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A Review of Analytical Methods for Determination of Antidiabetic and Antihypertensive Drugs in Pharmaceuticals

Tadvi Nidhi[1], Krishna Kalsara[2], Umesh Upadhyay[3]

Department of Pharmaceutical Quality Assurance, Sigma University, Bakrol, Vadodara, Gujarat, India

Abstract: ***SGLT2 inhibitors are generally well-tolerated, with low rates of hypoglycemia. However, adverse effects such as genital mycotic infections and volume depletion-related events may occur, particularly in older adults. Beta-blockers reduce the workload of the heart by decreasing heart rate and contractility, which can help prevent myocardial ischemia and reduce the risk of further cardiac damage. The rational use of Dapagliflozin and Metoprolol in patients with heart failure is grounded in their distinct yet complementary mechanisms of action. Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor known for its ability to reduce heart failure hospitalizations and cardiovascular events, particularly in patients with heart failure with reduced ejection fraction (HFrEF). Metoprolol, on the other hand, is a beta-blocker that has been a cornerstone in the treatment of heart failure for years, helping to reduce heart rate and improve cardiac function. Dapagliflozin and Metoprolol combination drug currently in phase 3. Our comprehensive literature survey has revealed an existing gap - there are no reported spectroscopic and chromatographic methods available for the precise determination of Dapagliflozin and Metoprolol, especially when used together. When used in combination, Dapagliflozin and Metoprolol offer a multifaceted approach to managing heart failure. Dapagliflozin addresses issues like fluid retention and cardiovascular risk, while Metoprolol helps to control heart rate and reduce the workload on the heart. This combination can potentially provide greater benefits to patients with heart failure, although its precise use and dosing should be determined by a healthcare professional based on the individual patient's medical history and condition. Clinical studies have shown promising results in the use of these medications together, and ongoing research continues to explore their effectiveness in improving outcomes for heart failure patients.***

Keywords: Chromatography, dapagliflozin, metoprolol, analytical methods

1. Introduction

The initiative objectives are to decrease, prevent and control the wide spread of cardiovascular disease, especially in developing countries. Heart failure is a gradual disease categorized by failure of the heart muscles to supply enough blood to meet the nutritious and oxygen need of the body. Dapagliflozin is a medication used in the treatment of type 2 diabetes mellitus. It belongs to a class of drugs known as sodium-glucose co-transporter 2 (SGLT2) inhibitors. The primary mechanism of action of dapagliflozin is to inhibit SGLT2, a protein responsible for reabsorbing glucose in the kidneys. By inhibiting SGLT2, dapagliflozin promotes the excretion of glucose in the urine, leading to a reduction in blood glucose levels. Regarding its metabolism, dapagliflozin undergoes minimal hepatic metabolism. The majority of dapagliflozin is excreted unchanged in the urine, with approximately 75% of the administered dose being eliminated this way. Renal excretion is the primary route of elimination for dapagliflozin. Metoprolol is a medication classified as a beta-blocker, specifically a selective beta-1 adrenergic receptor antagonist. Its mechanism of action involves blocking the effects of catecholamines, particularly adrenaline (epinephrine) and noradrenaline (norepinephrine), on beta-1 adrenergic receptors primarily located in the heart. When metoprolol is administered orally, it is almost completely absorbed in the gastrointestinal tract. The maximum serum concentration is achieved 20 min after intravenous administration and 1-2 hours after oral administration. The bioavailability of metoprolol is of 100% when administered intravenously and when administered orally it presents about 50% for the tartrate derivative and 40% for the succinate derivative. The prescribed dosage involves Dapagliflozin and Metoprolol at 10 mg and 50 mg, respectively.

2. Diagnosis

Diagnosis of antidiabetes can be by determining the method of blood glucose level. In fasting conditions, the blood glucose level could be >6.7 mmol/L or random glucose levels will be more than 10 mmol/considered as diabetes. If there occur any doubts in the diagnosis, glucose tolerance test must be conducted to measure the glucose level in blood. Before the test, the patient needs to be on fast at least 10–12 h. During the test, the patient is advised to take 75 mg glucose orally the test will be repeated after 2 h.

