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POLYMORPHISM IN RABEPRAZOLE SODIUM

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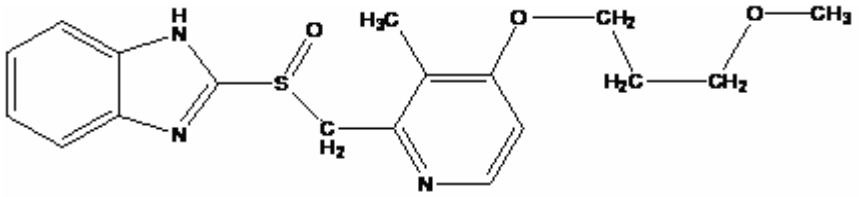
ABSTRACT
Rabeprazole sodium, a proton pump inhibitor, exhibits polymorphism and present article summarize the different polymorphic forms of rabeprazole sodium.
Keywords: Polymorphism, Rabeprazole, proton pump inhibitor, crystalline form, XRD and DSC

INTRODUCTION

Rabeprazole[1] is a compound with an alkoxyalkoxy group in the 4-position of the pyridine ring. Chemically rabeprazole is 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole and is represented by structural Formula-1.



Formula-1

Rabeprazole[1] is a proton pump inhibitor that can be used in the treatment of acid-peptic-related disorders (gastroesophageal reflux disease [GERD], duodenal ulcer, gastric ulcer, gastric acid hypersecretory syndromes) and *Helicobacter pylori*.

Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties such as unit packing, thermodynamic, spectroscopic, interfacial, and mechanical properties. Therefore a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different 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.

Polymorphic forms of a compound can be distinguished by X-Ray diffraction spectroscopy and by other methods such as, ^{1}H nuclear magnetic resonance spectroscopy, ^{13}C nuclear magnetic resonance spectroscopy, infrared spectroscopy, Raman spectroscopy and differential scanning calorimetry.

Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Many pharmaceutical solids exist in amorphous forms and because of their distinctive properties are sometimes regarded as a polymorph. Unlike true polymorphs, an amorphous form is not a single type of crystal and not considered a polymorph.

Rabeprazole sodium, a proton pump inhibitor is demonstrating polymorphism and several polymorphic forms of rabeprazole sodium have been reported in the literature and therefore an attempt has been made for the comprehensive study of different polymorphic forms of rabeprazole sodium along with their characterization method.

Polymorphism in Rabeprazole Sodium

Souda et al[1], reported amorphous form of rabeprazole sodium. 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 (2θ) in X-ray powder diffraction pattern as depicted in Figure 1. The differential scanning calorimetry thermogram of amorphous rabeprazole sodium exhibits significant endothermic peaks at about 66.46°C, 107.14°C, 147.63°C and an exothermic peak at 221.08°C.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 being prepared by spray-drying[2], heat drying[3], lyophilization[4], agitated thin film drying[5] techniques and by crystallization[1] from ether solvent, in the form of white to off-white powder.

Masahiko et al[6], reported crystalline form II of rabeprazole sodium. The crystalline form II of rabeprazole sodium is being characterized by powder X-ray diffraction patterns and infrared absorption spectrum in potassium bromide pellet. The crystalline form II of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having peaks at about 8.88, 9.64, 11.84, 12.54, 12.82, 13.20, 13.80, 14.22, 17.20, 17.60, 18.04, 19.52, 20.92, 21.20, 22.64, 24.16, 24.38, 24.76, 25.00, 25.92, 26.60, 27.56, 27.76, 28.50, 28.76, 29.40, 30.00, 31.62, 34.04 and 34.92 degrees 2θ. The X-ray diffraction pattern of crystalline form II of rabeprazole sodium is depicted in Figure 2.The crystalline form II of rabeprazole sodium is also being characterized by absorption bands in infrared absorption spectrum at 524.5, 621.0, 740.9, 822.8, 897.6, 971.6, 1024.4, 1099.0, 1154.1, 1193.8, 1268.2, 1296.1, 1381.2, 1464.6, 1583.6, 2929.5, 3036.0 and 3422.3 cm^{-1}.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 solvent such as methyl formate, ethyl formate, propyl formate, isopropyl formate, butyl formate, isobutyl formate, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, methyl propionate, ethyl propionate, n-propyl propionate, isopropyl propionate, butyl propionate, isobutyl propionate, methyl butyrate, ethyl butyrate, propyl butyrate, isopropyl butyrate, butyl butyrate, isobutyl butyrate, methyl isobutyrate, ethyl isobutyrate, propyl isobutyrate, isopropyl isobutyrate, butyl isobutyrate, isobutyl isobutyrate 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.

