REVIEW ARTICLE

A Review on Analytical Methods of Dapagliflozin: An Update

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ABSTRACT

Dapagliflozin is an antidiabetic drug that works on the kidneys of reabsorption of glucose in kidneys by the sodium-glucose co-transporter offer. It is used in patients with type 2 diabetes. It is administered as tablets. It has several analytical papers for estimation of active pharmaceutical ingredient (API) or drug formulation by reverse phase-high performance liquid chromatography (RP-HPLC) and ultraviolet spectroscopy (UV). It is very challenging to use of chemicals, drugs, and solvent of separation methods used in the pharmaceutical product to green chemistry. This review mostly used dihydrogen phosphate buffer and other toxic reagents for estimation and these agents harm instruments, as well as, environment and a lot of waste so that novel analytical techniques for quantifying and defining dapagliflozin should be built as easy as possible and secure for the individual and the community. This review pays attention to the critical condition of physicochemical, properties, action, and aims to focus on different analytical methods for the estimation of dapagliflozin in pharmaceutical formulations.

Keywords: Dapagliflozin, Pharmacokinetic, RP-HPLC methods, UV methods.

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INTRODUCTION

The dapagliflozin (DAPA) is an undoable, dynamic, and particular inhibitor of sodium-glucose co-transporter 2 (SGLT2). It works by the reabsorption of glucose from the liver, resulting in more glucose excretion in the urine, thereby increasing glycemic control in an individual with type 2 diabetes mellitus. It is defined in chemical terms as (1S)-1, 5-anhydro-1-C-[4-chloro-3-[(4-ethoxy phenyl) methyl]-D-glucite. Structure of Dapagliflozin shown in Figure 1. This is ethanol, methanol, dimethyl-sulfoxide, and dimethyl-formamide soluble white crystalline powder. Dapagliflozin is category III in the Biopharmaceutical Classification System (BCS) according to the European Medicines Agency (EMA), which is more soluble, and almost impermeable.[1]

These inhibitors are a new class of antidiabetic agents, called flozins. They have a novel mechanism of action that is insulin-independent and depends only on plasma glucose and renal function. These inhibitors provide benefits beyond glycemic regulation, including moderate body weight and blood pressure decreases, and improved insulin sensitivity and β-cell function. Dapagliflozin is orally available in the form of tablets.

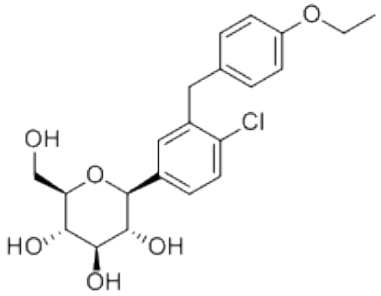

Figure 1: Structure of dapagliflozin

Single-agent, insulin supplement, or orally antihyperglycemic agent dapagliflozin is effective and decreases both weights of the body and blood pressure. This drug is efficient in type 2 diabetes mellitus (DM) patients, both as a single agent, as well as, in combination with other antidiabetic agents. In addition, recent studies have shown relatively fast action of dapagliflozin, with decreases in fasting plasma glucose levels within one week of treatment.[2] Its critical and important physic-chemical properties are showed in Table 1.[3]

Table 1: Critical physicochemical characterization of dapagliflozin

Parameter	*Description*
CAS number	461432-26-8
Molecular formula	$C_{21}H_{25}ClO_6$
Molecular weight	408.9
Appearance	Solid
Melting point	74–78°C
Solubility	Ethanol, dimethyl formamide
Drug type	Approved

