90% ethanol solutions of various pHs for 1 hour. The analysis was repeated a second time to check the reproducibility of the results. The results are shown in Table 25.

Table 25: Solubility of racemic ilaprazole, Forms A and F, in various pH environments

From	Solubility	pH								
	(mg/mL)	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5	11.0
A	Day 1	14.82	15.27	15.51	16.05	16.99	17.66	18.30	18.47	17.63
	Day 2	15.77	15.45	15.90	16.66	17.66	19.30	19.79	19.85	19.22
	Average	15.30	45.36	15.71	16.36	17.33	18.48	19.05	19.16	18.43
	% Diff.	6.41	1.18	2.51	3.80	3.94	9.29	8.14	7.47	9.02
B	Day 1	19.16	20.37	20.28	20.90	21.73	22.79	23.19	23.43	21.59
	Day 2	20.91	19.66	20.00	21.56	22.06	24.20	24.15	24.66	24.89
	Average	20.04	20.02	20.14	21.23	21.90	23.50	23.67	24.05	23.24
	% Diff.	9.13	3.49	1.38	3.16	1.52	6.19	4.14	5.25	15.28
F	Day 1	16.37	16.89	17.25	17.71	18.32	19.66	20.02	20.28	19.47
	Day 2	16.89	16.75	16.84	17.66	18.70	20.25	20.66	20.94	20.35
	Average	16.63	16.82	17.05	17.69	18.51	19.96	20.34	20.61	19.91
	% Diff.	3.18	0.83	2.38	0.28	2.07	3.00	3.20	3.25	4.52

[00184] **Example 7**: Preparation of Characterization of Racemic Ilaprazole, Form E

[00185] Approximately 82.0 mg Ilaprazole, Form A was added to a solution containing 6 mL MeOH and 6 μL triethylamine. The solid was dissolved using sonication. The solution was filtered through a 0.2 micron nylon filter into a glass vial. The vial opening was covered with aluminum foil containing five pinholes and left to evaporate at ambient temperature. A dark green solid resulted approximately 6 days later and was identified as Form E.

[00186] The XRPD pattern of racemic ilaprazole, Form E was obtained using an Inel XRG-3000 diffractometer. The measurement conditions are reported in Table 26. Fig. 49 shows the XRPD pattern for racemic ilaprazole, Form E. Table 27 reports the peaks identified in the XRPD pattern. In its XRPD racemic ilaprazole, Form E may be characterized by peaks at 8.1 °2θ ± 0.2 °2θ; 10.1 °2θ ± 0.2 °2θ; and 12.8 °2θ ± 0.2 °2θ. Another characteristic grouping includes the peak at 31.1 °2θ ± 0.2 °2θ.

Table 26: Measurement Conditions for XRPD Pattern of Racemic Ilaprazole, Form E.

Measurement Condition:	Data Process Condition:
X-ray tube target = Cu voltage = 40.0 (kV) current = 30.0 (mA) Slits divergence slit = 1.00000 (deg) scatter slit = 1.00000 (deg) receiving slit = 0.15000 (mm) Scanning drive axis = 2Theta/Theta scan range = 2.519 - 39.979 scan mode = Continuous Scan scan speed = 0.0040 (deg/min) sampling pitch = 0.0200 (deg) preset time = 300.00 (sec)	Smoothing [AUTO] smoothing points = 57 B.G. Subtraction [AUTO] sampling points = 27 repeat times = 30 Ka1-a2 Separate [MANUAL] Ka1 a2 ratio = 50.0 (%) Peak Search [AUTO] differential points = 35 FWHM threshold = 0.050 (deg) intensity threshold = 30 (par mil) FWHM ratio (n-1)/n = 2 System Error Correction: [NO] Precise Peak Correction: [NO]

Table 27: Peak Positions of Ilaprazole, Form E XRPD Pattern

Position (°2θ± 0.20 °2θ)	**Relative Intensity**
8.0	85
10.2	84
12.8	67
14.5	43
16.0	58

16.5	88
17.6	73
18.9	48
19.3	70
21.2	49
21.6	46
22.2	57
22.7	100
23.4	45
24.7	32
25.8	67
27.2	30
28.7	36
29.2	32
31.3	35
31.9	24
33.7	19
34.7	18
35.4	18
37.0	17
38.8	16

[00187] Fig. 50 is the TGA thermogram of ilaprazole, Form E. The TG curve shows a negligible weight loss (<0.02%) up to 100 °C, indicating the material is unsolvated. A weight loss of 5.3% is observed from 100 to 170 °C, mostly like due to decomposition.

