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# A Novel Method for Resolution of Amlodipine

Dinkar M. Gotrane, Rajendra D. Deshmukh, Prasad V. Ranade, Swapnil P. Sonawane,* Baburao M. Bhawal, Milind M. Gharpure, and Mukund K. Gurjar

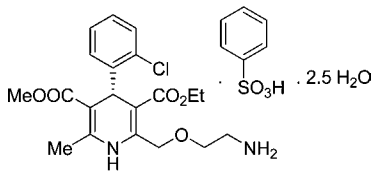
*API R&D Centre, Emcure Pharmaceuticals Ltd., ITBT Park, Phase-II, MIDC, Hinjewadi, Pune-411057, India*

**Abstract:**

**The present invention relates to an industrially feasible and cost-efficient process for the preparation of isomerically pure *S*-amlodipine besylate hemipentahydrate (1), a useful calcium antagonist inhibitor. Previous workers reported that *R*-amlodipine-tartrate was crystallized out preferentially from the reaction mixture when naturally occurring L-tartaric acid and racemic amlodipine base in DMSO are mixed. In order to crystallize *S*-amlodipine-tartrate, the use of unnatural D-tartaric acid as a resolving agent in DMSO was required. However, the cost of D-tartaric acid was not conducive to overall cost efficiency in the resolution protocol. Subsequent to the above observations, we have developed a novel resolving system in which amlodipine base with natural L-tartaric acid in DMF as a solvent gave preferentially the *S*-form of amlodipine tartrate directly from the reaction. The optimization of this approach by adjusting the water percentage in DMF ensured consistent purity of *S*-amlodipine (+99%) and satisfactory resolution efficiency.**

## Introduction

The last 20 years have seen outstanding discoveries of calcium (Ca) antagonists associated with multifaceted pharmacodynamic potential which includes not only the antiarrhythmic and antihypertensive effects of the drug but also the protection against excessive Ca entry into the cells of the cardiovascular system and subsequent cell damage.[1] Among many classes of calcium channel blockers the 1,4-dihydropyridine-based drug molecules represented by amlodipine, aranidipine, barnidipine, clevidipine, felodipine, nicardipine, etc. are by far the best candidates to reduce systemic vascular resistance and arterial pressure.[2] Amlodipine (**3**) and its salts are long-acting calcium channel blockers and are useful for the treatment of cardiovascular disorders.[3] Amlodipine is marketed in its racemic form in most major markets.




**1** S-(-)-Amlodipine besylate hemipentahydrate

During the systematic study on chiral isomers of amlodipine with respect to their biological activity, it was distinctively clear that the *S*-isomer (**1**) of amlodipine besylate had a better therapeutic profile than the corresponding *R*-isomer.[4] It has been demonstrated that only the *S*-(−)-isomer of amlodipine was having the calcium channel blocker activity while the corresponding *R*-(+)-isomer had little or no calcium channel blocking activity.[4] In fact our company has introduced *S*-amlodipine besylate for the first time in India under the brand name of *Asomex* and today chiral *S*-amlodipine is being marketed by us in more than 30 countries all over the world.[5] The post-marketing surveillance study[6a−c] by Emcure has proven beyond doubt that *S*-amlodipine besylate is a well-accepted drug for hypertension. Prior art for the preparation of *R*- and *S*-enantiomers of amlodipine are (a) resolution of amlodipine azide ester with optically active 2-methoxy-2-phenylethanol,[4] or (b) resolution of racemic amlodipine base with optically active camphanic acid,[7] or (c) resolution of racemic amlodipine base to *R*-(+)-and *S*-(−)-isomers with L- or D-tartaric acid, respectively, in the organic solvent, DMSO.[8] The separation of *R*- and *S*-amlodipine isomers was also achieved by the resolution of intermediate racemic azido acid cinchonidine salts, which were then eventually converted into the desired enantiomerically pure amlodipine (*R*)- and (*S*)-isomers.[9] Among these above methods reported, perhaps the tartaric acid resolution of racemic amlodipine in DMSO reported by Spargo[8] was most feasible. However, the patented method had the disadvantage of using expensive unnatural tartaric acid in DMSO to obtain the desired *S*-amlodipine isomer preferentially. This patent also mentioned explicitly that DMSO was essential for the unique separation process. In the process disclosed by Spargo et al.,[8] utilization of L-tartaric acid for resolution of racemic amlodipine first resulted in the separation of the undesired *R*-isomer of amlodipine, while the desired *S*-isomer passed into the mother liquor along with other impurities. The desired *S*-isomer was then isolated from the mother liquor by employing the costly D-tartaric acid in the subsequent step. These operations made the resolution process expensive and with too many operations to perform. Senanayake et al[10] describes the resolution process of racemic amlodipine base using L- or D-tartaric acid in dimethyl acetamide as a solvent. In this case the required (*S*)-

* Fax: +91-20-39821445. E-mail: Swapnil.Sonawane@emcure.co.in.

