SHORT NOTES

SUMMARY OF CHROMATOGRAPHIC ANALYSIS METHODS OF ANTI DIABETIC GLIFLOZINS EMPAGLIFLOZIN, CANAGLIFLOZIN AND DAPAGLIFLOZIN

ABSTRACT

Sodium glucose co-transporter-2 (SGLT-2) inhibitors are relatively new developed effective oral anti-diabetic agents used in treatment of type 2 Diabetes Mellitus. They present either alone or in combination with other ant diabetic agents such as linagliptin, Saxagliptin and metformin. Therefore, the necessity to explore and compare the existing analytical and bioanalytical assays used for determination of such drugs either single or in combination is crucial. Many methods were reported in the literature for the bio-analysis and analysis of three novel gliflozins with applying the method on different dosage forms and different chemical and biological samples. Furthermore, this review offered an overview of different methods used for determination of every drug alone in a tabulated comparative way. Moreover, the present review emphasized the most common stability indicating assays to be of interest to the analysts in the area of drug control.

Keywords: Review; Bioanalytical methods; Analytical methods; Empagliflozin; Dapagliflozin; Canagliflozin; SGLT-2

INTRODUCTION

Around the world, about 382 million patients are suffering from diabetes mellitus[1]. Global burden of disease study in 2010 shows that morbidity rate related to diabetes mellitus is doubled just in years from 1990 to 2010, also an increase with 30% in DALYs (disability adjusted life years)[2-4]. Other studies shows that diabetes mellitus patients will reach almost 600 million by the year of 2035[1]. These forecasts seems to be unobtrusive especially with an estimated nearly 300 million people having impaired glucose tolerance[5]. Global burden of diabetes mellitus is much higher in developing countries than the developed ones. About 80% of persons with diabetes mellitus are living currently in communities with low- to middle-income. Middle East and Asia are considered the regions which are hardest-hit.[1].

Dapagliflozin (DG), empagliflozin (EG), and canagliflozin (CG) (Fig.1) are phlorizin derivatives, approved by FDA for use in people with type 2 diabetes that inhibits sodium-glucose co-transporter-2 (SGLT2) and thereby reduces renal tubular glucose reabsorption and hence blood glucose concentrations by promoting urinary glucose excretion.

Table I: Chromatographic methods for analysis of empagliflozin either in bulk, dosage form or biological fluids

Stationary phase	Mobile phase	Application	Detection
C_{18} column	Phosphate buffer (pH 3): methanol, (30:70 V/V)	Tablet	UV 240 nm[14]
C_{18} column	Deionized water and acetonitrile in the ratio of (10:90, V/V)	Human plasma	MS/MS[15]
C_{18} column	Acetonitrile - water (75: 25, V/V)	Tablet impurities	MS/MS[16]
C_{18} column	Phosphate buffer (pH 4.8), acetonitrile, methanol (15:80:5, V/V/V)	Tablet	UV 227 nm[17]
C_{18} column	0.1% Formic acid: acetonitrile, (50:50, V/V)	Human plasma	MS/MS[18]
C_8 column	0.1 OPA: Acetonitrile, (70:30, V/V)	Tablet	UV 233 nm[19]

C_{18} column	Potassium dihydrogen phosphate buffer pH (4)-methanol (50 : 50, V/V)	Tablet	UV 225 nm [20]
C_{18} column	0.1% Aqueous formic acid: acetonitrile, 75:25, V/V	Tablet	MS/MS [21]

