World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

Synthesis and spectral characterization of esomeprazole sodium Polymorphic form

S. Suresh babu, AVGS Prasad *

Enal Drugs Pvt Ltd D-33, 34&35 Phase I IDA Jeedimetla, Hyderabad 500055, India

Received: 29-02-2016 / Revised: 18-03-2016 / Accepted: 24-03-2016 / Published: 27-03-2016

ABSTRACT

Regulatory authorities throughout the world require that all possible crystalline forms of the same active drug compound be synthesized and characterized as completely as possible. There is thus a continuing need to prepare new polymorphic forms of pharmacologically active compounds. Therefore it is need for preparation of highly pure polymorphic form N esomeprazole sodium by a repeatable process which guarantees stable physical form. Despite the fact that there are numerous known forms of omeprazole, the need continues to exist for novel, pharmaceutically-acceptable forms of omeprazole which may exhibit improved pharmacokinetic and metabolic properties and/or which may result in an improved therapeutic profile. Herein, we report our synthetic study of esomeprazole sodium Polymorphic form.

Key words: Proton Pump Inhibitors, polymorphism, Esomeprazole sodium, XRD, NMR, IR.

INTRODUCTION

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. Pharmaceutical polymorphic solids of the same chemical compound differ in internal solid-state structure and, therefore, possess different chemical and physical properties, including hygroscopicity, particle shape, density, flowability, and compactability, melting point, chemical reactivity, apparent solubility, dissolution rate, optical,vapor pressure, packing, thermodynamic, spectroscopic, kinetic, interfacial, and mechanical properties.*[1,2]

For a drug whose rate and extent of absorption is limited by its dissolution, large differences in the solubilities of the various polymorphic forms are likely to affect BA/BE. On the other hand, for a drug whose rate and extent of absorption is only limited by its intestinal permeability, differences in the solubilities of the various polymorphs are less likely to affect bioavailability/bioequivalence BA/BE.*[3]

It is desirable to investigate all the solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in the laboratory by powder X-ray diffraction spectroscopy. *[4]

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. *[5]

It is also important that the processes for the preparation of the polymorphic forms be robust and reproducible, so that the processes are easily scaled up in the plant. It has been observed that many antibiotics, antibacterials, transquilizers etc, exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibit superior bioavailability and consequently show much higher activity compared to other polymorphs. For some therapeutic indications one bioavailability pattern may be favored over another. *[6] PPIs are used to treat peptic ulcers (duodenal and gastric), gastroesophageal reflux disease (GERD) and drug-

***Corresponding Author Address: Dr**. A.V.G.S. Prasad, Enal Drugs Pvt Ltd D-33, 34&35 Phase I IDA Jeedimetla, Hyderabad 500055, India: E-mail: suresh@enaldrugs.com*

induced ulcers (e.g., non-steroidal anti-inflammatory drugs {NSAIDs}). For peptic ulcer disease, PPIs are given with antibiotics to eradicate Helicobacter pylori (H. pylori), the bacteria that cause ulcers. *[7-10]

Omeprazole is a proton pump inhibitor (PPIs) and inhibits the action of hydrogen/potassium adenosine triphosphatase (H+/K+ATPase) in parietal cells. Omeprazole was the first drug in this class introduced in 1988.

Since then, four other PPIs viz lansoprazole, rabeprazole, pantoprazole and esomeprazole have been introduced in 1995, 1999, 2000 and 2001 respectively. These drugs are referred to as proton pump inhibitors. *[11]

Omeprazole has a low water solubility and is chemically unstable in an acidic environment. Further, omeprazole degrades very rapidly in acidic aqueous solutions. While it is only slightly soluble in water, omeprazole is very soluble in alkaline solutions as a negatively charged ion. At pH 6.5, the half-life of degradation of omeprazole is about eighteen hours; at a pH of around 11, the half-life extends to several hundred days.

