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Original Article

Synthesis of highly pure esomeprazole sodium with polymorphic form J

Sandip Sadaphal, Huang Xiangliang, Xu Cong

R&D Centre, Menovo pharmaceutical Co. ltd., Shangyu, Zhejiang, China

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ABSTRACT

The present disclosure relates to a process of preparing excellent quality esomeprazole sodium, which is devoid of product related impurities. Esomeprazole sodium performed via preparation of sodium-salt using key starting material esomeprazole potassium. Herein, reported an excellent method to get polymorph J of esomeprazole sodium using acetonitrile maceration. In this development overall yield is 70-80% with purity more than 99%.

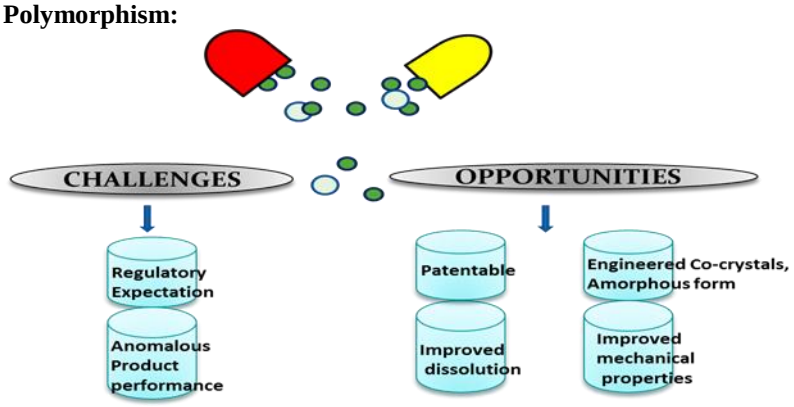
Keywords: Esomeprazole sodium, esomeprazole potassium, Proton Pump Inhibitors, polymorphism, maceration, XRD, DSC, HPLC, NMR, IR

INTRODUCTION

Polymorphs are different crystalline forms of the same pure substance in which molecules have different arrangements and/or different molecular conformation. Every Compound has different polymorphic forms and the number of forms known for a given compound is proportional to the time and energy spent in research on that compound.

Number of polymorphs α time and energy
Polymorphic solids have different unit cells, Display different properties such as unit packing, thermodynamic, spectroscopic, and mechanical properties. Clathrate and hydrates can exist in polymorphic forms. (Clathrate is a chemical substance consisting of a lattice that traps or contains molecules). An amorphous form is not a polymorph. (Random arrangement in unit cell), Many pharmaceutical solids exist in amorphous forms and because of their distinctive properties are sometimes regarded as polymorphs. Unlike true polymorphs, an amorphous form is not a single type of crystal and not considered a polymorph.[1-3] There are various parameter which influence polymorphism such as, molar volume and density, refractive index, melting and sublimation temperatures, enthalpy (i.e., heat content), solubility, vibration transitions (i.e., infrared absorption spectra and Raman spectra, dissolution rate, stability, hardness, compatibility, handling, flow, and blending.[2-3]

Polymorphism:



Corresponding Author Address: Dr. Sandip Sadaphal, R&D centre, Menovo pharmaceutical Co. ltd., Shangyu, Zhejiang, China: Email: sandip@menovopharm.com

In the view of regulatory, active pharma ingredient synthesis with desire polymorph is more advisable. With consideration of differences in the solubility's of the various polymorphs are less likely to affect bioavailability/bioequivalence. Polymorphic forms of a compound identified by powder X-ray diffraction spectroscopy.[4] Omeprazole, chemically 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1*H*-benzimidazole and its therapeutic uses were disclosed in European Patent No. 5129. Omeprazole is a well-known gastric acid secretion inhibitor, and is useful as an antiulcer agent. Omeprazole has a stereogenic center at sulfur and therefore exist as two optical isomers such as R-omeprazole and S-omeprazole (esomeprazole).

Injectable forms of esomeprazole use sodium salt due to their excellent solubility in water. In recent years 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. [5]

In literature various polymorphic forms for esomeprazole sodium available viz; form A, B, C, D, Form P, Q, Form J, K, L, M, N, form C, E, H.[6-10] In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity and with desired polymorph.

It's also mandatory to produce desired polymorph that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light or oxygen level.

In the present work prepared esomeprazole sodium with high purity, excellent yield and with polymorphic form J. The synthetic route for preparation is consistently reproducible. In this research work optimized process is easy to handle in laboratory scale as well as on industrial scale up.

MATERIAL AND METHODS

All chemicals were used as received from commercial sources without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 500 MHz spectrometer. The mass spectra were recorded with a Agilent 1260 LC/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 40° 2θ. DSC carried out on DSC Q200 V24.11 Build 124 instrument at 25°C and 75% RH.

