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Review Article

Polymorphic evaluation of Rabeprazole sodium

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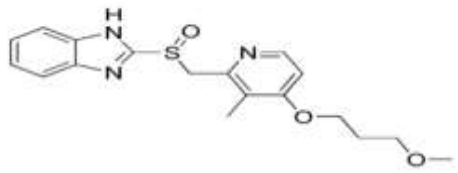
ABSTRACT
Regulatory authorities throughout the world require all possible crystalline forms of the same active drug compound be synthesized and characterized as completely as possible. Rabeprazole sodium, a proton pump inhibitor, exhibits polymorphism and the present article summarizes the different polymorphic forms of rabeprazole sodium.

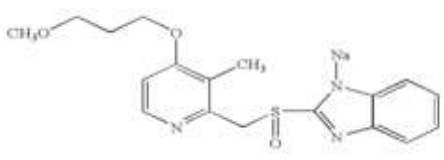
Keywords: Proton Pump Inhibitors, polymorphism, Rabeprazole sodium, XRD and crystalline forms.

INTRODUCTION

Discovery of new crystal forms of an active pharmaceutical ingredient provides more possibilities for improving to design prescriptions. Polymorphism is an ability of a chemical compound to crystallize – depending on crystallization conditions – in different crystal structures alias polymorphs. Molecules in the crystal structure of a polymorph are bonded by weak interactions. Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Therefore a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as solubility profiles, melting point temperatures and/or different X-Ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid forms of a drug and to determine the stability, dissolution and flow properties of each polymorphic form. Many pharmaceutical solids exist in crystalline/liquid crystalline/non crystalline (amorphous) forms or phases that have different arrangements and/or conformations of the molecules in the crystal lattice and thus exhibit polymorphism. Polymorphs may also undergo phase conversions, when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray-drying and compaction. Exposure to environmental conditions such as relative humidity and temperature may also induce phase conversions. Different forms of biologically active compounds, in particular the polymorphic forms, are known to be useful both in therapy, thanks to their different bioavailability, release times and solubility and in the pharmaceutical technique for the preparation of formulations as the physical characteristics often accompanying the different physical forms of the drug, such as hygroscopicity, flowability and/or powder compaction, can be advantageously exploited. [1-5] **Rabeprazole** is an antiulcer drug in the class of proton pump inhibitor developed by Eisai Co. in 1999 and is available worldwide under many brand names.



Rabeprazole



Rabeprazole Sodium

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Rabeprazole Sodium is chemically name as 2-[[[4-(methoxy propoxy)- 3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole sodium salt having molecular formula of C18H20N3O3S.Na (381) and it is a white to slightly yellowish white solid, very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate; and insoluble in ether and n-hexane. Rabeprazole sodium has an oral bioavailability of approximately 52%.

The polymorphic revolution in the recent years demanded to study the exploration of their polymorphism in rabeprazole sodium and therefore an attempt has been made for the comprehensive study of different polymorphic forms of rabeprazole sodium along with process and characterization.

Polymorphism in Rabeprazole Sodium

Andre S. Raw et al., [6] reported amorphous form of rabeprazole sodium. Formerly the pharmacologically permitted salt of rabeprazole sodium was manufactured as non-crystal (amorphous) or crystal solid (powder). Amorphous forms are generally more soluble, and thus they are desirable for pharmaceutical purposes because the bioavailability of amorphous compounds may be greater than their crystalline counterparts. Amorphous rabeprazole sodium does not show diffraction peaks (2Ɵ) in X-ray powder diffraction pattern.

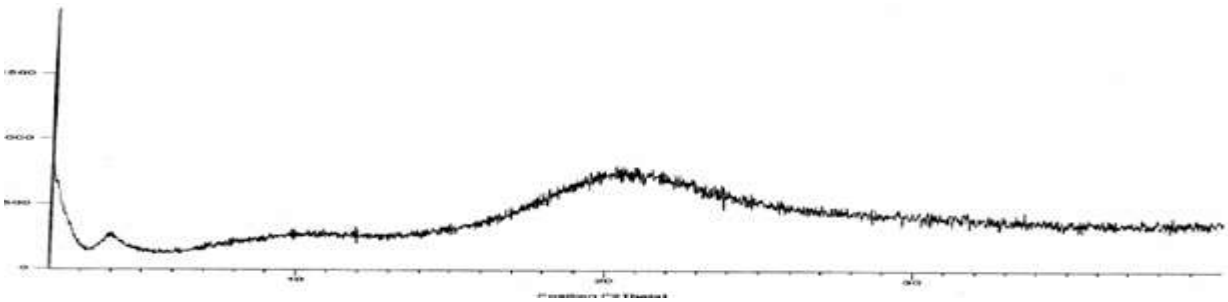

Figure 1 X ray diffraction pattern of amorphous form of rabeprazole sodium

The amorphous form of rabeprazole sodium does not shows clear melting point but was showing a decomposition at a temperature in the range of 140-141°C. The amorphous form of rabeprazole sodium is prepared by spray drying, heat drying, lyophilization, agitated thin film drying techniques and by crystallization from ether solvent, in the form of white to off-white powder. Rabeprazole sodium was dissolved in methanol previously treated with sodium methoxide at room temperature. Any undissolved particles were filtered and concentrated to an oily residue. Methylene chloride was added and evaporated to dryness. The obtained product was dried again in vacuo at 60^0C to obtain rabeprazole sodium and this was suspended in ether (diethyl ether or t-butyl methyl ether or diisopropyl ether) or alkanes (heptane or hexane) aged for two days at 20- 25°C. The product was filtered and dried in vacuo at 50^0C to obtain stable amorphous form. Masahiko et al., [7] reported crystalline form II of rabeprazole sodium. Crystal forms of Rabeprazole are designated as crystal I and II. However crystal I is not identified by recognized methods of crystal structure identification such as X-Ray diffraction.

