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Mini-Review: Analytical Procedures for Alogliptin Determination in Biological Fluids and Pharmaceutical Formulations

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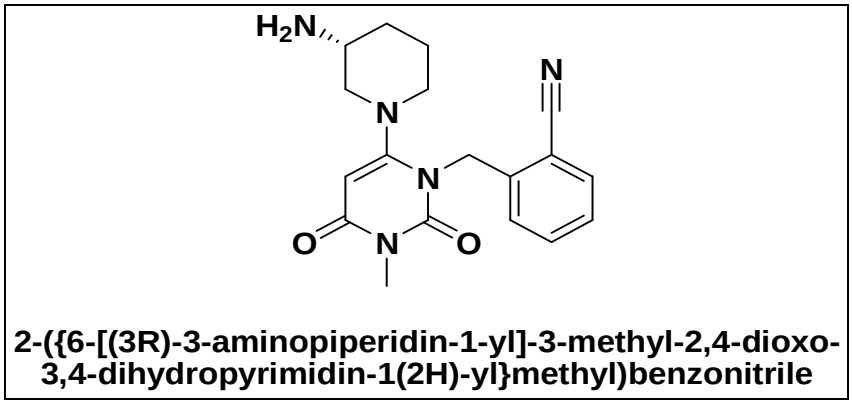
ABSTRACT

Many spectroscopic and chromatographic methods were reported for alogliptin analysis either in biological fluids or in pharmaceutical formulations including spectrophotometry, HPLC-UV, LC-MS/MS and HPTLC methods. This concise mini-review can be used by researchers to select the most suitable analytical procedure for their work according to the previously reported methods and corresponding applications.

INTRODUCTION

Alogliptin (figure 1) is one of the Dipeptidyl peptidase-4 (DPP-4) inhibitors that improve glycemic control in patients with type 2 diabetes mellitus. Its mechanism of action involves rising of the endogenous glucagon like peptide-1 (GLP-1), an incretin hormone, and other hormone levels by inhibiting the degrading enzyme DPP-4. The incretin effect is based on the greater stimulatory effect on insulin secretion than that of intravenous glucose [1]. Alogliptin was marketed as Nesina® tablets while its combination with metformin was marketed as Kazano® tablets and its combination with pioglitazone as Oseni® tablets.

Although some LC-MS/MS methods were reported for estimation of alogliptin in rat plasma [2], dog plasma [2], monkey plasma [2] and human plasma [3], LC-MS/MS parameters and analytical procedure details were not described in full details by the pharmacokinetic studies reported by lee et al [2] and Covington et al [3]. Another two pharmacokinetic studies were described for alogliptin in combination with pioglitazone [4], metformin [5], cimetidine [5] without any details regarding the used analytical procedures. On the other hand, many spectroscopic and chromatographic techniques were reported and described in full details [6-23] for alogliptin analysis either in biological fluids or in pharmaceutical formulations.



2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile

Figure 1: Chemical structure and IUPAC nomenclature of alogliptin

2. Spectroscopic methods for the analysis of alogliptin in pharmaceutical formulations

Some spectrophotometric methods were reported for determination of alogliptin alone in Nesina® tablets [6-7], determination of alogliptin in the presence of metformin in Kazano® tablets [8-9] and simultaneous determination of alogliptin and pioglitazone in Oseni® tablets [10]. Direct UV spectrophotometric method was developed and validated for the estimation of alogliptin benzoate using UV/Vis double beam spectrophotometer. The maximum absorbance was observed at 276 nm using methanol as solvent and linearity range of 5-35 μg mL^{-1} [6]. Also first derivative spectrophotometric method has been developed for the estimation of alogliptin in bulk and pharmaceutical formulations. Alogliptin showed a sharp peak at 278.0 nm in first order derivative spectrum with n =1. The drug followed Beer-Lambert's law in the concentration range of 2-16 μg mL^{-1} [7].

In addition, development and validation of two UV spectrophotometric methods for simultaneous estimation of alogliptin benzoate and metformin hydrochloride was achieved. First method is simultaneous equation method, which is based on the measurement of absorption at 224 nm and 237 nm for both alogliptin and metformin, respectively. Second method is an absorption ratio method, which is based on the measurement of absorption at 251 nm. Both the drugs were found to be linear in the concentration range of 0.5-18 μg mL^{-1} [8].

