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Exploring Chiral Separation Techniques For Amlodipine Enantiomers: A Review On Diverse Isolation Methods And HPLC Validation

Mr. Prashant Singh[1]Dr. Prashant Kamble[2]

1Ph.D. Scholar, Dept. of Chemistry, Patkar-Varde College, Mumbai.

2Research Guide & Asst. Prof., Dept. of Chemistry, Patkar-Varde College, Mumbai.

Abstract

Amlodipine, one of the most prescribed medications that act as calcium channel blockers, is found to exist as a racemic mixture. The (S)-enantiomer is clinically more beneficial when compared to its (R)- counterpart, warranting the chiral resolution of amlodipine enantiomers to enhance drug safety and efficacy. This review covers the latest developments in the synthesis of amlodipine derivatives, their chiral resolution by o,o-di-p-toluoyl-D-tartrate resolving agent, and the subsequent method development and validation by high-performance liquid chromatography (HPLC). The efficiency of enantioseparation by different methods, such as diastereomeric salt formation, capillary electrochromatography, and solid-phase extraction by bonded ionic liquids, is considered. Also discussed is the ICH-guided HPLC method validation for precise determination of the degree of enantiomeric excess. This review discusses the limited developments in chiral resolution methods that integrate automation and AI in the development of the chromatographic methods for pharmaceutical analysis to improve accuracy and sustainability.

Keywords : Amlodipine derivatives,Chiral separation,Enantioseparation,Diasteromeric

salt formation o,o-di-p-toluoyl-D-tartrate, HPLC validation, Pharmaceutical

Pharmaceutical analysis, Quality by Design (QbD).

Introduction

Chirality is super important in the world of pharmaceuticals because the different enantiomers of a chiral drug can show very different pharmacokinetic and pharmacodynamic behaviors. Take amlodipine, for example—it's a dihydropyridine calcium channel blocker that's commonly used to treat hypertension and angina. It comes as a racemic mixture, where the (S)-enantiomer is the one that actually helps lower blood

pressure, while the (R)-enantiomer doesn't have much pharmacological activity [1,2]. Regulatory bodies like the U.S. FDA and the European Medicines Agency (EMA) really stress the need for enantiomeric purity in chiral drugs, which is why enantioseparation is such a vital part of drug formulation [3].

The most effective way of enantiomer resolution of amlodipine is through diastereomeric salt formation, whereby a chiral resolving agent like O,O(-di-p-toluoyl-D-tartrate) forms individual crystalline salts with enantiomers and can be easily separated [4,5]. A number of studies have shown this method to deliver high enantiomeric purity (>99%) with good reproducibility [6]. Furthermore, HPLC-based enantioseparation methods like reversed-phase HPLC (RP-HPLC), stability-indicating HPLC, and capillary electrochromatography (CEC) are fast-developing highly dependable methods for quantitative enantioselective analysis [7,8].

This review discusses recent advancements in :

Synthesis of amlodipine derivatives

- Chiral resolution using O,O-di-p-toluoyl-D-tartrate
- Analytical method development and validation using HPLC
- Alternative enantioseparation technique.

Discussion

1. In the article "Development of a Quantitative Method for the Assessment of (S)- Amlodipine Di-P-Toluoyl-D-Tartaric Acid" [1], the researchers concentrated on working on a quantitative method for determination of the chiral purity of (S)-amlodipine by means of O,O-di-p- toluoyl-D-tartrate) as the resolving agent. The research had the objective of enhancing enantioselective resolution efficiency by optimizing diastereomeric salt formation conditions.Chiral resolution: The research proved that O,O-di-p-toluoyl-D-tartrate effectively separates (S)-amlodipine with an enantiomeric excess of more than 99%.A validated RP-HPLC method was established, following ICH guidelines for specificity, accuracy, androbustness.Industrial application: The research proved the applicability of the method forpharmaceutical quality control and bulk drug analysis.
2. In the article "A Novel Method for Resolution of Amlodipine" [2], the authors oriented towards the formation of an industrially scalable resolution process for amlodipine enantiomers. The research explored reaction kinetics, solvent performance, and crystallization properties in a systematic way.The process was tuned for industrial large-scale applications, with high efficiency and cost-effectiveness ensured.The optimized resolution conditions resulted in high enantiomeric purity and enhanced process yield, reducing solvent consumption and waste generation.The research showed uniform reproducibility across multiple batches, making it suitable for pharmaceutical production.
3. In the paper titled "Separation of Amlodipine Enantiomers by Diastereomeric Salt Formation" [3], the authors explored how O,O(-di-p-toluoyl-D-tartrate) can be used to separate amlodipine enantiomers. They took a close look at how factors like pH, the mix of solvents, and the time spent crystallizing affect the efficiency of the separation process.The research pinpointed the perfect solvent-to-solute ratio for selective crystallization, resulting in impressive enantiomeric purity.They employed techniques like X-ray diffraction (XRD) and differential scanning calorimetry (DSC) to

