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Journal of Pharmaceutical and Biomedical Analysis 43 (2007) 1262–1269
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Identification and characterization of potential impurities of rabeprazole sodium ☆

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Received 2 March 2006; received in revised form 5 October 2006; accepted 17 October 2006
Available online 28 November 2006

Abstract

Six impurities in rabeprazole sodium bulk drug substance were detected by a simple isocratic high performance chromatographic method (HPLC) whose area percentage ranged from 0.60 to 1.46%. LC-MS was performed to identify the mass of the impurities. A thorough study was undertaken to characterize these impurities. These impurities were synthesized, subsequently characterized and were co-injected with the sample containing impurities and are found to be matching with the impurities in the sample. Based on their spectral data (IR, NMR and MS), these impurities were characterized as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl]thio]-1*H*-benzimidazole (impurity I); 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] sulfonyl]-1*H*-benzimidazole (impurity II); 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl-1-oxide] methyl] sulfonyl]-1*H*-benzimidazole (impurity III); 2-[[[4-(3-methoxypropoxy)-3-methyl] pyridin-2-yl]methanesulfinyl]-1-[[4-(3-methoxypropoxy)-3-methyl]pyridin-2-ylmethyl]-1*H*-benzimidazole (impurity IV); 2-[[[4-methoxy-3-methyl-2-pyridinyl] methyl] sulfinyl]-1*H*-benzimidazole (impurity V); 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridine-1-oxide] methyl] sulfinyl]-1*H*-benzimidazole (impurity VI).

Keywords: Rabeprazole sodium; Impurities; Spectroscopy; Identification and characterisation

1. Introduction

Rabeprazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] sulfinyl]-1*H*-benzimidazole sodium salt is a proton pump inhibitor and inhibits the action of H^+-K^+ ATPase in parietal cells [1–4]. Preclinical studies indicated that, rabeprazole is 6.5 times more potent than omeprazole in inhibiting the enzyme activity of isolated gastric vesicles [5] and is an effective drug in the treatment of peptic ulcer [6].

During the analysis of laboratory batches of rabeprazole sodium, six impurities with area percentage ranging from 0.60 to 1.46% were detected, by an isocratic reverse phase LC method. In order to commercialize an active pharmaceutical ingredient (API), it is a mandatory requirement from regulatory authorities to identify and characterize all the unknown impurities that are present in it at a level as low as 0.05% [7]. In this context, a comprehensive study was undertaken to characterize all the six impurities present in the lab batches of rabeprazole sodium by spectroscopic and spectrometric techniques and results are presented in this article. The pathway for the formation of these impurities is also delineated. Among these six impurities, while impurity III and impurity IV are hitherto not reported, impurity V was described earlier as a process related one [8].

2. Experimental

2.1. Samples

Samples of rabeprazole sodium (Batch. No.: RAB/C082/III/02) bulk material were obtained from Research and Development Department, Active Pharmaceutical Ingredients-III,

☆ DRL Pub. No: DRL-IPDO-IPM 00022.

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doi:10.1016/j.jpba.2006.10.017

Dr. Reddy's Laboratories Ltd., Hyderabad, India. HPLC grade acetonitrile, acetic acid, ammonium acetate, potassium dihydrogen phosphate and potassium hydroxide were obtained (Merck, Mumbai, India) and used in the analysis. Water used for preparing mobile phase was purified using Millipore Milli-Q plus purification system.

2.2. High performance liquid chromatography (HPLC)

An in-house LC method was developed for the analysis of rabeprazole sodium and its impurities (Agilent with empower software, 1100 series, G1312A Binary pump, G1314A variable wavelength detector, Waldbronn, Germany) where a column Inertsil ODS-3V, 250 mm × 4.6 mm, 5 μm (GL Sciences Inc., Japan) with a mobile phase consisting of 0.01 M KH_2PO_4, with the pH adjusted to 6.0 with diluted potassium hydroxide and acetonitrile in the ratio of 65:35, with a flow rate of 1.0 ml/min and UV detection at 280 nm was used. This LC method was able to detect all these impurities.

2.3. Liquid chromatography-mass spectrometry (LC-MS)

Mass spectrometry compatible chromatographic method was developed for the analysis of rabeprazole sodium and its impurities, where a column Inertsil ODS-3V 250 mm × 4.6 mm, 5.0 μm particle size (GL Sciences Inc., Japan) with a mobile phase consisting of 0.01 M ammonium acetate (pH 6.0) adjusted with dilute acetic acid and acetonitrile in the ratio of 65:35, with a flow rate of 1.0 ml/min, UV detection at 280 nm was used. This LC method was able to detect all the impurities. The mass spectra of impurities were recorded on AB-4000 Q-trap LC-MS/MS mass spectrometer.