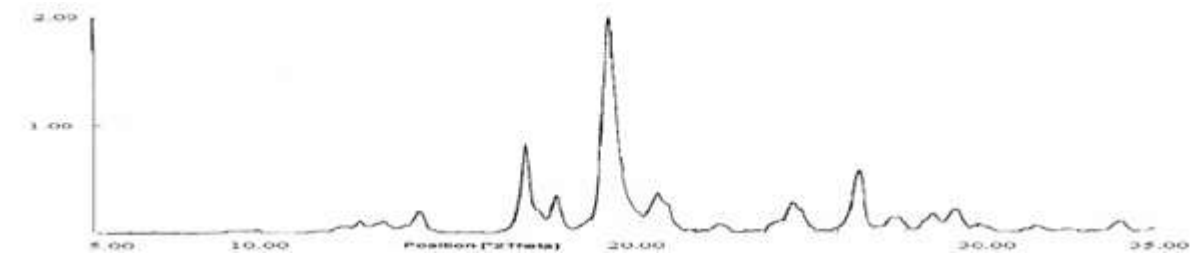

Figure 2 X ray diffraction pattern of crystalline form II of rabeprazole sodium

The crystalline form II of rabeprazole sodium characterized by x-ray powder diffraction having peaks at about 8.88, 9.64, 12.54, 12.82, 14.22, 18.04, 26.60, 27.56, and 34.92. The crystalline form II of rabeprazole sodium is being prepared by crystallization of amorphous rabeprazole sodium or acetone complex of rabeprazole sodium from lower fatty acid ester solvents or mixture(s) thereof. The crystalline form II of rabeprazole sodium usually is a needle shape crystal. The crystalline form II of rabeprazole sodium compared to amorphous rabeprazole sodium is stable up to 60% of relative humidity. Ashish pruthi et al., [8] reported crystalline form V and VI of rabeprazole sodium.

The crystalline form V of rabeprazole sodium is being characterized by x-ray powder diffraction peaks 9.69, 10.67, 13.62, 25.29, 36.09, 42.43, 44.94 and 55.28 ± 0.9 degrees. The crystalline form VI of rabeprazole sodium is being characterized by x-ray powder diffraction having peaks selected from the group consisting of 5.43, 9.70, 10.94, 20.36, 21.18, 25.58, 25.27, 27.95, 33.13, 33.90, 36.10, 40.40, 43.94, 44.91 and 55.71 ± 0.9. The crystalline forms V and VI of rabeprazole sodium are being prepared by freeze drying of rabeprazole sodium solution in water at cryogenic temperature. Bertha kothar et al., [9-16] reported Rabeprazole sodium forms A to I.