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Mechanism of Action

In the human excretion system, after 34 weeks of gestation, almost all the filtrate consumed by the human nephron very quickly, and per day limit is 180 grams of glucose. Epithelial cells lining the first section of the proximal convoluted tubule produces sodium-glucose co-transporter-2 and these reabsorbed ninety percent of the filtered glucose and just one percent of filtered glucose entered in the urine. Lower sodium-glucose co-transporter-1 reabsorbed the remaining 10 percent in the nephron. The proximal tubular epithelium's luminal surface is the starting point of cycle of glucose reabsorption then sodium-glucose co-transporter-2 plays a very important role in transfers glucose to the epithelial cells from the glomerular filtrate. At this time, the basolateral cells out sodium by the Na+ /K+-adenosine triphosphates pump through active transport so co-transporters transfer glucose along with sodium. Due to the concentration gradient, glucose transporters are passive transporters that carry glucose out of the cell across the basolateral membrane. The effect of this entire cycle is that glucose is transferred back into circulation from the proximal tubule.

Pharmacodynamics

More diuresis and dose-dependent glycosuria are allied with dapagliflozin. There is a temporary rise in sodium excretion in the urine, but this does not appear to affect sodium in the serum. There is a temporary rise in uric acid excretion but a persistent decline in uric acid levels in the serum.[4]

Pharmacokinetics

Dapagliflozin is absorbed comfortably and well following oral administration. Maximum plasma concentrations of dapagliflozin occur within two hours of administration. With the 10 mg once daily dose, bioavailability is 78%. It can be taken with a meal or without it. It is 91% protein-bound, and hepatic or renal disease does not affect this.[5-7]

Indication

For adults with type 2 DM, farxiga is recommended as a supplement to diet and exercise for improving glycemic control.

Dosage and Administration

The recommended starting dose of dapagliflozin is 5 mg once daily, taken before the first meal of the day.[8]

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHODS FOR DETERMINATION OF DAPAGLIFLOZIN

There are many developed methods for HPLC. Subrata *et al*. developed and validated a reverse phase HPLC method using methanol (75):acetonitrile (25):orthophosphoric acid (5) at 246 nm. The retention time was obtained to be 2.797 minutes. The phase was found to be accurate, easy, and linear.[9] Sanagapati *et al*. developed and validated the method using a mixture of orthophosphoric acid and acetonitrile (45:55 v/v) at 245 nm.[10] Rafaela *et al*. produce a new method and study degradation using acetonitrile and water acidified with 0.1% formic acid (42:58 v/v) at 245 nm. Forced degradation study has been done in acid media, basic, oxidative, heat, and photolytic condition.[11] Verma *et al*. define a method of stability using acetonitrile (40):di-potassium hydrogen phosphate (60) with maintaining pH-6.5 adjusted with orthophosphoric acid at 222 nm. The retention time was found to be 3.16 and 3.067 minutes for both API and dosage form, respectively.[12] Debata *et al*. developed a novel, easy, different, exact, fast, and precise technique using phosphate buffer (60) and acetonitrile (40) at 237 nm. The retention time of dapagliflozin was found to be 3.461 minutes.[13] Jeyabaskaran *et al*. present work is concerned with applying easy, exact, right, rugged, and selective method using 0.1% orthophosphoric acid buffer (50) and acetonitrile (50) at 245 nm using a photodiode array detector.[14] Sura *et al.* developed a novel simple, user-friendly, and stability representing high performance liquid chromatographic method for estimation of dapagliflozin in API and pharmaceutical forms with a mobile phase containing methanol:sodium 1-octanesulphonate in the proportion of 70:30 v/v was utilized for the chromatographic elution study. A forced degradation study has been done.[15] Patel *et al.* give specific, exact, and novel stability methods using acetonitrile (40):di-potassium hydrogen phosphate (60) with maintaining pH 6.5 with phosphoric acid at 222 nm.[16] Yunoos *et al*. gave a method for metformin and dapagliflozin using buffer 0.1% orthophosphoric acid with pH 6.8 triethylamine (50):acetonitrile (50) at 240 nm.[17] Shyamala *et al*. produced a method for a combination of metformin and dapagliflozin, and the chromatogram was obtained by using phosphate buffer (50): methanol (30):acetonitrile (20) at 240 nm. The buffer pH 6.5 was maintained.[18] Urooj *et al*. produce an easy, exact, and robust method at 285 nm.[19] Patel *et al.* gave a selective, right, sharp, rugged, and repeatable method at 227 nm using 0.05M potassium dihydrogen ortho phosphate buffer (50) and acetonitrile (50) with maintain pH 6.5.[20] Kommineni *et al*. gave a novel stability method in a combination of saxagliptin and dapagliflozin with phosphate buffer (50) and acetonitrile (50) maintaining pH 4 at 225 nm.[21] Patel *et al*. produced an easy, fast, exact, rugged, and robust stability method in a combination of saxagliptin hydrochloride and dapagliflozin using potassium dihydrogen phosphate buffer (45):acetonitrile (55) at 220 nm with maintaining pH 6.[22] Singh *et al.* presented an easy and novel stability method for the combination of dapagliflozin and saxagliptin with buffer (53) and acetonitrile (47) at 230 nm.[23] Patel *et al*. gave an accurate, rugged, and reproducible method for the combination of dapagliflozin propanediol and glimepiride at 288 and 224 nm, respectively. It is using a mixture of acetonitrile (70):10% orthophosphoric acid (30) pH 6.[24] Basha *et al*. produce a different, novel, and sharp method using separation with buffer (60):acetonitrile (40) at 245 nm wavelength.[25] Mante *et al*. gave a fast, novel, and exact method using acetonitrile (50):0.1% triethylamine (50) at 224 nm wavelength.[26] Bopudi *et al.* gave exact, sharp, and repeatable stability method using methanol (80): water (20)