2.4. Mass spectrometry

The LC-MS Analysis has been performed on AB-4000 Q-trap LC-MS/MS mass spectrometer [9]. The analysis was performed in positive ionization mode with Turbo Ion Spray interface with the following conditions. Ion source voltage

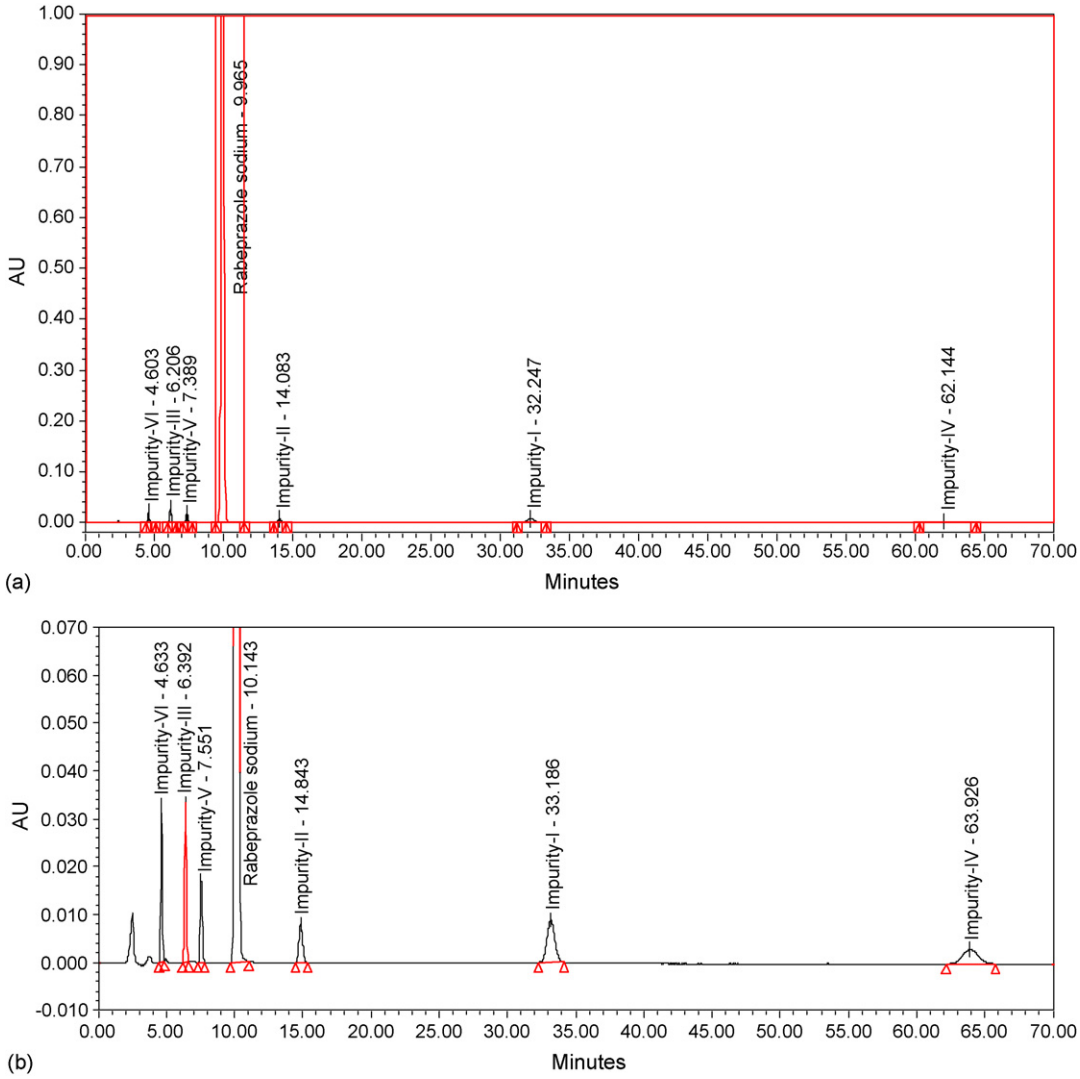

Fig. 1. (a) HPLC chromatogram of rabeprazole sodium laboratory sample. (b) HPLC chromatogram of rabeprazole sodium laboratory sample spiked with six impurities.