Furthermore, Two UV spectrophotometric methods have been developed for the simultaneous estimation of alogliptin and metformin. The first method is simultaneous equation method based on measurement of absorption at 277 nm and 232nm of alogliptin and metformin, respectively. The second method is Absorbance ratio (Q-analysis) method based on measurement of absorption at wavelength of 250 nm and 277 nm i.e. iso-absorptive point of alogliptin and metformin, respectively. Linearity was observed in the concentration range of 5-25 μg mL^{-1} for alogliptin and 1-10 μg mL^{-1} for metformin [9].

Moreover, UV spectroscopic methods have been developed for the simultaneous estimation of alogliptin and pioglitazone. First order derivative and Dual wavelength methods were developed and validated using methanol as solvent. Both methods showed linearity at 5-30 μg mL^{-1}. The first order derivative spectra of each solution were obtained. Zero crossing point (ZCP) of alogliptin was found to be 275.60 nm and ZCP of pioglitazone was found to be 268.20 nm. In Dual wavelength method, spectra of two wavelengths (270.20 nm and 265 nm) were selected for the estimation of alogliptin. Pioglitazone showed the same absorbance at these wavelengths. Similarly, wavelengths of 280 nm and 271 nm were selected for estimation of pioglitazone. Alogliptin shows the same absorbance at these wavelengths [10]. There is no published work yet regarding derivatization before UV detection as shown with similar gliptins [24] and there is no need for spiking technique as shown in some methods dealing with metformin analysis in combinations [25].

3. HPLC-UV methods for determination of alogliptin in pharmaceutical formulations

Many HPLC-UV methods [11-23] were reported for determination of alogliptin either alone (Nesina® tablets) or in combination with metformin (Kazano® tablets) or in combination with pioglitazone (Oseni® tablets). All the parameters affecting the chromatographic behavior are described in (table 1) including stationary phase, mobile phase and detection wavelength. Similar columns and similar chromatographic conditions were used for determination of similar gliptin, linagliptin, using LC-UV methods [26-28].

Table 1: HPLC-UV methods for analysis of alogliptin in different pharmaceutical formulations

Stationary Phase	Mobile Phase	Detection Wavelength	Application
Cyano column (150 mm × 4.6 mm, 5 µm)	Mixture of potassium dihydrogen phosphate buffer pH (4.6) and acetonitrile in the ratio of (20:80 %, *v/v*).	215 nm	Assay of Nesina® tablets [11]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture of 0.2 triethylamine buffer (pH 6.0) and methanol in the ratio of (30:70 %, *v/v*).	254 nm	Assay of Kazano® tablets [12]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture of potassium dihydrogen phosphate buffer (pH 4.0) and acetonitrile in the ratio of (70:30 %, *v/v*).	235 nm	Assay of Kazano® tablets [13]
C18 column (250 mm x 4.6 mm, 5µm).	Gradient elution of (0.1% perchloric acid pH 3 - acetonitrile in the ratio of 90:10, *v/v*) and (0.1% perchloric acid pH 3 - acetonitrile in the ratio of 40:60 %, *v/v*).	224 nm	Characterization of process-related impurities of Alogliptin [14]
Cellulose column (250 mm × 4.6 mm, 5 µm)	Mixture of ethanol and diethylamine in the ratio of (100:0.5 %, *v/v*).	230 nm	Method for the enantiomeric purity of alogliptin [15]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture of phosphate buffer and acetonitrile in ratio of (45:55 %, *v/v*).	215 nm	Stability indicating assay of Oseni® tablets [16]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture (pH 6.8) of methanol and double distilled water in the ratio of (80:20 %, *v/v*).	222 nm	Assay of Nesina® tablets [17]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture of phosphate buffer (pH 3.5) and methanol in the ratio of (70:30 %, *v/v*).	271 nm	Assay of Oseni® tablets [18]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture of Phosphate buffer (pH 3.6) and acetonitrile in the ratio of (35:65 %, *v/v*).	268 nm	Assay of Oseni® tablets [19]
Cyano column (250 mm x 4.6 mm, 5µm).	Gradient elution of (water, acetonitrile and trifluoroacetic acid in the ratio of 1900:100:1, *v/v/v*) and (acetonitrile, water and trifluoroacetic acid in the ratio of 1900:100:1, *v/v/v*).	278 nm	Determination of potential impurities in Nesina® tablets [20]
C18 column (150 mm x 4.6 mm, 5µm).	Mixture of potassium dihydrogen phosphate buffer (pH 3), methanol and acetonitrile in the ratio of (20:60:20 %, *v/v/v*).	290 nm	Assay of Kazano® tablets [21]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture of phosphate buffer (pH 4.8) and acetonitrile in the ratio of (48:52 %, *v/v*).	210 nm	Assay of Kazano® tablets [22]
C18 column (250 mm x 4.6 mm, 5µm).	Mixture of methanol and phosphate buffer (pH 3) in the ratio of (80:20 %, *v/v*).	269 nm	Assay of Oseni® tablets [23]