The literature discloses crystalline esomeprazole sodium polymorphic forms are less pure and less stable. Omeprazole sodium form A is highly soluble in water and as such, is suitable for parenteral formulations, providing an opportunity for physicians to treat patients suffering from gastroesophageal reflux disease (GERD) who are unable to take oral therapy. *[12]

Form B is said to be less hygroscopic than omeprazole form A. Form C of omeprazole sodium is relatively stable physical form and is less hygroscopic than Form A of omeprazole sodium. Form D of omeprazole sodium is thermally stable and free flowing solid. In general, the free flowing solids are recommended for pharmaceutical formulations.

During the preparation of esomeprazole sodium salt a number of novel crystal modifications are formed. Some of these novel intermediates are stable and thus possible to isolate and characterize. Others are too short-lived to characterize and still others are crystalline while in a damp and wet state, but are transformed into various amorphous forms upon drying and are as a consequence difficult to characterize. There is a constant need to prepare pharmaceutically stable crystalline form of the active substance omeprazole in an industrially simple and readily feasible way with high yield and quality.

Due to the huge requirement of omeprazole in the market, it is very important to synthesize stable crystalline form of omeprazole to the customers. Additionally, there is a continuing need for omeprazole forms which are stable over extended periods of time.

The present work relates to stable esomeprazole sodium for injection has characteristics of good stability and high purity. A process for preparing esomeprazole sodium crystalline form N in physically stable and highly pure form.

MATERIAL AND METHODS

All chemicals were used as received from commercial sources without further purification. 1H and 13C NMR spectra were recorded on a BrukerAvance 500 (500 MHz, 1H; 125 MHz 13C) spectrometer. The mass spectra were recorded with aAgilent 1260LC/MS instrument. XRD : Powder X – ray diffraction patterns were recorded on a D8 ADVANCE BRUKER axs model diffractometer equipped with vertical goniometer in θ / θ geometry. Copper K α (λ = 1.5406 A°) radiation was used, and the sample was scanned between 3 and 45° 2θ.3.4.

Example 1: 300 gr esomeprazole Potassium salt, methylene dichloride 1000ml and DM water. Neutralize with Glacial Acetic Acid upto 7-7.5 pH. Separate the MDC layer. Add this organic layer to 250 ml methanol containing 45 gr sodium methoxide. Maintain for 2 hours at Room temperature. Filter through hiflow bed. The solvent distilled atmospherically at 40° C. Add Isopropyl alcohol and cool to 10 ° C. The separated solid was filtered and washed with Isopropyl alcohol. The wet compound was dried at 60° C. for 4-6 hours to yield 197 g of the title compound. Purity by HPLC: 99.63%. Melting point: 233-235 ° C. R-isomer impurities: not detected. Optical Rotation: + 33 ^{0} (C=1 in water)

Example 2: 300 gr esomeprazole Potassium salt, methylene dichloride 1200ml and DM water. Neutralize with Glacial Acetic Acid upto 7-7.5 pH. Separate the MDC layer. Add this organic layer to 250 ml methanol containing 45 gr sodium methoxide. Maintain for 2 hours at Room temperature. Filter through hiflow bed. The mixture was then distilled atmospherically at 40° C to remove the solvents. Add diisopropyl ether and cool to 15 ° C. The separated solid was filtered and washed with diisopropyl ether. The wet compound was dried at 60° C. for 4-6 hours to yield 190 g of the title compound. Purity by HPLC: 99.59% Melting point: 233-234 ° C R-isomer impurities: 0.01%. Optical Rotation: + 34 ^{0} (C=1 in water).