at 225 nm wavelength.[27] Bonagani *et al*. gave a new, easy, rugged, and robust method for single drug dapagliflozin using phosphate buffer (35):methanol (65) at 215 nm wavelength.[28] Illendula *et al*. produce a method of drug, using buffer potassium hydrogen orthophosphate (65) with maintaining pH 4.2 and methanol (35) at 225 nm wavelength.[29] Iamail *et al*. gave a new and first method in combination with canagliflozin, dapagliflozin, empagliflozin, and metformin, using acetonitrile (65) and buffer 0.05M potassium dihydrogen phosphate at pH 4 at 212 nm wavelength.[30] Dhanaraju *et al*. gave a novel method in combination with drug dapagliflozin and metformin with mobile phase acetonitrile (70) and 0.1 M orthophosphoric acid (30) at 260 nm.[31] Hari babu *et al*. gave a method for the combination of dapagliflozin and metformin with a C8 column using buffer 0.1 M dipotassium hydrogen phosphate (60):acetonitrile (30):methanol (10) at 285 nm.[32] All methods mention above shown in Table 2.

SPECTROPHOTOMETRIC METHODS FOR DETERMINATION OF DAPAGLIFLOZIN

Mante *et al*. gave a spectrophotometric derivative method in methanol at two wavelengths 235 and 272 nm.[33] Jani *et al*. produced the first derivative spectrophotometric method in a combination of dapagliflozin and metformin hydrochloride in both drugs at two wavelengths 235 and 272 nm in methanol.[34] Sanagapati *et al*. produce easy, new, effective, selective, and cheap method at 237 nm.[35] Zameeruddin *et al.* gave easy, correct, and exact methods in a combination of dapagliflozin and saxagliptin using the equation of simultaneous estimation at two wavelengths 223 and 212 nm.[36] Chitra *et al.* produce a spectrophotometric method for single drug dapagliflozin at 233.65 nm.[37] All methods mention above shown in Table 2.

ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY METHOD FOR DAPAGLIFLOZIN

Madhavi *et al*. gave an ultra-performance liquid chromatography method in a combination of dapagliflozin and saxagliptin using C-18 column with 0.1% orthophosphoric acid (40) and acetonitrile (60) mobile phase at 254 nm wavelength.[38] Above method mention in Table 2.

LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY METHOD FOR DAPAGLIFLOZIN

Qinc *et al*. developed an liquid chromatography-mass spectrometry (LC-MS) method in human plasma. Plasma quantity 50 µL and a lower limit of quantitation were obtained at 0.2 ng/mL. This method gave a five-fold improvement in all assay of sensitivity and adduct of acetate was used for detection.[39] Anne-Francoise *et al*. produce a method of tandem mass spectrometry using mobile phase water and acetonitrile. It is useful in plasma as per the

Table 2: Analytical techniques used for estimation of dapagliflozin in pharmaceutical formulations

S. No.	*Matrix*	*Techniques*	*Mobile phase/ solvent used*	*Column/ spectrophotometer*	*Maximum absorbance wavelength (nm)*	*Flowrate (mL/min)*
1.	Dapagliflozin (tablet and bulk)	RP-HPLC	Methanol:acetonitrile:orthophosphoric acid (75:20:5)	C-18	246	1
2.	Dapagliflozin (tablet and bulk)	RP-HPLC	Orthophosphoric acid:acetonitrile (45:55)	BDS column	254	1
3	Dapagliflozin (tablet and bulk)	RP-HPLC	Acetonitrile:water acidified with 0.1% formic acid (42:58)	C-18	245	1
4	Dapagliflozin (tablet and bulk)	RP-HPLC	Acetonitrile:di-potassiumhydrogen phosphate (pH-6.5) maintain with ortho phosphoric acid (40:60)	C-18	222	1
5	Dapagliflozin (tablet and bulk)	RP-HPLC	Phosphate buffer:acetonitrile (60:40)	C-18	237	1
6	Dapagliflozin (tablet and bulk)	RP-HPLC	0.1% orthophosphoric acid buffer and acetonitrile 50:50	BDS	245	1
7	Dapagliflozin (tablet and bulk)		Methanol:sodium 1-octanesulphonate (70:3)	C-18	203	1
8	Dapagliflozin (tablet and bulk)	RP-HPLC	Acetonitrile:di-potassium hydrogen phosphate with pH-6.5 with OPA (40:60)	C-18	222	1
9	Dapagliflozin and metformin (tablet and bulk)	RP-HPLC	0.1% ortho phosphoric acid (pH 6.5) with triethylamine:acetonitrile (50:50)	C-18	240	1
10	Dapagliflozin and metformin (tablet and bulk)	RP-HPLC	Phosphate buffer (pH 6.5):methanol:acetonitrile 50:30:20	C-18	240	1
11	Dapagliflozin and metformin (tablet and bulk)	RP-HPLC	Acetonitrile: water (75:25)	C-18	285	1

Cont...