Reddy et al[7], reported crystalline forms X and Y of rabeprazole sodium. The crystalline form X of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having peaks at about 5.13, 6.606, 7.244, 8.569, 9.353, 10.565, 12.161, 12.923, 14.414, 14.864, 16.372, 17.309, 18.173, 19.072, 20.01, 20.539, 22.177, 23.469, 24.81 and 25.494 degrees 2θ. The X-ray diffraction pattern of crystalline form X of rabeprazole sodium is depicted in Figure 3.The differential scanning calorimetry thermogram of crystalline form X of rabeprazole sodium exhibits a significant endo-exo pattern at 154.62°C and 214.65°C.The crystalline form X of rabeprazole sodium is also being characterized by melting point (capillary method) at 140-150°C.The crystalline form X of rabeprazole sodium is being prepared by crystallization of Rabeprazole sodium from chlorinated C_1-C_3 hydrocarbon solvent and C_5-C_{10} alkane or a C_5-C_{10} cyclic alkane solvents or mixtures thereof.

The crystalline form Y of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having peaks at about 5.61, 7.207, 7.725, 9.649, 10.352, 11.231, 14.546, 16.418, 16.899, 19.442 and 24.943 degrees 2θ.The X-ray diffraction pattern of crystalline form Y of rabeprazole sodium is depicted in Figure 4.The differential scanning calorimetry thermogram of crystalline form Y of rabeprazole sodium exhibits a significant endo-exo pattern at 182.61°C and 215.57°C.The crystalline form Y of rabeprazole sodium is also being characterized by melting point (capillary method) at 160-170°C.The crystalline form Y of rabeprazole sodium is being prepared by crystallization of rabeprazole sodium from C_3-C_5 straight or branched chain alcohol and an ether solvent.

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.

Venkatraman et al[8], reported crystalline form Z of rabeprazole sodium. The crystalline form Z of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having peaks at about 4.694, 9.070, 9.417, 11.254, 14.712, 16.241, 17.264, 18.522, 19.320, 19.626, 19.920, 20.802, 21.477, 23.073, 24.814, 25.702, 27.470, 30.009, 30.653, 33.365 and 36.950 degrees 2θ.The X-ray diffraction pattern of crystalline form Z of rabeprazole sodium is depicted in Figure 5.The differential scanning calorimetry thermogram of crystalline form Z of rabeprazole sodium exhibits a significant endo-exo pattern at 106.5°C and 228.8°C.The crystalline form Z of rabeprazole sodium is also being characterized by melting point (capillary method) at 224-230°C.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.Malpezzi et al[9], reported crystalline hydrate forms α and β of rabeprazole sodium.

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 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 ± 0.2 degrees 2θ. The X-ray diffraction pattern of crystalline hydrate α form of rabeprazole sodium is depicted in Figure 6.The differential scanning calorimetry thermogram of crystalline hydrate α form of Rabeprazole sodium exhibits significant endothermic peaks at 123.93°C and 179.10°C.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 ± 0.2 degrees 2θ.The X-ray diffraction pattern of crystalline hydrate β form of rabeprazole sodium is depicted in Figure 7.The differential scanning calorimetry thermogram of crystalline hydrate β form of Rabeprazole sodium exhibits significant endo-exo pattern at 117.45, 165.31 and 208.83°C.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.Barreca et al[10], 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, 21.7, 22.9, 23.3, 27.1 and 31.6 ± 0.2 degrees 2θ.The X-ray diffraction pattern of crystalline hydrate form γ of rabeprazole sodium is depicted in Figure 8.The differential scanning calorimetry thermogram of crystalline hydrate γ form of Rabeprazole sodium exhibits significant endothermic peak at about 152°C.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, isobutyl propionate and ethyl butyrate at room temperature optionally in the presence of seed of crystalline hydrate γ form of rabeprazole sodium.Pruthi et al[11], reported crystalline form V and VI of rabeprazole sodium.

The crystalline form V of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having peaks selected from the group consisting of 9.69, 10.67, 13.62, 17.27, 18.82, 19.57, 20.39, 21.22, 22.09, 24.63, 25.29, 27.79, 36.09, 40.41, 42.43, 44.94 and 55.28 ± 0.9 degrees 2θ.The X-ray diffraction pattern of crystalline form V of rabeprazole sodium is depicted in Figure 9.

The crystalline form VI of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having peaks selected from the group consisting of 5.43, 9.70, 10.94, 13.60, 17.24, 18.74, 20.36, 21.18, 22.03, 25.58, 25.27, 27.95, 33.13, 33.90, 36.10, 40.40, 43.94, 44.91 and 55.71 ± 0.9 degrees 2θ.The X-ray diffraction pattern of crystalline form VI of rabeprazole sodium is depicted in Figure 10.

