Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Pharmaceutical and Biomedical Analysis 40 (2006) 605–613
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Identification and characterization of potential impurities of amlodipine maleate☆

P. Sudhakar[a], M. Nirmala[a], J. Moses Babu[a,*], K. Vyas[a], Ganta Madhusudan Reddy[b], B. Vijaya Bhaskar[b], P. Pratap Reddy[b], K. Mukkanti[c]

[a] *Department of Analytical Research, Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500 049, AP, India*
[b] *Dr. Reddy's Laboratories Ltd., Active Pharmaceutical Ingredients-III, Bollaram, Hyderabad 502 325, India*
[c] *Department of Chemistry, J.N.T. University, Kukatpally, Hyderabad 500 072, India*

Received 17 May 2005; received in revised form 20 October 2005; accepted 21 October 2005
Available online 1 December 2005

Abstract

Six impurities ranging from 0.43 to 1.42% in amlodipine maleate were detected by a simple isocratic reverse-phase high performance liquid chromatography (HPLC). LC–MS was performed to identify the mass of the impurities. Based on the spectral data (IR, NMR and MS), the structures of these impurities were characterized as 3-ethyl 5-methyl 4-(2-chlorophenyl)-2-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethoxymethyl]-6-methyl-1,4-dihydro-3,5-pyridinedicarboxylate (impurity I); 5-ethyl 3-methyl 4-(2-chlorophenyl)-2-methyl-6-[2-(2-methylcarbamoylphenyl-carboxamido)ethoxymethyl]-1,4-dihydro-3,5-pyridinedicarboxylate (impurity II); besylate salt of 3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate (impurity III); dimethyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydro-3,5-pyridinecarboxylate (impurity IV); 3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(4-chlorophenyl)-6-methyl-1,4-dihydro-3,5-pyridinedicarboxylate (impurity V); diethyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydro-3,5-pyridinedicarboxylate (impurity VI).

Keywords: Amlodipine impurities; Impurities; Spectroscopy; Identification; Elucidation

1. Introduction

A series of dihydropyridines (DHPs) substituted at the 2-position by basic chains are described and their potencies as calcium antagonists listed [1]. Due to the vasodilator properties, calcium channel blockers are important drugs in the treatment of angina [2].

Amlodipine maleate is used to control hypertension. It relaxes the blood vessels to the heart to control chest pain (angina) and it is one of the calcium channel blockers that work primarily on the arterial muscle [3].

During the analysis of laboratory, batches of amlodipine maleate, six impurities were detected whose area percentage ranged from 0.43 to 1.42%, by a simple isocratic reverse phase LC method. A comprehensive study has been undertaken to isolate and characterize these impurities by spectroscopic and spectrometric techniques. The impurity profile study has to be carried out for any final product to identify and characterize all the unknown impurities that are present at a level of even below 0.05%. The requirement of identifying and characterizing the impurities in the final product is extremely necessary in the wake of stringent purity requirements from the regulatory authorities. This paper not only describes the isolation and characterization of six impurities that are present in the range of 0.43–1.42% in the bulk drug of amlodipine maleate but, also, explains the formation of these impurities.

2. Experimental

2.1. Samples

The investigated samples of amlodipine maleate bulk material were obtained from Dr. Reddy's Laboratories Ltd., Bulk

☆ DRL Publication no.: IPM 00005.

* Corresponding author. Tel.: +91 40 23045439x258; fax: +91 40 23045438.
E-mail address: mosesbabuj@drreddys.com (J. Moses Babu).

0731-7085/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2005.10.029

Actives Unit-III, Hyderabad, India. The impurities detected in the HPLC were subjected to standard column chromatography for the isolation of the respective impurities and, further, subjected to spectroscopic studies.

2.2. High performance liquid chromatography (analytical)

An in-house LC method was developed for the analysis of amlodipine maleate and its impurities [4], where a column (Inertsil C8 3 (250 mm × 4.6 mm, 5 μm) with a mobile phase consisting of A: 0.01 M KH_2PO_4 (pH 3.0) adjusted with phosphoric acid); B: ACN:MeOH (1:1), with a Timed gradient program of T/%B: 0/40, 5/40, 20/80, 25/80, 30/40, 35/40 with a flow rate of 1.5 ml/min, UV detection at 237 nm was used. This LC method was able to detect all these impurities.