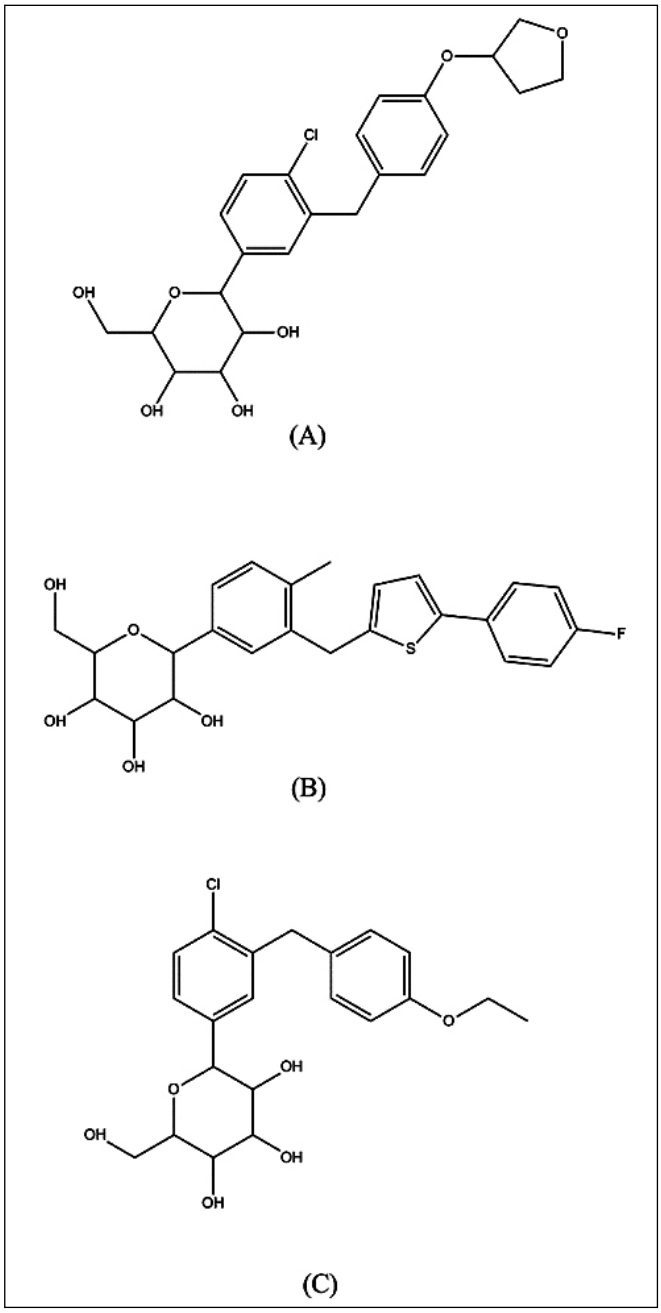

Fig. 1: Chemical structures of empagliflozin (A), canagliflozin (B) and dapagliflozin (C)

Table II: Chromatographic methods for analysis of dapagliflozin either in bulk, dosage form or biological fluids

Stationary phase	Mobile phase	Application	Detection
C_{18} column	Acetonitrile : Ortho phosphoric acid the (55:45, V/V)	Bulk	UV at 203 nm[22]
C_{18} column	Ortho phosphoric acid : acetonitrile (pH 4.5) (45:55 V/V)	Bulk	UV at 245 nm[23]
C_{18} column	Phosphate Buffer: methanol: acetonitrile (pH 6.5) (50:30:20 V/V/V)	Tablet	UV at 240 nm [24]
C_{18} column	Triethylamine: acetonitrile pH (6.8) (50:50, V/V)	Tablet	UV at 240 nm[25]
C_{18} column	Acetonitrile: di-potassium hydrogen phosphate (pH 6.5) (40:60 V/V)	Tablet	UV at 222 nm[26]
C_{18} column	Water: acetonitrile (60/40 V/V).	Rat plasma	MS/MS[27]

Table III: Chromatographic methods for analysis of canagliflozin either in bulk, dosage form or biological fluids

Stationary phase	Mobile phase	Appli-cation	Detection
C_{18} column	Ammonium acetate: acetonitrile (pH 3.5) (65:35, V/V)	Tablet	UV at 254 nm [28]
C_{18} column	Phosphate buffer : acetonitrile (pH 4.5) (65:35, V/V)	Tablet	UV at 248 nm[29]
C_{18} column	Phosphate buffer : acetonitrile (pH 4.5) (53:47, V/V)	Tablet	UV at 240 nm [30]

C_{18} column	Phosphate buffer : Acetonitrile : methanol (pH 4.5) (40:40:20, V/V)	Tablet	UV at 212 nm [31]
C_{18} column	20 mM Potassium dihydrogen orthophosphate : acetonitrile (pH 3.2) (45 : 55, V/V)	Human Plasma	Fluorescence detection at 280 and 325 nm (excitation and emission)[32]
C_8 column	36.46 mM Acetate buffer : acetonitrile : methanol(pH 4.5) (30:50:20, V/V)	Human Plasma	UV at 290 nm [33]
C_{18} column	0.05% V/V Triethylamine : Acetonitrile (pH 6.5) (45:55, V/V)	Tablet	UV at 215 nm [34]
C_{18} column	Acetonitrile : Ammonium acetate buffer (pH 4.5) (45:55, V/V)	Tablet	UV at 252 nm [35]
C_{18} column	Acetonitrile: water (80:20, V/V)	Rat plasma	MS/MS [36]
C_{18} column	Acetonitrile: 0.1% formic acid (90:10,V/V)	Rat plasma	MS/MS [37]