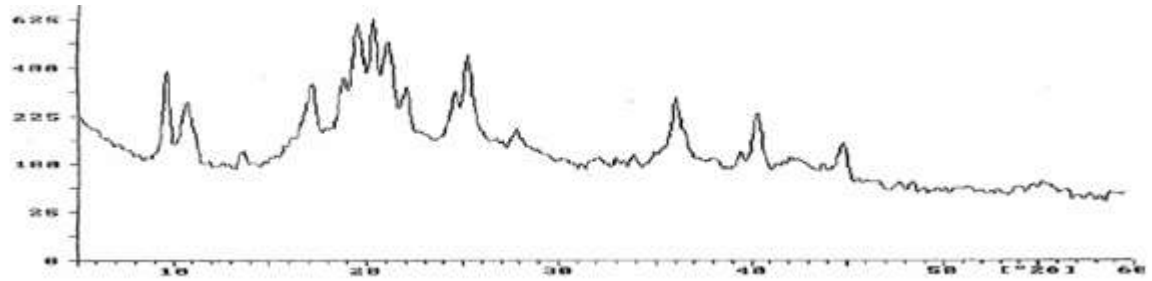

Figure 3 X ray diffraction pattern of crystalline form V of rabeprazole sodium

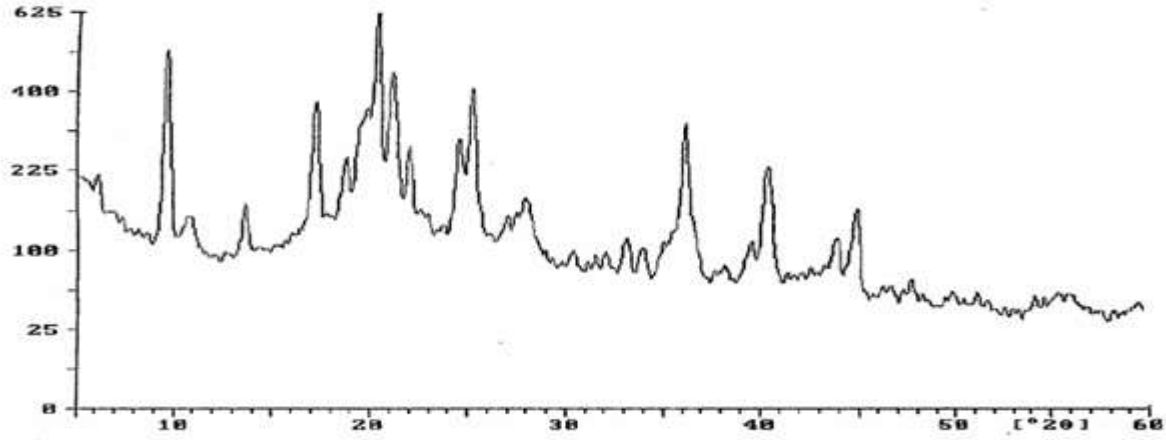

Figure 4 X ray diffraction pattern of crystalline form VI of rabeprazole sodium

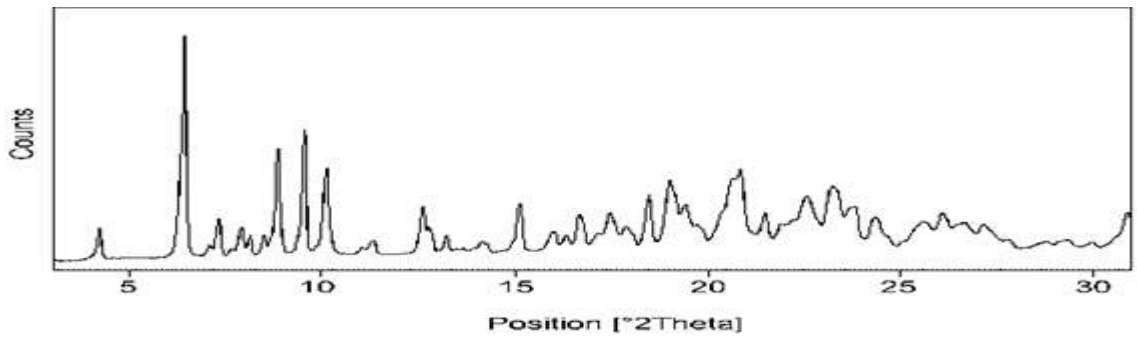

Figure 5 X ray diffraction pattern of crystalline form A of rabeprazole sodium

The crystalline form A rabeprazole sodium characterized by x-ray powder diffraction having peaks at 6.5, 8.9, 9.6, 12.6, 15.1, 19.0, 20.9, 23.2 ± 0.2. Rabeprazole was dissolved in a solution of sodium hydroxide in methanol/ethanol at room temperature. Any undissolved particles were filtered off to get a clear solution. The solution was concentrated to an oily residue; methylene chloride was added and evaporated to dryness. The obtained dry product was dissolved in of ethyl acetate, concentrated to minimum volume and stirred for 12 hours at 20-25^{0}C. The suspension was cooled to 0-5^{0}C for one hour, filtered, washed with ethyl acetate. The product was dried in vacuo at 40^{0}C to obtain crystalline form A. Example 2: Rabeprazole sodium as amorphous form was dissolved in ethyl acetate, previously treated with sodium methoxide in methanol. The solution was partially concentrated and aged for 12 hours at 20-25^{0}C. The product was filtered, washed with ethyl acetate and dried in vacuo at 40^{0}C to obtain crystalline form A.

The crystalline form B rabeprazole sodium characterized by x-ray powder diffraction having peaks 10.5, 13.4, 18.1, 18.5, 19.5, 22.9, 23.3, 27.1 ± 0.2. Rabeprazole was dissolved in a solution of sodium hydroxide in methanol at room temperature. Any undissolved particles were filtered off to get a clear solution. The solution was concentrated to an oily residue; methylene chloride was added and evaporated to dryness to obtain amorphous form. This was suspended in of ethyl acetate, previously treated with rabeprazole sodium of crystalline form Z and maintained for 12 hours at 20-25^{0}C. The product was filtered, washed with ethyl acetate and dried in vacuo at 50^{0}C to obtain crystalline form B. The crystalline form C rabeprazole sodium characterized by x-ray powder diffraction having peaks at 4.8, 6.3, 8.1, 12.6, 14.8, 19.8, 20.8, 22.0 ± 0.2. Rabeprazole was dissolved in a solution of sodium hydroxide in methanol at room temperature. Any undissolved particles were filtered off to get a clear solution. The solution was concentrated to an oily residue; methylene chloride was added and evaporated to dryness to obtain amorphous form. This was dissolved in iso-butyl methyl ketone, aged at 20-25^{0}C to begin crystallization. The product was filtered, washed with iso-butyl methyl ketone and dried in vacuo at 25°C for 12 hours, then 7 hours at 50^{0}C to obtain Rabeprazole sodium form C.