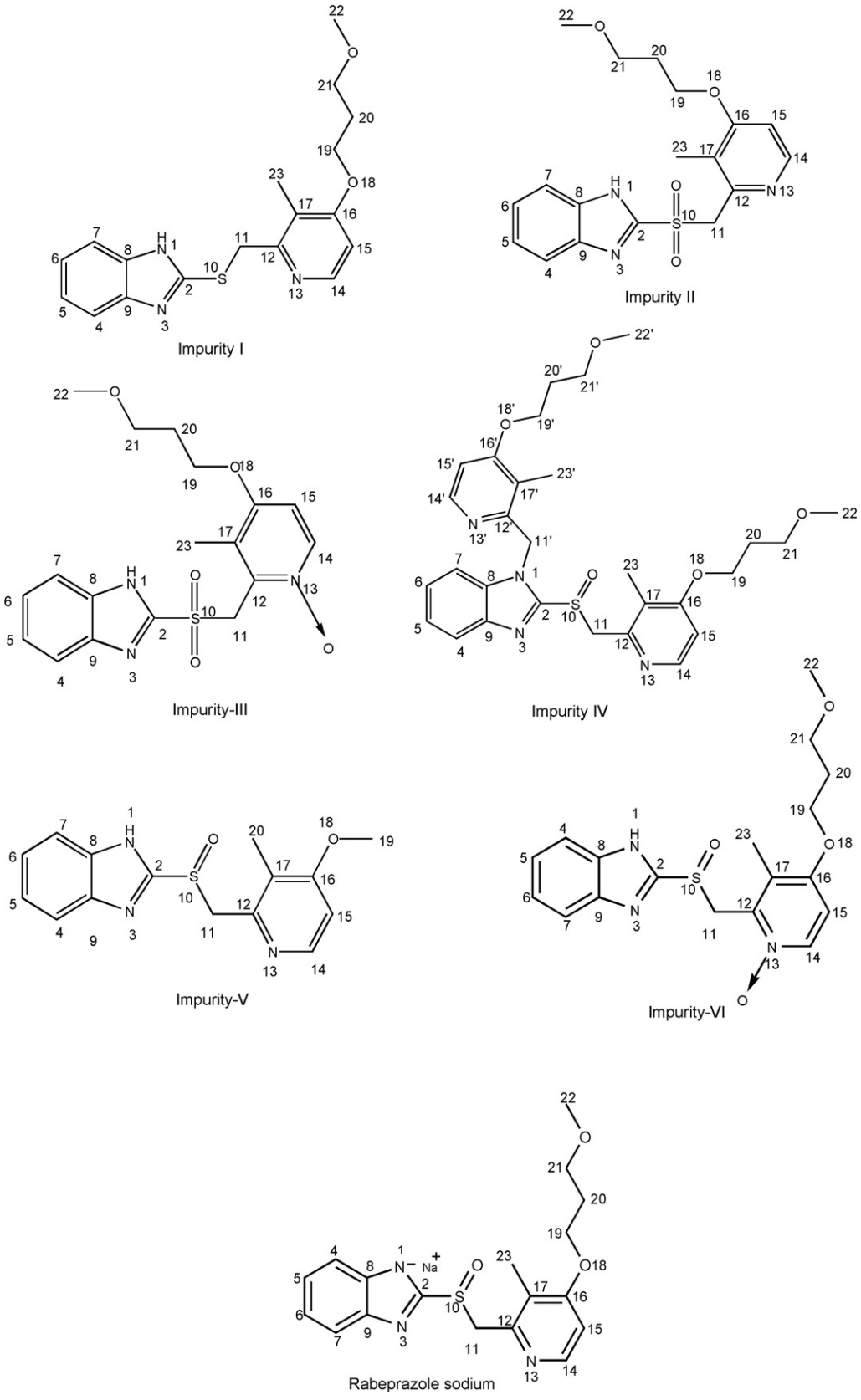

Fig. 2. Atom numbering used for NMR assignments.