REFERENCES

1. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. **Lancet Diabetes & endocrinology.** 2014;2(1):56-64.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. **Lancet.** 2013;380(9859):2095-128.
3. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. **Lancet**. 2013;380(9859):2197-223.
4. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. **Lancet.** 2013;380(9859):2163-96.
5. Alberti KGM, Zimmet P. Epidemiology: Global burden of disease—where does diabetes mellitus fit in? **Nature Rev. Endocrinol.** 2013;9(5):258-60.
6. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. **Lancet.** 2017.
7. Association AD. Diagnosis and classification of diabetes mellitus. **Diabetes Care**. 2004;27(suppl 1):s5-s10.
8. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. **Lancet.** 2014;383(9922):1084-94.
9. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. **Lancet.** 2014;383(9922):1068-83.
10. Ehrenkranz JR, Lewis NG, Ronald Kahn C, Roth J. Phlorizin: a review. **Diabetes/metabolism Res. Rev.** 2005; 21(1):31-8.
11. Wilding JP, Rajeev SP, DeFronzo RA. Positioning SGLT2 inhibitors/incretin-based therapies in the treatment algorithm. **Diabetes Care.** 2016;39(Supplement 2):S154-S64.
12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. **New England J. Med.**. 2015;373(22):2117-28.
13. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. **New England J. Med.** 2017.
14. Madana Gopal N, Sridhar, C. A validated stability indicating ultra-performance liquid chromatographic method for simultaneous determination of metformin hydrochloride and empagliflozin in bulk drug and tablet dosage form. **Int. J. Appl. Pharm.** 2017;9(3):45.
15. Ayoub BM, Mowaka S, Elzanfaly ES, Ashoush N, Elmazar MM, Mousa SA. Pharmacokinetic Evaluation of Empagliflozin in Healthy Egyptian Volunteers Using LC-MS/MS and Comparison with Other Ethnic Populations. **Scientific Reports.** 2017;7.
16. Hao Z, MENG F-h, Lei S, QIAO S-y, ZHANG G-g. Related substances in empagliflozin determined by LC-MS/MS. J. **Int. Pharma. Res.** 2016:753-6.
17. Geetha Swarupa P, Lakshmana Rao, K., Prasad, K.R.S., Suresh Babu, K. Development and validation of stability indicating reversed phase high-pressure liquid chromatography method for simultaneous estimation of metformin and empagliflozin in bulk and tablet dosage form **Asian J. Pharm. Clin. Res.** 2016;9:126.
18. Ayoub BM. Enhancement of plasma extraction recovery of empagliflozin and metformin combination using liquid-liquid extraction and vacuum evaporation techniques. **Der Pharma Chemica**. 2016;8(10):163.
19. Shyamala KN, Mounika J, Nandini B. Validated stability-indicating RP-HPLC method for determination of Empagliflozin. **Der Pharmacia Lettre**. 2016;8(2):457-64.