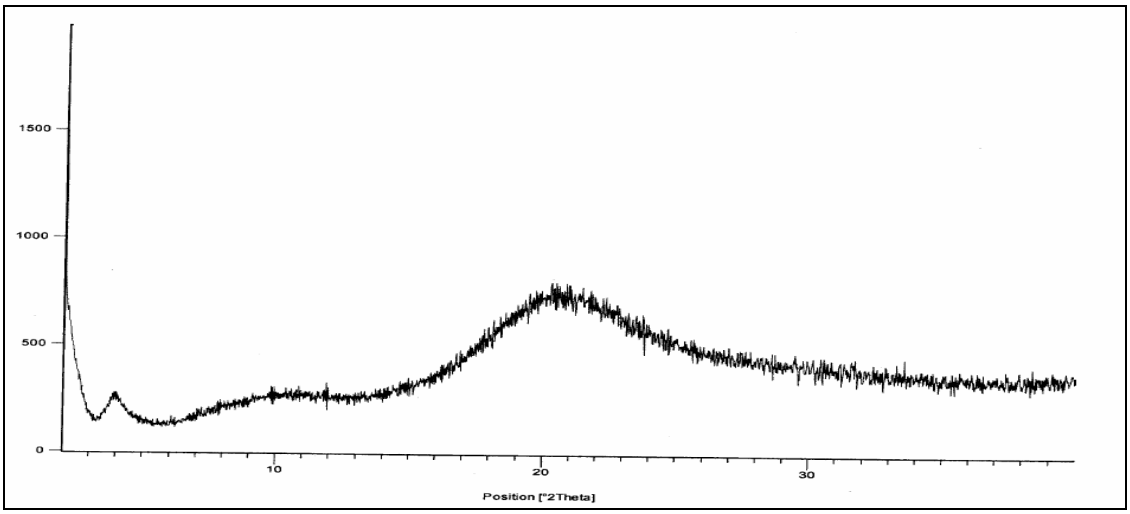


Fig.-1: Depicts X-ray diffraction pattern of amorphous form of rabeprazole sodium

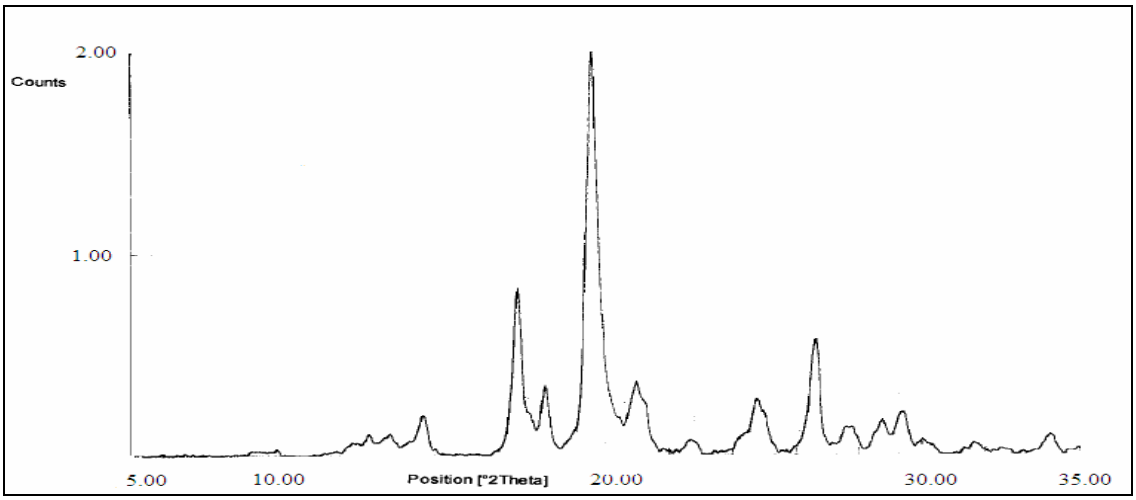


Fig.-2:Depicts X-ray diffraction pattern of crystalline form II of rabeprazole sodium