3. Analytical Methods

Table 1.1: UV spectrophotometric method of Dapagliflozin

Sr No.	Title	Description
1	Estimation of Dapagliflozin from its Tablet Formulation by UV-Spectrophotometry	**Solvent-** Methanol with water **λmax -** 224 nm **Linearity**-5-40µg/ml
2	Development and validation of UV Spectroscopic method for Dapagliflozin in its API and its Tablet Formulation	**Solvent-** Methanol **λmax -** 226 nm **Linearity**-0.5-2.5 µg/ml
3	Unique UV spectrophotometric method for reckoning of dapagliflozin in bulk and pharmaceutical dosage forms	**Solvent**- Ethanol,DMSO, and Dimethyl formamide **λmax -** 233.65 nm **Linearity**- 10-35 µg / ml
4	Quantitative Estimation of Dapagliflozin in Blood Plasma by Using UV Spectroscopy	**Solvent**- Methanol **λmax -** 224 nm **Linearity**- 20-100 µg/ml
5	Method Development And Validation For The Estimation Of Dapagliflozin In Bulk And Tablet Dosage Formby UV Visible Spectroscopy	**Solvent**- Methanol **λmax -** 225 nm **Linearity**- 2-10µg/ml
6	Development and Validation of UV Spectroscopic First Derivative Method for Simultaneous Estimation of Dapagliflozin and Metformin Hydrochloride in Synthetic Mixture.	**Solvent**- Methanol **λmax –** DAPA - 235.0 nm MET at 272.0 nm **Linearity-** DAPA- 0.5-2.5 µg/ml MET-25-125 µg/ml
7	Development and Validation of UV Spectroscopic Method for Simultaneous Estimation of Dapagliflozin and Saxagliptin in marketed formulation	**Solvent**- Phosphate buffer pH 6.8 **λmax –** DAPA- 276 nm SAXA- 222 nm **Linearity**- 5-25µg/ml(Both)
8	Development And Validation Of UV Spectrophotometric Method For Estimation Of Saxagliptin And Dapagliflozin In Bulk And Dosage Form	**Solvent**- Methanol **λmax –** SAXA - 224 nm DAPA- 274 nm **Linearity-** SAXA-2-10 µg/ml DAPA- 4-20 µg/ml
9	A Novel Method Development and Validation of Dapagliflozin and Metformin Hydrochloride 222 nm using Simultaneous Equation Method by UV– Visible Spectroscopy in Bulk and Combined Pharmaceutical Formulation including Forced Degradation Studies	**Solvent- Water** **λmax –** DAPA 222 nm MET 232 nm **Linearity-** DAPA -2 – 32 µg/ml MET- 1 – 20µg/ml
	Development and validation of UV spectroscopic method for simultaneous estimation of dapagliflozin and metformin hydrochloride in synthetic mixture	**Solvent**- Methanol **λmax –** DAPA - 225.0 nm MET at 237.0 nm **Linearity-** DAPA- 0.5-2.5 µg/ml MET- 0.5-2.5 µg/ml
11	Ultraviolet-Spectrophotometric Method For Simultaneous Estimation Of Dapagliflozin Propanediol And Metformin Hydrochloride	**Solvent-** Methanol **λmax –** **1 -Simultaneous Estimation** DAPA - 223.0 nm MET at 233.0 nm **2-Area under curve method** DAPA - 220-229 nm MET- 229-236 nm **Linearity-** DAPA- 2-30 µg/ml µg/ml MET- 3-15 µg/ml
12	Analytical method development and validation for Simultaneous estimation of Dapagliflozin and Teneligliptin hydrobromide hydrate from synthetic mixture by three different UV spectrophotometric Methods	**Solvent** -Water **λmax -** 223 or 243 nm **Linearity**- 5-75 µg/ml **1)Simultaneous equation method λmax-** Dapagliflozin 223nm Teneligliptin hydrobromide hydrate 243 nm 2) **Q absorbance ratio method λmax -** Dapagliflozin 230nm Teneligliptin hydrobromide hydrate 223nm

		3) **First derivative signal λmax -** Dapagliflozin 223nm Teneligliptin hydrobromide hydrate 243 nm