[00188] Fig. 51 is the DSC thermogram of racemic ilaprazole, Form E. Form E exhibits a minor endotherm near 99 °C, and an endotherm near 163 °C (onset: 157 °C) followed immediately by a sharp exotherm. The nature of the minor endotherm was not investigated. The remaining DSC events are most likely due to concomitant melt and decomposition.

[00189] Fig. 52 is the ^{1}H NMR spectra of racemic ilaprazole, Form E, in CD_2Cl_2. Any peaks near 5.32 ppm are due to solvent – not to ilaprazole.

[00190] Fig. 53 is the solid state ^{13}C CP/MAS NMR spectrum of racemic ilaprazole, Form E. The spectrum is externally referenced against glycine at 176.5 ppm. The peaks positions in the solid state ^{13}C NMR spectrum are reported in Table 28, rounded to the nearest 0.1 ppm. The peak occurring at 62.4 may overlap with excipient peaks.

Table 28: Solid State ^{13}C NMR Peaks for Racemic Ilaprazole, Form E.

PPM	HEIGHT
165.7	85.1
153.2	84.6
148.0	91.7
141.2	99.3
137.7	86.6
135.4	90.9
123.9	67.3
122.0	75.8
119.0	95.2
117.0	49.5
116.2	51.5
112.2	66.2
103.6	64.3
62.4	25.8
56.4	141.8
13.2	74.1

[00191] Fig. 54 shows the IR spectrum of racemic ilaprazole, Form E. The IR peaks are listed in Table 29.

Table 29. Peak Positions of Ilaprazole, Form E IR Spectrum.

Position ($cm^{-1} \pm 4\ cm^{-1}$)
688
732
756
823
866
890
950
963
1019
1046
1054
1066
1083
1095
1119
1147
1182

1232
1259
1285
1300
1339
1359
1392
1434
1482
1517
1525
1585
1629
1733
1905
2363
2594
2800
2840
2889
2980
3008
3068
3128

[00192] Example 8: Delayed Release Tablet Formulations

[00193] Delayed release tablets containing 40 mg racemic ilaprazole, Form A, B, or F, were prepared and the dissolution rates of the tablets studied. The tablets were identical, with the exception of the crystalline form of ilaprazole. The qualitative and quantitative compositions of racemic ilaprazole delayed release tablets, 40 mg (inclusive of the compositions made using Forms A, B, and F) are described in Table 30. The delayed release tablets, 40 mg, were prepared according to the manufacturing process shown in Figure 55.

Table 30. Composition of Delayed Release Tablets, 40 mg

Ingredient	Quality Standard	Listed	Function	mg/tablet
Core Tablet				
Racemic Ilaprazole (Form A, B, or F)	Internal	-	Active	40.00
Magnesium Hydroxide	USP	IID	Stabilizer	40.00
Microcrystalline Cellulose (Avicel PH 101)	NF	IID	Diluent/ Binder	58.75
Lactose Monohydrate (Foremost Lactose 312)	NF	IID	Diluent	58.75
Microcrystalline Cellulose (Avicel PH 102)	NF	IID	Diluent/ Binder	58.75
Lactose Monohydrate (Foremost Fast-Flo 316)	NF	IID	Diluent	58.75
Sodium Starch Glycolate (Explotab)	NF	IID	Disintegrant	12.14
Colloidal Silicon Dioxide (Cab-O-Sil M5P)	NF	IID	Glidant	0.8983
Magnesium Stearate	NF	IID	Lubricant	1.980
Subcoat				
Opadry YS-1-19025-A Clear[1]	Internal	IID	Coating Material	36.67
Purified Water*	USP	N/A	Solvent	q.s.
Enteric Coating				
Acryl-EZE 93F19255 Clear[2]	Internal	-	Enteric Coating	36.67
Purified Water*	USP	N/A	Solvent	q.s.
Total				403.4

