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A REVIEW ON ESTIMATION OF DAPAGLIFLOZIN AND METFORMIN HCL IN BULK AND IN PHARMACEUTICAL DOSAGE FORM

Priyanka R. Varade*[1], Dr. N. S. Dighe[1], Prof. G. S. Shinde[1] and Sachin K. Nawathe[2]

[1]Pravara Rural College of Pharmacy, Pravaranagar, Tal-Rahata, Dist-Ahmednagar Department of Pharmaceutical Chemistry.

[2]S. N. D. College of Pharmacy, Babhulgaon Tal-Yeola, Dist-Nashik Department of Pharmaceutical Chemistry.

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***Corresponding Author**
Dr. Priyanka R. Varade
Pravara Rural College of Pharmacy, Pravaranagar, Tal-Rahata, Dist-Ahmednagar Department of Pharmaceutical Chemistry.

ABSTRACT

Diabetes mellitus is a chronic, progressive, incompletely understood metabolic condition chiefly characterize by hyperglycemia. Dapagliflozin is a sodium-glucose co transporter 2 inhibitors (SGLT2) as a new class of oral antidiabetic drugs. It is indicated for treatment of Diabetes mellitus type 2, either alone or in combination with Metformin hydrochloride. The aim of this review is to focus on update of determination of Dapagliflozin and Metformin hydrochloride in bulk and in pharmaceutical preparation using RP-HPLC and UV spectrophotometric method. This review provides detailed information on separation for Dapagliflozin alone and in combination with Metformin hydrochloride.

KEYWORD: Dapagliflozin, Metformin hydrochloride, RP-HPLC, UV- Spectroscopy.

INTRODUCTION

Dapagliflozin increases urinary glucose excretion by selectively inhibiting renal sodium-glucose transporter 2 (SGLT2), an insulin independent mechanism of action that may be complementary to that of other oral antidiabetes drugs.[24] The chemical name of dapagliflozin is (2S,3R,4R,5S,6R)-2-[-4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol, molecular formula $C_{21}H_{25}CLO_6$ with molecular weight 408.875 g/mol.[2] Dapagliflozin (INN) is a white to off-white powder, non-hygroscopic and soluble in many polar organic solvents eg. DMSO, water, ethanol.

Dapagliflozin is a chiral molecule with five stereogenic centres. Only one polymorphic form has been observed.[4]

Metformin hydrochloride (metformin), a biaguanide reduces HbAlc, FPG and PPG concentrations in type 2 diabetes patients and getting better glycaemic control by decreasing hepatic glucosecreation, reducing intestinal absorption of glucose, and recovering insulin sensitivity and productivity by improving peripheral glucose uptake and utilisation.[6] The chemical name of metformin hydrochloride (metformin HCL) is 1,1-Diamethylbiaguanidehyrochloride, molecular formula $C_4H_{11}N_5$.HCL with molecular weight 165.63 g/mol. Metformin soluble in water, methanol, practically insoluble in acetone, ether, and chloroform.

A new combination dosage form of Metformin and Dapagliflozin is indicated for the treatment and management of diabetes. Combination of Dapagliflozin and Metformin is marketed as a Tablet (XIGDUEO XR) containing 5mg/500mg, 5mg/1000mg, 10mg/500mg, 10mg/1000m.and in Xigduo 5mg/850mg, 5mg/1000mg.[9]

Mechanism of action

Dapagliflozin inhibits subtype 2 of the sodium glucose transport proteins (SGLT2) which are responsible for at least 90% of the glucose reabsorption in the kidney. Blocking this transporter mechanism causes blood glucose to be eliminated through the urine. In clinical trials, dapagliflozin lowered HbA1c by 0.6 versus placebo percentage point when added to metformin.[12]

Pharmacokinetic Data

1. **Routes of administration -** By oral / mouth (tablets)
2. **Distribution –** Extravascular distribution (mean volume of

i. distribution 118 L

3. **Bioavailability -** 78% (after 10 mg dose)
4. **Protein binding -** ~ 91%
5. **Metabolism -** In liver and kidney [(UGT1A9 - major) urine

i. diphosphate Glucuronosyltransferase – 1A9 and

ii. (CYP – minor) cytochrome P450.