Table 1.2: HPLC method of Dapagliflozin

Sr No.	Title	Description
1	RP-HPLC Method for Estimation of Dapagliflozin from its Tablet.	**Mobile Phase-** Acetonitrile: 0.1% Triethylamine (pH-5.0) in the ratio of (50:50%v/v) **Stationary phase =** C18 **λmax** -224nm **Flow Rate**: 1mL/min **Retention time**-5.16min **Linearity** - 10-70µg/ml
2	Development and validation of Dapagliflozin by reversed-phase high-performance liquid chromatography method and it's forced degradation studies.	**Mobile Phase-** Buffer: Acetonitrile (%60:40V/V) **Stationary phase =** BDS (250 mm × 4.6 mm, 5 µ), **λmax** - 245 nm **Flow Rate**: 1mL/min **Retention time** - 2.789 min **Linearity** – 25-150µg/ml
3	Development and Stability Indicating HPLC Method for Dapagliflozin in Api and Pharmaceutical Dosage Form.	**Mobile Phase** - Acetonitrile: Di-potassium hydrogen phosphate with pH-6.5 adjusted with OPA (40:60 %v/v) **Stationary phase :** C18 (4.6 , 150mm,5 µm) **λmax** - 222 nm **Flow Rate**: 1ml/min **Retention time-** Dapa API-3.160 min Dapagliflozin tablet- 3.067 min **Linearity** - 50-150µg/ml
4	Development and Validation of stability-Indicating RP-HPLC method for determination of Dapagliflozin.	**Mobile Phase-** Acetonitrile: Ortho phosphoric acid (55:45%v/v) **Stationary phase =** BDS column **λmax** -245nm **Flow Rate**: 1mL/min **Retention time** -2.873 min **Linearity** - 10-70µg/ml
5	Stability-indicating HPLC method development and validation for simultaneous estimation of metformin, dapagliflozin, and saxagliptin in bulk drug and pharmaceutical dosage form.	**Mobile Phase-** Phosphate buffer (pH = 3) Acetonitrile (60:40%v/v) **Stationary phase** -Kromasil C18 column (150 × 4.6 mm, 5 µm) **λmax** -230 nm **Flow Rate**: 1mL/min **Retention time** - 4 min **Linearity –** MET-125–750 µg/mL, DAPA-1.25–7.5 µg/mL SAXA-0.625 -3.75 µg/mL

Table 1.3 HPTLC method of Dapagliflozin

S. No.	Title	Description
1	A New High-Performance Thin Layer Chromatographic Method Development and Validation of Dapagliflozin In Bulk And Tablet Dosage Form.	**Mobile Phase**-Chloroform: Methanol (90:10%v/v) **Stationary phase**: Merck precoated silica gel aluminum plate 60 F_{254} **λmax** -223nm **Concentration range**= 400 ng/band to 1200 ng/band
2	HPTLC Method for the Determination of Metformin Hydrochloride, Saxagliptin Hydrochloride, and Dapagliflozin in Pharmaceuticals	**Mobile Phase- acetonitrile**: 1% w/v Ammonium Acetate in Methanol (90: 10, v/v%) **Stationary Phase** : HPTLC sheets coated with silica gel 60 F254 λmax -210 nm. **Concentration range-** 0.25-10 µg/band for SAXA and DAPA MET-0.25-25 µg/band
3	Development and validation of stability-indicating HPTLC method for simultaneous estimation of Metformin, Saxagliptin, and Dapagliflozin in their combined matrix using AQbD	**Mobile Phase-** Methanol: 0.5 % aqueous ammonium sulphate (8:2, %v/v), pH 5.5 **Stationary phase**: pre-coated silica gel 60 F254 HPTLC aluminum plates, **λmax** -222 nm **Concentration range**= 50,000–150,000 ng/band for MET and 250–750 ng/band for SAXA and DAPA
4	Development and validation of hptlc Technique for assessment of dapagliflozin And metformin hcl	**Mobile Phase-** Toluene, ethyl acetate, and formic acid (3: 6.5: 0.5 v/v/v) **Stationary phase**: TLC aluminium plate precoated with silica gel 60 F254 **λmax** -235 nm **Concentration range**= DAPA-50-300 MET-2500-15000 ng band
5	Development and Validation of HPTLC Method for Simultaneous	**Mobile Phase-** Toluene: Ethyl Acetate: Methanol: Ammonia (6.0: 2.0: 2.0: 0.1, v/v/v/v)

	Quantification of Dapagliflozin and Vildagliptin in Tablet Dosage Form	**Stationary phase**: TLC aluminium plate precoated with silica gel 60 F^{254} **λmax** -217 nm **Concentration range**= DAPA-200-1400 VILG-2000-14000 ng/band

Table 1.4 LC-MS Method of Dapagliflozin

Sr no.	Title	Description
1	Development and Validation of a LC-ESI-MS/MS Based Bioanalytical Method for Dapagliflozin and Saxagliptin in Human Plasma	**Stationary phase**- hypersil Gold C 18 (50mmx3.0mm, 5µm) **Mobile Phase**: Ammonium acetate and methanol (20:80,% v/v) **Flow rate**: 0.5 ml/min **Detection:** Quantification was achieved using an electro spray ion interface operating in positive mode, under multiple reaction monitoring (MRM) conditions.