* Removed during processing.
IID - indicates use of the ingredient is supported by FDA Inactive Ingredient Database.
q.s. - sufficient quantity
N/A - not applicable, solvents are removed during processing.
1 Contains hypromellose, USP and polyethylene glycol 400, NF.
2 Contains methacrylic acid copolymer type C, NF; polyethylene glycol 8000, NF; sodium bicarbonate, USP; colloidal anhydrous silica, NF; sodium lauryl sulfate, NF; and talc, USP.

[00194] The dissolution rate procedure was modified to be consistent with USP <711>, Delayed Release Method A and to change the UV detection wavelength in the acid stage of the test. For the acid stage, a wavelength of 340 nm was used, and for the buffer stage, a wavelength of 306 nm was used. The desired dissolution profile was Q = 70% in 60 minutes. The dissolution profiles of the tablets containing racemic ilaprazole Forms A, B, and F are presented in Table 31.

Table 31 Dissolution Comparison of Delayed Release Tablets, 40 mg using Racemic Ilaprazole, Forms A, B, and F

Racemic Ilaprazole Form in Tablet	**Acid Stage % Dissolved in 2 hrs** Average Min-Max	**Buffer Stage Drug Release, % Dissolved** Average Min-Max (% RSD)			
		15 min	30 min	45 min	60 min
Form A	1 0-2	54 48-61 (9.8)	75 70-78 (4.1)	82 79-87 (3.6)	86 84-91 (3.3)
Form B*	0 0-0	34 1-43 (33.6)	53 43-59 (8.3)	60 52-68 (7.5)	65 56-74 (7.4)
Form F	0 0-0	43 33-47 (13.0)	71 66-74 (4.8)	83 79-87 (4.6)	89 85-95 (5.0)

* Stage 1-3 testing conducted per USP. N = 24 results reported.

[00195] The relatively slower dissolution profile for the Form B tablet was unexpected based on the relative solubility data for of ilaprazole Forms A, F, and B (A<F<B). The tablets containing Form B drug had a relatively smaller particle size distribution compared to Form A and Form F. Form B was slower to wet and dissolve in the dissolution buffer than Form A and Form F.

[00196] **Example 9: Bioavailability Study of Ilaprazole from Delayed-Release Tablets Containing Racemic Ilaprazole, Forms A, B, or F**

[00197] The bioavailability of ilaprazole from delayed-release tablets containing racemic ilaprazole, Form A, F, and B. This study were to assessed the bioavailability of ilaprazole from ilaprazole 40-mg delayed-release tablets manufactured as described in Example 8.

[00198] **Study Design and Dose Administration:** The subjects were randomly assigned in equal numbers to one of three sequence groups (Table 32).

Table 32 **Regimen Sequences**

Sequence	**Number of Subjects**	**Regimen Sequence**		
		Period 1	**Period 2**	**Period 3**
1	16	Form A	Form F	Form B
2	16	Form B	Form A	Form F
3	16	Form F	Form B	Form A

Form A as a single ilaprazole 40-mg delayed-release tablet. **Form B** as a single ilaprazole 40-mg delayed-release tablet. **Form F** as a single ilaprazole 40-mg delayed-release tablet. **Note:** Study drug was administered with 240 mL of water following a minimum 10-hour fast. Subjects fasted for 4 hours post-dose.

[00199] Subjects received all regimens in a crossover fashion, according to the sequence group to which they were randomized. For each period, confinement began on Day 1 and ended on Day 2 after all procedures had been completed. There was a washout interval of at least 5 days between the doses of each period. Each subject received 3 doses of racemic ilaprazole 40 mg, each dose administered with 240 mL of water. On Day 1 of each period, subjects received the regimen to which they had been assigned at approximately 0800 hours. Subjects were fasted for 10 hours prior to dosing and remained fasted until 4 hours postdose when a standardized lunch was served.