20. Ayoub BM. UPLC simultaneous determination of empagliflozin, linagliptin and metformin. **RSC Advances.** 2015;5(116):95703-9.
21. Ayoub BM, Mowaka S. LC–MS/MS Determination of Empagliflozin and Metformin. **J. Chromatogr. Sci.** 2017: 1-6.
22. Manasa S, Dhanalakshmi K, Nagarjuna Reddy G, Sreenivasa S. Method Development and Validation of Dapagliflozin in API by RP-HPLC and UV-Spectroscopy. **Int. J. Pharm. Sci. Drug Res.** 2014;6(3):250-2.
23. Sarkar S, Patel VP. Method Development and Validation of Dapagliflozin Drug in Bulk and Tablet Dosage form by RP-HPLC. **Int. J. Pharma. Res. Health Sci.** 2017;5(4):1755-59.
24. Sabbagh B, BVS L, Akouwah G. Validated RP-HPLC and UV-Spectroscopy Methods for the Estimation of Dapagliflozin in Bulk and In Tablets. 2017.
25. Yunoos M, Sankar D. A validated stability indicating high-performance liquid chromatographic method for simultaneous determination of metformin HCl and dapagliflozin in bulk drug and tablet dosage form. **Asian J Pharm Clin Res.** 2015;8:320-6.
26. Patel C, Verma MV, Patel M. Simultaneous Estimation of Dapagliflozin in API and Pharmaceutical Dosage Form by Development and Stability Indicating HPLC Method. 2017.
27. Aubry A-F, Gu H, Magnier R, Morgan L, Xu X, Tirmenstein M, et al. Validated LC–MS/MS methods for the determination of dapagliflozin, a sodium-glucose co-transporter 2 inhibitor in normal and ZDF rat plasma. 2010.
28. Panigrahy UP, Reddy ASK. A novel validated RP-HPLC-DAD method for the simultaneous estimation of Metformin Hydrochloride and Canagliflozin in bulk and pharmaceutical tablet dosage form with forced degradation studies. **Oriental J. Chem.,** 2015;31(3):1489-507.
29. Gaware D, Patil R, Harole M. A validated stability indicating RP-HPLC method for simultaneous determination of metformin and canagliflozin in pharmaceutical formulation. **world J. pharm. pharma. Sci.** 2015;4(12):631-40.
30. Suneetha DS. A Validated Stability Indicating RP-HPLC Method for Estimation of Canagliflozin in Dosage Form. **Res J Pharm. Biol Chem Sci.** 2015;6(5):1186-94.
31. Reddy NP, Chevela NT. RP-HPLC Method development and validation for the Simultaneous Estimation of Metformin and Canagliflozin in Tablet Dosage Form. **Int. J. Pharm Sci**. 2015;5(4):1155-9.
32. Iqbal M, Khalil NY, Alanazi AM, Al-Rashood KA. A simple and sensitive high performance liquid chromatography assay with a fluorescence detector for determination of canagliflozin in human plasma. Analytical Methods. 2015; 7(7):3028-35.
33. Dudhe P, Kamble M. RP-HPLC Method Development and Validation forthe Determination of Canagliflozin in Human Plasma.
34. Aditya Trivedi ND, d. N. Jhade. Modified quantification through high-performance liquid chromatography analysis for canagliflozin and metformin hydrochloride in bulk and tablets using ecofriendly green solvents. **Int. J. appl. pharm.** 2017;9(5):97.
35. D'souza S, Krishna M, Sushmitha GS, Vasantharaju S. Stability indicating assay method development and validation to simultaneously estimate metformin hydrochloride and canagliflozin by RP-HPLC. **Curr. Trends in Biotechnol. Pharm.** 2016;10(4):334-42.
36. Iqbal M, Ezzeldin E, Al-Rashood KA, Asiri YA, Rezk NL. Rapid determination of canagliflozin in rat plasma by UHPLC–MS/MS using negative ionization mode to avoid adduct-ions formation. **Talanta.** 2015;132:29-36.
37. Kobuchi S, Yano K, Ito Y, Sakaeda T. A validated LC-MS/MS method for the determination of canagliflozin, a sodium–glucose co-transporter 2 (SGLT-2) inhibitor, in a lower volume of rat plasma: application to pharmacokinetic studies in rats. **Biomed. Chromatogr.** 2016;30(10):1549-55.

Zaghary W. A.[a], Mowaka S.[b,c,d], and Hendy M. S.[b,d]

[a] **Pharmaceutical Chemistry Department, Faculty of Pharmacy, Helwan University, Ein Helwan, Cairo 11795, Egypt.**
[b] **Pharmaceutical Chemistry Department, Faculty of Pharmacy, The British University in Egypt, El-Sherouk city, Cairo 11837, Egypt.**
[c] **Analytical Chemistry Department, Faculty of Pharmacy, Helwan University, Ein Helwan, Cairo 11795, Egypt.**
[d] **The Center for Drug Research and Development (CDRD), Faculty of Pharmacy, The British University in Egypt, El-Sherouk city, Cairo 11837, Egypt.**

***For Correspondence :E-mail: moataz.sobhy@gmail.com**

(Received 01 July 2018) (Accepted 26 November 2018)

https://doi.org/10.53879/id.56.07.11477