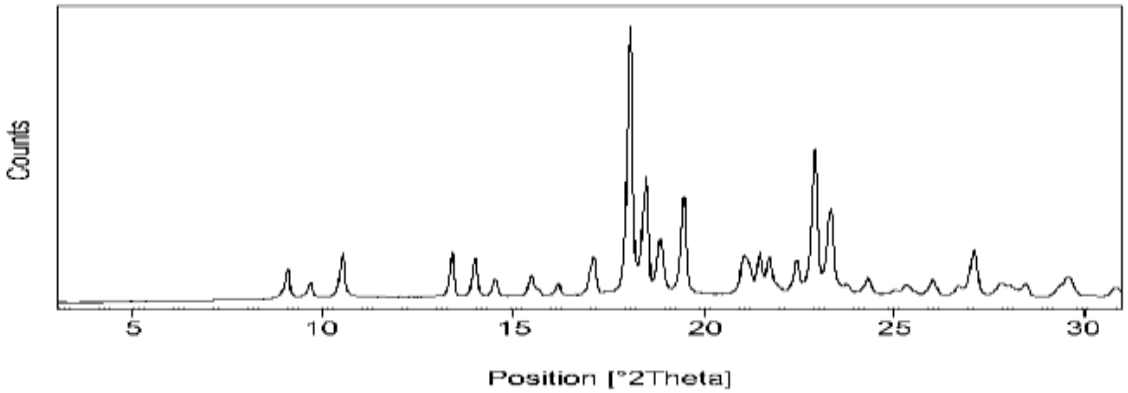

Figure 6 X ray diffraction pattern of crystalline form B of rabeprazole sodium

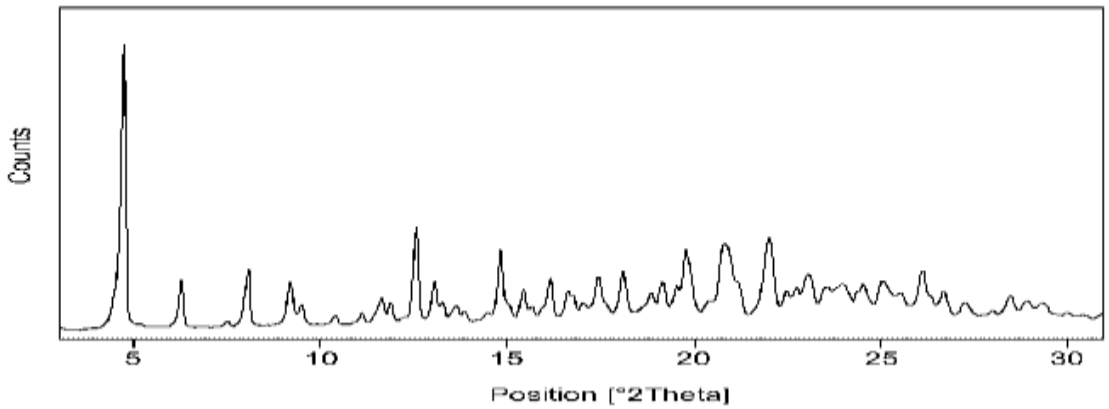

Figure 7 X ray diffraction pattern of crystalline form C of rabeprazole sodium

The crystalline form D rabeprazole sodium characterized by x-ray powder diffraction having peaks at about 6.5, 7.3, 7.9, 9.9, 14.3, 16.5, 17.6, 23.2. Rabeprazole sodium as amorphous form was suspended in acetone, previously treated with seeding crystals of form D. The suspension was stirred for 12 hours, filtered and washed with acetone. The product was dried in vacuo at 25°C to obtain crystalline form D. The crystalline form F rabeprazole sodium characterized by x-ray powder diffraction having peaks at about 3.9, 5.6, 7.7, 11.6, 14.2, 19.5, 24.6 ± 0.2. Rabeprazole sodium as amorphous form was dissolved in acetonitrile with addition of 30% aqueous sodium hydroxide at 20-25^{0}C. The solution was gradually dropped to diisopropyl ether/ TBME at 20-25^{0}C. The oily solution was maintained at the same temperature to begin crystallization and aged for 16 hours. The product was filtered, washed with acetonitrile and once again slurred in acetonitrile for one hour. Filtered product was dried in vacuo at 40 ^{0}C to obtain crystalline form F. The crystalline form G rabeprazole sodium characterized by x-ray powder diffraction having peaks at about 5.0, 5.4, 6.8, 7.5, 9.6, 16.2 ± 0.2. Rabeprazole sodium as amorphous form was suspended in diisopropyl ether at 20-25^{0}C and ethanol was added to this suspension and maintained for 16 hours at the same temperature. The oily product was cooled to 5-10^{0}C and stirred to start crystallization. The white product was filtered, washed with diisopropyl ether and dried in vacuo at 40 °C to obtain crystalline form G. The crystalline form H rabeprazole sodium characterized by x-ray powder diffraction having peaks at about 4.1, 5.7, 7.2, 8.2, 9.6, 15.0, 19.3 ± 0.2. Rabeprazole sodium form F was dried in a dryer over P2O5 at the final temperature 8O^{0}C. The crystalline form I rabeprazole sodium characterized by x-ray powder diffraction having peaks at about 4.8, 9.3, 11.5, 13.9, 14.7 ± 0.2. Rabeprazole sodium form F was held at 25°C and at relative humidity 70% for 10 hours. Song Weiguo et al., [17-18] reported Rabeprazole sodium Form P and Q.

The crystalline form P rabeprazole sodium characterized by x-ray powder diffraction having peaks 16.5,16.9,25,32,34,36,37,40,43,45 and 57. Amorphous sodium rabeprazole is added to acetonitrile at room temperature till complete dissolution and filter for insoluble and the filtrate is slowly volatilize to get form P rabeprazole sodium. The crystalline form Q rabeprazole sodium characterized by x-ray powder diffraction having peaks7.72,9.04,16.52,16.88,21.37,22.03 and 22.50. Amorphous sodium rabeprazole iis added to n-butanol , stirred at room temperature until the solid was completely dissolved, insoluble matter filtered , the filtrate was slowly volatilize in the fume hood, 14 days after the container precipitated solid was filtered and dried in vacuo to give an off-white powder.