Table 1
Melting range, FT-IR and mass spectral data of rabeprazole sodium and impurities I, II, III, IV, V and VI

S. no.	Compound	Melting point (°C)	IR[a]	MS
1	Impurity I	116–118	3435 (Moisture O—H stretching), 3049 (Aromatic C—H stretching), 2888 (Aliphatic C—H stretching), 1585 (Aromatic C=C, C=N stretching), 1463, 1439 (Aliphatic C—H bending), 1303, 1010 (C—O stretching), 1263 (C—N stretching), 746 (Aromatic C—H bending)	+ve ES-MS:344 $(M+H)^+$, 687 $(2M+H)^+$ −ve ES-MS: 342 $(M-H)^-$, 378.1 $(M+Cl)^-$
2	Impurity II	138–142	3435 (Moisture O—H stretching), 3063 (Aromatic C—H stretching), 2933 (Aliphatic C—H stretching), 1585 (Aromatic C=C, C=N stretching), 1461, 1443 (Aliphatic C—H bending), 1339, 1046 (C—O stretching), 1301 (C—N stretching), 1132 (S=O stretching), 756 (Aromatic C—H bending)	+ve ES-MS: 376 $(M+H)^+$, 398.1 $(M+Na)^+$ −ve ES-MS: 373.9 $(M-H)^-$
3	Impurity III	170–174	3435 (Moisture O—H stretching), 3058 (Aromatic C—H stretching), 2927 (Aliphatic C—H stretching), 1616 (Aromatic C=C, C=N stretching), 1455, 1442 (Aliphatic C—H bending), 1323, 1094 (C—O stretching), 1301 (C—N stretching), 1135 (S=O stretching), 747 (Aromatic C—H bending)	+ve ES-MS: 391.9 $(M+H)^+$, 783.8 $(2M+H)^+$, 414.3 $(M+Na)^+$, 805.8 $(2M+Na)^+$, 430.9 $(M+K)^+$ −ve ES-MS: 390.2 $(M-H)^-$
4	Impurity IV	Liquid	3273 (Moisture O—H stretching), 2953 (Aromatic C—H stretching), 2923 (Aliphatic C—H stretching), 1578 (Aromatic C=C, C=N stretching,) 1458, 1377 (Aliphatic C—H bending), 1291, 1019, (C—O stretching), 1244 (C—N stretching), 1123 (S=O stretching), 743 (Aromatic C—H bending)	+ve ES-MS:553.6 $(M+H)^+$
5	Impurity V	162–166	3045 (Aromatic C—H stretching), 2967 (Aliphatic C—H stretching), 1588 (Aromatic C=C, C=N stretching, 1482, 1441 (Aliphatic C—H bending), 1297, 1043 (C—O stretching), 1267 (C—N stretching), 1080 (S=O stretching), 741 (Aromatic C—H bending)	+veES-MS:302.2 $(M+H)^+$, 603.3 $(2M+H)^+$, 1206.5 $(4M+H)^+$, 324 $(M+Na)^+$, 625.4 $(2M+Na)^+$ −ve ES-MS:300.3 $(M-H)^-$
6	Impurity VI	158–164	3429 (Moisture O—H stretching), 3035 (Aromatic C—H stretching), 2984 (Aliphatic C—H stretching), 1567 (Aromatic C=C, C=N stretching), 1459, 1428 (Aliphatic C—H bending), 1404, 1098 (C—O stretching), 1265 (C—N stretching), 1059 (S=O stretching), 742 (Aromatic C—H bending)	+ve ES-MS:376.2 $(M+H)^+$, 398 $(M+Na)^+$, 1148.7 $(3M+Na)^+$, 414.2 $(M+K)^+$
7	Rabeprazole sodium	163–168	3441 (Moisture O—H stretching), 3047 (Aromatic C—H stretching), 2926 (Aliphatic C—H stretching), 1584 (Aromatic C=C, C=N stretching, 1465, 1369 (Aliphatic C—H bending), 1299, 1011 (C—O stretching), 1269 (C—N stretching), 1094 (S=O stretching), 747 (Aromatic C—H bending)	+ve ES-MS:360.5 $(M+H)^+$, 720.3 $(2M+H)^+$, 1079.2 $(3M+H)^+$, 1438.7 $(4M+H)^+$, 382.8 $(M+Na)^+$, 741.8 $(2M+Na)^+$, 1101.2 $(3M+Na)^+$, 1460.1 $(4M+Na)^+$, 398.5 $(M+K)^+$ −ve ES-MS: 358.5 $(M-H)^-$, 395 $(M+Cl)^-$, 718 $(2M-H)^-$

[a] KBr—impurities I, II, III, IV, VI and rabeprazole sodium; neat—impurity IV.

5500 V, declustering potential 80 V, entrance potential 10 V, with the nebuliser gas as nitrogen at 30 psi. Whereas the negative ionization was performed by switching the polarity of the ion source voltage to −4500 V.