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

A LC–MS compatible method was developed for the analysis of amlodipine maleate and its impurities, where a column (Inertsil C8 3 (250 mm × 4.6 mm, 5 μm) with a mobile phase consisting of A: 0.01 M ammonium acetate (pH 3.0) adjusted with formic acid), B: ACN:MeOH (1:1), with a timed gradient program of T/%B: 0/40, 5/40, 20/80, 25/80, 30/40, 35/40 with

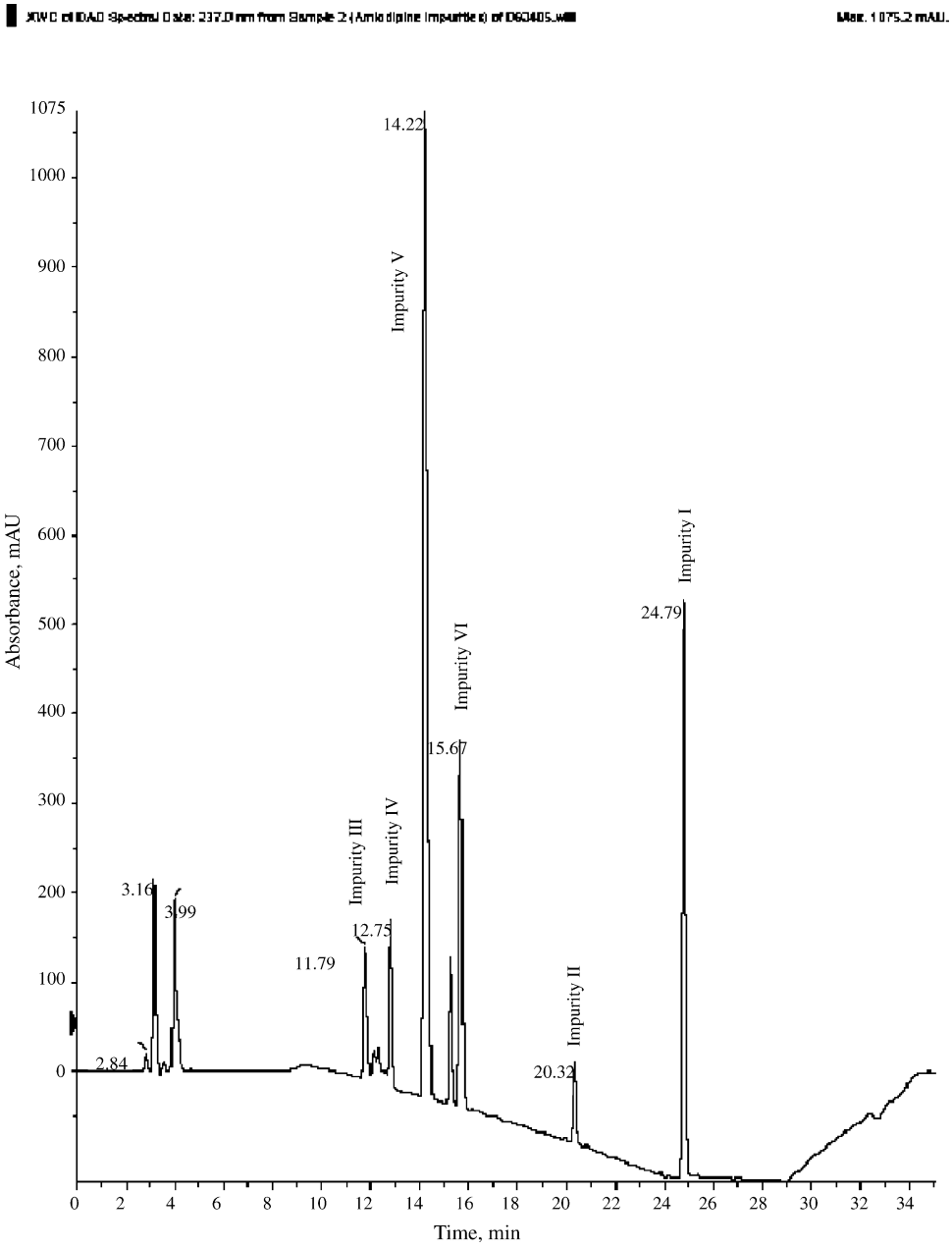


Fig. 1. LC method used for LC–MS.