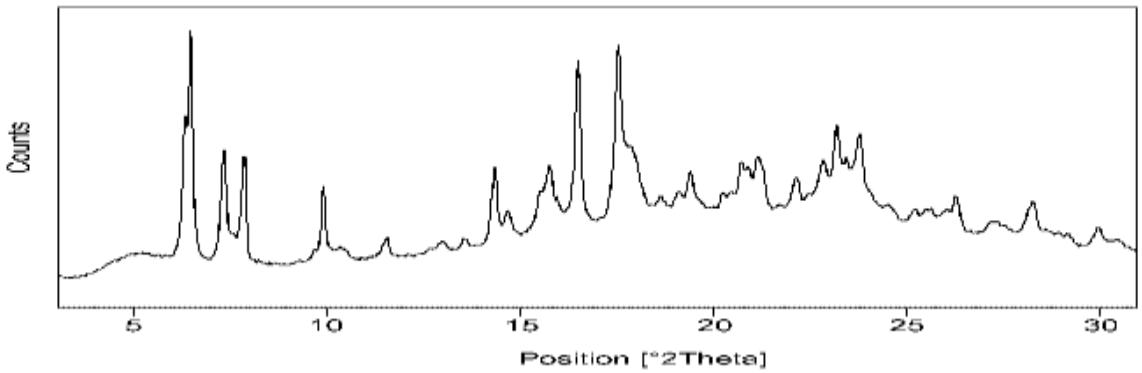

Figure 8 X ray diffraction pattern of crystalline form D of rabeprazole sodium

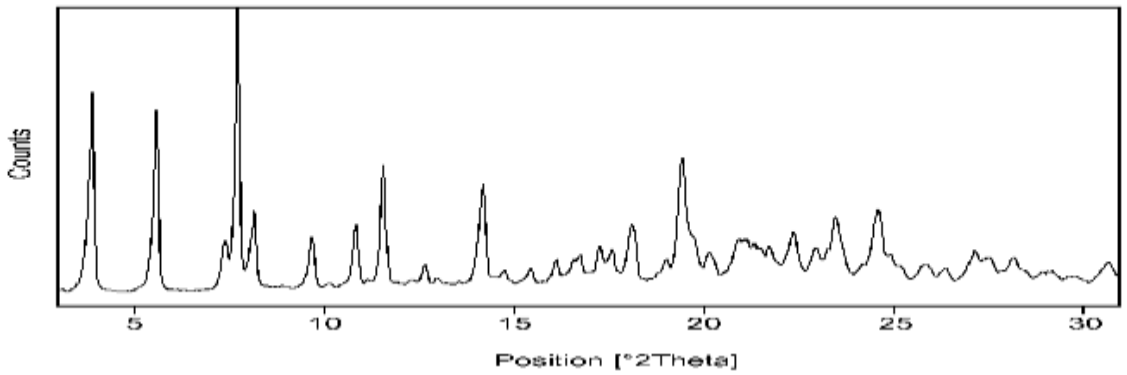

Figure 9 X ray diffraction pattern of crystalline form F of rabeprazole sodium

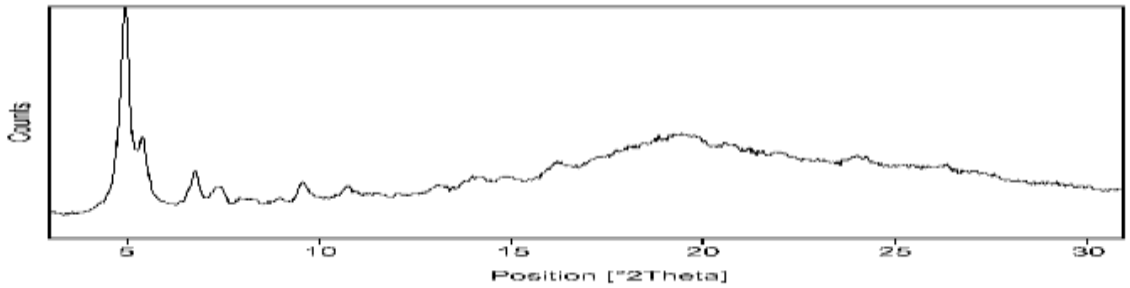

Figure 10 X ray diffraction pattern of crystalline form G of rabeprazole sodium

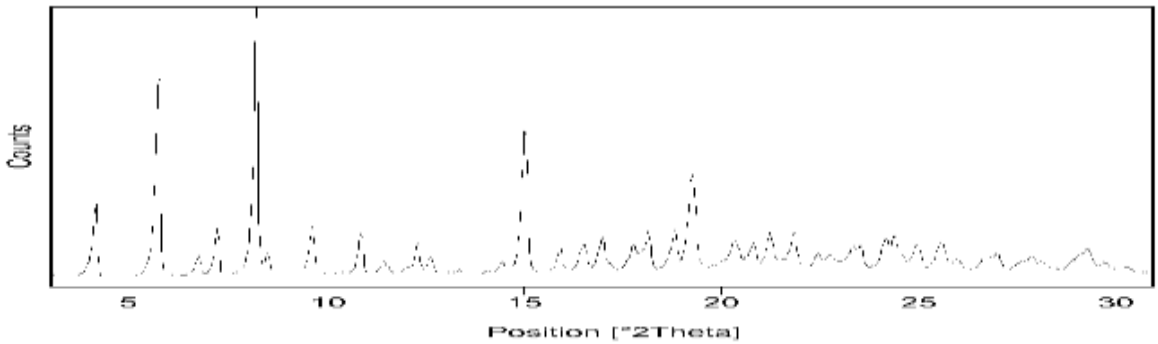

Figure 11 X ray diffraction pattern of crystalline form H of rabeprazole sodium

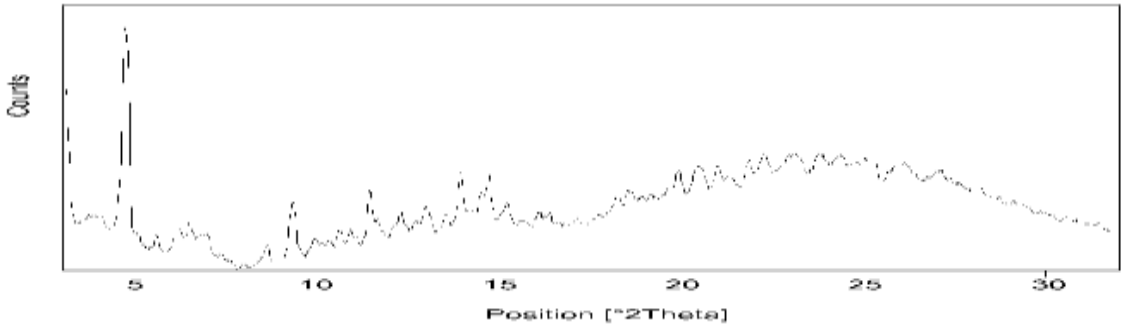

Figure 12 X ray diffraction pattern of crystalline form I of rabeprazole sodium

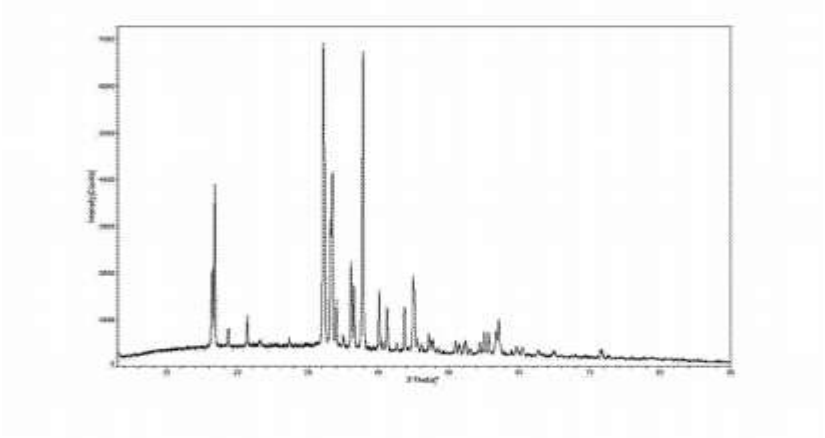

Figure 13 X ray diffraction pattern of crystalline form P of rabeprazole sodium

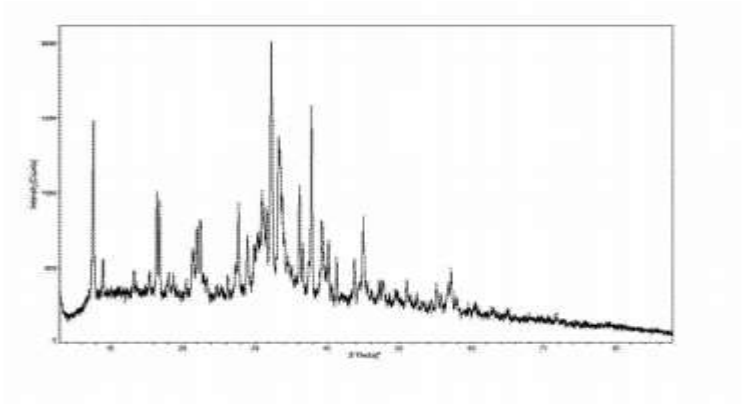

Figure 14 X ray diffraction pattern of crystalline form Q of rabeprazole sodium

Vijaya Bhaskar Bolugoddu et al., [19] reported Rabeprazole sodium X and Y. The crystalline form X rabeprazole sodium characterized by x-ray powder diffraction having peaks 5.13, 6.606, 7.244, 9.353, 12.923, 14.414, 18.173, 20.01, 22.177, 24.81 and 25.494. Rabeprazole base is dissolved in a mixture of sodium hydroxide and methanol. The reaction solution is filtered through hi-flow and washed with methanol. Methanol from the filtrate is distilled off under high vacuum. The reaction mass is cooled to ambient temperature followed by addition of dichloromethane accompanied by distillation to remove traces of methanol. Dichloromethane and petroleum ether is then added to the residual mass, which is then stirred at 25-30°C for about 6-8 hours. The solid