6. **Metabolites -** Dapagliflozin 3-0-glucuronide (inactive)
7. **Excretion -** Urine (75%), feces (21%): 5

8. Elimination half life - ~ 12.9 hours

Typical spectroscopic graph in Methanol for selection of wavelength

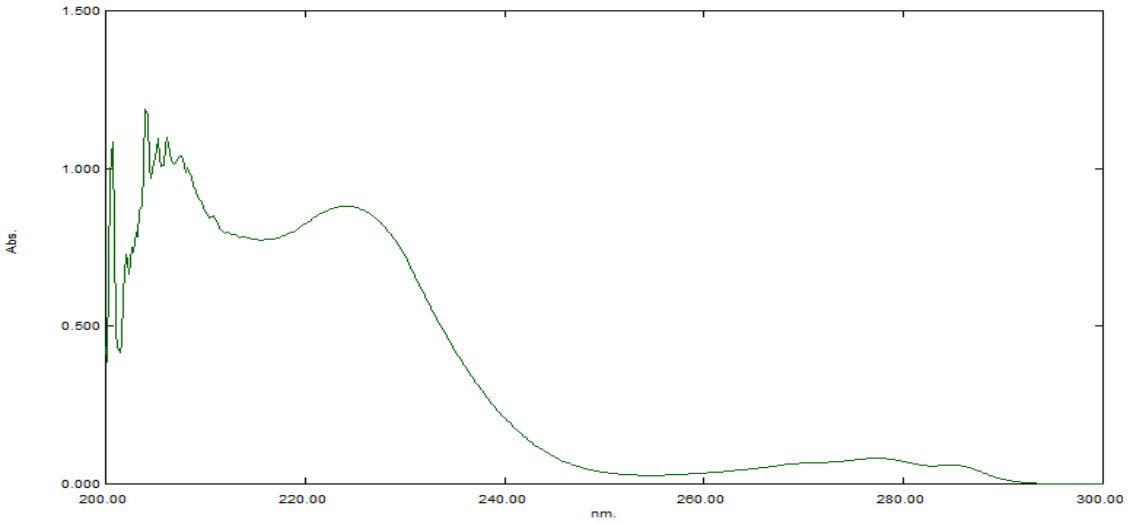

Fig. 1: Dapagliflozin UV spectra.

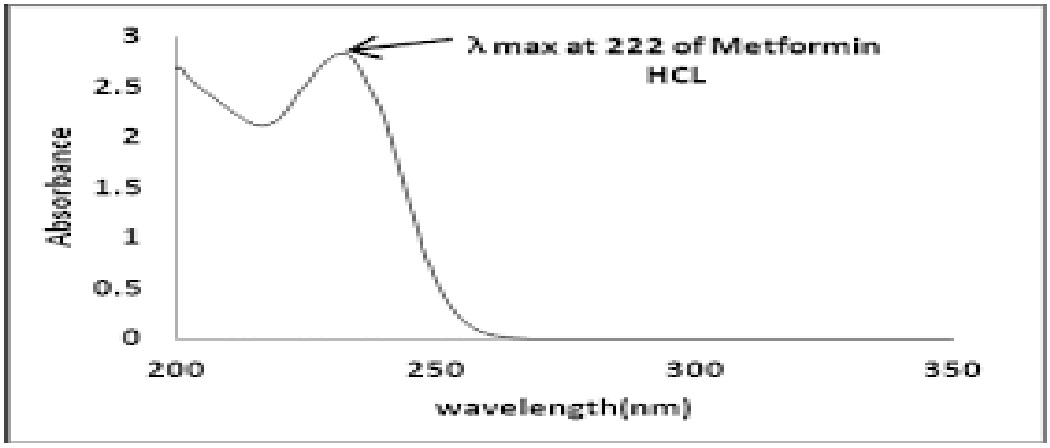

Fig. 2: UV-Spectra of metformin HCL.

Reported method are categorized depending on the following consideration.