DISCUSSION

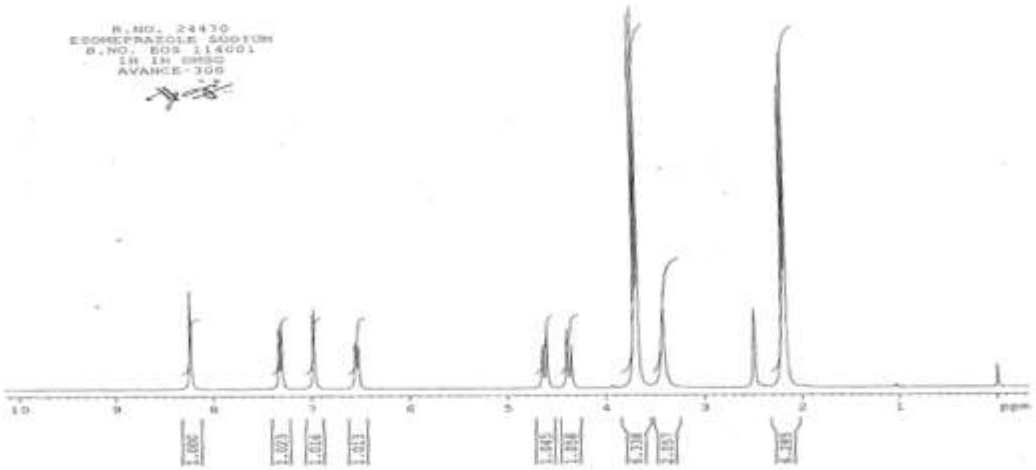

Figure 1 The 1 H NMR spectra of esomeprazole sodium

Table 1 The 1 H NMR spectra of esomeprazole sodium

	1H-NMR (δ) ppm	
	esomeprazole	Esomeprazole sodium
H6	8.17 s	8.25 s
H7	7.54 brs	7.37 brs
H4	7.02 brs	7.09 brs
H6	6.60 dd	6.81 dd
CH2S	4.46 d and 4.72 d	4.67 d and 4.75 d
OCH3	3.75 s	3.8 s
OCH3	3.70 s	3.67 s
CH3	2.19 s	2.21 s
CH3	2.16 s	2.16 s

The NMR spectra show similar signals to that of sulfide compound, except the signals of methylene group attached to S=O. Two proton signals of methylene group that appeared as the singlet at 4.34 ppm were found at 4.67 and 4.75 ppm as 2 doublets.

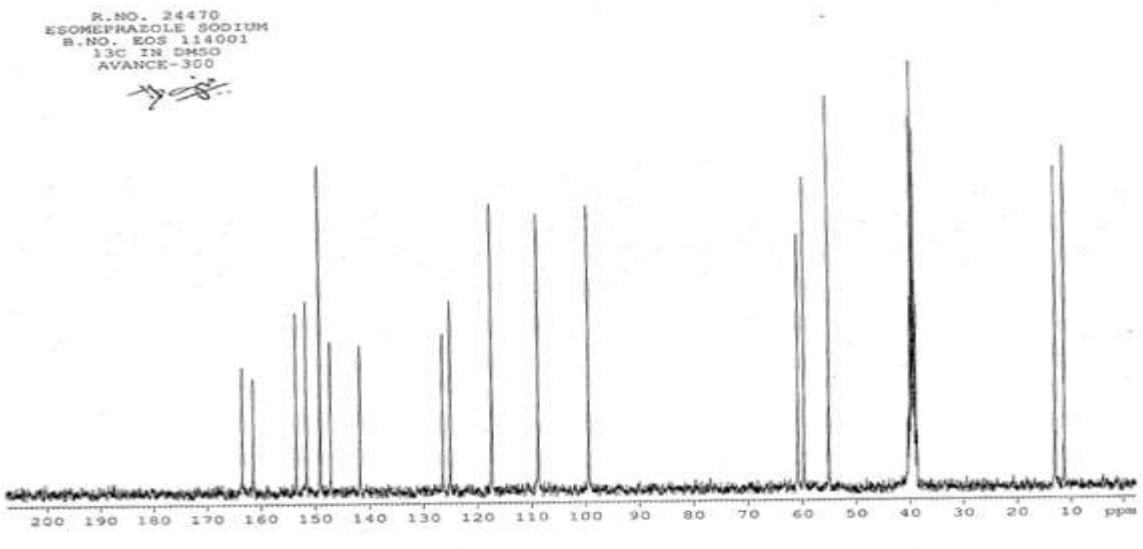

Figure 2: The 13 C NMR spectra of esomeprazole sodium

Table 2 The 13 C NMR spectra of esomeprazole sodium

	13C-NMR (δ) ppm	
	esomeprazole	Esomeprazole sodium
C 4	163.3	163.6
C5	159	159
C2	157	154
C6	150	149
C 2	148	147
C9	139	141
C8	131	129
C3	127	126
C 5	125	124
C4	116	117
C6	110	109
C7	100	101
OCH3	60	61
OCH3	56	59
CH2S	59	59.8
CH3	13	12
CH2	11	11