(1) Gasser, R. *Angiology* **1990**, *41*, 36–43.
(2) Resnekov, L. *Chest* **1980**, *78*, 121–247.
(3) Campbell, S.; Cross, J.; Stubbs, K. EP0089167, 1983.
(4) Arrowsmith, J. E.; Campbell, P. E.; Cross, J. K. *J. Med. Chem.* **1986**, *29*, 1696–1702.
(5) Gharpure, M.; Bhawal, B.; Ranade, P.; Deshmukh, R.; Mehta, S. U.S. Patent 2008/0262239, 2008.
(6) (a) Gurjar, M. *J. Indian Med. Assoc.* **2007**, *105*, 177–178. (b) Thacker, H. *J. Indian Med. Assoc.* **2007**, 180–190. (c) Hiremath, J. *Indian Med. Gaz.* **2005**, (CXXXIX), 403–408.
(7) Goldman, S.; Stoltefuss, J.; Born, L. *J. Med. Chem.* **1992**, *35*, 3341–3344.
(8) Spargo, P. U.S. Patent 6,046,338, 2000.
(9) Arrowsmith, J. E. EP 0331315, 1989.
(10) Senanayake, H.; Tanoury G.; Wilkinson, H.; Bakale, R.; Zlota, A. U.S. Patent 6,822,099, 2003.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isomer of amlodipine needed unnatural D-tartaric acid as a resolving agent. The process disclosed by Chung et al.,[11] utilizes L-tartaric acid for resolution; however, major lacunas of this process are the use of the class II solvent dichloromethane, the reaction time, and most importantly, the low ee, i.e. 97.9%. Kim et al.,[12] showed the resolution using expensive optically active *O*,*O*′-dibenzoyl tartaric acid. Similar strategies for the resolution of racemic amlodipine were reported by other groups of Zhang et al.[13] and Joshi et al.[14] The basic premise of our studies was directed to design experiments in which the required *S*-isomer of amlodipine could be isolated with the use of inexpensive naturally occurring tartaric acid.

## Results and Discussion

As reported in the literature,[8] *R*-amlodipine-tartrate was crystallized out preferentially from the reaction mixture when naturally occurring L-tartaric acid and racemic amlodipine base in DMSO were used. For *S*-amlodipine-tartrate, the use of unnatural D-tartaric acid as a resolving agent in DMSO was required. However, the cost of D-tartaric acid was rather high for developing a cost-efficient process to seed generic markets. In order to make the resolution of amlodipine commercially feasible, we sought to reverse this process and attempted to force the crystallization of the *S*-isomer from the reaction by keeping the L-tartaric acid segment constant by changing the solvent system.

In order to decide which solvent system is suitable for crystallization of *S*-amlodipine-L-tartrate salt, we independently prepared the L-tartrate salts of both *S*- and *R*-amlodipine by the literature method.[8] The solubility of both ot these salts in different solvents were carefully studied. It was gratifying to realize that the L-tartrate salt of the *S*-form was significantly less soluble than the L-tartrate salt of the *R*-form in DMF solvent. This observation gave us a clue to focus the resolution of racemic amlodipine base with natural L-tartaric acid in DMF. Indeed, amlodipine base with 0.25 equiv of L-tartaric acid in pure DMF at room temperature for 4 h gave a solid precipitate whose analytical data confirmed that it contained 76.17% of *S*-form and 23.83% of *R*-form as tartrate salts (see entry 12, Table 1).