that is obtained further diluted with petroleum ether and stirred at 25-30°C for about 6-8 hours. The precipitated solid is filtered and washed with petroleum ether and dried at 50-60°C for 12 hours to afford the desired Form X of Rabeprazole sodium. The crystalline form X of rabeprazole sodium is also being characterized by melting point (capillary method) at 140-150°C. The crystalline form Y rabeprazole sodium characterized by x-ray powder diffraction having peaks at 5.61, 7.207, 7.725, 9.649, 10.352, 11.231, 16.899, 18.816 and 24.943.

Rabeprazole base is dissolved in a mixture of sodium hydroxide and methanol and filtered through hi-flow and washed with methanol. Methanol from the filtrate is distilled off under high vacuum. The reaction mass is cooled to ambient temperature followed by addition of dichloromethane accompanied by distillation to remove traces of methanol.

The reaction mass is cooled to ambient temperature and n-butanol and tertiary butyl methyl ether is added to the residual mass which is stirred at 25-30°C for 6-8 hours. The reaction mixture is further cooled to 5-15°C and then stirred for another 3-5 hours. The solid is thus obtained is filtered and washed with tertiary butyl methyl ether and dried at 50-60°C for 7 hours to afford the desired crystalline Form Y of Rabeprazole sodium. The crystalline form Y of rabeprazole sodium is also being characterized by melting point (capillary method) at 160-170°C. The crystalline forms X and Y of rabeprazole sodium are high melting solids with residual solvents within permissible limits and are very well suited for formulation.