2.5. NMR spectroscopy

The ^1H, ^{13}C, DEPT and 2D experiments for rabeprazole sodium, impurities IV and VI were done at 400 MHz and 100 MHz on Varian Mercury plus 400 MHz FT NMR Spectrometer and similar experiments for impurities I, II, III and V were performed on Gemini-2000 (200 MHz) in DMSO-d_6. The solvent used for rabeprazole sodium, impurity IV was DMSO-d_6 and $CDCl_3$ was used for impurity VI. The ^1H chemical shift values were reported on the δ scale in ppm, relative to TMS ($\delta = 0.00$ ppm) and in the ^{13}C NMR the chemical shift values were reported relative to $CDCl_3$ ($\delta = 77.00$ ppm) and DMSO-d_6 ($\delta = 39.50$ ppm) as internal standards, respec-

Table 2
^{1}H and ^{13}C NMR assignments for rabeprazole sodium and impurities I, II and III

Position[a]	Rabeprazole sodium				Impurity I				Impurity II				Impurity III			
	^{1}H	ppm/J	^{13}C	DEPT	^{1}H	ppm/J	^{13}C	DEPT	^{1}H	ppm/J	^{13}C	DEPT	^{1}H	ppm/J	^{13}C	DEPT
1	–	–	–	–	NH	12.61	–	–	NH	13.8/s	–	–	NH	13.91/s	–	–
2	–	–	162.15	–	–	–	150.29	–	–	–	138.04	–	–	–	138.32	–
4	1H	7.45/m	117.39	CH	1H	7.46/m	110.51	CH	1H	7.69/m	116.84	CH	1H	7.68/b	116.96	CH
5	1H	6.86/m	118.40	CH	1H	7.13/m	119.75	CH	1H	7.38/m	124.40	CH	1H	7.38/m	124.27	CH
6	1H	6.86/m	118.40	CH	1H	7.13/m	119.75	CH	1H	7.38/m	124.40	CH	1H	7.38/m	124.27	CH
7	1H	7.45/m	117.39	CH	1H	7.46/m	117.39	CH	1H	7.69/m	116.84	CH	1H	7.67/b	116.96	CH
8	–	–	146.91	–	–	–	147.74	–	–	–	147.09	–	–	–	148.52	–
9	–	–	146.91	–	–	–	147.74	–	–	–	147.09	–	–	–	148.52	–
11	2H	4.43/d, 13.2	61.13	CH_2	2H	4.70/s	36.28	CH_2	2H	5.07/s	60.51	CH_2	2H	5.44/s	54.09	CH_2
12	–	–	151.96	–	–	–	154.68	–	–	–	148.04	–	–	–	138.86	–
14	1H	8.28/d, 5.6	148.17	CH	1H	8.23/d, 5.6	147.74	CH	1H	8.0/d, 5.6	147.91	CH	1H	8.03/d, 7.2	136.61	CH
15	1H	6.93/d, 5.6	106.17	CH	1H	6.95/d, 5.6	106.22	CH	1H	6.9/d, 5.6	106.83	CH	1H	7.08/d, 7.6	108.94	CH
16	–	–	162.84	–	–	–	162.68	–	–	–	162.95	–	–	–	153.89	–
17	–	–	121.80	–	–	–	121.35	–	–	–	123.14	–	–	–	126.45	–
19	2H	4.10/t, 6.2	65.09	CH_2	2H	4.10/t, 6.2	65.04	CH_2	2H	4.10/t, 6.2	65.12	CH_2	2H	4.12/t, 6.2	65.88	CH_2
20	2H	1.98/m	28.74	CH_2	2H	2.00/m	28.66	CH_2	2H	1.98/m	28.59	CH_2	2H	1.97/m	28.62	CH_2
21	2H	3.49/t, 6.2	68.39	CH_2	2H	3.49/t, 6.4	68.28	CH_2	2H	3.48/t, 6.2	68.24	CH_2	2H	3.49/t, 6.0	68.22	CH_2
22	3H	3.25/s	58.02	CH_3	3H	3.25/s	57.92	CH_3	3H	3.25/s	57.93	CH_3	3H	3.25/s	57.95	CH_3
23	3H	2.18/s	10.76	CH_3	3H	2.22/s	10.35	CH_3	3H	2.18/s	11.02	CH_3	3H	2.20/s	12.12	CH_3

[a] Refer structural formula (Fig. 2) for numbering: s, singlet; d, doublet; t, triplet; m, multiple; b, broad.

tively. DEPT spectra revealed the presence of methyl and methine groups as positive peaks and methylenes as negative peaks.

2.6. Melting point determination

Melting points of all the impurities were determined in a Polmon digital melting point apparatus Model no. MP96.