12	Dapagliflozin and metfotmin (tablet and bulk)	RP-HPLC	0.05M potassium dihydrogenortho phosphate buffer (pH-3.5, adjusted with 0.1% orthophosphoric acid): acetonitrile 50:50	C-18	227	1
13	Dapagliflozin and saxagliptin (tablet and bulk)	RP-HPLC	Phosphate buffer (pH 4) and acetonitrile (50:50)	C-18	225	1
14	Dapagliflozin and saxagliptin (tablet and bulk)	RP-HPLC	Potassium dihydrogen phosphate buffer (pH 6.0):acetonitrile (45:55)	C-18	220	1.5
15	Dapagliflozin and saxagliptin (tablet and bulk)	RP-HPLC	20 mM sodium dihydrogen phosphate (pH 5.5 ± 0.02 with orthophosphoric acid acetonitrile (53:47)	C-18	230	1.2
16	Dapagliflozin and glimepiride (tablet and bulk)	RP-HPLC	Acetonitrile:10% orthophosphoric acid in water pH 6 (70:30)	C-18	228	1
17	Dapagliflozin (tablet and bulk)	RP-HPLC	Orthophosphoric acid:acetonitrile (60:40)	BDS	245	1
18	Dapagliflozin (tablet and bulk)	RP-HPLC	Acetonitrile: 0.1% triethylamine (pH-5) in the ratio of 50:50	C-18	224	1
19	Dapagliflozin (tablet and bulk)	RP-HPLC	Phosphate buffer:methanol (35:65)	C-18	215	1
20	Dapagliflozin (tablet and bulk)	RP-HPLC	Potassium hydrogen orthophosphate (pH-4.2):methanol (65:35)	C-18	225	1
21	Dapagliflozin canagliflozin empagliflozin metformin (combination)	RP-HPLC	Acetonitrile: 0.05M di-potassium hydrogen phosphate with pH-4 (65:35)	C-18	212	1
22	Dapagliflozin and metfotmin (tablet and bulk)	RP-HPLC	Acetonitrile: O.1M orthophosphoric acid (70:30)	C-18	260	1
23	Dapagliflozin and metfotmin (tablet and bulk)	RP-HPLC	0.1M dipotassium hydrogen phosphate:acetonitrile:methanol (60:30:10)	C-8	285	1.2
24	Dapagliflozin (tablet and bulk)	UV-Visible	Methanol	Double beam	224	-
25	Dapagliflozin and metfotmin (Tablet and bulk)	UV-Visible	Methanol	Double beam	235 270	-
26	Dapagliflozin (tablet and bulk)	UV-Visible	Methanol	Double beam	203	-
27	Dapagliflozin and saxagliptin (tablet and bulk)	UV-Visible	Water: Methanol (80:20)	Double beam	223 212	-
28	Dapagliflozin (tablet and bulk)	UV-Visible	Methanol	Double beam	233.65	-
29	Dapagliflozin (tablet and bulk)	RP-HPLC	Methanol: water (80:20% v/v)	C-18	225	0.8
30	Dapagliflozin saxagliptin	UPLC	0.1% orthophosphoric acid (40) :acetonitrile (60)	C-18	254	0.3
31	Dapagliflozin	LC-MS/MS	-	C-18	-	-
32	Dapagliflozin	LC-MS/MS	Water/acetonitrile	C-18	-	-

report of studies in normal, as well as, diabetic rat.[40] All methods mention above shown in Table 2.

ANALYTICAL AWARENESS OF DAPAGLIFLOZIN WITH GREEN CHEMISTRY

It is very challenging to use chemicals, drugs, and solvent of separation methods used in pharmaceutical products to green chemistry. Mostly volatile organic compounds are used for the laboratory, research, and industry for method development. Pollution spread through these types of organic compounds that's why the different analytical methods with some parameters, such as, simplicity, accuracy, sensitivity, and cost-effectiveness are of major consideration. The use of toxic reagents is strictly limited. Nowadays developed methods are very simple and less harmful to the environment, humans, and animals.

In green chemistry mainly focused on new analytical method and techniques reduces unsafe chemicals. Thus, new is very important to post-marketing surveillance so that use of green solvents increasing instead of harmful solvents. Green solvents, like water, ethanol, butanol, isopropyl alcohol, butyl acetate, isopropyl acetate, anisole, and sulfolane. Hence, green chemistry should be applied for the drug dapagliflozin in method development and validation. In this review, mostly buffers are used which are decreasing the life of the equipment, pump, and column of HPLC. The cleaning of the instrument is necessary for a proper way.

CONCLUSION

Dapagliflozin (SGLT2), an inhibitor used in diabetes has many HPLC and spectrophotometric methods, those mentioned in Table 2. Mostly used dihydrogen phosphate buffer and other toxic reagents harm instruments, as well as, environment and a lot of waste so that novel analytical techniques for quantifying and defining dapagliflozin should be built as simple as possible and safe for the chemist analyst and the community.

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