[00200] **Sample Collection and Bioanalysis:** Ilaprazole, ilaprazole sulfide and ilaprazole sulfone plasma concentrations were determined from 3 mL blood samples collected starting on Day 1 at 0 hour (predose), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 28 and 32 hours postdose in each period. Plasma concentrations of ilaprazole were determined using a validated LC-MS/MS method at PPD (Middleton, WI). The lower limit of quantitation (LLOQ) for ilaprazole and its metabolites was 5.00 ng/mL with a 0.100 mL aliquot of plasma.

[00201] **Pharmacokinetic and Statistical Analyses:** Pharmacokinetic parameters for ilaprazole were estimated using standard noncompartmental methods with WinNonlin Professional Version 4.1 (Pharsight Co., Mountain View, CA).

[00202] Pharmacokinetic endpoints included time to reach the first quantifiable concentration (t_{lag}), time to reach the peak concentration (t_{max}), the peak plasma concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from time zero to the last quantifiable concentration (AUC_t) and to infinity (AUC_∞), terminal-phase elimination half-life ($t_{1/2z}$), apparent oral clearance (CL/F) and apparent volume of distribution (V_z/F).

[00203] For ilaprazole t_{lag}, t_{max}, and the natural logarithms of C_{max} and AUCs, an analyses of variance (ANOVA) model was fitted that included fixed effects of sequence, period, and crystal form as well as a random effect of subject nested within sequence. Pairwise comparisons between racemic ilaprazole, Forms B or F and Form A, were conducted. Ninety percent confidence intervals for relative bioavailability between regimens were computed.

[00204] **Pharmacokinetic Results:** Mean concentration vs. time profiles for ilaprazole (linear and log-linear Formats) following administration of a single 40 mg oral dose of ilaprazole as racemic ilaprazole, Form A, B or F, are presented in Figure 56.

[00205] Mean pharmacokinetic parameter estimates for plasma ilaprazole concentrations following administration of a single 40 mg oral dose of racemic ilaprazole, Form A, B, or F, are presented in Table 33.

Table 33: Plasma Pharmacokinetic Parameter Estimates of Ilaprazole in Healthy Adult Subjects Following Administration of a Single 5 mg Oral Dose of Racemic Ilaprazole, Forms A, B or F

	t_{lag} (h)	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_∞ (ng·h/mL)	$t_{1/2z}$ (h)[a]	CL/F (L/h)	Vz/F (L)
	Form A							
N	44	44	44	44	44	44	44	44
Mean	1.16	4.14	651.68	5066.75	5454.11	8.89 (6.95)	9.34	111.60
CV%	62	24	49	40	38	60	70	81
	Form B							
N	44	44	44	44	44	44	44	44
Mean	1.22	3.50	522.51	3812.50	4087.99	9.48 (7.76)	11.70	160.34
CV%	65	36	38	37	36	63	52	76
	Form F							
N	44	44	44	44	44	44	44	44
Mean	1.18	4.01	554.18	4256.66	4672.37	9.66 (7.29)	11.29	134.72
CV%	90	26	50	43	40	52	81	54

a: Arithmetic mean (harmonic mean).

[00206] Ilaprazole t_{lag} and t_{max} were similar regardless of the crystal form of racemic ilaprazole that was administered. Ilaprazole mean t_{lag} averaged about 1.2 hours, and the mean t_{max} ranged from 3.5 to 4.1 hours. Ilaprazole mean C_{max} and AUC values were highest for Form A and lowest for Form B. The mean C_{max} and AUC_∞ values for ilaprazole from Form B were approximately 20% and 25% lower, respectively, than those values observed for Form A. The mean C_{max} and AUC_∞ values for ilaprazole from Form F were approximately 15% and 14% lower, respectively, than those values observed for Form A. The harmonic mean $t_{1/2z}$ values were similar for the Forms A, B, and F, and ranged from approximately 7.0 to 7.8 hours. The mean apparent oral clearance and volume of distribution values were highest for Form B and

lowest for Form A. The results of the statistical analysis of the ANOVA are summarized in Table 34.