UV-Spectroscopy and RP-HPLC techniques

Sr. no.	Drug	Method	Description	Ref. no.
1.	Dapagliflozin in tablet formulation	UV Spectrophotometric Method	**Wavelength:** 224 nm **Solvent:** Methanol	[1]
2.	Dapagliflozin in API	UV Spectrophotometric Method	**Wavelength:** 237 nm **Solvent:** Ethanol	[2]
3.	Dapagliflozin in bulk and pharmaceutical dosage form	UV Spectrophotometric Method	**Wavelength:** 233.65 nm **Solvent:** Ethanol: Phosphate buffer (1:1)	[3]

4.	Dapagliflozin in API	RP-HPLC method and UV- spectroscopy.	**Column:** BDS **Mobile phase:** Acetonitrile: Ortho phosphoric acid (55-45%) **Flow rate:** 1.2 ml/min **Wavelength:** 203 nm **Retention time:** 2.072 min	[4]
5.	Dapagliflozin and Metformin hydrochloride in synthetic mixture	UV Spectrophotometric Method	**Wavelength:** Dapagliflozin-225nm metformin - 237 nm **Solvent:** Methanol	[19]
6.	Dapagliflozin and Metformin hydrochloride in synthetic mixture	UV Spectrophotometric Method	**Wavelength:** Dapagliflozin-235nm metformin - 272 nm **Solvent:** Methanol	[20]
7.	Dapagliflozin in bulk and pharmaceutical dosage form	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Buffer (potassium hydrogen orthophosphate): Methanol (65:35%) **Flow rate:** 1.0 ml/min **Wavelength:** 225 nm **Retention time:** 2.93min	[5]
8.	Dapagliflozin in raw and tablet formulation	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Methanol:Water (75:25v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 230 nm **Retention time:** 2.797 min	[6]
9.	Dapagliflozin forced degradation studies	RP-HPLC method	**Column:** BDS **Mobile phase:** Buffer: Acetonitrile (60:4o %v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 245 nm **Retention time:** 2.789 min	[7]
10.	Dapagliflozin in bulk and tablet dosage form	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Methanol: Acetonitrile: 1% OPA(75:25:05v/v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 246 nm **Retention time:** 2.797 min	[8]
11.	Dapagliflozin in bulk and pharmaceutical dosage form	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Phosphate Buffer: Methanol (35:65v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 215 nm	[9]
12.	Dapagliflozin in bulk and tablet formulation	RP-HPLC method	**Column:** BDS **Mobile phase:** Ortho phosphoric acid Buffer: Acetonitrile (50:50 %v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 245 nm **Retention time:** 2.226 min	[10]

13.	Dapagliflozin in tablet form	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Acetonitrile:0.1% Triethylamine (50:50%v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 224 nm **Retention time:** 5.163 min	[11]
14.	Dapagliflozin in API	RP-HPLC method	**Column:** BDS **Mobile phase:** Ortho phosphate acid: Acetonitrile (45:55%v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 245 nm **Retention time:** 2.963 min	[12]
15.	Dapagliflozin	RP-HPLC method	**Column:** BDS **Mobile phase:** Ortho phosphoric acid: Methanol (55:45%v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 245 nm **Retention time:** 2.873 min.	[13]
16.	Dapagliflozin in API and pharmaceutical dosage form	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Acetonitrile: Di-potassium hydrogen phosphate (40:60%v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 222 nm **Retention time:** 3.16o min	[14]
17.	Dapagliflozin in bulk and tablet dosage form	RP-HPLC method	**Column:** BDS **Mobile phase:** Ortho phosphoric acid buffer: Acetonitrile (50:50%v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 245 nm **Retention time:** 2.226 min	[15]
18.	Dapagliflozin in bulk and tablet dosage form	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Phosphate Buffer: Acetonitrile (60:40%v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 237 nm **Retention time:** 3.461	[16]
19.	Dapagliflozin in API and pharmaceutical dosage form	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Acetonitrile: Di-potassium hydrogen phosphate (40:60%v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 222 nm **Retention time:** API-3.160 min Tablet-3.067 min	[17]