These experiments suggested that pure DMF might not be sufficiently polar to differentiate the solubility of these isomers. Therefore, addition of water was proposed. With 10% addition of water in DMF, we saw a dramatic enhancement. The ratio of the *S*-form increased to 86% with the *R*-form being 14% in the isolated solid. Table 2 summarizes three valuable experimental results. It is apparent that the 85:15 ratio of DMF/water yields the best results with the *S*-form being crystallized out with 99% purity. Table 2 also indicates the resolution efficiency of 0.70 was by far the best we could obtain (see entry 2). The resolution efficiency of 0.70 is quite satisfactory; however, we wished to optimize the resolution efficiency with new experiments as indicated in Table 3. In short, Table 3 reiterates that entry 2 of Table 2 was the best experiment so far in this series.

(11) Chung, S.; Ha Mun, C. U.S. Patent 7,482,464, 2007.
(12) Kim, S.; Kim, H.; Lee, K. EP1831166, 2007.
(13) Xitian, Z. U.S. Patent 6,646,131, 2003.
(14) Joshi, R.; Joshi, R.; Gurjar, M. U.S. Patent 7,148,358, 2005.

***Table 1.*** **Resolution of (*R*,*S*)-amlodipine (3) with L-(+)-tartaric acid using various solvents**

| entry | solvent[a] | % *S*-isomer in solid precipitated[b] |
|---|---|---|
| 1 | acetone | 49.75 |
| 2 | 2-butanone | 49.01 |
| 3 | methyl isobutyl ketone | 44.98 |
| 4 | methanol | 51.82 |
| 5 | ethanol | 48.19 |
| 6 | *n*-propanol | 49.50 |
| 7 | 2-propanol | 49.37 |
| 8 | *n*-butanol | 50.07 |
| 9 | ethyl acetate | 39.76 |
| 10 | isopropyl acetate | 49.51 |
| 11 | butyl acetate | 53.85 |
| 12 | DMF | 76.17 |
| 13 | DMAc | 49.39 |
| 14 | sulfolane | —[c] |
| 15 | dichloromethane | 48.89 |
| 16 | chloroform | —[c] |
| 17 | DIPE | —[d] |
| 18 | MTBE | —[d] |
| 19 | DIPE | —[d] |
| 20 | diethyl ether | —[d] |
| 21 | hexanes | —[d] |
| 22 | cyclohexane | —[d] |
| 23 | toluene | 49.48 |

[a] Reactions were carried out on 50 mmol scale using 0.25 equiv of L-(+)-tartaric acid for 4.0 h at 25 °C wrt **3**. [b] By chiral HPLC. [c] No precipitation. [d] **3** is insoluble.

***Table 2.*** **Effect of water on resolution of (*R*,*S*) amlodipine (3) with L-(+)-tartaric acid**

| entry | solvent[a] DMF/Water | yield (%)[b] | enantiomeric excess (%)[c] | resolution efficiency[d] |
|---|---|---|---|---|
| 1 | 9/1 (10%) | 59.94 | 74.00 | 0.44 |
| 2 | 8.5/1.5 (15%) | 70.58 | 99.00 | 0.70 |
| 3 | 8/2 (20%) | 50.21 | 97.72 | 0.49 |

[a] Reactions were carried out on 50 mmol scale using 0.25 equiv of L-(+)-tartaric acid for 4.0 h at 25 °C wrt **3**. [b] Yield is based on a half amount of racemate mono DMF solvate. [c] By chiral HPLC. [d] Resolution efficiency = yield × ee.

The enantiomerically pure salt **2** was then converted to a biologically active pharmaceutical ingredient **1** by reacting it with benzenesulfonic acid in isopropanol/water mixture at ambient temperature to obtain *S*-amlodipine besylate (**1**) (Scheme 1). Interestingly, we carried out the single-crystal X-ray diffraction studies on *S*-amlodipine besylate (**1**) (Figure 1) and observed that **1** existed as a hemipentahydrate. The single crystal (Figure 1) shows that five water molecules are shared by two molecules of *S*-(−)-amlodipine besylate.