In the 13C-NMR, the signal of CH2S=O moved to 59.8 ppm from 35.0 ppm in the spectrum of sulfide

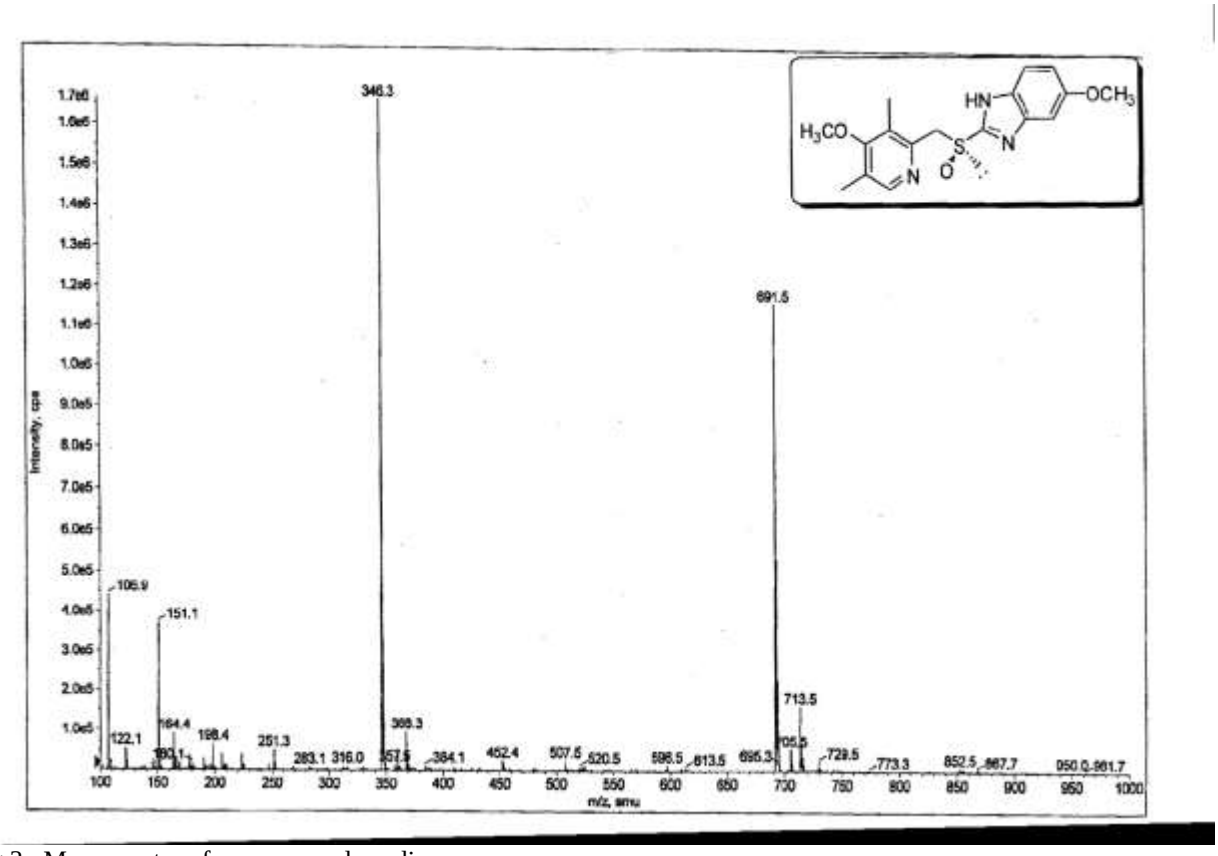

Fig 3 Mass spectra of esomeprazole sodium

The molecular ion peak [M+H]+ was found at 346 in the ESI-MS, hence the chemical formula is C17H19N3O3S.