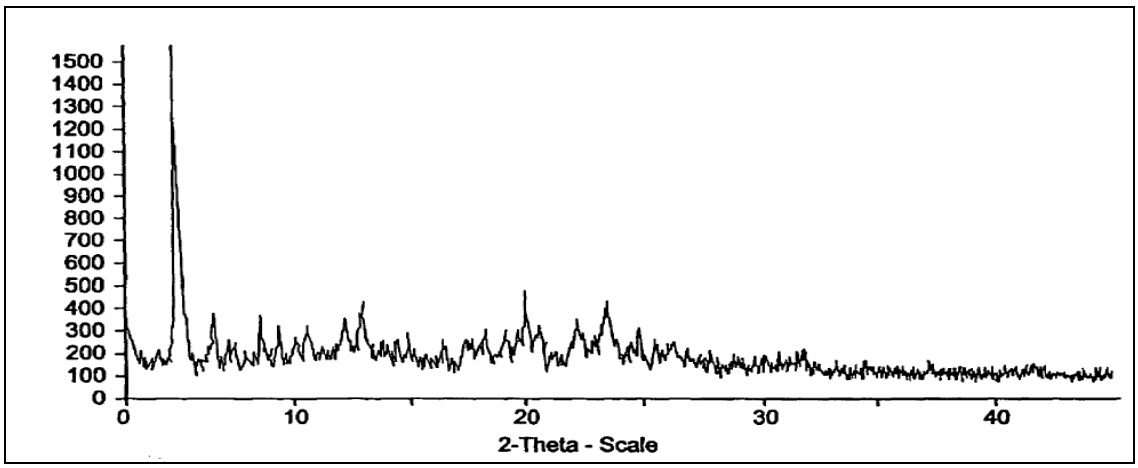


Fig.-3:Depicts X-ray diffraction pattern of crystalline form X of rabeprazole sodium

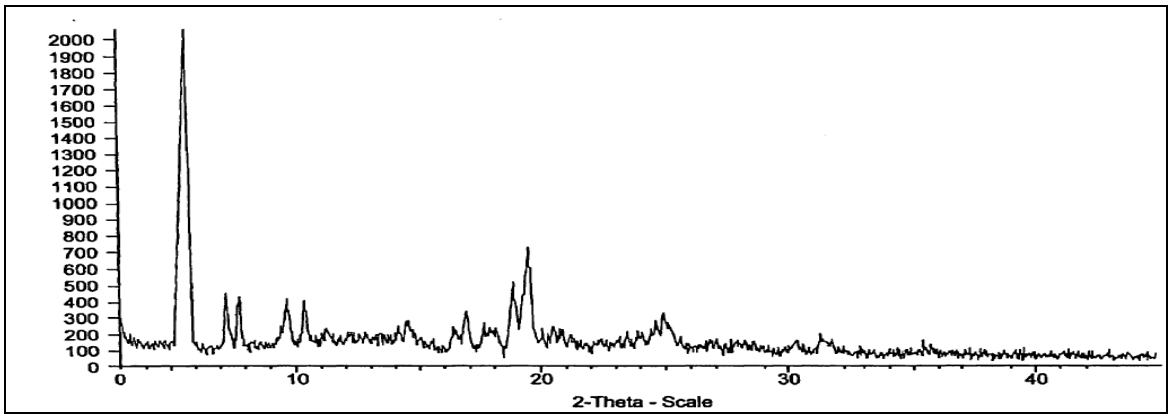


Fig.-4: Depicts X-ray diffraction pattern of crystalline form Y of rabeprazole sodium

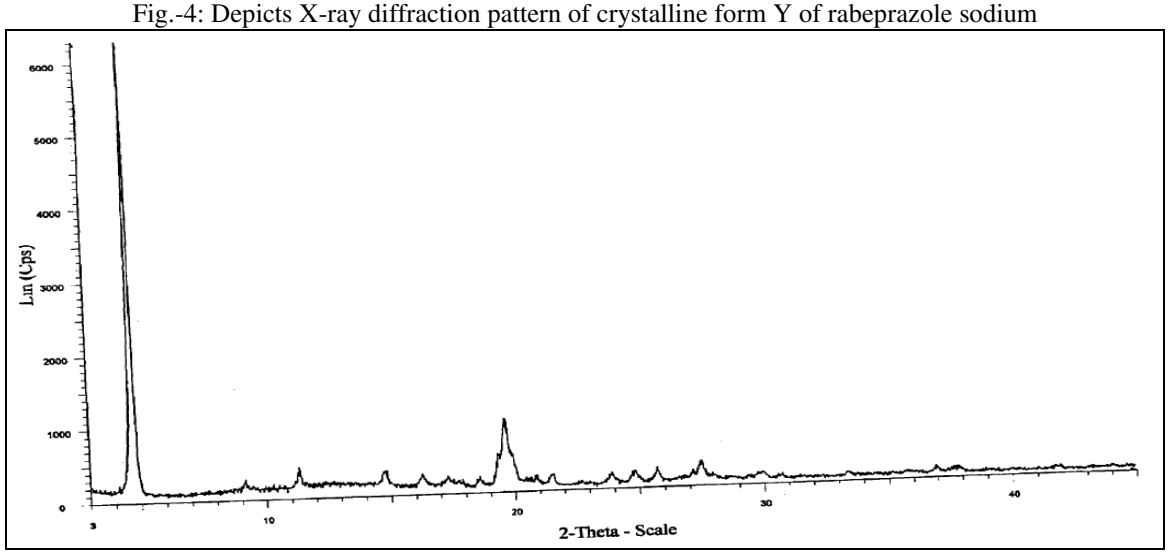


Fig.-5: Depicts X-ray diffraction pattern of crystalline form Z of rabeprazole sodium