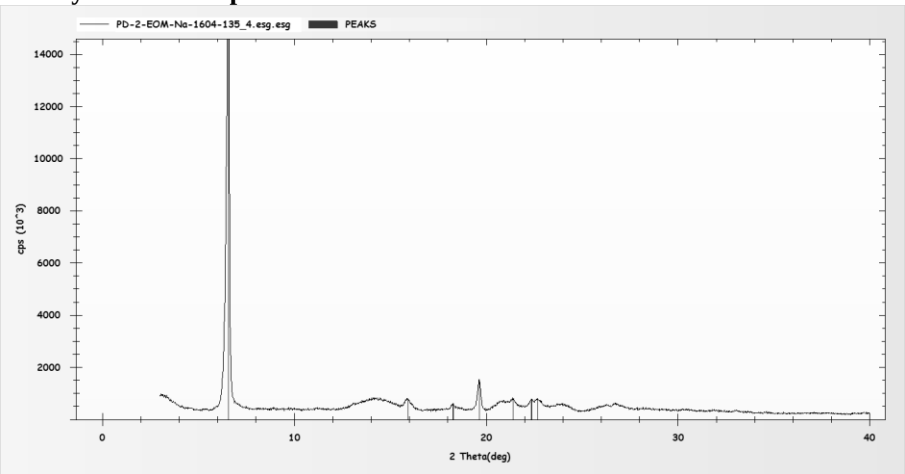
Esomeprazole sodium with from J, obtained and optimized using different solvents such as, acetonitrile, acetone, methyl tertiary butyl ether, methyl isobutyl ketone and isopropyl alcohol.

Whereas ethyl acetate, methyl ethyl ketone, 2-methyl tetrahedrofuran gives form J with traces of unknown form.

The obtained form is analyzed for XRD, compared and conformed using literature data for form J.[8]

Example 1:
In this experiment we have used esomeprazole potassium (100.0 g on dry basis) with purity 98.85% and sulfone impurity 1.07%. Here used water (2.0 V) as a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization and dichloromethane (DCM, 3*2.5 V) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using methanol (1.25 V). Further, reaction mass dissolved in methanol (5.0 V), charged methanolic NaOH (1.6eq NaOH in 2.5 V methanol) slowly and maintained for 1-2 h. Then perform activated carbon treatment and distilled out up to 30% conc. of reaction mass (300.0 g). Age reaction mass overnight at 0-5°C and filtered out and washed by methanol (0.5 V). After filtration suck dry obtained wet cake. The obtained wet cake dry for 24h under vacuum at 39°C and check water content, LOD, residual solvent and purity. Then transfer dry product in another flask and use 4V (wrt esomeprazole potassium) acetonitrile for maceration at 0-5°C. Age reaction mass for 2h at same temperature. Obtained solid filter under nitrogen, wash by ACN (0.5V) and suck dry. Wet product dry under vacuum for 8h at 39°C. Sieve dry product under nitrogen and dry again for 24h at 39°C under vacuum to yield 68.8g (71.74%) of the title compound. Purity by HPLC: 99.94%, Sulphone impurity is 0.03%. Melting point: 233-234°C. R-isomer impurities: not detected.

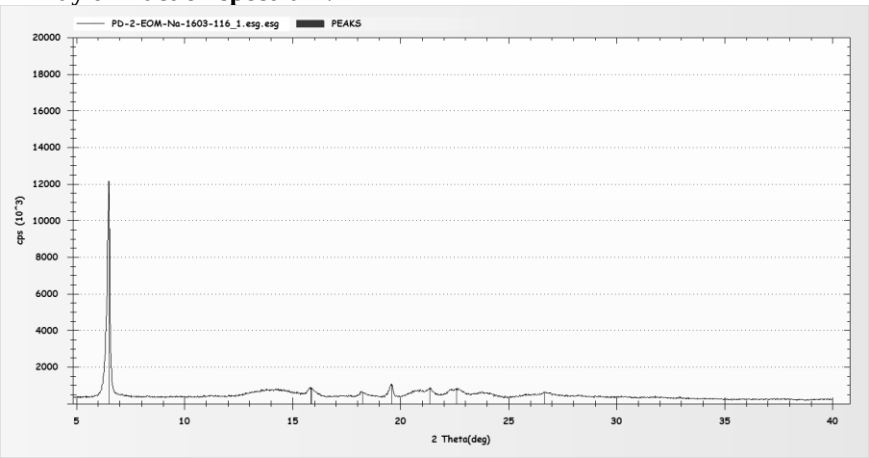
X – ray diffraction spectrum:



Example 2:

In this experiment we have used esomeprazole potassium (50.0 g on anhydrous basis) with purity 99.73% and sulfone impurity 0.28%. Here used water (2 V) a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization and dichloromethane (DCM, 3*2.5 V)) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using methanol (2.0 V). Further, reaction mass dissolved in methanol (5.0 V), charged methanolic NaOH (1.6eq NaOH in 2.5 V methanol) slowly and maintained for 1-2 h. Then perform activated carbon treatment and distilled out up to 30% conc. of reaction mass (150.0 g). Age reaction mass overnight at 0-5°C and filtered out and washed by methanol (0.5V). After filtration suck dry obtained wet cake. The obtained wet cake dry for 16h under vacuum at 39°C. Then transfer dry product in another flask and use 9 V (wrt esomeprazole potassium) acetone for maceration at 20-25°C for 1h and then 2h at 0-5°C. Obtained solid filter under nitrogen, wash by acetone (0.5V) and suck dry. Wet product dry under vacuum for 6h at 39°C. Sieve dry product under nitrogen and dry again for 24h at 39°C under vacuum to yield 27.8g (58.03% yield) of the title compound. Purity by HPLC: 99.91%, Sulphone impurity is 0.04%. Melting point: 232-234°C. R-isomer impurities: not detected.

X – ray diffraction spectrum:

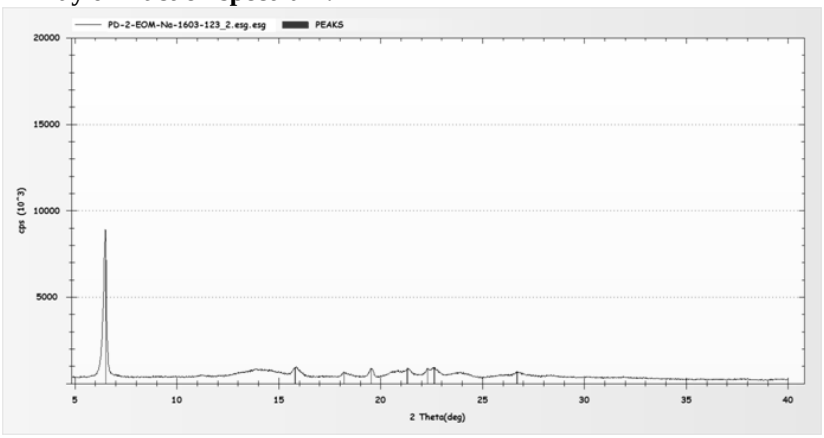


Example 3:

In further investigation used esomeprazole potassium (25.0 g on anhydrous basis) with purity 98.97% and sulfone impurity 0.94%. Here used water (2 V) a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization and dichloromethane (DCM, 3*2 V)) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using methanol (2.0 V). Further, reaction mass dissolved in methanol (5.0 V), charged methanolic NaOH (1.6eq NaOH in 2.5 V methanol) slowly and maintained for 1-2 h. Then perform activated carbon treatment and distilled out up to 30% conc. of reaction mass (150.0 g). Age reaction mass overnight at 0-5°C and filtered out and washed by

methanol (0.5 V). After filtration suck dry obtained wet cake. The obtained wet cake strip out using acetone (2* 2V) under vacuum at 39°C. Then transfer dry product in another flask and use 8 V (wrt esomeprazole potassium) MTBE for maceration at 0-5°C for 2h. Obtained solid filter under nitrogen, wash by MTBE (0.5V) and suck dry. Wet product dry under vacuum for 6-8h at 39°C. Sieve dry product under nitrogen and dry again for 16h at 39°C under vacuum to yield 18.4g (76.86% yield) of the title compound. Purity by HPLC: 99.65%, Sulphone impurity is 0.28%. Melting point: 233-235°C. R-isomer impurities: not detected.

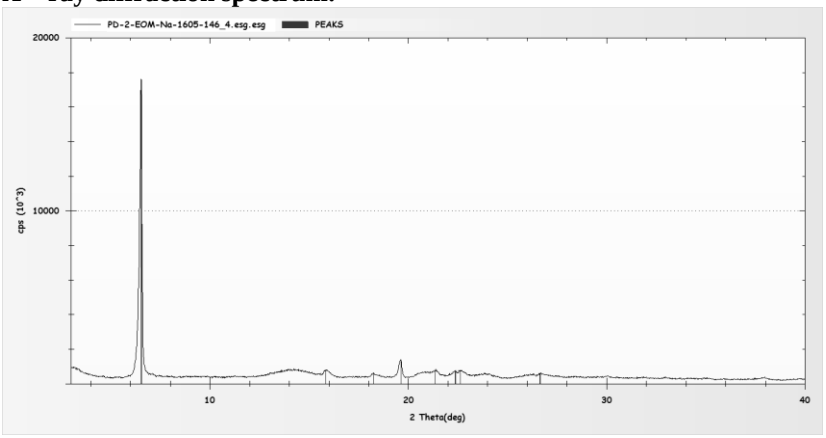
X – ray diffraction spectrum:



Example 4:

In this experiment we have used esomeprazole potassium (25.0 g on anhydrous basis, 150106) with purity 99.85% and sulfone impurity/IMP-I 1.07%. Here used water (2 V) a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization and dichloromethane (DCM, 3*2.5 V) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using MiBK (1.25V). Further, reaction mass dissolved in MiBK (5 V), charged NaOH (1.6eq, 4.17g) in methanol 62.5 ml slowly and maintained for 1-2 h. Then perform activated carbon treatment and distilled out up to reaction mass (125.0 g). Age reaction mass overnight at 0-5°C and filtered out and washed by MiBK (0.5 V). After filtration suck dry under nitrogen, obtained wet cake. Dry obtained product under vac. at 39°C for 8 h, Sieve dry product under nitrogen and dry again for 24h at 35°C under vacuum to yield 22g (92% yield) of the title compound. Purity by HPLC: 98.86%, Sulphone impurity is 0.88%. Melting point: 231-234°C. R-isomer impurities: not detected.

X – ray diffraction spectrum:

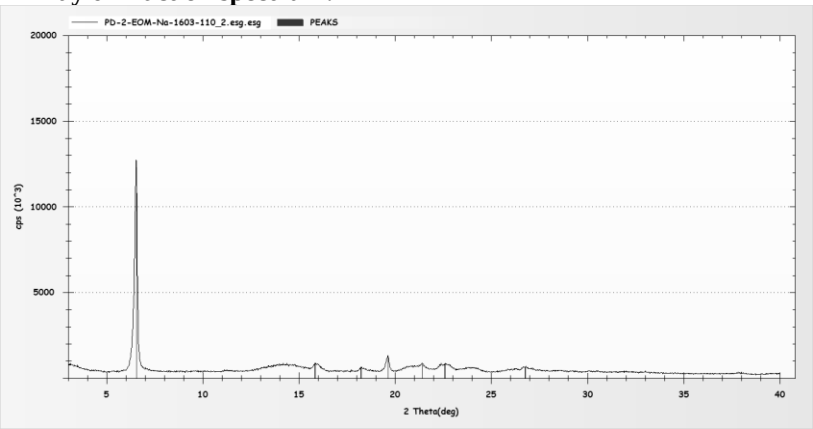


Example 5:

In next experiment we have used esomeprazole potassium (25.0 g on anhydrous basis, PD-2/EOM-Na/1601/097) with purity 99.73% and sulfone impurity/IMP-I 0.28%. Here used water (2 V) a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization and dichloromethane (DCM, 3*2.5 V)) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using IPA (2V). Further, reaction mass dissolved in IPA (8 V), charged NaOH (1.75eq,

4.55g) slowly and maintained for 1-2 h. Then perform activated carbon treatment and distilled out up to 30% conc. of reaction mass (75.0 g). Age reaction mass overnight at 0-5°C and filtered out and washed by IPA (0.5 V). After filtration suck dry under nitrogen, obtained wet cake. Dry obtained product under vac. at 39°C for 8 h, Sieve dry product under nitrogen and dry again for 24h at 35°C under vacuum to yield 17g (71.13% yield) of the title compound. Purity by HPLC: 99.68%, Sulphone impurity is 0.29%. Melting point: 233-235°C. R-isomer impurities: not detected.

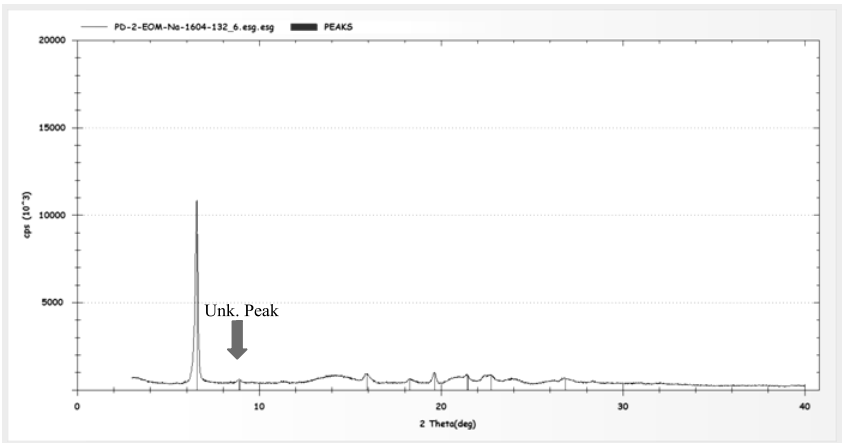
X – ray diffraction spectrum:



Example 6:

In this experiment, we have used esomeprazole potassium (25.0 g, 150106) with purity 98.85% and sulfone impurity/ IMP-I 1.07%. Here used water (2V) a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization (pH is 6.9) and dichloromethane (DCM, 3*2.5 V)) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using methanol (1.25 V). Further, reaction mass dissolved in methanol (5.0 V), charged methanolic NaOH solution (1.6eq NaOH in 2.5 V methanol) slowly and maintained for 1-2 h. Then perform activated carbon, sodium sulphate treatment and distilled out up to 30% conc. of reaction mass (75.0 g). Age reaction mass overnight at 0-5°C and filtered out and washed by methanol (0.5 V). After filtration suck dry obtained wet cake. Wet cake transferred in single neck rotatory flask charged EA (10 V) strip out at 39°C two times. Then charged 10V ethyl acetate and cool to 0-5°C. Maintain for 1h. Filter reaction mass under nitrogen; wash by ethyl acetate (25 ml). Dry product at 6-8h sieve and dry again for 24h under vacuum at 39°C to yield 16.9g (70.71% yield) of the title compound. Purity by HPLC: 99.73%, Sulphone impurity is 0.22%. Melting point: 232-233°C. R-isomer impurities: not detected.

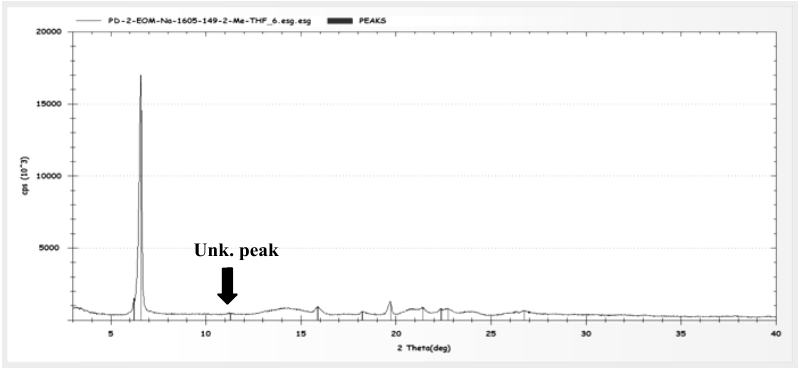
X – ray diffraction spectrum:



Example7:

In another experiment we have used esomeprazole potassium (25.0 g, 150106) with purity 98.85% and sulfone impurity/IMP-I 1.07%. Here used water (2 V) a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization and dichloromethane (DCM, 3*2.5 V)) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using MEK (1.25 V). Further, reaction mass dissolved in MEK (7.0 V), charged sodium methoxide solution (29%) (1.6eq NaOH, 14.4 ml) slowly and maintained for 1-2 h. Then perform activated carbon treatment and distilled out up to 5V of reaction mass (125.0 g). Age reaction mass overnight at 20-25°C and filtered out and washed by MEK (0.5 V). After filtration suck dry obtained wet cake. The obtained wet cake dry for 8h under vacuum at 39°C. Sieve dry product under nitrogen and dry again for 24h at 39°C under vacuum to yield 12.70g (53.14% yield) of the title compound. Purity by HPLC: 99.33%, Sulphone impurity is 0.64%. Melting point: 232-233°C. R-isomer impurities: not detected.

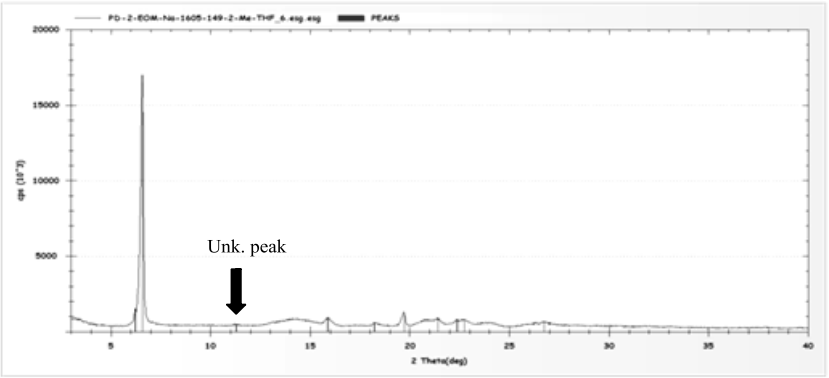
X – ray diffraction spectrum:



Example 8:

In this experiment we have used esomeprazole potassium (10.0 g on anhydrous basis) with purity 99.85% and sulfone impurity/IMP-I 1.07%. Here used water (2 V) a solvent for esomeprazole potassium dissolution, dil. HCl (1:1) for neutralization and dichloromethane (DCM, 3*2.5 V) for extraction of neutralized EOM free base. After complete distillation of dichloromethane, reaction mass strip out using 2-Me THF (1.25V). Further, reaction mass dissolved in 2-Me THF (5 V), charged NaOH (1.6eq, 4.17g) in methanol 62.5 ml slowly and maintained for 1-2 h. Then perform activated carbon treatment and distilled out up to reaction mass (125.0 g). Age reaction mass overnight at 0-5°C and filtered out and washed by 2-Me THF (0.5 V). After filtration suck dry under nitrogen, obtained wet cake. Dry obtained product under vac. at 39°C for 8 h, Sieve dry product under nitrogen and dry again for 24h at 35°C under vacuum to yield 3.49g (41.21% yield) of the title compound. Purity by HPLC: 99.69%, Sulphone impurity is 0.19%. Melting point: 233-235°C. R-isomer impurities: not detected.