2.7. FT-IR spectroscopy

The IR spectra were recorded in the solid state as KBr dispersion medium using Perkin-Elmer Spectrum One FT IR spectrophotometer.

2.8. Synthesis of impurities

Impurity I, 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] thio]-1*H*-benzimidazole is the precursor of rabeprazole. mCPBA oxidation of I results in rabeprazole. Impurity II, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] sulfonyl]-1*H*-benzimidazole is a sulphone and it was prepared from the peracid-mediated oxidation of rabeprazole, further oxidation of sulphone II with mCPBA yielded the corresponding N-oxide, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl-1-oxide] methyl] sulfinyl]-1*H*-benzimidazole, impurity III. In the synthesis of impurity I, 2-[[4-(3-methoxypropoxy)-3-methyl] pyridin-2-yl]methanethio]-1-[[4-(3-methoxypropoxy)-3-methyl]pyridin-2-ylmethyl]-1*H*-benzimidazole was the byproduct. mCPBA oxidation of 2-[[[4-(3-methoxypropoxy)-3-methyl] pyridin-2-yl]methanethio]-1-[[4-(3-methoxypropoxy)-3-methyl]pyridin-2-ylmethyl]-1*H*-benzimidazole gave as sulphoxide, impurity IV. Impurity V was prepared by the oxidation of 4-methoxy rabeprazole sulfide, impurity VI, which is N-oxide of rabeprazole, was prepared by the oxidation of rabeprazole using mCPBA.

3. Results and discussion

3.1. Detection of impurities I, II, III, IV, V and VI

A typical analytical LC chromatogram of a laboratory batch of rabeprazole sodium bulk drug was recorded using the LC method as described in Section 2.2. The target impurities under study are marked as impurity I (retention time (RT): 32.24, molecular weight (MW): 343), impurity II (RT: 14.08, MW: 375), impurity III (RT: 6.20, MW: 391), impurity IV (RT: 62.14, MW: 552), impurity V (RT: 7.38, MW: 301), impurity VI (RT: 4.60, MW: 375). The LC-MS compatible method is described in Section 2.3 which is used to detect all the impurities Fig. 1. The structures of these impurities and rabeprazole sodium are shown in Fig. 2. Impurities III, V, and VI are polar and impurities I, II and IV are non-polar, respectively, with respect to rabeprazole sodium.

Table 3
^{1}H and ^{13}C NMR assignments for rabeprazole sodium and impurities IV, V and VI

Position[a]	Impurity IV				Impurity V				Impurity VI			
	^{1}H	ppm/J	^{13}C	DEPT	^{1}H	ppm/J	^{13}C	DEPT	^{1}H	ppm/J	^{13}C	DEPT
1					NH	13.6/b	–	–	NH	#	–	–
2	–	–	150.72	–	–	–	154.39	–	–	–	153.93	–
4	1H	7.79/m	120.10	CH	1H	7.63/m	116.15	CH	1H	7.69/m	116.32	CH
5	1H	7.31/m	122.81	CH	1H	7.29/m	123.19	CH	1H	7.33/m	123.40	CH
6	1H	7.31/m	123.99	CH	1H	7.29/m	123.19	CH	1H	7.33/m	123.40	CH
7	1H	7.79/m	111.20	CH	1H	7.63/m	116.15	CH	1H	7.69/m	116.32	CH
8	–	–	141.84	–	–	–	138.50	–	–	–	139.23	–
9	–	–	136.25	–	–	–	138.50	–	–	–	139.23	–
11, 11′	Ha	4.98/d, 13.6 5.81/q (17.2)	56.58 45.95	CH_2	Ha	4.80/d, 13.6	60.19	CH_2	Ha	4.97/d, 12.6	54.23	CH_2
	Hb	4.67/d, 13.6	–	–	Hb	4.70/d, 13.8	–	–	Hb	5.21/d, 12.8	–	–
12, 12′	–	–	154.19 153.27	–	–	–	149.99	–	–	–	141.47	–
14, 14′	1H	8.22/d, 6.0 8.03/d, 5.6	148.06 147.79	CH	1H	8.23/d, 5.6	148.16	CH	1H	8.21/d, 7.0	137.35	CH
15, 15′	1H	6.90/d, 5.6 6.94/d (5.6)	106.30	CH	1H	6.96/d, 5.6	105.82	CH	1H	6.75/d, 7.2	107.44	CH
16, 16′	–	–	162.89 162.70	–	–	–	163.59	–	–	–	156.23	–
17, 17′	–	–	121.85	–	–	–	121.76	–	–	–	126.91	–
19, 19′	2H	4.07/m	65.14	CH_2	3H	3.85/s	55.74	CH_3	2H	4.08/t, 6.2	65.89	CH_2
20, 20′	2H	1.98/m	28.78	CH_2	3H	2.13/s	10.68	CH_3	2H	2.06/p, 6	28.96	CH_2
21, 21′	2H	3.47/m	68.39	CH_2	–	–	–	–	2H	3.51/t, 6	68.38	CH_2
22, 22′	3H	3.30/s 3.17/s	57.94 48.67	CH_3	–	–	–	–	3H	3.33/s	58.58	CH_3
23, 23′	3H	2.27/s	10.45 9.47	CH_3	–	–	–	–	3H	2.24/s	12.01	CH_3