Table 1
Retention time, molecular weight of the impurities from LC–MS

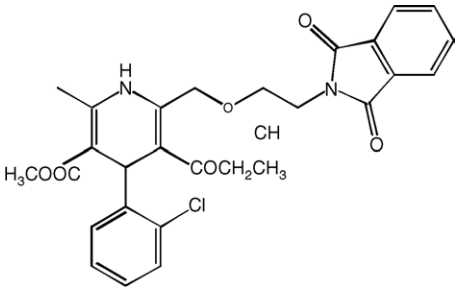
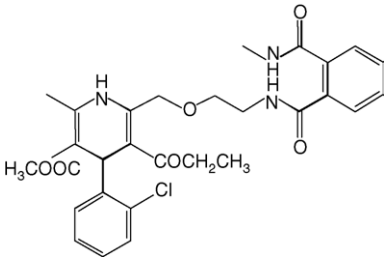
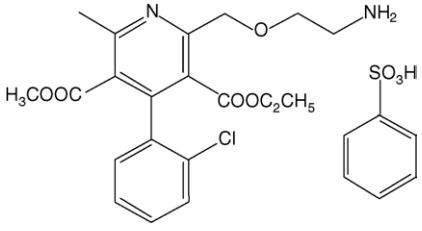
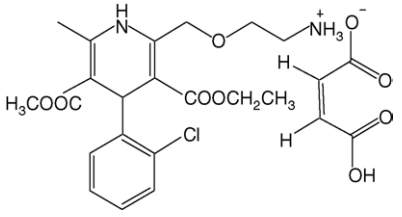
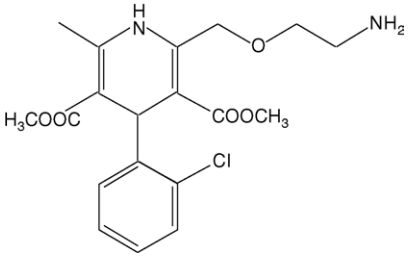
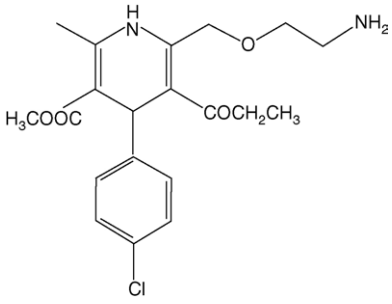
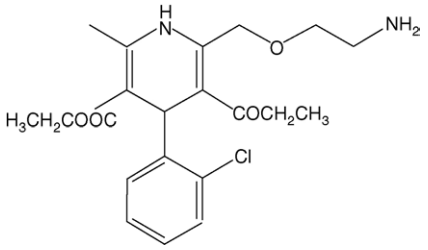
Sl. no.	Retention time[a] (min)	Compound	Molecular weight	Structure	Nature
1	24.8	Impurity I	538		–
2	20.3	Impurity II	569		Process related
3	11.9	Impurity III	406		Process related
4	15.4	Amlodipine maleate	408		–
5	12.8	Impurity IV	394		Process related
6	14.2	Impurity V	408		Process related

Table 1 (*Continued*)

Sl. no.	Retention time[a] (min)	Compound	Molecular weight	Structure	Nature
7	15.7	Impurity VI	422		Process related

[a] Retention time of impurities in LC–MS.

a flow rate of 1.0 ml/min (using split), UV detection at 237 nm was used. This LC method was able to detect all the impurities.

2.4. Mass spectrometry

The electrospray ionization and MS–MS studies were performed on a triple quadrupole mass spectrometer PE Sciex model API 3000. The positive and negative electrospray MS data was obtained by switching the capillary voltage between $n + 5000$ and -4500 V, respectively. The MS–MS data was generated with the collision energy ramping from 30 to 60 V in nitrogen atmosphere.

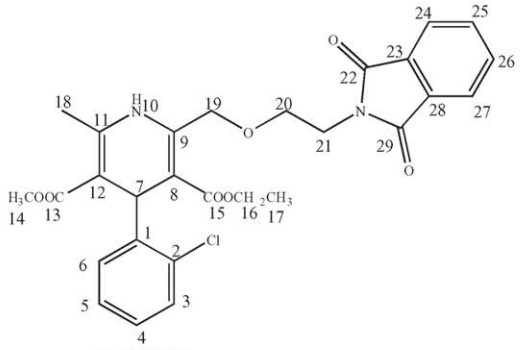
2.5. NMR spectroscopy

The ^{1}H, ^{13}C, DEPT and 2D experiments (gDQCOSY, gHSQC and gHMBC) for Amlodipine maleate, impurities I, II, IV–VI were performed in $CDCl_3$ and impurity III in DMSO-d_6 solvents using Mercury plus 400 MHz FT-NMR spectrometer. The ^{13}C experiment for amlodipine maleate was performed in mixture of $CDCl_3$ and DMSO-d_6. The ^{1}H chemical shift values were reported on the δ scale in ppm, relative to TMS ($\delta = 0.00$ ppm) and 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, respectively.

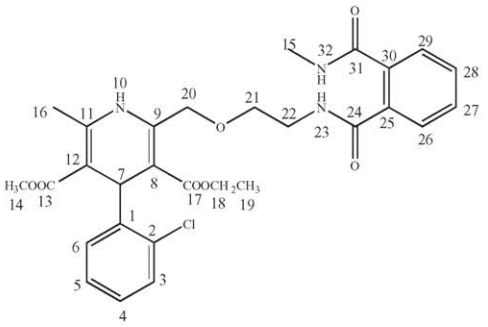
Table 2
FT-IR and mass spectral data of amlodipine maleate and impurities I–VI