X – ray diffraction spectrum:



RESULT AND DISCUSSION

In concern with the role of polymorphic form of esomeprazole sodium for formulation or in drug industry, we have reported here synthesis of highly pure esomeprazole sodium synthesis using easy laboratory method. Using different solvents we can synthesize esomeprazole sodium with form J. But, among the all solvent acetonitrile provide excellent reaction condition over all optimized methods. The quality and quantity obtained using acetonitrile as a maceration solvent is excellent over all optimized methods. The following table represents consistency of reported method from 50-200g scale with IMP-1 less than 0.1% and API purity more than 99%. On the basis of above data found that, esomaprazole sodium prepared with excellent quality (<99%) and quantity (70-80% yield) with all used residual solvents in limit. The synthesized product analyzed with NMR, Mass, IR, XRD, DSC and compared with standard results. The all obtained results indicate, synthesized product is esomeprazole sodium with form J.

Table: Experimental details of esomeprazole sodium using acetonitrile maceration.

Sr. No.	Experiment No.	Input (dry basis)	LOD	HPLC Purity (%)		solvent for maceration	Out put	Yield	water	HPLC Purity (%)		Residual solvent (ppm)			Assay
		(g)	(%)	EOM-2	IMP-D		(g)	%	%	EOM-Na	IMP-D	MeOH	DCM	ACN	(%)
1	EOM-Na/001	50	13.5	98.85	1.07	acetonitrile (8V)	35.4	73.90	0.4	99.9	0.04	264	5	ND	100.30
2	EOM-Na/002	200	12.43	99	0.4	acetonitrile (8V)	153.4	80.06	0.39	99.86	0.02	18	ND	ND	100.2

Figure 1: The ^{1}H NMR spectra of esomeprazole sodium

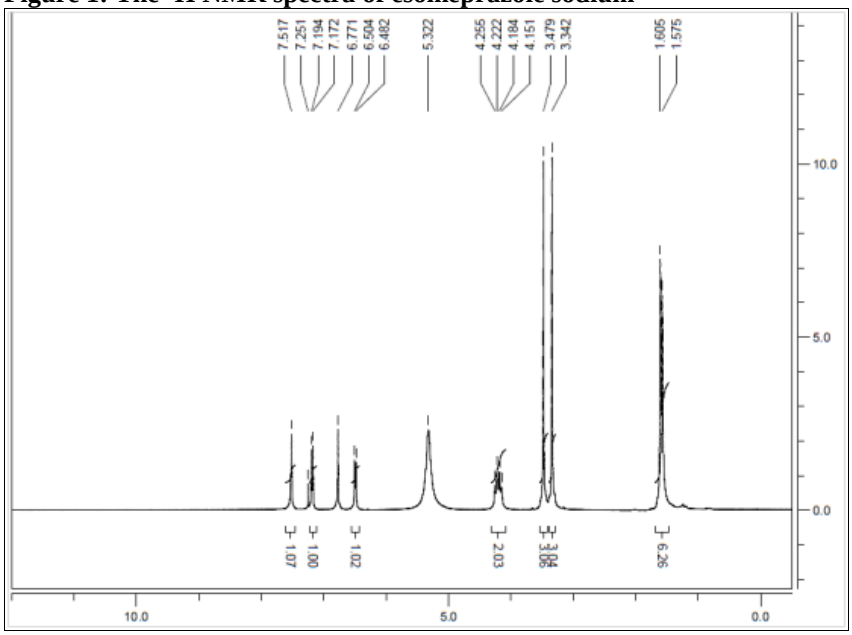


Table 1: The 1H NMR spectra of esomeprazole sodium

Proton No.	δ (ppm)	Multiplicity[A]	No. of Proton
1	7.51	s	1H
2	7.17-7.19	d	1H
3	6.77	s	1H
4	6.48-6.50	d	1H
5	4.15-4.25	q	1H
6	3.47	s	3H
6’	3.34	s	3H
7	1.60	s	3H
7’	1.57	s	3H

[A] brs = broad siglet, s = singlet, d = doublet, dd = doublet of doublet, q = quartet, m = multiplate