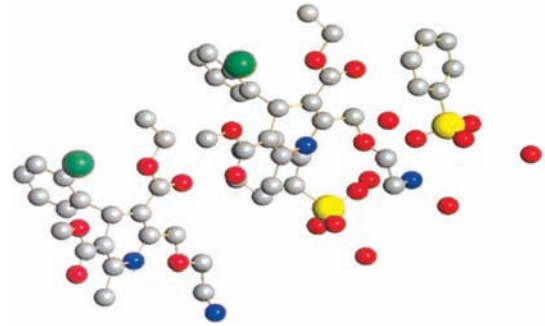


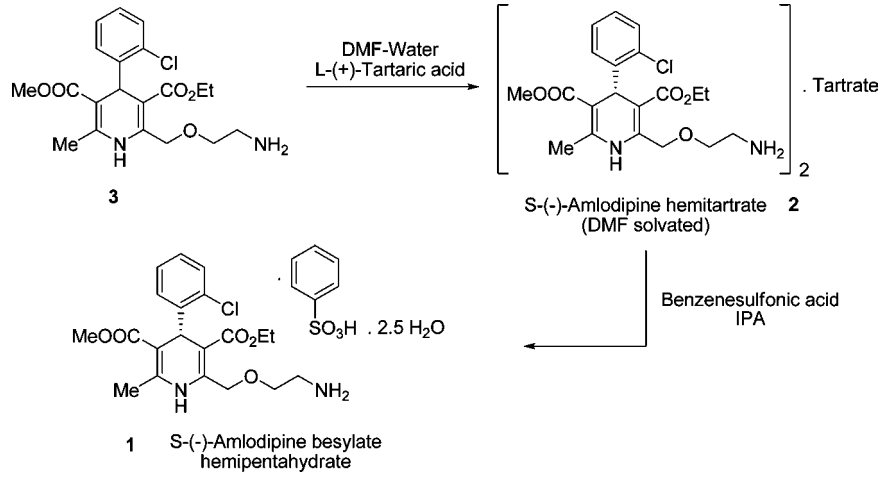
***Figure 1.*** **Single crystal X-ray structure of *S*-(−)-amlodipine besylate hemipentahydrate.**

***Table 3.*** **Effect of L-(+)-tartaric acid and solvent dilution on resolution of (*R,S*)-amlodipine (3)**

| entry | solvent[a] DMF/water | molar ratio (equiv) | yield (%)[b] | enantiomeric excess (%)[c] | resolution efficiency[d] |
|---|---|---|---|---|---|
| 1 | 4.25/0.75 (5 vol, 15%) | 0.25 | 89.70 | 69.54 | 0.62 |
| 2 | 5.95/1.05 (7 vol, 15%) | 0.25 | 78.67 | 77.46 | 0.60 |
| 3 | 7.65/1.35 (9 vol, 15%) | 0.25 | 80.88 | 79.76 | 0.64 |
| 5 | 8.5/1.5 (10 vol, 15%) | 1.0 | 200[e] | 00 | 00 |
| 6 | 8.5/1.5 (10 vol, 15%) | 0.5 | 200[e] | 00 | 00 |
| 7 | 8.5/1.5 (10 vol, 15%) | 0.3 | 98.01 | 54.5 | 0.53 |

[a] Reactions were carried out on 50 mmol scale using L-(+)-tartaric acid for 4.0 h at 25 °C wrt **3**. [b] Yield is based on a half amount of racemate mono DMF solvate. [c] By chiral HPLC. [d] Resolution efficiency = yield × ee. [e] (*R,S*)-Amlodipine tartarate isolated in quantitative yield.

***Scheme 1***




## Conclusion

The work reported in this communication has significance as it discloses how a systematic screening of solvents to study solubilities of *R*- and *S*-forms of amlodipine tartrate can result in an economically viable process. The L-tartrate salt of amlodipine in DMSO crystallized the unwanted *R*-isomer while the same salt in DMF provided the required *S*-form of amlodipine.

## Experimental Section

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. Melting points were determined by open air capillary with an X-6 melting point apparatus, Beijing Tech Instrument Co. Ltd., and are uncorrected. $^1$H NMR spectra and $^{13}$C NMR spectra (100 MHz) were recorded on a Varian 400 MR spectrometer in $CDCl_3$ and DMSO-$d_6$, and mass spectra were determined on an API-2000LCMS mass spectrometer, Applied Biosciences. The HPLC system was Ultron Es-OVM (4.6 mm × 250 mm) 10 $\mu$, 1.0 mL/min, 237 nm; mobile phase, Buffer: acetonitrile (78:22), buffer 0.9 g of disodiumhydrogen orthophosphate and 0.72 g of potassium dihydrogen orthophosphate, the pH adjusted to 7.0 with either of the salts used.