Table 1.5: Official methods of Metoprolol

Sr No	Title	Description
1	BP-2018 (HPLC)	**Mobile Phase** – **(1)** Trifluoro acetic acid Acetonitrile For Chromatography -Water For Chromatography (1:29:70, %v/v) **(2)** Trifluoro acetic acid R Acetonitrile For Chromatography -Water For Chromatography (1:24:75, v/v) **Stationary phase**- 0.15m,=3.0mm Base detective end-capped octadecylsilane silica gel for chometographyR3µm) **λmax** - 242 nm **Flow Rate: -** 0.75 ml/min **Retention time –** 25min
2	IP-2018 (RP-HPLC)	**Mobile Phase**: 58 vol of a buffer sol prepared by dissolving 1.54 g of ammonium acetate in 900ml of water adjust with 4.00ph glacial acetic acid and dilute to 1000mk of water, 360 vol of acetonitrile and 50 vol of tetrahydrofuran. **Stationary phase** : (25cm × 4.6mm, packed with octadecylsilane bonded to porous silica 5µm) **λmax:** 248 nm **Flow rate**: 1.5 ml/min
3.	Liquid Chromatographic Method **(USP 2020)**	**Stationary Phase:** (3.2 mm× 25 cm;5µm) L1. **Mobile Phase:** Acetonitrile, Sol A. and Water (37:1:62) **Sol A:** 1% Trifluoroacetic acid in water **Flow Rate**: 0.75 ml/min **Injection Volume**: 10µl **λmax:**242nm

Table 1.6: UV spectrophotometric method of Metoprolol

S. No.	Title	Description
1	UV- Spectrophotometric Determination of Metoprolol Succinate	**Solvent**- Methanol **λmax** - 222 nm **Linearity**-2-16 µg/mL
2	UV spectrophotometric method development and validation for the determination of metoprolol succinate in bulk and its pharmaceutical dosage form	**Solvent**- Methanol **λmax** - 275 nm **Linearity**-50-250 µg/mL
3	Spectrophotometric Determination of Metoprolol Tartrate in Pharmaceutical Dosage Forms on Complex Formation with Cu(II)	**Solvent**- Methanol/water (1:1 v/v) **Λmax**- 675 nm **Linearity**- 8.5-70 µg/mL
4	Development And Validation of Spectrophotometric Method For Determination of Metoprolol Succinate	**Solvent**- D/W **Λmax**- 223 nm **Linearity**- 5-25 µg/ml.
5	Development and validation of UV spectrophotometric method for simultaneous estimation of cilnidipine and metoprolol succinate in bulk drugs and combined dosage form	**Solvent**- Methanol **λmax** – MET-230 nm CLI-223.40nm **Linearity-** MET-2-10 µg/ml CLI-10-50 µg/ml
6	Development and validation of the simultaneous UV spectrophotometric method for estimation of metoprolol succinate and olmesartan medoxomil in the tablet dosage form	**Solvent**- D/W **λmax** – MET-221nm OLM-257nm **Linearity-** MET-5-25 µg/ml OLM -4-20 µg/ml
7	Sensitive and Reproducible Study for UVSpectrophotometric Method for Analysis of Clopidogrel and Metoprolol in a Combined Tablet Dosage Form	**Solvent**- Ethanol: Water 60: 40% v/v **λmax -** MET- 276.13 nm CLO- 245.7nm