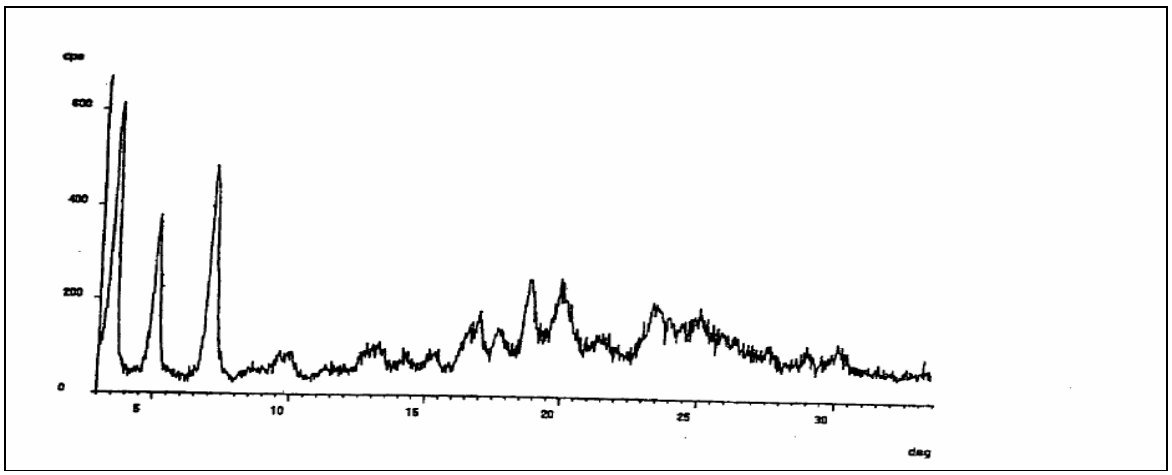


Fig.-6: Depicts X-ray diffraction pattern of crystalline hydrate α form of rabeprazole sodium

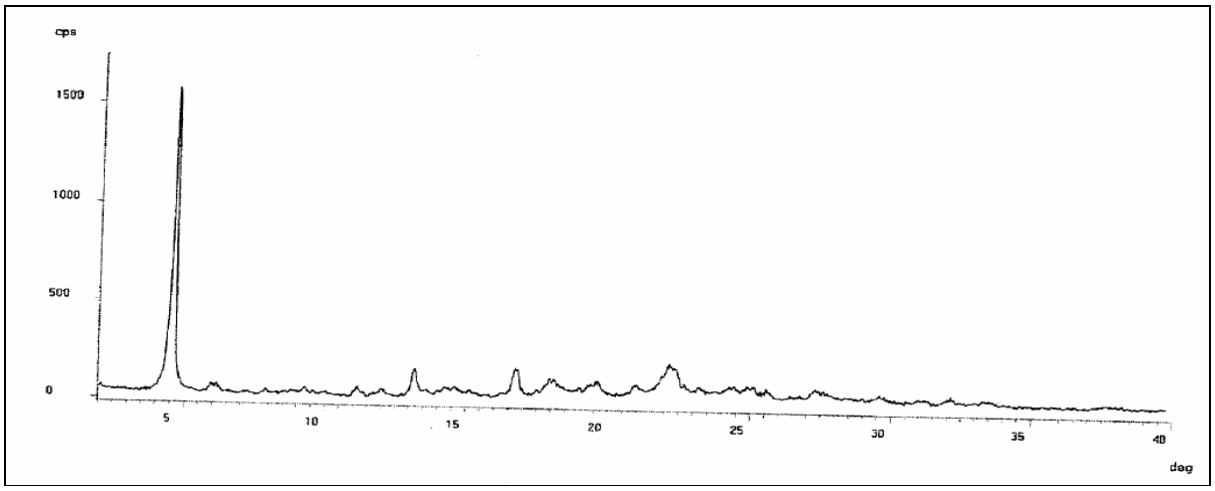


Fig.-7:Depicts X-ray diffraction pattern of crystalline hydrate β form of rabeprazole sodium