verify both the enantiomeric purity and the stability of the crystals.The study underscored how cost-effective and reproducible this method is for large-scale use in the pharmaceutical industry.

4. In the article "Direct Chiral Separation and Quantitative Determination of S- Amlodipine by RP-HPLC-PDA Method" [4], the authors synthesized an RP-HPLC-PDA method for the direct enantioseparation of amlodipine.The method employed a Lux-2 chiral column with acetonitrile-triethylamine-acetic acid, obtaining very good enantiomeric separation.The (S)- and (R)-enantiomers were resolved within 7 minutes, lowering analysis time for day-to-day applications.The procedure was in accordance with ICH guidelines for linearity, specificity, and robustness, and hence suited for pharmaceutical quality control.
5. In the article titled "Chiral Analysis of Amlodipine by HPLC Method" [5], the authors came up with a stability-indicating HPLC technique to investigate degradation routes of amlodipine enantiomers. The research explored acidic, basic, oxidative, and photolytic stress conditions on amlodipine enantiomers.The procedure conformed to ICH standards for robustness, repeatability, and specificity, proving useful for pharmaceutical stability testing.
6. In the article titled "RP-HPLC Method Development and Validation for Simultaneous Estimation of Amlodipine, Telmisartan, and Rosuvastatin" [6], the authors constructed an RP-HPLC technique for multi-drug quantitation.The technique effectively quantified amlodipine with telmisartan and rosuvastatin, demonstrating high specificity and reproducibility.The technique proved high stability in case of slight variations in experimental conditions, which makes it appropriate for pharmaceutical formulations.
7. In the paper titled "QbD Based RP-HPLC Method Development and Validation" [7], the authors utilized a Quality by Design (QbD) approach to validate their RP-HPLC method.By applying QbD, they were able to fine-tune the mobile phase composition, column temperature, and flow rate, which significantly improved both resolution and accuracy.The method successfully fulfilled all the ICH validation criteria.
8. Gao et al. (2022) studied the application of capillary electrochromatography (CEC) for amlodipine enantioseparation with reference to traditional HPLC approaches. The findings demonstrated that CEC offered better selectivity and shorter analysis time and thus was an better and efficient alternative to RP-HPLC. This study highlights the possibility of CEC as a next-generation enantioseparation method, especially in instances involving high.
9. Liu et al. (2020) investigated solid-phase extraction (SPE) with immobilized ionic liquids for enantioseparation of amlodipine. The work proved that SPE based on ionic liquid enhances enantioselectivity and decreases solvent waste, hence an environmentally friendly alternative to conventional separation techniques. The results indicate that future studies should aim at establishing ionic liquid-based methods for commercial-scale pharmaceutical applications, promoting enantiomeric drug manufacturing sustainability.
10. Attimarad et al. (2020) targeted HPLC method validation for quantification of amlodipine and celecoxib, with high specificity and high robustness in pharmaceutical analysis.The outcome affirmed that the method proved is accurate, precise, and appropriate for regular drug testing, hence an important resource in the pharmaceutical quality control laboratories.
11. Tomikj et al. (2024) established a green HPLC method for the simultaneous determination of atorvastatin and amlodipine, focusing on sustainability and lesser solvent consumption. This study

emphasizes the significance of environmentally friendly analytical pharmaceutical science techniques, in accordance with green chemistry principles.

12. Zhou et al. (2021) investigated the application of sulfobutylether-β-cyclodextrin-based capillary electrochromatography (CEC) for enantioseparation, with great selectivity and efficiency. The research indicates that CEC possesses great potential as a high-resolution separation method, especially for intricate chiral molecules.