4. HPTLC methods for determination of alogliptin in pharmaceutical formulations

A high performance thin layer chromatographic (HPTLC) method was developed and validated for simultaneous determination of metformin and alogliptin. Chromatographic separation was carried out on Merck HPTLC aluminium sheets of silica gel 60F254 using acetonitrile: 1% ammonium acetate in methanol (4.5:5.5 (v/v)) as mobile phase followed by densitometry analysis at 253 nm. The reliability of the method was assessed by evaluation of linearity (100-2500 ng/spot for metformin and 100-2500 ng/spot for alogliptin) [29].

5. Bioanalytical methods for determination of alogliptin in biological fluids

A liquid chromatography-tandem mass spectrometric method was developed and validated for the evaluation of alogliptin in monkey. The analytes were extracted through a liquid-liquid extraction with ethyl acetate. The linear detection range in monkey plasma was from 0.5 to 2000 ng mL^{-1} with lower limit of quantification of 0.5 ng mL^{-1}. The relative standard deviation was measured to be less than 10.4% for determination of inter- and intra-day precisions, and the relative error was determined to be within ±7.2% for all accuracy measurements. The developed LC-MS/MS method could be used for the pharmacokinetics studies in monkeys [30].

In addition, ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method for determination of alogliptin in rat plasma was developed and validated. After addition of diazepam as an internal standard (IS), protein precipitation by acetonitrile-methanol (9:1, v/v) was used to prepare samples.

Chromatographic separation was achieved on a UPLC BEH C18 column (2.1 × 100 mm, 1.7 μm) with 0.1% formic acid and acetonitrile as the mobile phase with gradient elution. An electrospray ionization source was applied and operated in positive ion mode; multiple reactions monitoring (MRM) mode was used for quantification using target fragment ions m/z 340.2 → 116.0 for alogliptin, and m/z 285.1 → 193.1 for IS. Calibration plots were linear throughout the range 2-2000 ng mL^{-1} for alogliptin in rat plasma. Mean recoveries of alogliptin in rat plasma ranged from 81.5% to 91.4%, matrix effect of alogliptin in rat plasma ranged from 105.9 to 110.5%. RSD of intra-day and inter-day precision were both <10%. The accuracy of the method was between 95.2% and 110.3%. The method was successfully applied to pharmacokinetic study of alogliptin after either oral or intra-venous administration. The absolute bioavailability of alogliptin was reported as high as 30.9% [31].

Furthermore, RP-HPLC method for the quantitative determination of metformin and alogliptin in human plasma was developed. The drug was spiked in the plasma and extracted with mobile phase by precipitation method. The extracted analyte was injected into X-Terra C18 (4.6 × 150 mm, 3.5 μm, Make: ACE) or equivalent, maintained at 25°C temperature and effluent was monitored at 235 nm. The mobile phase was consisted of sodium dihydrogen ortho phosphate [pH 4.0]: acetonitrile [HPLC Grade] (70:30, v/v). The calibration curve for metformin and alogliptin was linear from 300.0 to 700.0 μg mL^{-1} and 7.5 to 17.5 μg mL^{-1}, respectively. The inter-day and intra-day precision was found to be within limits. The Lower limit of quantification (LLOQ) for metformin and alogliptin were 5.936 and 1.983 μg mL^{-1}, respectively. The average % recovery for metformin and alogliptin were 100.17 and 99.40-99.55%, respectively and reproducibility was found to be satisfactory [32].