**Preparation of *S*-(−)-Amlodipine Hemitartrate DMF Solvate (2).** A mixture of DMF (425 L) and purified water (75 L) were prepared. From this solution 50 L was removed, and to it was added L-tartaric acid (4.6 kg, 30.7 mol); the mixture was stirred to form a homogeneous solution and was filtered. Separately, a solution of racemic amlodipine base (50.0 kg, 122.3 mol) in (450 L) followed by filtration was prepared. To the solution of racemic amlodipine was added the tartaric acid solution over a period of 1 h. At this point, seeding with pure *S*-amlodipine-L-tartrate DMF solvate (0.3 g) was carried out. The reaction mass was further stirred at RT for 4 h, filtered, and washed with cold acetone (25 L). The residue was dried to give *S*-amlodipine-L-tartrate as a DMF solvate (24 kg, 70.6%), off-white solid, mp: 135−138 °C, MS (CI): Calcd for $C_{40}H_{50}Cl_2N_4 \cdot C_4H_6O_6 \cdot C_3H_7NO$ (M + H)/*z*: 409.9. Found: (M + H)/*z*: 409.9; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.15 (t, 3 H), 2.31 (s, 3 H), 2.28 (s, 3 H), 3.0 (s, 3 H), 3.28 (m, 2 H), 3.57 (s, 3 H), 3.77 (m, 2 H), 4.02 (m, 2 H), 4.36 (s, 1 H), 4.72 (qq, 2 H), 5.40 (s, 1 H), 7.04−7.41 (m, 4 H), 8.01 (s, 1 H); Anal. for $C_{20}H_{25}ClN_2O_5 \cdot 1/2C_4H_6O_6 \cdot C_3H_7NO$. Calcd: C, 53.90; H, 6.33; N, 7.54. Found: C, 53.81; H, 6.29; N, 7.5. Optical purity by chiral HPLC (Ultron Es-OVM (4.6 mm × 250 mm) 10 $\mu$, 1.0 mL/min, 237 nm): 99.37%. $[\alpha]^{25}_D = -15.15°$ (1% in methanol).

**Preparation of *S*-(−)-Amlodipine Besylate Hemipentahydrate (1).** A suspension of *S*-amlodipine-L-tartrate DMF solvate **2** (24 kg, 43 mol) in isopropanol (24 L) and purified water (144 L) at RT was stirred for 15 min, and then benzene sulphonic acid (7.8 kg, 49 mol) dissolved in purified water (24 L) was added over a period of 30 min. After stirring for 40−45 min at RT, the solid was filtered, washed with water, and air-dried for 6−8 h to give *S*-amlodipine-besylate as a hemipentahydrate (1) (24 kg, 91%). *Note: S-(−)-amlodipine besylate hemipentahydrate is unstable under elevated temperature and becomes a dark-yellow to greenish solid*; off-white to pale-yellow solid, mp: 60−63 °C; MS (CI): Calcd for $C_{20}H_{25}ClN_2O_5 \cdot C_6H_5SO_3H \cdot 2.5H_2O$ as a free base (M + H)/*z*: 409.9, Found: (M + H)/*z*: 409.9, $^1$H NMR (400 MHz,

$CDCl_3$): $\delta$ 1.2 (t, 3 H), 2.1 (s, 3 H), 3.1 (s, 1 H), 3.5 (s, 3 H), 3.5 (3 H), 3.6 (t, 2 H), 4.0 (m, 2 H), 4.6 (q, 3 H), 5.3 (s, 1 H), 6.9−8.0 (m, 9 H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 12, 20, 36, 40, 51, 60, 67, 68, 102, 103, 124−132, 143, 145.2, 145.4, 146, 167, 168; Anal. for $C_{20}H_{25}ClN_2O_5 \cdot C_6H_5SO_3H \cdot 2.5H_2O$ Calcd: C, 51.02; H, 6.03; N, 4.6; S, 5.23. Found: C, 51.41; H, 6.00; N, 4.55; S, 5.16%. Optical purity by HPLC (Ultron Es-OVM (4.6 mm × 250 mm) 10 $\mu$, 1.0 mL/min, 237 nm): 99.77%; $[\alpha]^{25}_D = -26.54°$ (1% in methanol).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## Supporting Information Available

Additional characterization data of compounds **2** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.


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