Table 34 Statistical Comparison of Pharmacokinetic Parameter Estimates for Racemic Ilaprazole, Forms A, B, and F

Parameter	Point Estimate	90% Confidence Interval
(i)	**Regimen B vs. Regimen A**	
C_{max}	0.8292	0.7185 – 0.9570
AUC_t	0.7630	0.6646 – 0.8759
AUC_∞	0.7609	0.6624 – 0.8740
(ii)	**Regimen C vs. Regimen A**	
C_{max}	0.8456	0.7327 – 0.9759
AUC_t	0.8288	0.7220 – 0.9515
AUC_∞	0.8456	0.7362 – 0.9713

Regimen A: Form A as a single ilaprazole 40-mg delayed-release tablet.
Regimen B: Form B as a single ilaprazole 40-mg delayed-release tablet.
Regimen C: Form F as a single ilaprazole 40-mg delayed-release tablet.

[00207] The lower bounds of the 90% confidence intervals for the ratios of the central values when racemic ilaprazole was administered as a single oral dose of the 40-mg tablet as Form B (Regimen B), relative to a single oral dose of the 40-mg tablet as Form A (Regimen A), were below the lower bioequivalence limit of 0.80 for C_{max}, AUC, and AUC_∞, and the confidence intervals did not include 1. For C_{max} and AUC, the point estimate indicated that the values for Form B were approximately 17% and 24% lower, respectively, than those observed for Form A.

[00208] The lower bounds of the 90% confidence intervals for the ratios of the central values when ilaprazole was administered as a single oral dose of the 40-mg tablet as Form F (Regimen C), relative to a single oral dose of the 40-mg tablet as Form A (Regimen A), were below the lower bioequivalence limit of 0.80 for C_{max}, AUC, and AUC_∞, and the confidence intervals did not include 1. The point estimates indicated that ilaprazole C_{max} and AUC values following administration of Form F were approximately 15% and 15-17% lower, respectively, than those observed for Form A.

[00209] **Pharmacokinetic Summary:** Following administration of a single 40-mg oral dose of ilaprazole as delayed-release tablets containing Form B, the total systemic exposure, as

measured by ilaprazole C_{max} and AUC, was approximately 17% and 24% lower, respectively, relative to a single 40-mg oral dose of ilaprazole as delayed-release tablets containing Form A.

[00210] Following administration of a single 40-mg oral dose of ilaprazole as delayed-release tablets containing Form F, the total systemic exposure, as measured by ilaprazole C_{max} and AUC, was approximately 15% and 15-17% lower, respectively, relative to a single 40-mg oral dose of ilaprazole as delayed-release tablets containing Form A.

[00211] **Example 10**: Solid State ^{13}C NMR Study of Racemic Ilaprazole, Forms A, B, F, in 40 mg Extended-Release Formulations

[00212] The delayed release tablets containing 40 mg of racemic ilaprazole, Forms A, B, and F, were studied using ^{13}C CP/MAS ssNMR. The estimated level of detection for each form as a minor impurity in the major form was approximately 15% for all three forms. To ensure that approximately the same response can be obtained for all three forms and to ensure that the observed forms do not have a high or low response, the relaxation delay and cross-polarization contact times were independently optimized for each crystalline form of ilaprazole. All three forms had an optimal relaxation delay of 10 seconds, and an optimal cross-polarization contact time of 4 milliseconds, which conditions were used for the study. As shown in Fig. 57, ^{13}C CP/MAS ssNMR shows good specificity for each form. Fig. 57 demonstrates that the regions with the best specificity for the three forms do not overlap with the peaks of the 40 mg excipient-only placebo blend. The peak positions for each form and placebo blend are summarized in Table 35. Four characteristic peaks were chosen for each form that are suitable for form identification as a neat API and in tableted form and are listed in Table 36.