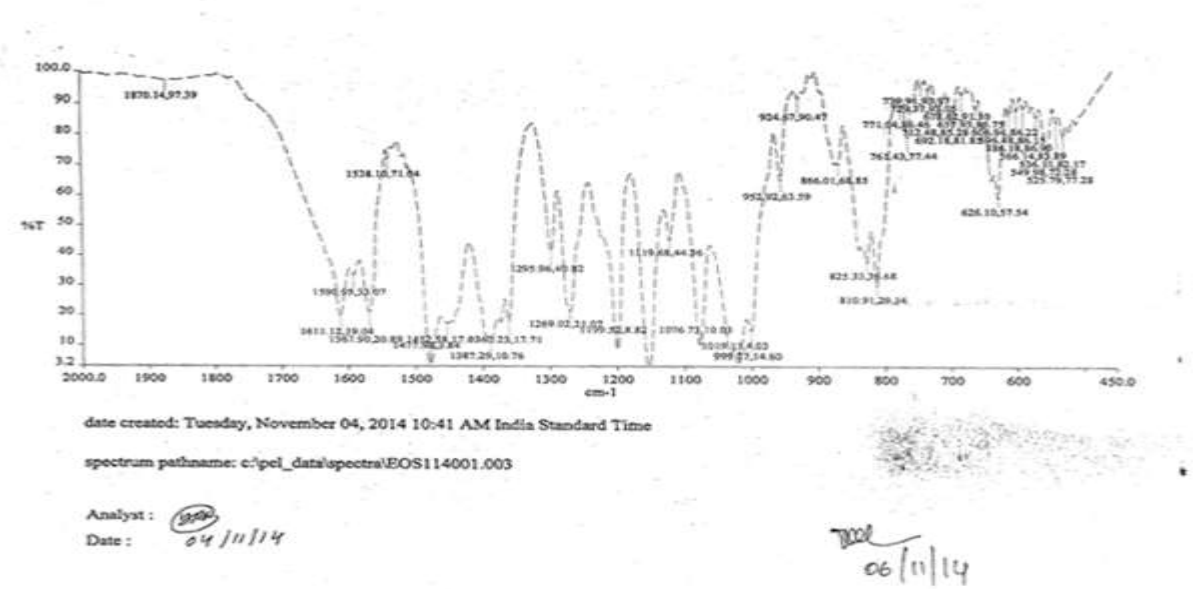

Figure 4: The IR spectra of esomeprazole sodium

Table 3: IR interpretation data

Wave No	assignment	Mode of vibration
3378	N-H	Stretching
2953	Aliphatic C-H	Stretching
1613,1698	C=C, C=N	Stretching
1476,1409	Aliphatic C-H	bending
1271,1288	C-O-C	Asymmetric Stretching
1174	S=O	Stretching
1077, 1029	C-O-C	Symmetric Stretching
807	Aromatic C-H	bending
632	C-S	Stretching

