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RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF METFORMIN, DOPAGLIFLOZIN, SAXAGLIPTIN IN TABLET DOSAGE FORMS

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ABTRACT

A SIMPLE, ACCURATE, PRECISE METHOD WAS DEVELOPED FOR THE SIMULTANEOUS ESTIMATION OF THE METFORMIN, DAPAGLIFLOZIN AND SAXAGLIPTIN IN PHARMACEUTICAL DOSAGE FORM. CHROMATOGRAM WAS RUN THROUGH ZORBAX C18 250X4.6MM, 5 . MOBILE PHASE CONTAINING 0.01N KH_2PO_4AND ACETONITRILE IN THE RATIO OF 55:45 V/V WAS PUMPED THROUGH COLUMN AT A FLOW RATE OF 1.0ML/MIN. TEMPERATURE WAS MAINTAINED AT 30°C. OPTIMIZED WAVELENGTH FOR METFORMIN. DAPAGLIFLOZIN AND SAXAGLIPTIN WAS 230.0 NM. RETENTION TIME OF SAXAGLIPTIN, METFORMIN AND DAPAGLIFLOZIN WERE FOUND TO BE 2.253MIN, 2.701MIN AND 3.598MIN. %RSD OF SYSTEM PRECISION FOR METFORMIN, SAXAGLIPTINANDDAPAGLIFLOZINWEREANDFOUNDTOBE1.1,1.7AND1.1RESPECTIVELY.%RSDOFM ETHOD PRECISION FOR METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN WERE AND FOUND TO BE 0.8, 1.1 AND 0.6 RESPECTIVELY. % RECOVERY WAS OBTAINED AS 98.94%, 100.35% AND 100.13% FOR METFORMIN, SAXAGLIPTINANDDAPAGLIFLOZINRESPECTIVELY.LODVALUESAREOBTAINEDFROMREGRESSION EQUATIONSOF METFORMIN,SAXAGLIPTINANDDAPAGLIFLOZIN.WERE4.50PPM,0.02PPM,0.10PPMANDLOQVALUESA RE OBTAINED FROM REGRESSION EQUATIONS OF METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN WERE 13.65PPM, 0.05PPM ,0.31PPM RESPECTIVELY. REGRESSION EQUATION OF METFORMIN WAS Y = 5934X + 13728., DAPAGLIFLOZIN WAS Y = 119948X + 2393.4.AND OF SAXAGLIPTIN WAS Y = 101914X + 5013. RETENTION TIMES ARE DECREASED SO THE METHOD DEVELOPED WAS SIMPLE AND ECONOMICAL THAT CAN BE ADOPTED IN REGULAR QUALITY CONTROL TEST ININDUSTRIES.

KEY WORDS: METFORMIN. DAPAGLIFLOZIN, SAXAGLIPTIN, RP-HPLC

INTRODUCTION:

AS OPPOSED TO NP-HPLC, RP-HPLC EMPLOYS MAINLY DISPERSIVE FORCES (HYDROPHOBIC OR VANDERWAL'S INTERACTIONS). THE POLARITIES OF MOBILE AND STATIONARY PHASES ARE REVERSED, SUCH THAT THE SURFACE OF THESTATIONARY PHASE IN RP-HPLC IS HYDROPHOBIC AND MOBILE PHASE IS POLAR, WHERE MAINLY WATER-BASED SOLUTIONS ARE EMPLOYED. RP-HPLC IS BY FAR THE MOST POPULAR MODE OF CHROMATOGRAPHY. ALMOST 90 % OF ALL ANALYSES OF LOW-MOLECULAR-WEIGHT SAMPLES ARE CARRIED OUT USING RP-HPLC. DISPERSIVE FORCES EMPLOYED IN THIS SEPARATION MODE ARE THE WEAKEST INTERMOLECULAR FORCES, THEREBY MAKING THE OVERALL BACKGROUND INTERACTION

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ENERGYINTHE CHROMATOGRAPHICSYSTEMVERYLOWCOMPAREDTOOTHERSEPARATIONTECHNIQUES[1].THISLO WBACKGROUND ENERGYALLOWSFORDISTINGUISHINGVERYSMALLDIFFERENCESINMOLECULARINTERACTIONSO FCLOSELYRELATED ANALYTES. ADSORBENTS EMPLOYED IN THIS MODE OF CHROMATOGRAPHY ARE POROUS RIGID MATERIALS WITH HYDROPHOBIC SURFACES. THE MAJORITY OF PACKING MATERIALS USED IN RP-HPLC ARE CHEMICALLY MODIFIEDPOROUSSILICA.INDATAANALYSISTHEQUA;ITYASSURANCEOFTHEBULKDRUGSANDPHA RMACEUTICAL PREPARATIONS PLAYS A VITALROLE.