Conclusion

1. This research was able to show successfully that O,O(-di-p-toluoyl-D-tartrate) is a highly efficient resolving agent for enantio-separation of amlodipine enantiomers. The established RP-HPLC method is accurate, precise, and rugged and can be used in routine pharmaceutical quality control. Future studies should aim to construct other green resolving agents to eliminate environmental footprint while ensuring high enantioselectivity. Further improvement in yield and efficiency can be obtained by exploring automated crystallization methods.
2. This study reaffirmed that diastereomeric salt formation is a scalable and reproducible technique for resolving amlodipine enantiomers in large-scale pharmaceutical manufacturing. The research proved that maximized crystallization conditions improve enantioselective efficiency, lowering processing time and cost. Future research should aim at incorporating real-time process monitoring and automation to also improve industrial usability and reduce material loss.
3. This research supported the efficacy of diastereomeric salt formation with O,O(-di-ptoluoyl-D-tartrate) in achieving high-purity (S)-amlodipine (>99%). The findings yielded unequivocal proof that solvent composition, pH, and temperature control are important in enantiomeric separation optimization. Future studies should investigate solvent-free chiral separation methods to come up with more eco-friendly solution approaches.
4. This study was able to construct an extremely sensitive and validated RP-HPLC-PDA method for the quantitative determination of (S)-amlodipine, providing rapid, reliable, and precise enantioseparation. The research offered a cost-effective alternative to conventional chiral separation methods, with a brief run time of less than 7 minutes. Future work ought to aim for incorporating nano-LC or UHPLC techniques to be more sensitive and minimize solvent use for enhanced analytical effectiveness.
5. This research illustrated the significance of stability-indicating HPLC techniques in assessing amlodipine enantiomer degradation under stress conditions. The study demonstrated that acidic conditions strongly affect (S)-amlodipine stability, emphasizing the necessity for strict formulation and storage regulations. Future studies must integrate HPLC-MS techniques to identify degradation byproducts more accurately and enhance pharmaceutical stability tests.
6. This research effectively created a multi-drug RP-HPLC system for simultaneous quantification of telmisartan, amlodipine, and rosuvastatin in pharmaceutical formulations. The findings validated high accuracy and specificity, illustrating the method's potential for routine quality control. Future research should explore AI-driven Optimization of HPLC method to improve automated peak detection and analysis for improved efficiency of multi-component drug measurement.
7. This study confirmed that Quality by Design (QbD) improves RP-HPLC method reliability and reproducibility in the estimation of amlodipine besylate and lisinopril dihydrate. Systematic method optimization was emphasized by the study to guarantee minimal variability across various

laboratory conditions. Future studies ought to incorporate machine learning QbD optimization models to further optimize HPLC method development.

8. This research validated that capillary electrochromatography (CEC) is a potential alternative to RP-HPLC for enantioseparation, providing higher selectivity, shorter analysis time, and reduced solvent usage. The results indicate that CEC may be incorporated into high-throughput pharmaceutical analysis for cost-saving and environmentally friendly enantioselective separation. Current and future research must emphasize hyphenated methods such as CEC-MS for improved enantioselective detection and characterization.
9. This study proved that ionic liquid-mediated solid-phase extraction (SPE) is an eco-friendly and highly selective enantioseparation process for racemic amlodipine. The study established that immobilized ionic liquids enhance efficiency and reusability, minimizing solvent loss. Future work will involve ionic liquid-based extraction for industrial-scale pharmaceutical use and exploration of new chiral ionic liquids with increased enantioselectivity.
10. This study created and validated a high-performance liquid chromatography (HPLC) method that can simultaneously measure amlodipine and celecoxib, boasting impressive specificity, precision, and reliability. The results suggest that this method is ideal for use in pharmaceutical quality control labs. Looking ahead, future research should delve into HPLC-MS applications for structural characterization and consider automated data processing to enhance high-throughput analysis.
11. This research introduced a sustainable and eco-friendly HPLC method that allows for the simultaneous determination of amlodipine and atorvastatin. The focus was on cutting down solvent use while still delivering top-notch analytical performance. The findings lay a solid foundation for green analytical chemistry practices in the realm of pharmaceutical analysis. Looking ahead, future efforts should concentrate on broadening the use of green solvents and energy-efficient chromatographic techniques in pharmaceutical quality control.
12. This study delved into capillary electrochromatography with sulfobutylether-β-cyclodextrin for enantioseparation, showcasing impressive resolution and better selectivity. The findings indicate that CEC might be a viable alternative for handling complex chiral pharmaceutical compounds. Looking ahead, future research should aim to automate CEC systems and combine them with mass spectrometry (CEC-MS) to boost analytical capabilities.

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