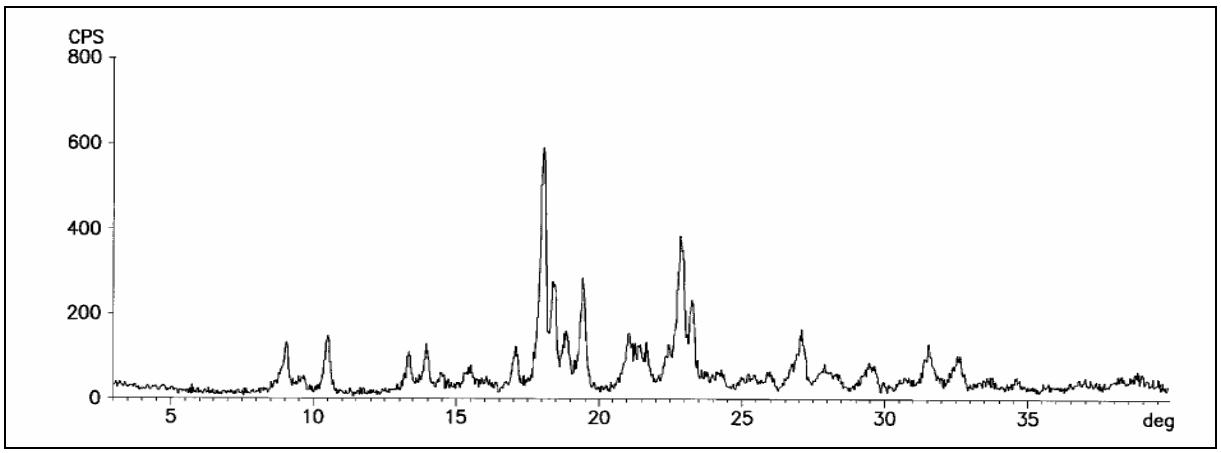


Fig.-8: Depicts X-ray diffraction pattern of crystalline hydrate form γ of rabeprazole sodium

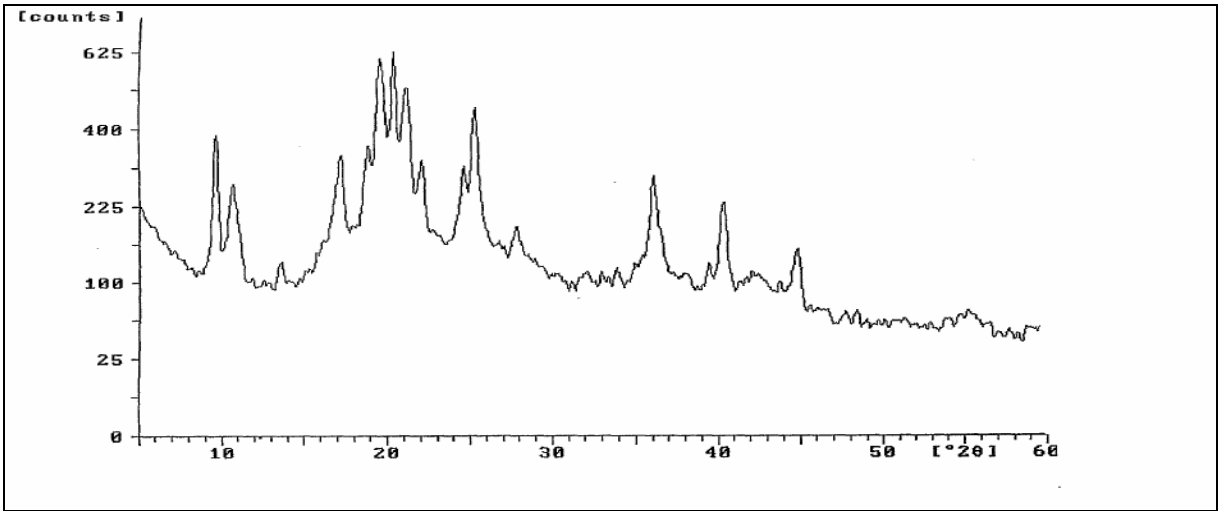


Fig.-9: Depicts X-ray diffraction pattern of crystalline form V of rabeprazole sodium