Table 35. Racemic Ilaprazole ^{13}C CP/MAS ssNMR Peak Positions for Delayed-Release Formulations Containing Forms A, B, and F and the Placebo Blend

Peak Position (ppm)			
Form A	**Form B**	**Form F**	**40 mg Placebo Blend**
165.1	163.5	164.2	179.3
163.9		156.1	152.4
154.7	155	148.4	105.5
	152.2		
148.5	149.5		92.8
145.3	142.2	143.2	89.3

Peak Position (ppm)			
Form A	**Form B**	**Form F**	**40 mg Placebo Blend**
141.8			87.2
139.1			84.0
137.2	135.7	137.5	74.7
127.4			72.7
124.1			71.8
122.2	121.5	121.0	69.4
120.1	118.3		65.5
	116.2		
111.8[a]	**110.3**[a]	**110.6**[a]	62.0
108.6[a]	**107.8**[a]	**107.8**[a]	45.5
105.2[a]	**104.5**[a]		37
61.1[a]		**60.4**[a]	33.4
57.7[a]			21.8
56.2[a]	**55.7**[a]	**56.4**[a]	14.4
12.6	11.5	10.5	

a. Peaks that do not show specificity compared to placebo blend peaks.

Table 36. Racemic Ilaprazole ^{13}C CP/MAS ssNMR Peak Positions for Delayed-Release Formulations Containing Forms A, B, and F Characteristic Peak Positions

Approximate Peak Positions (ppm)		
Form A	**Form B**	**Form F**
139.1	152.2	156.1
127.4	135.7	143.2
124.1	116.2	110.6
12.6	11.5	10.5

The claimed invention is:

1. Crystalline racemic ilaprazole characterized by characterized by a powder x-ray diffraction pattern having a peak at 15.8 °2θ ± 0.2 °2θ.

2. A pharmaceutical composition for inhibiting gastric acid secretion, comprising a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 1 and a pharmaceutically acceptable carrier.

3. A pharmaceutical composition of claim 2, containing about 5 to about 80 mg of ilaprazole.

4. A pharmaceutical composition of claim 3 wherein the pharmaceutical composition is a delayed release pharmaceutical composition.

5. A method for treating a gastrointestinal inflammatory disorder in a mammal, comprising administering to a patient in need thereof a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 1.

6 The method of claim 5, wherein the amount of ilaprazole administered ranges from about 0.001 mg/kg to about 50 mg/kg of subject body weight per day.

7. A crystalline form of racemic ilaprazole characterized by a solid state ^{13}C CP/MAS NMR spectra having peaks at 139.1, 127.4, 124.1, and 12.6.

8. The crystalline form of racemic ilaprazole of claim 7, further characterized by on differential scanning calorimetry thermogram having an onset temperature of about 167 °C.

9. The crystalline for of racemic ilaprazole of claim 7, further characterized by a powder x-ray diffraction pattern having peaks at 8.0 °2θ ± 0.2 °2θ, 13.2 °2θ ± 0.2 °2θ, and 24.1 °2θ ± 0.2 °2θ.

10. A pharmaceutical composition for inhibiting gastric acid secretion, comprising a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 7 and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition of claim 10, containing about 10 to about 50 mg of ilaprazole.

12. A pharmaceutical composition of claim 11 wherein the pharmaceutical composition is a delayed release pharmaceutical composition.

13. A method for treating a gastrointestinal inflammatory disorder in a mammal, comprising administering to a patient in need thereof a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 7.

14. The method of claim 13, wherein the amount of ilaprazole administered ranges from about 0.001 mg/kg to about 50 mg/kg of subject body weight per day.

15. A crystalline form of racemic ilaprazole characterized by a solid state ^{13}C CP/MAS NMR spectra having peaks at 156.1, 143.2, 110.6 and 10.5.

16. The crystalline form of racemic ilaprazole of claim 15, further characterized by on differential scanning calorimetry thermogram having an onset temperature of about 170 °C.

17. The crystalline form of racemic ilaprazole of claim 15, further characterized by a powder x-ray diffraction pattern having peaks at 9.4 °2θ ± 0.2 °2θ, 17.5 °2θ ± 0.2 °2θ, 18.8 °2θ ± 0.2 °2θ; and 32.8 °2θ ± 0.2 °2θ.

18. A pharmaceutical composition for inhibiting gastric acid secretion, comprising a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 15 and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition of claim 18, containing about 10 to about 50 mg of ilaprazole.