Figure 2: The ^{13}C NMR spectra of esomeprazole sodium

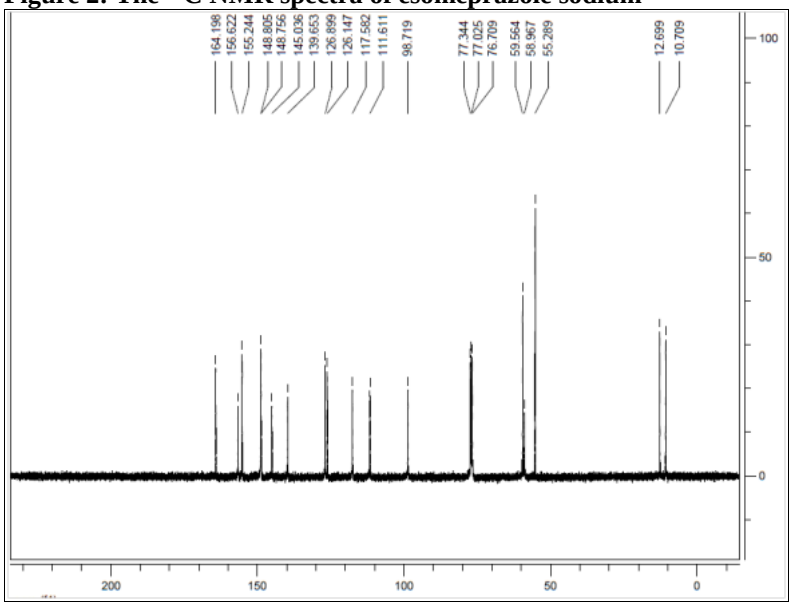
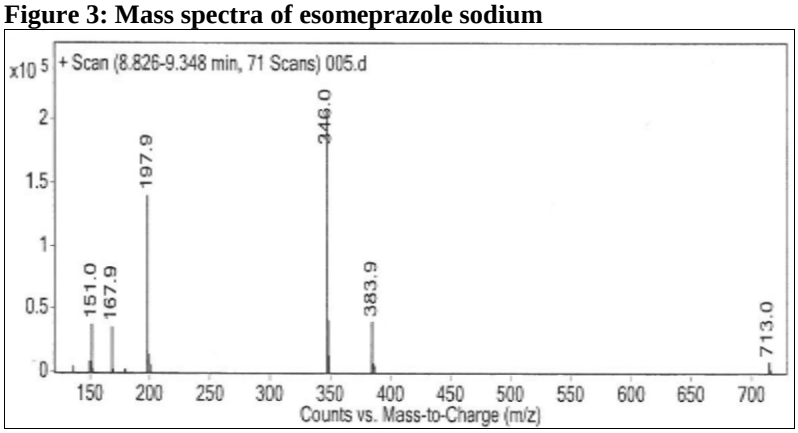


Table 1: The ^{13}C NMR spectra of esomeprazole sodium

Carbon No.	δ (ppm)
1	164.19
2	156.62
3	155.24
4	148.80
5	148.75
6	145.03
7	139.65
8	126.89
9	126.14
10	117.58
11	111.61
12	98.71
13	59.56
14	58.96
15	55.28
16	12.69
17	10.70

Figure 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 $C_{17}H_{19}N_3O_3S$.