METFORMIN[2] IS AN ANTIHYPERGLYCEMIC AGENT OF THE BIGUANIDE CLASS, USED FOR THE MANAGEMENT OF TYPE II DIABETES). DAPAGLIFLOZIN[3] IS A SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR INDICATED FOR MANAGING DIABETES MELLITUS TYPE 2. DAPAGLIFOZIN IS AN INHIBITOR OF SGLT2. BY INHIBITING SGLT2, DAPAGLIFLOZIN REDUCES REABSORPTION OF FILTERED GLUCOSE AND THEREBY PROMOTES URINARY GLUCOSE EXCRETION. DAPAGLIFLOZEN ALSO REDUCES SODIUM REABSORPTION AND INCREASES THE DELIVERY OF SODIUM TOTHEDISTALTUBULE[4].SAXAGLIPTIN(RINN)ISANORALLYACTIVEHYPOGLYCEMIC(ANTI-DIABETICDRUG)OFTHE NEW DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITOR CLASS OF DRUGS. FDAAPPROVED

DRUG PROFILE

METFORMIN:

DESCRIPTION: METFORMIN IS AN ANTIHYPERGLYCEMIC AGENT OF THE BIGUANIDE CLASS, USED FOR THE MANAGEMENT OF TYPE II DIABETES).CURRENTLY, METFORMIN IS THE FIRST DRUG OF CHOICE FOR THE MANAGEMENT OF TYPE II DIABETES.

STRUCTURE:

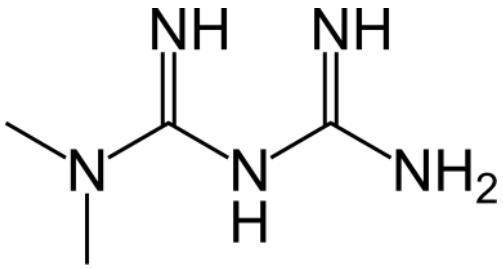

FIG NO: 1

SYNONYM:	N,N-DIMETHYLIMIDODICARBONIMIDICDIAMIDE-D6,HYDROCHLORIDE; DIABETOSAN-D6; DIABEX-D6, METFORMIN-D6; METIGUANIDE-D6
APPLICATION:	A DEUTERIUM LABELED ORAL HYPOGLYCEMIC AGENT
MOLECULAR WEIGHT:	171.66
MOLECULAR FORMULA:	$C_4H_6D_6CL_5\ N_5$
APPEARANCE:	CRYSTALLINE
PHYSICAL STATE:	SOLID

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SOLUBILITY: SOLUBLE IN DMSO, AND METHANOL.

STORAGE: STORE AT -20° C

MELTING POINT: 215-218°C

DAPAGLIFLOZIN

DESCRIPTION: DAPAGLIFLOZIN IS A SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR INDICATED FOR MANAGING DIABETES MELLITUS TYPE 2. WHEN COMBINED WITH DIET AND EXERCISE IN ADULTS, DAPAGLIFLOZIN HELPS TO IMPROVE GLYCEMIC CONTROL BY INHIBITING GLUCOSE RESORPTION IN THE PROXIMAL TUBULE OF THE NEPHRON AND CAUSING GLYCOSURIA. DAPAGLIFLOZIN WAS APPROVED BY THE FDA ON JAN 08, 2014[10].