Sl. no.	Compound	IR[a]	MS
1	Impurity I	3361 (N—H stretching), 2950 (aliphatic C—H stretching), 1707 (C=O stretching), 1607 (C=C aromatic stretching), 1490 (N—H bending), 1392 (aliphatic C—H stretching), 1287, 1101 (C—O stretching), 1209 (C—N stretching) and 723 (aromatic C—H bending)	+ve ES–MS: 539.0 $(M+H)^+$, 561.2 $(M+Na)^+$, 577.0 $(M+K)^+$; −ve ES–MS: 537.3 $(M-H)^-$, 573.3 $(M+Cl)^-$
2	Impurity II	3424 (N—H stretching), 2932 (aliphatic C—H stretching), 1690 (C=O stretching), 1639 (C=C aromatic stretching), 1482 (N—H bending), 1209 (C—N stretching) and 753 (aromatic C—H bending)	+ve ES–MS: 570.3 $(M+H)^+$, 592.2 $(M+Na)^+$, 1139.3 $(2M+H)^+$, 1161.3 $(2M+Na)^+$; −ve ES–MS: 568.5 $(M-H)^-$, 604.5 $(M+Cl)^-$
3	Impurity III	3374 (N—H stretching), 2981 (aliphatic C—H stretching), 1728 (C=O stretching), 1561 (C=C stretching), 1480 (C—N stretching), 1436 (aliphatic C—H bending), 1237, 1111 (C—O stretching) and 756 (C—S stretching)	+ve ES–MS: 407.3 $(M+H)^+$, 429.3 $(M+Na)^+$, 435.4 $(M+K)^+$, 813.5 $(2M+H)^+$, 841.8 $(2M+K)^+$; −ve ES–MS: 405.3 $(M-H)^-$, 451.5 $(M+Cl)^-$
4	Impurity IV	3391 (N—H stretching), 2945 (aliphatic C—H stretching), 1692 (C=O stretching) 1650 (C=C aromatic stretching), 1480 (N—H bending), 1432 (aliphatic C—H bending), 1284, 1102 (C—O stretching), 1210 (C—N stretching) and 759 (aromatic C—H bending)	+ve ES–MS: 395.0 $(M+H)^+$, 417.1 $(M+Na)^+$, 433.0 $(M+K)^+$, 789.3 $(2M+H)^+$, 811.3 $(2M+Na)^+$; −ve ES–MS: 405.3 $(M-H)^-$ 451.5, $(M+CH_3COO)^-$
5	Impurity V	3391 (N—H stretching), 1686 (C=O stretching), 1642 (C=C aromatic stretching), 1483 (N—H bending), 1308 (aliphatic C—H bending), 1278, 1101 (C—O stretching), 1201 (C—N stretching) and 862 (aromatic C—H bending)	+ve ES–MS: 409.3 $(M+H)^+$, 431.0 $(M+Na)^+$, 817.3 $(2M+H)^+$, 839.3 $(2M+Na)^+$; −ve ES–MS: 407.5 $(M-H)^-$, 453.5 $(M+HCOO)^-$
6	Impurity VI	3254 (N—H stretching), 2983 (aliphatic C—H stretching), 1685 (C=O stretching), 1639 (C=C stretching), 1485 (N—H bending), 1280, 1098 (C—O stretching), 1202 (C—N stretching) and 759 (aromatic C—H bending)	+ve ES–MS: 423.1 $(M+H)^+$, 445.1 $(M+Na)^+$, 845.3 $(2M+H)^+$, 867.32 $(M+Na)^+$; −ve ES–MS: 421.5 $(M-H)^-$, 457.4 $(M+Cl)^-$, 481.4 $(M+CH_3COO)^-$
7	Amlodipine maleate	3369 (N—H stretching), 1691 (C=O stretching), 1484 (N—H bending), 1289, 1105 (C—O stretching), 1204 (C—N stretching) and 741 (aromatic C—H bending)	+ve ES–MS: 409.4 $(M+H)^+$, 431.0 $(M+Na)^+$, 817.3 $(2M+H)^+$; −ve ES–MS: 407.5 $(M-H)^-$

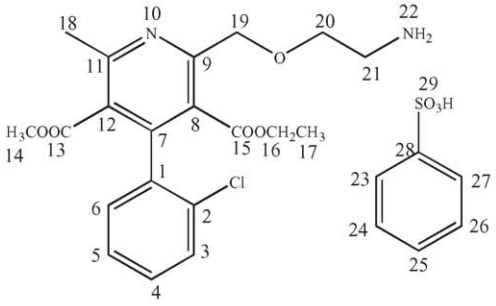
[a] KBr (impurities I, II, IV–VI, amlodipine maleate) and neat (III).