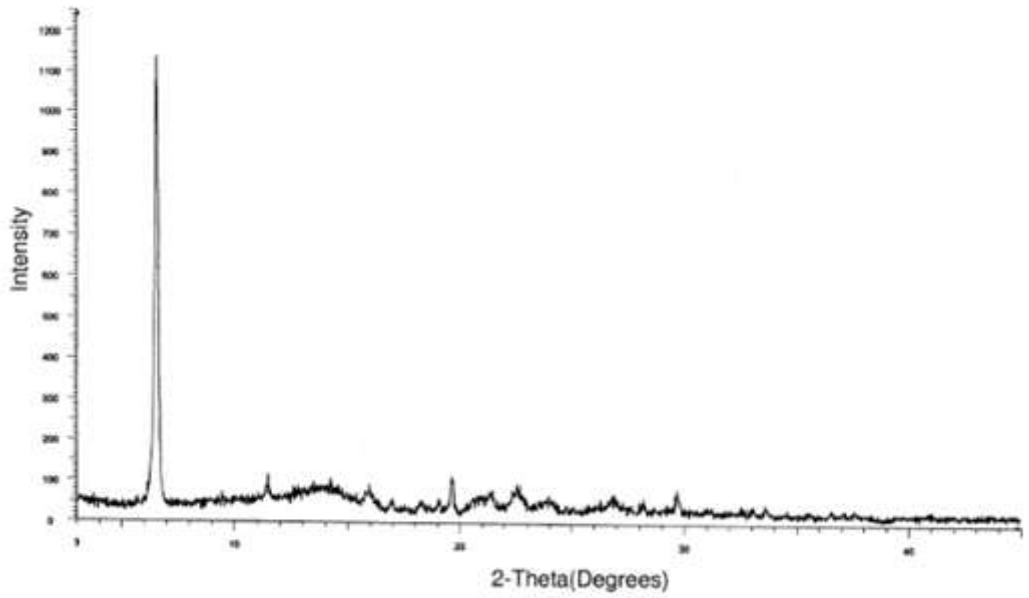

Figure 5: XRD of esomeprazole sodium
XRPD pattern having significant peaks at about 6.3, 8.5, and 15.7, ±0.2 degrees 2θ.
It is also characterized by the additional XRPD peaks at about 19.5 and 22.4, ±0.2 degrees 2θ.

CONCLUSION

Significant advantages of the present method of synthesis reside in that polymorphic crystalline esomeprazole Sodium Form N can be provided repeatedly in pure form for injection have characteristics of good stability and high purity.

ACKNOWLEDGEMENTS

The author expresses thanks to P. Shankar and P. Sarath (process R&D) for providing necessary facilities to carry out this research work. We are grateful to Chief Executive Officer, Crystal morphix Technologies Pvt Ltd., for providing XRD data and Director IICT for NMR, Mass and IR spectral data.

REFERENCES

1. DJW Grant. "Effect of polymorphism and solid-state solvation on solubility and dissolution rate." In HG Brittain (ed.) Polymorphism in Pharmaceutical Solids. Marcel Dekker, Inc., New York, (1999) pp. 279-330.
2. Bauer.J, Polymorphism". Pharmaceutical Research *(2004) (*6): 859–866.
3. Daniel A. Snider*, William Addicks, Walter Owens Polymorphism in generic drug product development, Advanced Drug Delivery Reviews 56 (2004) 391 – 395
4. R. Jenkins, and R.L. Snyder, Introduction to X-Ray Powder Diffractometry, Vol. 138, (1996), Wiley Interscience, New York 378, pp.355-556 and 371
5. Andre S. Raw, et al., Regulatory considerations of pharmaceutical solid polymorphism in Abbreviated New Drug Applications, Advanced Drug Delivery Reviews, (2004) 56(3), 397–414
6. Karpinski, PH polymorphism of active Pharmaceutical ingredients, Chem Eng Technology (2006) 29(2) 233-7.
7. G. Sachs, J. M. Shin and C.W. Hoden the clinical pharmacology of proton pump inhibitors Alimentary Pharmacology and Therapeutics (2006) 23: 2–8.
8. Mc Tavish, D. and Buckley M.M.T. Omeprazole: an updated review of its pharmacology and therapeutic use in acid-related disorders Drugs; (1991) 42:138-70.
9. M. J. Kendall, esomeprazole--the first proton pump inhibitor to be developed as an isomer Aliment Pharmacol Ther; (2003) 17 (Suppl. 1): 1–4.
10. Evangelos Kalaitzakis and Einar Björnsson A review of esomeprazole in the treatment of gastroesophageal reflux disease (GERD) Ther Clin Risk Manag, (2007) 3(4): 653–663.
11. Lindberg, P Omeprazole: the first proton pump inhibitor. Med. Res. Rev., (1990) 10, 1–60
12. Olbe, L., Carlsson, E. and Lindberg, P. A proton-pump inhibitor expedition: the case histories of omeprazole and esomeprazole Nat. Rev. Drug Discov., (2003) 2(2), 132-139.