[a] Refer structural formula (Fig. 2) for numbering: s, singlet; d, doublet; t, triplet; q, quartet; m, multiple; b, broad. 11′–23′ applicable for impurity IV.

3.2. Structural elucidation of rabeprazole sodium and its impurities

The +ve ES-MS spectrum of the impurity showed peaks at *m/z* 344, and 687 corresponding to the adduct ions $(M+H)^+$ and $(2M+H)^+$. Further the −ve ES-MS spectrum showed peaks at *m/z* 342 and 378.1 corresponding to $(M-H)^-$ and $(M+Cl)^-$. The ES-MS-MS spectrum displayed daughter ions at *m/z* 102.2, 119.4, 149.3, 159.4 and 226.1 in which 226.1 is the dominant fragment. The adduct ions confirm the molecular ion of the impurity I to be *m/z* 343. The DEPT spectra displayed four negative signals due to four methylene groups and five positive peaks due to the presence of two methyl groups and the rest are due to the methine groups (all in aromatic). IR spectrum displayed characteristic absorptions at 1585 corresponding to C=C, C=N stretching which was supported by the appearance of quaternary carbon signal characteristic of a C=N group in ^{13}C NMR spectrum. The peaks at 1303 and 1010 cm^{-1} in the IR spectrum are indicative of ether functionality. Based on the above spectral data the molecular formula of impurity I could be $C_{18}H_{21}N_3O_2S$ and the corresponding structure was characterized as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl]thio]-1*H*-benzimidazole.

The spectral data of rabeprazole is compared with those of impurities I to VI. It is interesting to note that impurities I, II, III and VI have same skeletal system as evident by the number of NMR signals. The mass spectra of the impurities I and II displayed molecular ion at *m/z* 343 and 375, which is 16 amu less and 16 amu more than that of rabeprazole (*m/z* 359), respectively. The chemical shift of methylene carbon adjacent to sulphur appeared at 36 and 60 ppm for impurities I and II, respectively. Thus the impurities I and II structure can be explained in terms of removal and addition of oxygen on sulphur, respectively.

Though the molecular ion for both impurities II and VI is same, the diagnostic change in the aromatic protons in pyridine moiety in both the cases indicates the formation of respective N-oxide impurities of rabeprazole.

On comparison of impurity II with impurity III, the chemical shift change in the aromatic protons in the pyridine moiety indicates that impurity III is an N-oxide of impurity II.

The spectral data of impurity IV have several additional resonances both in the aliphatic and aromatic region. The molecular ion at *m/z* 552 can be attributed to the *N*-alkylated product of rabeprazole and 2-chloromethyl-3-methyl-4-(3-methoxy propoxy) pyridine moieties.

It is also interesting to note that impurity V displayed molecular ion at *m/z* 301 with 58 amu less than that rabeprazole. In