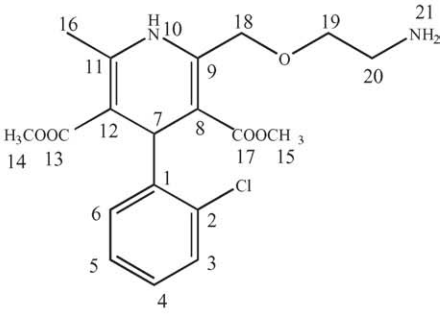
IMPURITY I



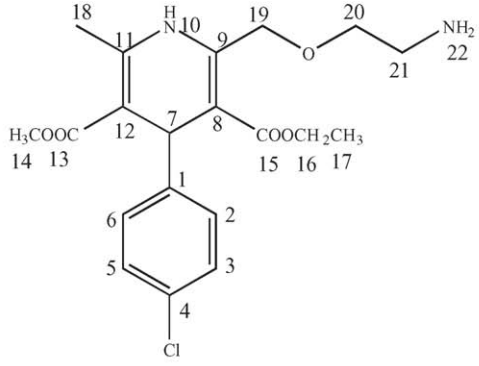
IMPURITY II



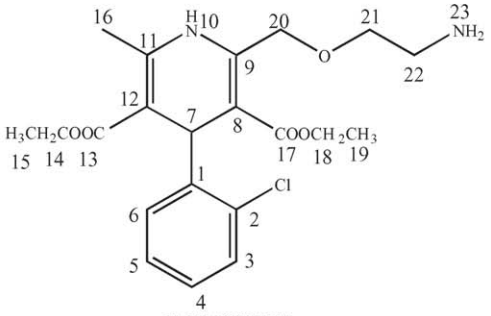
IMPURITY III



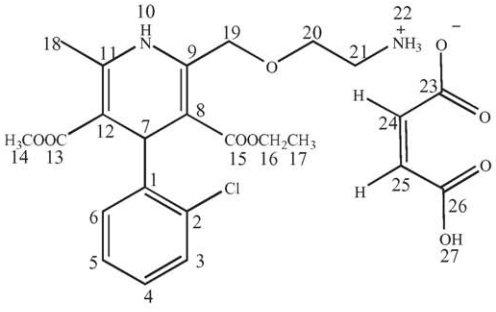
IMPURITY IV



IMPURIY V



IMPURITY VI



Amlodipine Maleate

Fig. 2. Atom numbering used for NMR assignments.

Table 3
^{1}H and ^{13}C NMR assignments for amlodipine maleate and impurities I–III

Position[a]	Amlodipine maleate				Impurity I				Impurity II				Impurity III			
	^{1}H	ppm/*J*	^{13}C[b]	DEPT	^{1}H	ppm/*J*	^{13}C	DEPT	^{1}H	ppm/*J*	^{13}C	DEPT	^{1}H	ppm/*J*	^{13}C	DEPT
1	–	–	131.07	–	–	–	145.86	–	–	–	132.27	–	–	–	134.79	–
2	–	–	144.92	–	–	–	131.86	–	–	–	145.91	–	–	–	132.67	–
3	1H	7.34/dd 1.2, 7.2	130.43	CH	1H	7.20/dd 1.6, 8.0	128.97	CH	1H	7.38/dd 1.6, 8.0	131.43	CH	1H	7.40/dd 1.2, 8.0	128.99	CH
4	1H	7.23/dt 1.2, 7.2	126.01	CH	1H	7.01/dt 1.6, 7.6	127.13	CH	1H	7.11/dt 1.6, 7.6	126.83	CH	1H	7.29–7.36/m	130.01	CH
5	1H	7.13/dt 1.6, 7.6	126.43	CH	1H	7.09/dt 1.2, 7.6	126.73	CH	1H	7.03/dt 1.6, 8.0	127.29	CH	1H	7.26/dt 1.2, 7.6	126.07	CH
6	1H	7.28/dd 1.6, 7.6	128.13	CH	1H	7.34/dd 1.6, 7.6	131.32	CH	1H	7.22/dd 1.2, 8.0	129.17	CH	1H	7.14/dd 1.6, 7.2	130.10	CH
7	1H	6.03/s	36.10	CH	1H	5.37/s	36.80	CH	1H	7.26/s	37.09	CH	–	–	145.13	–
8	–	–	101.13	–	–	–	103.58	–	–	–	144.85	–	–	–	128.33	–
9	–	–	143.67	–	–	–	144.98	–	–		101.78	–	–	–	155.58	–
10	NH	8.38/s	–	–	NH[c]	–	–	–	NH		–	–	–	–	–	–
11	–	–	144.08	–	–	–	144.55	–	–		103.56	–	–	–	156.13	–
12	–	–	102.16	–	–	–	100.92	–	–	–	145.02	–	–	–	129.79	–
13	–	–	166.87	–	–	–	168.00	–	–	–	168.66	–	–	–	166.89	–
14	3H	3.51/s	49.63	CH_3	3H	3.61/s	50.59	CH_3	3H	2.96/d 4.8	26.98	CH_3	3H	3.51/s	52.08	CH_3
15	–	–	165.96	–	–	–	167.03	–	3H	3.60/s	50.68	CH_3	–	–	166.32	–
16	2H	3.98/m	58.71	CH_2	2H	4.03/m	59.61	CH_2	3H	2.331/s	18.99	CH_3	2H	3.95/q 7.2	61.64	CH_2
17	3H	1.12/t 6.8	13.24	CH_3	3H	1.16/t 7.2	14.10	CH_3	–	–	167.21	–	3H	0.826/t 7.2	13.23	CH_3
18	3H	2.31/s	17.84	CH_3	3H	2.42/s	18.79	CH_3	2H	4.04/m	59.78	CH_2	3H	2.603/s	22.90	CH_3
19	2H	4.64/q 14.0	66.82	CH_2	2H	4.68/q 16.6	68.03	CH_2	3H	1.18/t 7.0	14.23	CH_3	2H	4.76/q 14.0	71.83	CH_2
20	2H	3.66/t 4.4	65.96	CH_2	2H	3.75/m	68.88	CH_2	2H	4.75/q 15.2	68.06	CH_2	2H	3.77/t 4.8	66.99	CH_2
21	2H	3.09/t 4.4	38.27	CH_2	2H	4.00/m	37.87	CH_2	2H	3.67/m	70.16	CH_2	2H	3.23/b	39.82	CH_2
22	NH_3	7.81/s	–	–	–	–	168.45	–	2H	3.67/m	39.62	CH_2	NH_2	8.10/b	–	–
23	–	–	168.15	–	–	–	132.09	–	NH		–	–	1H	7.82/dd 1.6, 7.2	125.76	CH
24	1H	6.03/s	135.02	CH	1H	7.76/m	168.45	CH	–	–	168.09	–	1H	7.29–7.36/m	128.18	CH
25	1H	6.03/s	135.02	CH	1H	7.88/m	123.28	CH	–		134.08	–	1H	7.29–7.36/m	126.07	CH
26	–	–	168.15	–	1H	7.88/m	123.28	CH	1H	7.49–7.46/m	130.44	CH	1H	7.29–7.36/m	128.18	CH
27	OH[c]	–	–	–	1H	7.76/m	168.45	CH	1H	7.49–7.46/m	130.16	CH	1H	7.82/dd 1.6, 7.2	125.76	CH
28	–	–	–	–	–	–	132.09	–	1H	7.49–7.46/m	127.66	CH	–	–	144.12	–
29	–	–	–	–	–	–	168.45	–	1H	7.73/m	129.28	CH	SO_3H[c]	–	–	–
30	–	–	–	–	–	–	–	–	–		134.08	–	–	–	–	–
31	–	–	–	–	–	–	–	–	–	–	170.68	–	–	–	–	–
32	–	–	–	–	–	–	–	–	NH		–	–	–	–	–	–