		Linearity- MET & CLO 5-30 µg/ml

Table 1.7: HPLC method of Metoprolol

S. No.	Title	Description
1	Estimation of metoprolol in human plasma by hplc method	**Mobile Phase-** acetonitrile-potassium phosphate (pH 3.0) buffer in the ratio of (60:40 %v/v) **Stationary phase** -C18 **λmax** - 262 nm **Flow Rate: -** 1. ml/min **Retention time** – 4.07±0.02 min **Linearity** – 0.2-20 (µg/ml)
2	Rp-hplc method for the estimation of metoprolol succinate in bulk and in dosage forms	**Mobile Phase** - Aqueous phosphoric acid solution (0.1% v/v) **Stationary phase** - 150 mm ×4.6 mm zorbax SB phenyl RP 18, 5 µm **λmax** -252 nm **Flow Rate**:- 0.8 ml/min **Retention time** – 3.765 mins **Linearity** - 50-300 µg/m
3	Development and validation of a stability indicating RP-HPLC method for simultaneous estimation of Olmesartan Medoxomil and Metoprolol Succinate in pharmaceutical dosage form	**Mobile Phase**- 0.05% Trifluoro acetic acid (TFA) and Acetonitrile (ACN) (70:30% v/v) **Stationary phase**- YMC-Pack CN (250 × 4.6 mm, 5.0 µm) **λmax** - 220 nm **Flow Rate**:- 1.0 ml/min **Retention time** –METO-7.9 min OLM-4.1min **Linearity** –METO- & OLM 5-35µg/ml
4	Analytical Method for the Simultaneous Estimation of Hydrochlorothiazide and Metoprolol Tartrate using RP HPLC	**Mobile Phase-** mixture of buffer and methanol in the proportion (60:40 % v/v) **Stationary phase**- C18, 5µm 4.6 mm×250 mm column **λmax** - 226 nm **Flow Rate:-** 1.0 ml/min **Retention time** – HCL-4.13min MET-10.81min **Linearity** – HCL- a 0.013 to 0.075 mg/ml MET- d 0.10 to 0.60 mg/ml
5	Development of Reverse-Phase HPLC Method for Simultaneous Analysis of Metoprolol Succinate and Hydrochlorothiazide in a Tablet Formulation	**Mobile Phase** - Di-sodium hydrogen phosphate:methanol:acetonitrile in a ratio of (525:225:250) **Stationary phase-** RP C8 (4.6mm x 100mm, 5µm) column **λmax** - 222 nm **Flow Rate:-** 1.0 ml/min **Retention time** – HCL-3.04min MET-5.38 min **Linearity** – 2 to 32 µg/ml for both drugs
6	Simultaneous determination of metoprolol succinate and amlodipine besylate in pharmaceutical dosage form by HPLC.	**Mobile Phase** -buffer (aqueous triethylamine pH 3) and acetonitrile in the ratio of 85:15 (%v/v) **Stationary phase-** n Hypersil BDS cyano (250 mm × 4.6 mm, 5m) column **λmax** - 254 nm **Retention time** – AMI- 16.838min MET-4.99min **Linearity** – AMI- a 0.013 to 0.075 mg/ml MET- d 0.10 to 0.60 mg/ml
7	Method development and validation for the simultaneous determination of metoprolol and atorvastatin by reversed-phase high-performance liquid chromatography in its bulk and pharmaceutical tablet dosage form using biorelevant dissolution media (fasted state small intestinal fluid)	**Mobile Phase** - phosphate buffer 4.8 pH: acetonitrile (35:65% v/v), **Stationary phase-** Inertsil ODS-3 (4.6×150 mm, 5 µm). **λmax** -224 nm **Flow Rate**: - 1.00 ml/min **Retention time –** MET- 2.227 min ATO - 5.819 min **Linearity** – MET- 50–250 µg/ml ATO - 10–50 µg/m

Table 1.8: HPTLC method of Metoprolol

Sr no.	Title	Description
1	Comparative HPTLC study for simultaneous determination	**Mobile Phase-** chloroform: methanol: formic acid: ammonia (8.5:1.5:0.2:0.1, v/v) **Stationary phase** : TLC silica 60 F254 plates and non-fuorescent TLC silica gel 60