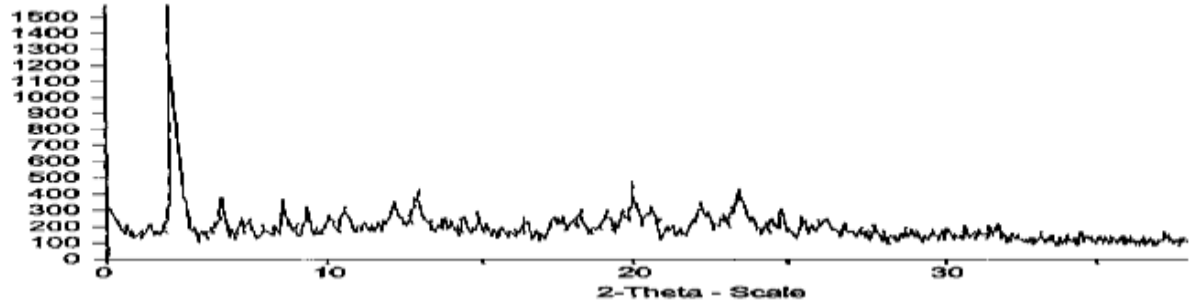

Figure 15 X ray diffraction pattern of crystalline form X of rabeprazole sodium

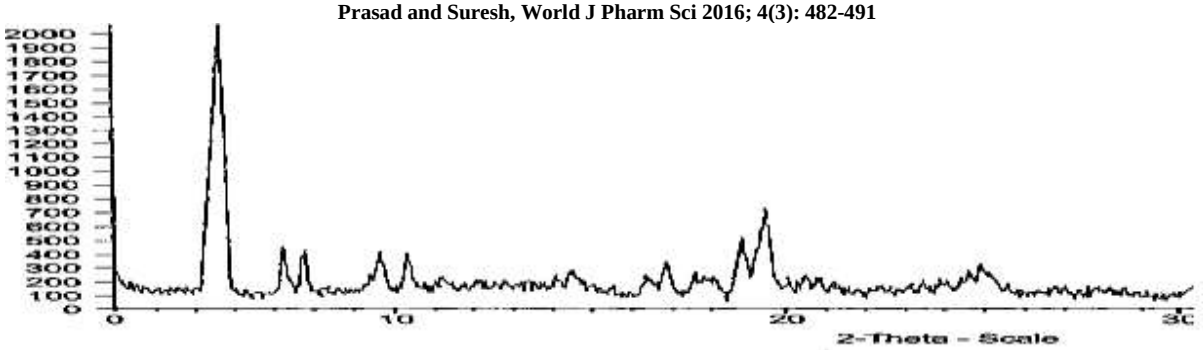

Figure 16 X ray diffraction pattern of crystalline form Y of rabeprazole sodium

Sundaram Venkatraman et al., [21] reported Form Z of rabeprazole sodium. The crystalline form Z rabeprazole sodium characterized by x-ray powder diffraction having peaks at 4.69 , 9.07, 11.25, 18.52, , 19.63, , 25.70, 27.47, 30.01, 30.65, 33.37, and 36.95. The crystalline form Z of rabeprazole sodium is being prepared by crystallization of rabeprazole sodium from aromatic hydrocarbon solvents such as toluene, xylenes or mixture(s) thereof. The crystalline form Z of rabeprazole sodium is also being characterized by melting point (capillary method) at 224-230°C. Luciana Malpezzi et al., [22] reported crystalline hydrate forms α and β of rabeprazole sodium. The crystalline hydrate α form of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having more intense peaks at about 3.8, 5.1, 7.1, 16.9, 17.6, 18.8 and 19.9. The crystalline hydrate α form of rabeprazole sodium has water content ranging between 2.2 and 3.0% in weight, so that it can be defined as hemihydrate form. The crystalline hydrate α form of rabeprazole sodium is being prepared by crystallization of Rabeprazole sodium from aprotic polar solvents such as ethyl acetate, butyl acetate, isopropyl acetate, ethyl propionate, isobutyl propionate and ethyl butyrate. The crystalline hydrate β form of rabeprazole sodium has water content ranging between 6.0 and 7.2% in weight, so that it can be defined as sesquihydrate form. The crystalline hydrate β form of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having more intense peaks at about 4.7, 9.4, 13.2, 16.8 and 22.2. The crystalline hydrate β form of rabeprazole sodium is being prepared by crystallization of Rabeprazole sodium from a solution of organic polar aprotic solvent such as ethyl acetate, butyl acetate, isopropyl acetate, ethyl propionate, isobutyl propionate and ethyl butyrate and alkaline water solution. The isomorphic forms alpha and beta are characterized by low hygroscopicity, which makes handling and storing easy. Giuseppe Barrecaa et al., [23] reported crystalline hydrate form γ of rabeprazole sodium. The crystalline hydrate γ form of rabeprazole sodium has water content ranging between 4.5 and 5.0% in weight, so that it can be defined as monohydrate form. The crystalline hydrate γ form of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having more intense peaks at about 10.5, 18.0, 18.4, 19.4, 21.1, 22.9, 23.3. The crystalline hydrate γ form of rabeprazole sodium is being prepared by crystallization of rabeprazole sodium from organic polar aprotic solvent such as ethyl acetate, butyl acetate, isopropyl acetate, ethyl propionate, and isobutyl propionate and ethyl butyrate at room temperature optionally in the presence of seed of crystalline hydrate γ form of rabeprazole sodium.