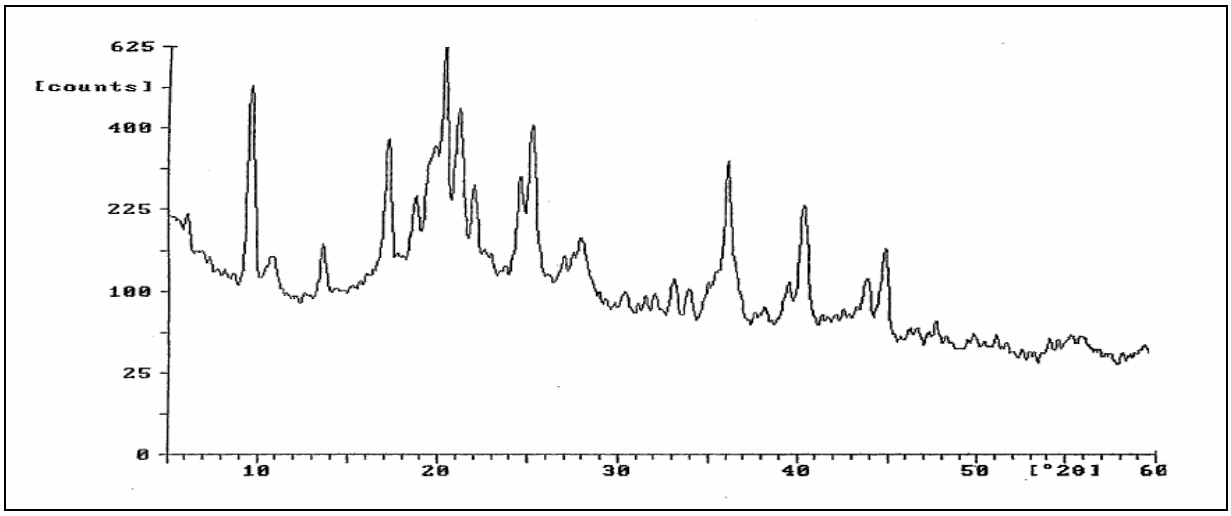


Fig.-10: Depicts X-ray diffraction pattern of crystalline form VI of rabeprazole sodium

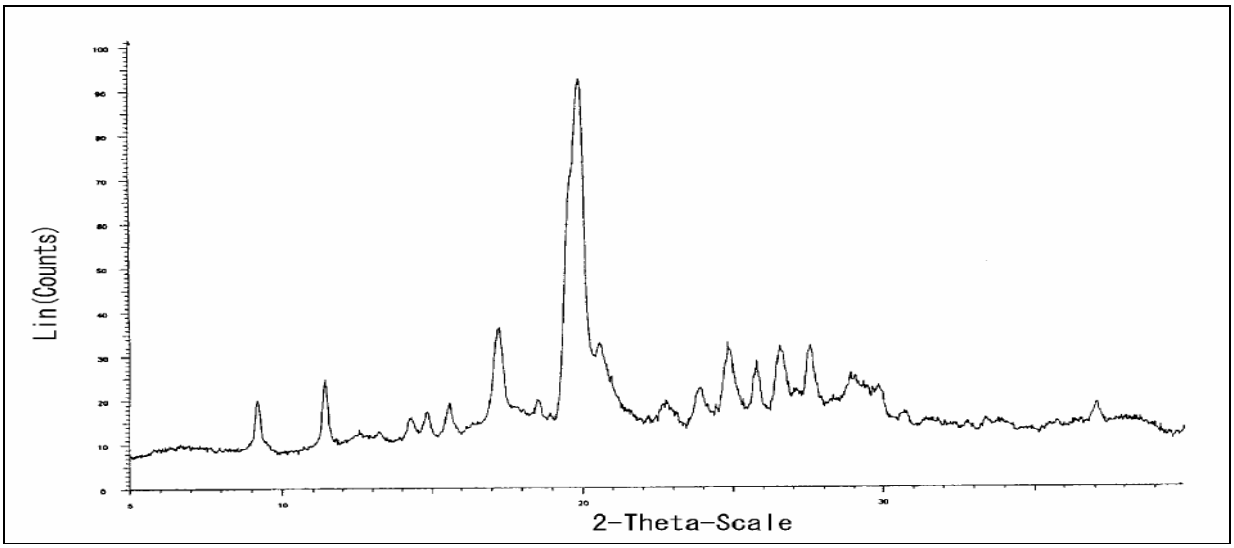


Fig.-11:Depicts X-ray diffraction pattern of crystalline form F of rabeprazole sodium

Table-1: Characteristic peaks and their intensity ratio in XRD pattern of rabeprazole sodium polymorphic form II, X, Y, Z and α.

Form II 2θ°	Intensity I/I_0	Form X 2θ°	Intensity I/I_0	Form Y 2θ°	Intensity I/I_0	Form Z 2θ°	Intensity I/I_0	Form α 2θ°	Intensity I/I_0
14.22	10	5.13	100	5.61	100	4.69	100	3.8	100
17.20	41	6.60	19	7.20	15	9.07	3	5.1	70
17.60	10	8.56	14	7.72	17	11.25	4	7.1	85
18.04	17	10.56	10	9.64	14	14.71	3	16.9	23
19.52	100	12.16	9	10.35	13	16.24	3	17.6	16
20.92	18	12.92	13	19.44	33	18.52	5	18.8	35
21.20	12	20.01	18	16.89	11	19.32	15	19.9	32
24.76	25	22.17	7	18.81	20	19.62	6		
25.00	10	23.46	16	19.44	33	24.81	3		
26.60	28	24.81	11	24.94	10	27.47	3		

The crystalline forms V and VI of rabeprazole sodium are being prepared by freeze drying of rabeprazole sodium solution in water at cryogenic temperature.