	of ivabradine and metoprolol using UV and fluorescence detectors	plates **λmax** - 275 nm Concentrationrange- **IVA**- 50.0–600.0 ng/band **MET**- 50.0–900.0 ng/band
2	A robust high-performance thin-layer chromatography method for the simultaneous estimation of chlorthalidone and metoprolol succinate using quality risk assessment and design of experiments-based enhanced analytical quality by design approach	**Mobile Phase**- Toluene–methanol–triethylamine (8:2:0.5, V/V) **Stationary phase:** silica gel GF254 **λmax** - 230 nm **Concentration range-** CLO - 200–1000 ng/band MET - 800–4000 ng/band
3	Development and Validation of HPTLC Method for Simultaneous Determination of Amlodipine Besylate and Metoprolol Succinate in Bulk and Tablets	**Mobile Phase**- toluene:ethyl acetate:methanol:triethylamine (4:1:1:0.4 v/v/v) **Stationary phase:** HPTLC aluminum plates precoated with silica gel 60F-254 (10×10) **Concentration range-** AMB - e 400-1400 ng /spot MET- 3800–13300 ng /spot.
4	High-performance thin-layer chromatographic method for simultaneous analysis of metoprolol succinate and amlodipine besylate in pharmaceutical preparations	**Mobile Phase**- Methanol ethyl acetate-water-toluene-25% ammonia 1.5:5.0:0.3:3.0:0.3 (v/v) **Stationary phase:** silica gel 60 F 254 plates **Concentration range-** AMLO - 180 to 280 μg mL −1 MET- 18 to 28 μg mL −1
5	Validated HPTLC method for simultaneous estimation of metoprolol succinate and ramipril in bulk drug and marketed formulation	**Mobile Phase**- Methanol: Toluene: Ethyl Acetate: Ammonia (2.5:3:5:0.7v/v/v/v) **λmax –** 209 nm **Stationary phase:** silica gel 60 F 254 plates **Concentration range-** AMLO - 2000-12000 ng/spot RAM- 200–1200 ng/spot

Table 1.9: LC-MS method of Metoprolol

S. no.	Title	Description
1	Rapid and Sensitive LC-MS/MS Method for the Determination of Metoprolol in Beagle Dog Plasma with a Simple Protein Precipitation Treatment and Its Pharmacokinetic Applications	**Column**- Ultimate XB-C18 (150 × 2.1 mm ID, 5 μm **Mobile Phase**- methanol-water containing 0.2% formic acid (65:35, v/v) **Flow** rate- 0.2 mL/min **Monitoring ions**- 268.1/115.6 and m/z 373.1/150.2 **Linearity Range**- 3.03–416.35 ng/mL

Table 1.10: Literature Summary

METHOD	DAPA	MET	DAPA+ MET
UV SPECTROPHOTOMETRY	√	√	-
HPLC	√	√	-
RP-HPLC	√	√	-
LC-MS/MS	√	√	-
HPTLC	√	√	-
STABILITY INDICATING HPLC METHOD	√	√	-

Table 1.11: PSARS Report

S. No.	Patent Application Number	Title of Patent
1.	US 2016/0214953 A1	Process for the preparation of dapagliflozin
2.	WO2018/029611A1,2018	Novel processes for preparation of dapagliflozin or its solvates or co - crystals thereof
3.	US 2005/0107635A1	Metoprolol manufacturing process
4.	US 2009/0247642 A1	Synthesis and preparations of metoprolol and its salts
5.	WO2013/137839 A1	Tablet formulation comprising dapagliflozin and extended-release metformin

1) **As per described in patent 1**: The present invention provides an improved process for the preparation of dapagliflozin of Formula (II) wherein the pro cess comprises the step of hydrolyzing the compound of Formula (III) in the presence of an amine base.
2) **As per described in patent 2**: The present generally relates to an improved process for the preparation of dapagliflozin of Formula I or its solvates or co - crystals thereof. The present invention also encompasses the novel intermediates and their use in the preparation of dapagliflozin.
3) **As per described in patent 3**: Metoprolol manufacturing process with optimized reaction temperatures and reactant molar ratios, to avoid the manu facture of excessive epoxide intermediates, thus avoiding the need for purification of epoxide intermediates, thus achieving higher yields and higher-purity product than that Seen in the prior art teachings.
4) **As per described in patent 4:** The invention relates to an improved process for preparing metoprolol and its salts.
5) **As per described in patent 5:** The present invention is

related to combination formulation prepared by being coated with a coating solution comprising dapagliflozin or pharmaceutically acceptable salts , solvents or hydrates thereof on the extended release metformin tablet.

4. Conclusion

From the above Literature review, all Spectroscopic methods for Dapagliflozin and Metoprolol were done by using Methanol as a common solvent.

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