REFERENCES

[1] A.J. Scheen, *Expert Opin. Pharmacother.*, **2015**, 16, 43-62.
[2] B. Lee, L. Shi, D.B. Kassel, T. Asakawa, K. Takeuchi, R.J. Christopher, *Eur. J. Pharmacol.*, **2008**, 589, 306-314.
[3] P. Covington, R. Christopher, M. Davenport, P. Fleck, Q.A. Mekki, E.R. Wann, A. Karim, *Clin. Ther.*, **2008**, 30, 499-512.
[4] A.J. Scheen, Expert Opin. Drug Metab. Toxicol., **2015**, 11, 1005-1020.
[5] A. Karim, P. Covington, R. Christopher, M. Davenport, P. Fleck, X. Li, E. Wann, Q. Mekki, *Int. J. Clin. Pharmacol. Ther.*, **2010**, 48, 46-58.
[6] P. Supriya, N. Madhavi Latha, K.B.V. Rohith, G.V. Ramana, U. Harini, A.K.M. Pawar, Asian J. Pharm. Clin. Res., **2016**, 9, 264-269.
[7] P.J. Yadav, V.N. Kadam, S.K. Mohite, J. Curr. Pharm. Res., **2014**, 4, 1286-1290.
[8] D.B. Sen, A.K. Sen, A. Zanwar, R. Balaraman, A.K. Seth, *Int. J. Pharm. Pharm. Sci*., **2015**, 7, 380-383.
[9] Chirag, A. Parle, *Der Pharma Chem.*, **2014**, 6, 303-311.
[10] R. Kashyap, U. Srinivasa, *Int. J. Pharm. Pharm. Sci.*, **2014**, 6, 730-738.
[11] R.I. El-Bagary, E.F. Elkady, B.M. Ayoub, *Int. J. Biomed. Sci.*, **2012**, 8, pp. 215-218.
[12] A.P. Kumar, G. Aruna, K. Rajasekar, P.J. Reddy, *Int. Bull. Drug Res.*, **2013**, 3, 58-68.
[13] G.S. Sri, S.A. Kumar, J. Saravanan, M. Debnath, V. Greeshma N.S. Krishna, *World J. Pharm. Pharm. Sci.*, **2013**, 2, 6720-6743.
[14] Y. Zhou, W. Zhou, L. Sun, Q. Zou, P. Wei, P. OuYang, *J. Sep. Sci*., **2014**, 37, 1248–1255.
[15] G.S. Rao, K. Mallesh, G.V. Kumar, C. Surekha, B.V. Rao, *Der Pharma Chem.*, **2014**, 6, 234-239.
[16] B. Neelima, P.R. Kumar, V.H. Bindu, Y.R. Prasad, *Int. J. Pharm.*, **2014**, 4, 458-464.
[17] P.J. Yadav, S.S. Jadhav, S.K. Mohite, *Int. J. Pharm. Pharm. Drug Res.*, **2014**, 1, 1-9.
[18] R. Kashyap, U. Srinivasa, *Int. J. Curr. Res*., **2014**, 6, 10201- 10207.
[19] M. Ahmed, M. Anusha, S.A. Satishkumar, I.J. Kuppast, M.S. Siddalingaswamy, M.C. Ravi, *World J. Pharm. Pharm. Sci.*, **2014**, 4, 863-874.
[20] K. Zhang, P. Ma, W. Jing, X. Zhang, *Asian J. Pharm. Sci*., **2015**, 10, 152-158.
[21] K. Swathi, K. Swathi, M. Chaitanya, *Int. J. Pharm. Res. Health Sci.*, **2015**, 3, 747-753.
[22] C. Runja, P. Ravikumar, S.R. Avanapu, *Int. J. Pharm. Pharm. Sci.*, **2016**, 8, 116-120.
[23] M.M. Mabrouk, S.F. Hammad, F.R. Mansour, M.M. Amer, *Pharm. Sin.*, **2016**, 7, 32-40.
[24] R.I. El-Bagary, E.F. Elkady, B.M. Ayoub, *Int. J. Biomed. Sci.*, **2012**, 8, 204-208.
[25] B.M. Ayoub, *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, **2016,** doi: 10.1016/j.saa.2016.06.010
[26] R.I. El-Bagary, E.F. Elkady, B.M. Ayoub, *Int. J. Biomed. Sci.*, **2012**, 8, 209-214.
[27] R.I. El-Bagary, E.F. Elkady, B.M. Ayoub, *Int. J. Biomed. Sci.*, **2013**, 9, 41-47.
[28] B.M. Ayoub, *RSC Advances*, **2015**, 5, 95703-95709.
[29] K. Sharma, A. Parle, *Pharm. Lett.*, **2015**, 7, 321-328.

[30] J. Deng, J. Guo, R. Dai, G. Zhang, H. Xie, *J. Pharm. Biomed. Anal.*, **2016**, 117, 99-103.
[31] H. Chen, X. Xia, L. Li, W. Jiang, Y. Wang, H. Xia, Z. Wang, Y. Wang, *LAT. AM. J. Pharm.*, **2016**, 35, 233-238.
[32] K.S. Ashutosh, D. Manidipa, R.J.V.L.N. Seshagiri, S.D. Gowri, *J. Chromatogr. Sep. Tech.*, **2015**, 6, 1-6.