20.	Dapagliflozin	RP-HPLC method	**Column:** c_{18} **Mobile phase:** Methanol: Acetonitrile: 1% OPA(75:25:05v/v/v) **Flow rate:** 1.0 ml/min **Wavelength:** 246 nm **Retention time:** 2.797 min	[18]
21.	Dapagliflozin and Metformin hydrochloride in degradation product	RP-HPLC method	**Column**- C18 **Mobile phase** -0.05M Potassium Dihydrogen Phosphate Buffer: Acetonitrile: methanol.(5:4:1) **Flow rate**-0.5ml/min **UV wavelength**-236 **Retention time**- DAPA-8.314±0.05 min MET-2.274±0.04min	[29]
22.	Metformin hydrochloride and Dapagliflozin in tablet dosage form	RP-HPLC method	**Column**-BDS **Mobile phase** –phosphate buffer: Methanol: Acetonitrile(50:30:20 %v/v/v) **Flow rate**-1ml/min **Retention time**-DAPA-3.647 min MET -2.475 min **UV wavelength**- 240 nm	[24]
23.	Dapagliflozin and Metformin HCL	RP-HPLC method	**Column:** C18 **Mobile phase:** 0.05 M Potassium dihydrogen orthophosphate buffer: Acetonitrile (50:50%v/v) **Flow rate:** 1 ml/min **Retention time:** Dapaglifiozin: 2.633 min Metformin: 5.620 min	[23]
24.	Dapagliflozin and Metformin in bulk and in synthetic mixtute	RP-HPLC method	**Column**: C18 **Mobile phase**: Acetonitrile: Water (75:25%v/v) **UV Wavelength**: 285nm **Flow rate**: 0.5 ml/min **Retention time**: Metformin:3.2 min Dapagliflozin-5.4min	[31]
25.	Metformin and Dapagliflozin in tablet form	RP-HPLC metod	**Column**: C18 **Mobile phase**: Buffer: Acetonitrile (60:40%v/v) **Flow rate:** 1 ml/min **UV wavelength**: 266 nm **Retention time**: Metformin: 2.330 min Dapaglifolizin:3.098 min	[25]
26.	Metformin and Dapagliflozin	RP-HPLC method	**Column**: C 18 **Mobile phase**: Acetonitrile:0.1 M Ortho phosphoric acid buffer (70:30%v/v)	[30]

			UV wavelength: 260 nm **Retention time:** MET - 2.097min DAPA:3.691min **Flow rate:** 1ml/min	
27.	Dapagliflozin and Metformin	RP-HPLC method	**Column**: C18 **Mobile phase:** 0.1M dipotassium hydrogen phosphate: Acetonitrile: Methanol (60:30:10%v/v/v) **Flow rate**: 1.2 ml/min **UV Wavelength**: 285 nm **Retention time**: DAPA:2.847min MET: 3.804 min	[22]
28.	Metformin and Dapagliflozin in bulk and pharmaceutical dosage form	RP-HPLC method	**Column**: C_{18} **Mobile phase**: 0.1M Orthophosphoric acid: Acetonitrile: Methanol (35:40:25%v/v/v) **UV Wavelength**: 234nm **Retention time**: MET: 2.102min DAPA: 4.105min	[27]
29.	Metformin and Dapagliflozin in bulk and pharmaceutical dosage form	RP-HPLC method	**Column**: C18 **Mobile phase**: Acetonitrile: Phosphate buffer (70:30%v/v) **Flow rate**: 1ml/min **Retention time**: MET: 2 .463 min DAPA: 3.760min	[26]
30.	Metformin HCL and Dapagliflozin in bulk drug and tablet dosage form	RP-HPLC method	**Column**: C_{18} **Mobile phase**: Buffer: Acetonitrile (50:50 %v/v) **Flow rate:** 1 ml/min **Retention time**: MET: 2.791 min DAPA: 3.789 min	[28]
31.	Dapagliflozin and Metformin	RP-HPLC method	**Column**-C18 **Mobile phase** – Acetonitrile:0.05 m potassium dihydrogen phosphate buffer (65:35% v/v) **Flow rate**-1ml/min **UV wavelength**-212nm **Retention time**- MET- 1.898 min DAPA-3.560 min	[21]

CONCLUSION

Various method for determination of Dapagliflozin have been reported. Some RP-HPLC assay method were used to estimation Dapagliflozin alone or in combination with Metformin

HCL also it was found that the mobile phase containing Acetonitrile, Water, and Phosphate buffer were common for most of the RP-HPLC method to provide more resolution. UV-Spectrophotometric methods are also reported. For most of the spectroscopic methods common solvent is Methanol. Hence this all methods found to be simple, accurate, economic, precise and reproducible in nature. Most of methods were of RP-HPLC and UV absorbance detection because these method provided with best available, reliability, repeatability, analysis time and sensitivity.

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