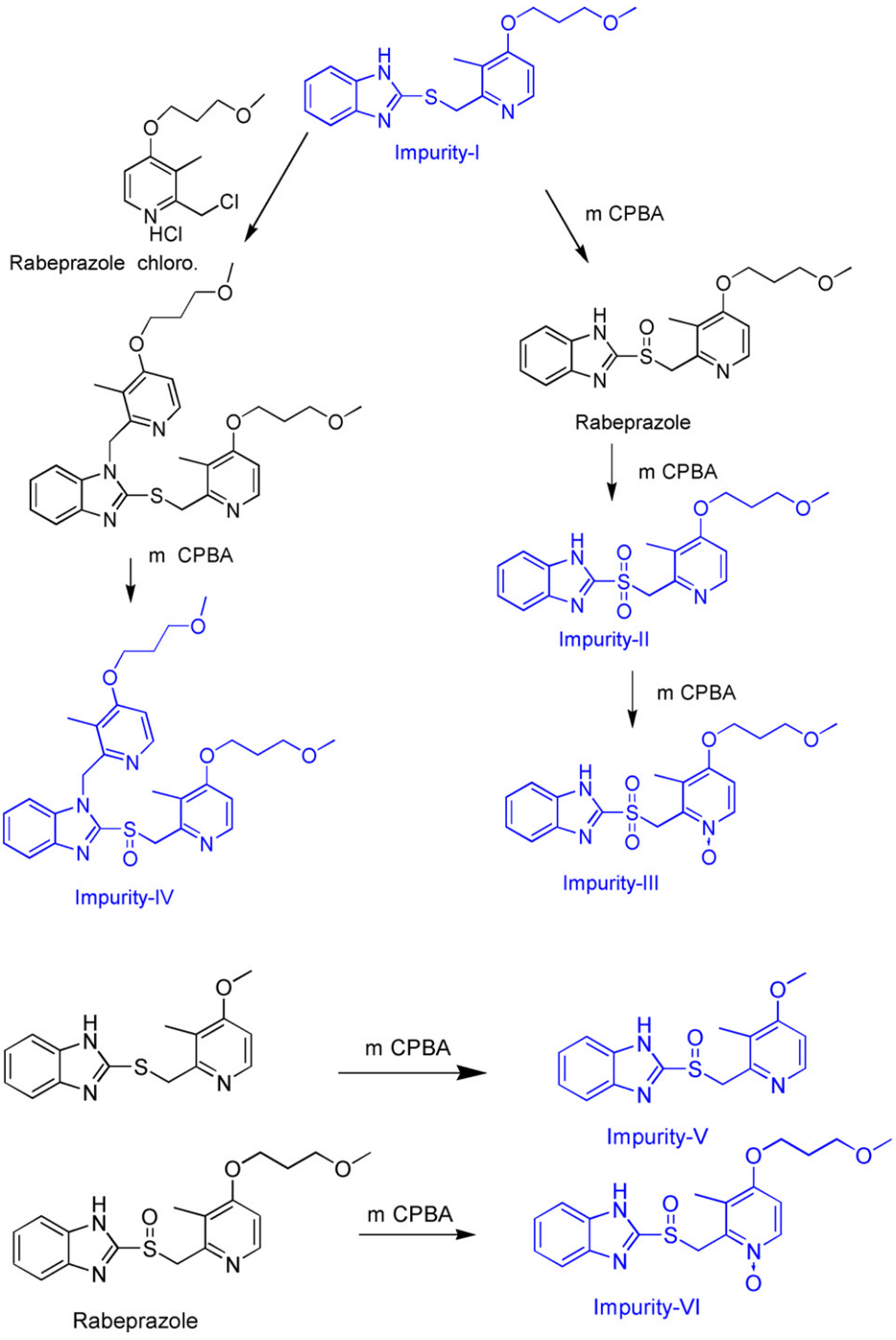

Fig. 3. Formation of impurities.

the NMR data three methylenes were missing in which one of them was oxygen attached methylene, Thus impurity V structure explains the absence of alkyl ether moiety.

The spectral data used for elucidation of the impurities from I to VI, are tabulated (Figs. 1 and 2, Tables 1–3).

3.3. Formation of impurities

One of the intermediate used in the synthesis of rabeprazole is impurity I. Rabeprazole on further oxidation yields impurities II and VI. Impurity II on further oxidation yields impurity III. Due to the presence of 2-chloromethyl-3-methyl-4-methoxy pyridine hydrochloride, 2-[[[4-methoxy-3-methyl-2-pyridinyl] methyl] thio]-1*H*-benzimidazole is formed which undergoes oxidation to give impurity V. Due to the condensation of rabeprazole chloro compound (a key starting material, 2-chloromethyl-3-methyl-4-(3-methoxypropoxy) pyridine hydrochloride) with impurity I, 2-[[[4-(3-methoxypropoxy)-3-methyl]pyridin-2-yl]methylthio]-1-[[4-(3-methoxypropoxy)-3-methyl]pyridin-2-yl methyl]-1*H*-benzimidazole is formed

which undergoes oxidation to impurity IV. The schematic diagram for the formation of impurities I, II, III, IV, V and VI are shown in Fig. 3.

Acknowledgements

The authors wish to thank the colleagues of Analytical Research Department of Discovery Research and the colleagues of Active pharmaceutical ingredients Unit-III, Dr. Reddys Laboratories Ltd.

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