Figure 4: The IR spectra of esomeprazole sodium

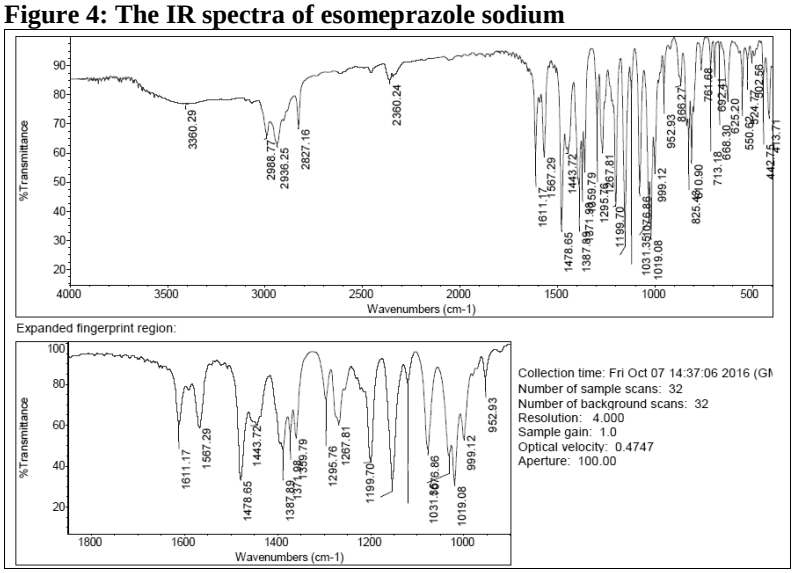
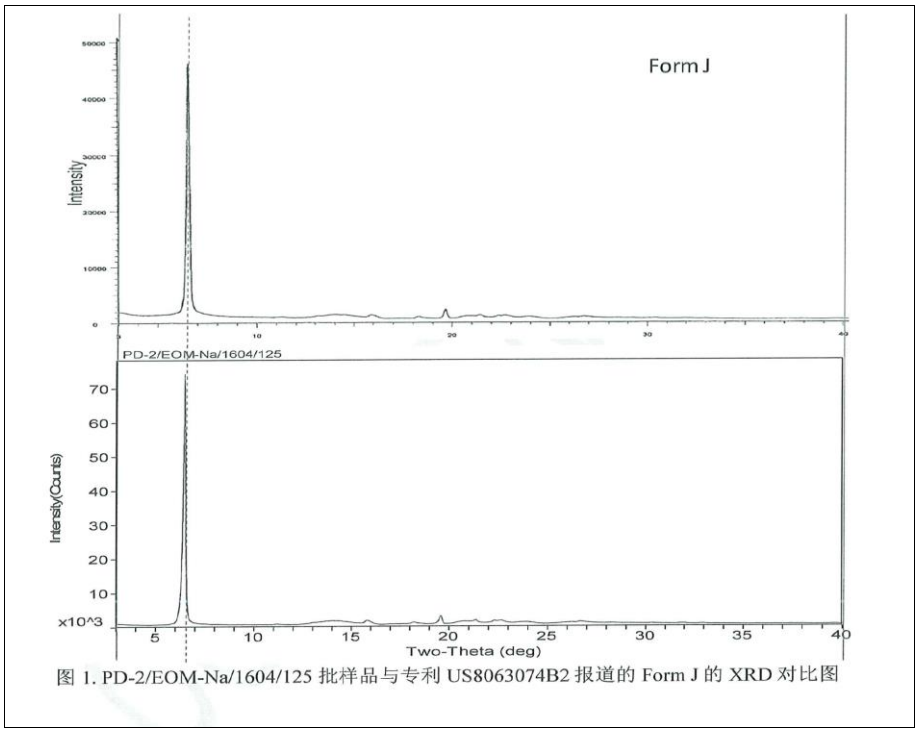


Table 4: IR interpretation data

Sr. No.	Bands (cm^{-1})	Intensity[A]	Group
1	3360	brs	N-H Stretching
2	2935	m	Aliphatic C-H Stretching
3	1611	s	C=C,
4	1297,1267	s	C-O-C Asymmetric Stretching
5	1199	s	S=O Stretching
	625	s	C-S Stretching

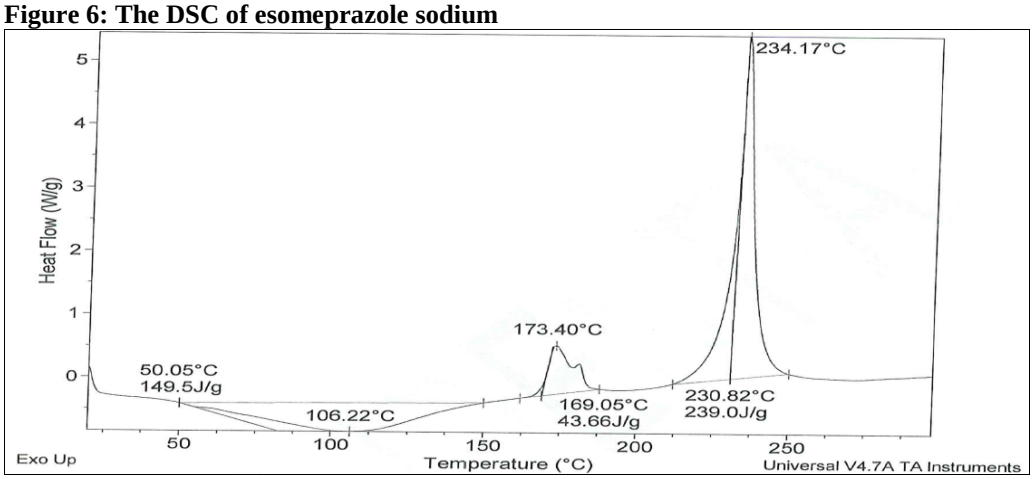
[A] brs = braod signal, s = strong, m = moderate, w = weak

Figure 5: Comparison data of XRD of esomeprazole sodium with literature report (US8063074 B2) for form J.



XRPD pattern having significant peaks at about 6.3±0.2 degrees 2θ.
It is also characterized by the additional XRPD peaks at about 15.8, 19.5 ±0.2 degrees 2θ.

Figure 6: The DSC of esomeprazole sodium



All above data shown that, using acetonitrile solvent for maceration give desired form J with excellent yield and quality.

Conclusion:

Reported method for synthesis of polymorphic crystalline esomeprazole sodium form J is highly reliable method. Herein, reported method gives excellent yield (70-80%) with purity more than 99%. In this research we developed a method which is easy to carry out on different scales. The obtained polymorphic form of esomeprazole sodium is J and its reproduces consistently using acetonitrile maceration.

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