s, singlet; d, doublet; m, multiple; b, broad.

[a] Refer structural formula (Fig. 2) for numbering.

[b] DMSO + $CDCl_3$.

[c] Proton not observed.

2.6. FT-IR spectroscopy

The IR spectra were recorded in the solid state as KBr dispersion medium using Perkin-Elmer 1600 series FT-IR spectrophotometer.

2.7. Synthesis of impurities

The impurity II was synthesized by amination of impurity I. Impurity III was synthesized from impurity I by dehydration followed by amination. Impurity IV was synthesized from impurity I by aminolysis. Impurity V was synthesized from parachloro phthalimido amlodipine by aminolysis. Impurity VI was synthesized from diethoxy phthalimido amlodipine by aminolysis.

3. Results and discussions

3.1. Detection of impurities II–VI

A typical analytical LC chromatogram of a laboratory batch of amlodipine maleate bulk drug recorded using the LC method as described in Section 2.2. The LC–MS compatible method is described in Section 2.3, which is used to detect the impurities Fig. 1. The impurity I is not detected by the LC method described in Section 2.2 as it is one of the intermediate materials for the preparation of the active pharmaceutical ingredient (API). Retention times in LC–MS and structures of these impurities and amlodipine maleate are shown in Table 1. Impurities III, IV are polar and impurities II, V and VI are non-polar, respectively with respect to amlodipine maleate.

3.2. Structural elucidation of amlodipine maleate and its impurities

3.2.1. Structural elucidation of impurity I

The +ve ES–MS spectrum of the impurity showed peaks at *m*/*z* 539.0, 561.2, and 577.0 corresponding to the adduct ions $(M+H)^+$, $(M+Na)^+$ and $(M+K)^+$. The −ve ES–MS spectrum showed peaks at *m*/*z* 537.3 and 573.3 corresponding to $(M-H)^-$ and $(M+Cl)^-$.