Hori et al[12], reported crystalline form F of rabeprazole sodium, which is free from the storage stability problems of raw drug and the solid drug formulation. The crystalline form F of rabeprazole sodium is being characterized by x-ray powder diffraction spectrum having peaks at 18.0, 20.9 and 21.2 ± 0.1 degrees 2θ. The X-ray diffraction pattern of crystalline form F of rabeprazole sodium is depicted in Figure 11.The differential scanning calorimetry thermogram of crystalline form F of rabeprazole sodium exhibits significant endo-exo pattern at 128.93 and 237.67°C.The crystalline form F of rabeprazole sodium is being prepared by crystallization of rabeprazole sodium from an ether base organic solvent.

CONCLUSION

Rabeprazole sodium exhibit polymorphism and ten crystalline polymorphic forms along with an amorphous form are reported in the literature. Polymorphism is meaningless unless solid physical properties exert an influence on biological activity, physiochemical properties or an industrial manufacturing method of the substance and therefore researchers have been attracted toward the development of new polymorphic form of rabeprazole sodium, study of 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.

Table-2: Characteristic peaks and their intensity ratio in XRD pattern of rabeprazole sodium polymorphic form β, γ, V, VI and F.

Form β 2θ°	Intensity I/I_0	Form γ 2θ°	Intensity I/I_0	Form V 2θ°	Intensity I/I_0	Form VI 2θ°	Intensity I/I_0	Form F 2θ°	Intensity I/I_0
4.7	100	10.5	10	9.69	56	9.70	76	11.39	27
9.4	5	18.0	100	17.27	39	17.24	50	17.20	39
13.2	12	18.4	38	18.82	45	18.74	27	19.52	74
16.8	12	19.4	38	19.57	95	20.36	100	19.84	100
22.2	15	21.1	20	20.39	100	21.18	66	20.55	35
		21.7	19	21.22	75	22.03	33	24.85	34
		22.9	47	22.09	39	24.58	37	25.76	31
		23.3	26	24.63	37	25.27	60	26.56	34
		27.1	17	25.29	67	36.10	48	27.53	34
		31.6	12	36.09	36	40.40	30	28.92	28

REFERENCES

1. Shigeru Souda, Norihiro Ueda, Shuhei Miyazawa, Katsuya Tagami, Makoto Okita, Naoyuki Shimomura, Toshihiko Kaneko, Masatoshi Fujimoto, Manabu Murakami, Kiyoshi Oketani, Hideaki Fujisaki, Hisashi Shibata and Tsuneo Wakabayashi, US 5,045,552 (1991).
2. IP.com Number, IPCOM000153804D, June 8, 2007.
3. Masahiko Tsujii (Japan), Yukio Morita (Japan), WO 2004/085424 (2004).
4. Masahiko Tsujii (Japan), Nobuo Niikawa (Japan), Keizo Takayanagi (Japan), Shigeharu Nochi (Japan), US 6,545,024 (2003).
5. Pingili Ramchandra Reddy, Vurimidi Himabindu, Lilakar Jaydeepkumar, Boluggdu Vijaya Bhaskar, Ghanta Mahesh Reddy, *Rasayan Journal of Chemistry*, **1**, 166, (2008).
6. Tsujii Masahiko, Shinkawa Nobuo and Hasebe Takashi, JP 2001/039975 A2 (2001).
7. Manne Satyanarayana Reddy, Sajja Eswaraiah, Vijava Bhaskar Bolugoddu, Ramchandra Reddy Pingili and Madhusudhan Reddy Ganta, US 2005/0234103 (2005).

8. Sundaram Venkatraman, Manne Satyanarayana Reddy, Sajja Eswaraiah, Vijava Bhaskar Bolugoddu, Ramchandra Reddy Pingili, Ireddy Rajiv, Thirunava Karasu Ananda Babu, US 2004/0180935 (2004).
9. Luciana Malpezzi, Tommaso Giovenzana, Pietro Allegrini, Gianpiero Ventimiglia, US 2006/0135565 (2006).
10. Giuseppe Barreca, Alessandro Restelli, Pietro Allegrini, US 2008/0161359 (2008).
11. Ashish Pruthi, Gianchand Sharma, WO 2007/091276 (2007).
12. Noriyuki Hori, Youko Kiyosawa, Yoshitaka Nakata, WO 2008/152753 (2008).

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