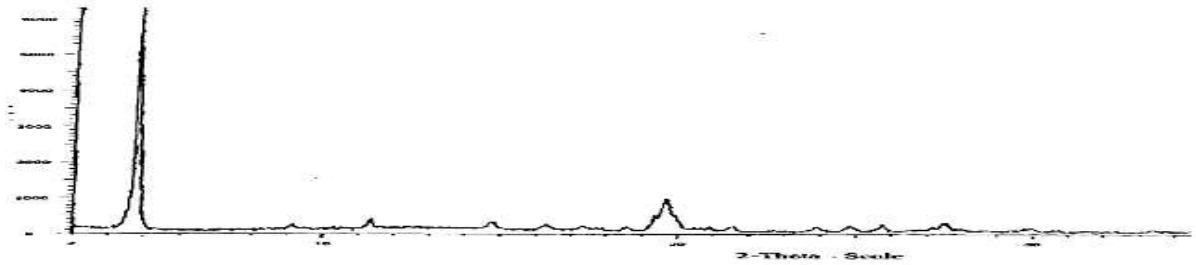

Figure 17 X ray diffraction pattern of crystalline form Z of rabeprazole sodium

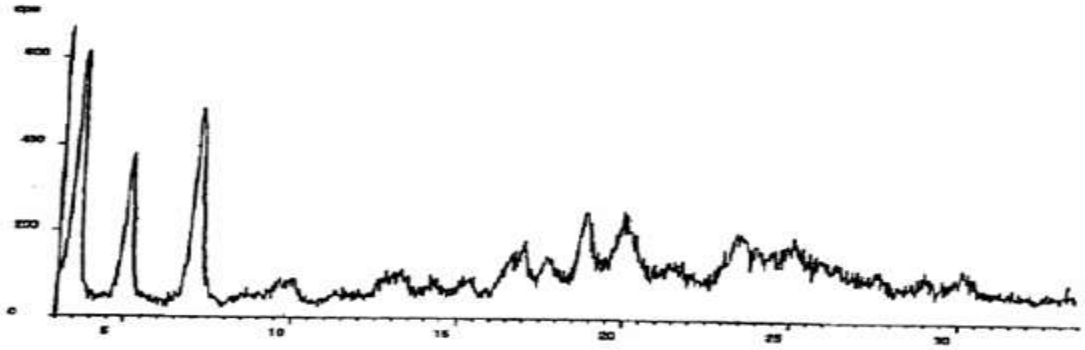

Figure 18 X ray diffraction pattern of crystalline form α of rabeprazole sodium

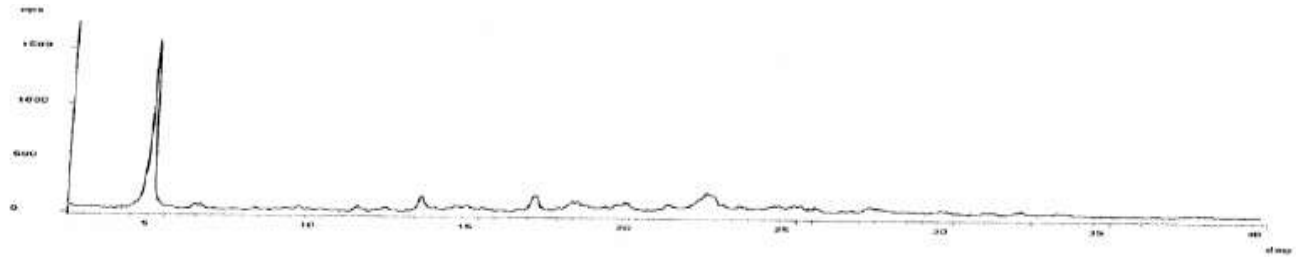

Figure 19 X ray diffraction pattern of crystalline form β of rabeprazole sodium

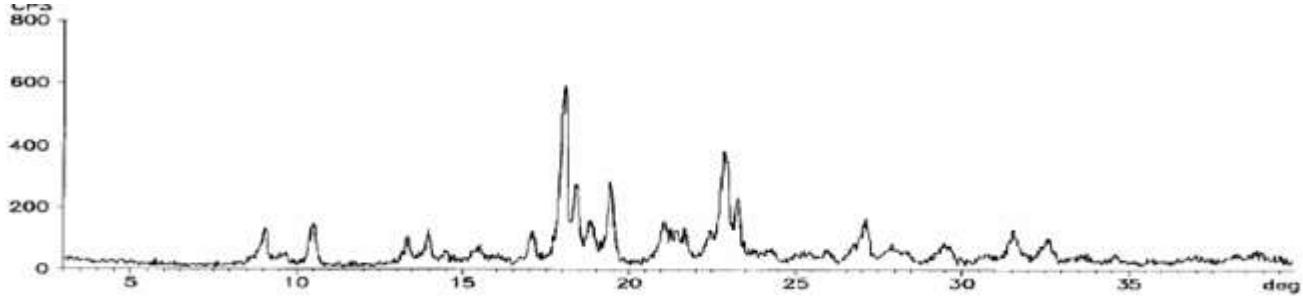

Figure 20 X ray diffraction pattern of crystalline form γ of rabeprazole sodium

CONCLUSION

Rabeprazole sodium exhibit polymorphism and crystalline polymorphic forms along with an amorphous form are reported. Therefore this work has been attempted towards the development of new polymorphic form of rabeprazole sodium, study the correlation of process parameters such as type of solvent, volume of the solvent, sequence of addition, temperature, rate of agitation, pH of reaction mixture etc on the polymorphism and the study of impact of different polymorphic forms of rabeprazole sodium on the biological activity, physiochemical properties or an industrial manufacturing method.

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