Both +ve and −ve ES–MS spectra showed characteristic chlorine isotope peaks. The ES–MS–MS spectrum displayed daughter ions at *m*/*z* 174.1, 208.1 and 288.3 in which 174.1 is the dominant fragment. From the mass spectral data, the molecular ion of impurity is 538. The DEPT spectra displayed four negative signals due to four methylene groups and 11 positive peaks due to the presence of four methyl groups and the rest are due to the methine groups (one in aliphatic and rest in aromatic). One methyl peak in the DEPT corresponds to the acetic acid peak. IR spectrum displayed characteristic absorptions at 3361 and 1707 cm^{-1} corresponding to NH and C=O stretching, which was supported by the appearance of quaternary carbon signal characteristic of a carbonyl functional group in ^{13}C NMR spectrum. The peaks at 1287 and 1102 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 $C_{28}H_{27}ClN_2O_7$. This molecular formula matched

Table 4
^1H and ^{13}C NMR assignments for amlodipine maleate and impurities IV–VI

Position[a]	Impurity IV				Impurity V				Impurity VI			
	^1H	ppm/*J*	^{13}C	DEPT	^1H	ppm/*J*	^{13}C	DEPT	^1H	ppm/*J*	^{13}C	DEPT
1	–	–	145.97	–	–	–	144.60	–	–	–	145.62	–
2	–	–	132.30	–	1H	7.16–7.21/m	127.93	CH	–	–	132.31	–
3	1H	7.37/dd 1.6, 8.0	131.30	CH	1H	7.16–7.21/m	129.20	CH	1H	7.38/dd 1.6, 7.6	131.62	CH
4	1H	7.13/t 7.6	126.90	CH	–	–	131.66	–	1H	7.12/dt 1.2, 7.2	126.59	CH
5	1H	7.03/dt 1.2, 7.6	127.26	CH	1H	7.16–7.21/m	129.20	CH	1H	7.03/dt 1.6, 7.2	127.20	CH
6	1H	7.22/d 7.6	129.20	CH	1H	7.16–7.21/m	127.93	CH	1H	7.22/dd 1.2, 7.6	129.14	CH
7	1H	5.42/s	37.13	CH	1H	4.95/s	39.04	CH	1H	5.41/s	37.39	CH
8	–	–	101.02	–	–	–	101.09	–	–	–	100.96	–
9	–	–	146.08	–	–	–	146.28	–	–	–	145.83	–
10	NH	7.84/s	–	–	NH	7.83/s	–	–	NH	7.77/s	–	–
11	–	–	144.41	–	–	–	145.75	–	–	–	144.15	–
12	–	–	103.98	–	–	–	103.56	–	–	–	103.85	–
13	–	–	167.99	–	–	–	167.85	–	–	–	167.60	–
14	3H	3.58/m	50.72	CH_3	3H	3.63/s	50.84	CH_3	2H	4.07/m	59.60	CH_2
15	3H	3.58/m	50.69	CH_3	–	–	166.91	–	3H	1.19/t 7.2	14.18	CH_3
16	3H	2.36/s	19.12	CH_3	2H	4.07/m	59.68	CH_2	3H	2.35/s	19.15	CH_3
17	–	–	167.59	–	3H	1.21/t 7.0	14.19	CH_3	–	–	167.21	–
18	2H	4.74/q 16.4	67.90	CH_2	3H	2.37/s	19.25	CH_3	2H	4.07/m	59.60	CH_2
19	2H	2.97/t 5.2	73.59	CH_2	2H	4.74/q 16.4	67.92	CH_2	3H	1.19/t 7.2	14.18	CH_3
20	2H	3.58/m	41.31	CH_2	2H	3.57/t 5.0	73.54	CH_2	2H	4.74/q 16.4	67.91	CH_2
21	NH_2	1.45/br	–	–	2H	2.96/t 5.0	41.24	CH_2	2H	2.96/t 5.6	41.21	CH_2
22	–	–	–	–	NH_2	1.45/br	–	–	2H	3.58/m	73.36	CH_2
23	–	–	–	–	–	–	–	–	NH_2	1.58/br	–	–

