SYNTHESIS OF DESGLYMIDODRINE FROM MIDODRINE BY CONVENTIONAL AMIDE HYDROLYSIS METHOD

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ABSTRACT

Objective: The term prodrug involves chemically modifying inert compound which upon administration releases the active parent drug to elicit its pharmacological response within the body. Acting as a α-adrenergic agonist, desglymidodrine an active metabolite of amide prodrug midodrine is used for the treatment of essential and orthostatic hypotension. In the present study synthesis of desglymidodrine from midodrine was reported.

Methods: The synthesis was done by the conventional amide hydrolysis method.

Results: A novel synthesis of desglymidodrine was successfully achieved and spectrally elucidated by infrared spectroscopy (IR), ¹H, ¹³C nuclear magnetic resonance (NMR) and mass analysis.

Conclusion: The acquired results were found to be accurate, the synthetic route appeared to be simple, cost-effective and time efficient. Hence the synthesized desglymidodrine can be as a reference standard for the estimation of the same.

Keywords: Midodrine, Desglymidodrine, Amide hydrolysis.

Midodrine (N-glycyl derivative of Desglymidodrine), consisting of glycine promoiety linking to the amine group, undergoes enzymatic deglycination to give desglymidodrine. Desglymidodrine is α-adrenergic receptor agonist which increases the vascular tone and causes elevation of blood pressure [1]. Chemically midodrine is 2-amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl] acetamide. It has an empirical formula of C₁₂H₁₈N₂O₄ and a molecular weight of 254.28 g/mol [2].

The literature survey revealed different simultaneous estimation techniques like HPLC [3-6], Spectrometric [7], HPTLC [8] and to the best of our knowledge, plasma estimation in healthy human volunteers by UPLC-MS/MS [9] and ascetic patients using liquid chromatography-tandem mass spectroscopy [10] have been reported earlier. However, despite the significance of these analytical efforts in the simultaneous estimation of both prodrug and its active metabolite no synthetic route has been reported in the literature for the synthesis of desglymidodrine.

Midodrine is a glycaminamide prodrug consisting of a secondary amide linkage between glycine and desglymidodrine. The possible mechanism involves attack of hydroxide anion towards positively charged carbonyl carbon causing localization of the pi bond to carbonyl oxygen. This leads to the formation of a tetrahedral intermediate which eventually generates neutral amine and glycine anion. Here the amide linkage was cleaved by approaching conventional amide hydrolysis method under basic conditions giving desglymidodrine.

The midodrine hydrochloride reference standard was supplied by PAR formulations, Chennai synthetic work was done by procuring analytical grade solvents. TLC was performed to monitor the reaction and to determine the purity of the sample product. The melting point of the synthesized compounds was determined on Shimadzu FT-IR spectrometer using KBr pellet technique and is expressed in °C and are uncorrected. The IR spectrum of compounds was recorded on Shimadzu FT-IR spectrometer using KBr pellet technique and is expressed in cm⁻¹. ¹H-NMR and ¹³C-NMR spectra were recorded on the Agilent (400MHz FT-NMR) using Vnmrj 3.2 V as processing software. Mass spectra were recorded with Shimadzu LC-MS/MS 8030 system using lab solution software. DSC analysis was carried out by DSC Q 200 system.

To a solution of midodrine hydrochloride (3 g, 0.01M) in 1N NaOH solution (200 ml) was refluxed in a water bath for 30 h. The completion of the reaction was monitored by TLC (n-butanol: water, 4.5:0.5 v/v) and LC-MS/MS. White crystals of desglymidodrine were obtained upon the addition of sodium hydroxide (q. s) which was filtered, dried and recrystallized using acetonitrile as solvent (fig. 1).

Fig. 1: Synthesis of desglymidodrine from midodrine
Yield = 96%, White crystalline, m.p: 148-151 °C, IR (KBr) (υ in cm⁻¹) = 3628.22 (OH str), 3350.46 and 3390.97 (NH₂ str), 2992.66 and 2935.76 (Aliphatic CH str), 1279.81 (C-O str), 3121 (Ar C-H str); ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 4.71 (s, 1H, OH), 2.67 (s, 2H, NH₂), 1.73 (s, 3H, OCH₃), 1.60 (s, 3H, OCH₃), 6.69-6.94 (m, 3H, Ar-H) ppm; ¹³C NMR (400 MHz, DMSO-d₆, δ ppm): 39.33, 40.62, 49.02, 56.22, 111.88, 112.1, 113.14, 133.99, 150.18, 153.62 ppm; MS (ESI) m/z (%): 198.05 [M+H]+.

Midodrine hydrochloride was hydrolyzed into desglymidodrine in the presence of basic medium and the IR spectra (fig. 2), of synthesized compound, have shown OH stretching at 3628.22 cm⁻¹, symmetrical and unsymmetrical NH₂ stretching bands at 3350.46 cm⁻¹ and 3390.97 cm⁻¹, aryl aliphatic ether C-O-C stretching at 1279.81 cm⁻¹, aromatic C-H stretching band at 3121 cm⁻¹, aliphatic symmetrical and unsymmetrical stretching at 2992.66 and 2935.76 cm⁻¹. A highly intense molecular ion peak at [M+H]+ m/z 198.05 (fig. 2), signifies the formation of desglymidodrine.

In the ¹H NMR spectrum (fig. 3), singlet signals at δH 4.71 and 2.67 revealed the presence of hydroxyl and amino protons respectively. Two singlets at δH 1.73 and 1.60 represent six methoxyl protons along with multiplet signals at δH 6.6-6.9 for aromatic protons. In ¹³C NMR spectrum (fig. 3) signals at δC 69.19 and 49.02 indicate the presence of carbinolic carbon and carbon attached to an amine respectively. Two methoxy carbons are attributed to signals at δC 55.68 and 56.22. The percentage purity of the synthesized compound was found to be 96.89 %, which was estimated by DSC analysis as shown in fig. 4.

Fig. 2: IR spectra and scan mass spectra of synthesized desglymidodrine

Fig. 3: NMR (¹H) and (¹³C) analytical data for synthesized desglymidodrine

Fig. 4: DSC analysis of synthesized desglymidodrine
Apparently, the present work previews the first reported method for synthesis of desglymidodrine from midodrine using conventional amide hydrolysis method. The formation of desglymidodrine was observed in mass spectrum as a gradual rise in the intensity of the peak at 198.05 m/z with respect to time. The spectral interpretation of synthesized desglymidodrine by IR, $^1$H and $^{13}$C NMR, the mass analysis showed consistency with the assigned structure, whereas the obtained purity by DSC explains the practical applicability of this synthesis method. Despite its applicability as a standard in numerous bio-analytical estimation methods the high cost of desglymidodrine and its availability in synthetic form seems to be a bottleneck for the budding researchers, where the current developed synthetic route appeared to be simple, cost-effective and time efficient.

AUTHORS CONTRIBUTIONS
All the authors have contributed equally to this synthesis work.

CONFLICT OF INTERESTS
All authors have no conflict of interest

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