20. A pharmaceutical composition of claim 19 wherein the pharmaceutical composition is a delayed release pharmaceutical composition.

21. A method for treating a gastrointestinal inflammatory disorder in a mammal, comprising administering to a patient in need thereof a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 15.

22. The method of claim 21, wherein the amount of ilaprazole administered ranges from about 0.001 mg/kg to about 50 mg/kg of subject body weight per day.

23. A crystalline form of racemic ilaprazole characterized by a powder x-ray diffraction pattern having peaks at 11.9 2θ ± 0.2 °2θ, 17.1 2θ ± 0.2 °2θ, 21.5 °2θ ± 0.2 °2θ, and 25.1 2θ ± 0.2 °2θ.

24. The crystalline form of racemic ilaprazole of claim 23, further characterized by on differential scanning calorimetry thermogram having an onset temperature of about 113 °C.

25. A pharmaceutical composition for inhibiting gastric acid secretion, comprising a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 23 and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition of claim 25, containing about 10 to about 50 mg of ilaprazole.

27. A pharmaceutical composition of claim 26 wherein the pharmaceutical composition is a delayed release pharmaceutical composition.

28. A method for treating a gastrointestinal inflammatory disorder in a mammal, comprising administering to a patient in need thereof a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 23.

29. The method of claim 28, wherein the amount of ilaprazole administered ranges from about 0.001 mg/kg to about 50 mg/kg of subject body weight per day.

30. A crystalline form of racemic ilaprazole characterized by a solid state ^{13}C CP/MAS NMR spectra having peaks at 152.2, 135.7, 116.2, and 11.5.

31. The crystalline form of racemic ilaprazole of claim 30, further characterized by on differential scanning calorimetry thermogram having an onset temperature of about 159 °C.

32. The crystalline form of racemic ilaprazole of claim 30, further characterized by a powder x-ray diffraction pattern having peaks at 6.8 2θ ± 0.2 °2θ, 9.1 2θ ± 0.2 °2θ, 22.0 2θ ± 0.2 °2θ, and 25.5 2θ ± 0.2 °2θ.

33. A pharmaceutical composition for inhibiting gastric acid secretion, comprising a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 30 and a pharmaceutically acceptable carrier.

34. A pharmaceutical composition of claim 33, containing about 10 to about 50 mg of ilaprazole.

35. A pharmaceutical composition of claim 34 wherein the pharmaceutical composition is a delayed release pharmaceutical composition.

36. A method for treating a gastrointestinal inflammatory disorder in a mammal, comprising administering to a patient in need thereof a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 30.

37. The method of claim 36, wherein the amount of ilaprazole administered ranges from about 0.001 mg/kg to about 50 mg/kg of subject body weight per day.

38. A crystalline form of racemic ilaprazole characterized by a solid state ^{13}C CP/MAS NMR spectra having peaks at 165.7, 141.2, and 62.4.

39. The form of crystalline racemic ilaprazole of claim 38, further characterized by on differential scanning calorimetry thermogram having an onset temperature of about 151 °C.

40. The crystalline form of racemic ilaprazole of claim 38 further characterized by a powder x-ray diffraction pattern having a peak at 8.1 °2θ ± 0.2 °2θ, 10.1 °2θ ± 0.2 °2θ, and 12.8 °2θ ± 0.2 °2θ.

41. A pharmaceutical composition for inhibiting gastric acid secretion, comprising a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 38 and a pharmaceutically acceptable carrier.

42. A pharmaceutical composition of claim 41, containing about 10 to about 50 mg of ilaprazole.

43. A pharmaceutical composition of claim 42 wherein the pharmaceutical composition is a delayed release pharmaceutical composition.

44. A method for treating a gastrointestinal inflammatory disorder in a mammal, comprising administering to a patient in need thereof a therapeutically effective amount of a crystalline form of racemic ilaprazole of claim 38.

45. The method of claim 44, wherein the amount of ilaprazole administered ranges from about 0.001 mg/kg to about 50 mg/kg of subject body weight per day.