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

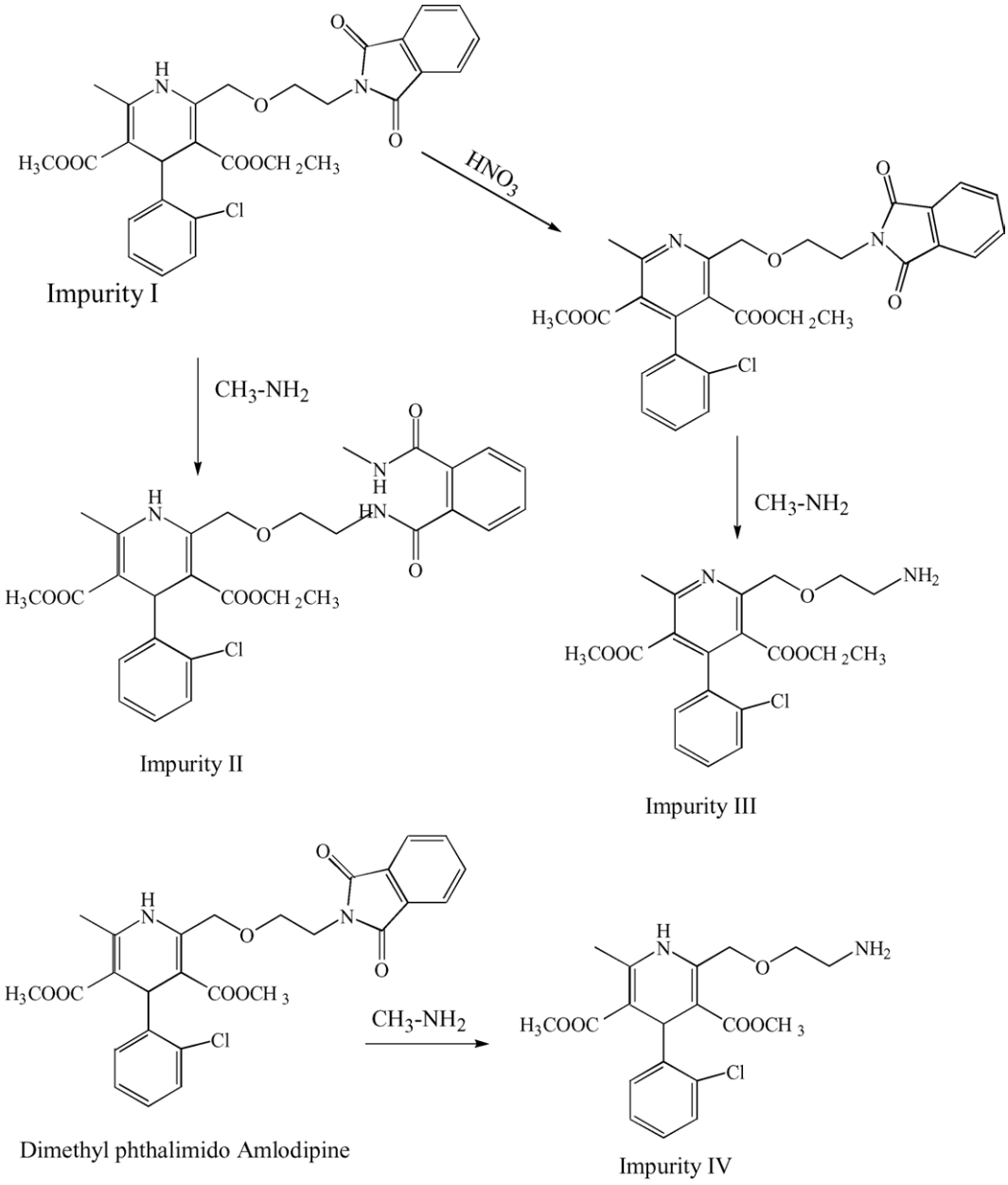


Fig. 3. Formation of impurities.

well with the molecular ion observed at *m/z* 538 in the mass spectral data. The data obtained form the spectral studies can be rationalized in terms of impurity I having the molecular formula $C_{28}H_{27}ClN_2O_7$ and the corresponding structure was characterized as 3-ethyl 5-methyl 4-(2-chlorophenyl)-2-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethoxymethyl]-6-methyl-1,4-dihydro-3,5-pyridinedicarboxylate.

The above-mentioned strategies were used for elucidation of the impurities from II to VI [5] (Figs. 1 and 2 and Tables 1–4).

3.3. Formation of impurities

One of the intermediate used in the synthesis of amlodipine maleate is impurity I. This on hydrolysis yields impurity II. Impurity III is formed from I by aromatization followed by hydrolysis. Due to the presence of methyl-4-[2′-(phthalimido)ethoxy]-2-[2″-(chloro)benzylidine]-acetoacetate, dimethyl phthalimido amlodipine is formed, which undergoes hydrolysis to give IV. The presence of 4-chloro benzaldehyde in the starting material contributes to the formation of impurity V. The presence of ethyl-3-amino contributes to the formation diethyl phthalimido amlodipine. This undergoes hydrolysis to give VI. The schematic diagram for the formation of impurities I–IV are shown in Fig. 3.

Acknowledgements

The authors wish to thank the colleagues of Analytical Research Department of Discovery Research and the colleagues

of Bulk Actives-III, Dr. Reddy's Laboratories Ltd., for providing the compounds.

References

[1] J.E. Arrowsmith, et al., J. Med. Chem. 29 (1986) 1696–1702.
[2] P. Theroux, Y. Taeymans, D.D. Waters, Drugs 25 (1983) 178–195.
[3] F.R. Buhler, U.L. Hulthen, W. Kiowski, F.B. Muller, P.J. Bolli, Cardiovasc. Pharmacol. 4 (1982) S350–S357.
[4] Z. Zanko, G. Rok, Z. Teofil, F. Borut, Acta Chim. Slov. 47 (2000) 63–68.
[5] K.V.S.R. Krishna Reddy, J. Moses Babu, P. Anil Kumar, E.R.R. Chandrashekar, T.M. Vijayavitthal, S. Eswaraiah, M. Satyanarayana Reddy, K. Vyas, J. Pharm. Biomed. Anal. 35 (2004) 1007–1058.