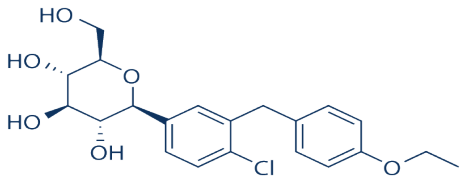

FIG NO:2 DAPAGLIFLOZIN

IUPACNAME:(2S,3R,4R,5S,6R)-2-(4-CHLORO-3-(4-ETHOXYBENZYL)PHENYL)-6- (HYDROXYMETHYL)TETRAHYDRO-2H-PYRAN-3,4,5-TRIOL

APPLICATION:SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

MOLECULAR WEIGHT: 408.87

MOLECULAR FORMULA: $C_{12}H_{25}CLO_6$

PHYSICAL STATE: WHITE COLOUR SOLID

SOLUBILITY: SOLUBLE IN ORGANIC SOLVENTS , ETHANOL, DMSO, DIEHYL FORMAMIDE.

SAXAGLIPTIN:
DESCRIPTION: SAXAGLIPTIN (RINN) IS AN ORALLY ACTIVE HYPOGLYCEMIC (ANTI-DIABETIC DRUG) OF THE NEW DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITOR CLASS OF DRUGS. FDA APPROVED ON JULY 31, 2009[13].

STRUCTURE:

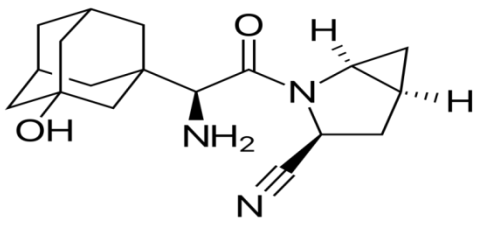

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FIG NO:3

IUPAC:(1S,3S,5S)-2-((2S)-AMINO(3-HYDROXYTRICYCLO(3.3.1.13,7)DEC-1-YL)ACETYL)-2-AZABICYCLO(3.1.0)HEXANE-3-CARBONITRILE

THERAPEUTICCATEGORY	DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS
MOLECULAR WEIGHT:	315.41
T½	2.5 HOURS
PLASMAPROTEINBINDING	<10%
METABOLISM	50%
ELIMINATION	RENAL AND HEPATIC
CHEMICALFORMULA	$C_{18}H_{25}N_3O_2$
SOLUBILITY:	IN WATER
BRAND NAMES	ONGLYZA,

MATERIALS:

INSTRUMENTS USED-

1. ELECTRONICS BALANCE-DENVER
2. P^H METER -BVK ENTERPRISES,INDIA
3. ULTRASONICATOR-BVK ENTERPRISES

WATERS HPLC 2695 SYSTEM EQUIPPED WITH QUATERNARY PUMPS,PHOTO DIODE ARRAY DETECTOR AND AUTO SAMPLER INTEGRATED WITH EMPOWER 2 SOFTWARE.

UV-VIS SPECTROPHOTOMETER PG INSTRUMENTS T60 WITH SPECIAL BANDWIDTH OF 2MM AND 10MM AND MATCHED QUARTZ CELLS INTEGRATED WITH UV WIN 6 SOFTWARE WAS USED FOR MEASURING ABSORBANCES OF METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN SOLUTIONS

CHEMICALS AND REAGENTS:

DRUGS- METFORMIN, DAPAGLIFLOZIN, SAXAGLIPTIN

OPTIMIZED METHOD:

MOBILE PHASE	0.01N KH2PO4: ACETONITRILE (55:45 V/V)
BUFFER	0.01N KH2PO4
DILUENT	WATER : ACETONITRILE (50:50 V/V).
COLUMN	ZORBAX C18 150 X 4.6 MM, 5µM..
FLOW RATE	1.0 ML /MIN

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INJECTION VOLUME	10µL
RUN TIME:	8MIN
WAVE LENGTH	221NM
BUFFER	0.01N KH2PO4
TEMPERATURE	30°C

TABLE-I : OPTIMIZED METHOD CONDITIONS

SAMPLE PREPARATION.

DILUENTS: BASED UP ON THE SOLUBILITY OF THE DRUG DILUENTS WAS SELECTED WATER: ACETONITRILE (50:50 V/V)

PREPARATION OF STANDARD STOCK SOLUTIONS: ACCURATELY WEIGHED 250MG OF METFORMIN, 2.5MG OF DAPAGLIFLOZIN AND 1.25MG OF SAXAGLIPTIN AND TRANSFERRED TO THREE 50ML VOLUMETRIC FLASKS SEPARATELY. 10ML OF DILUENT WAS ADDED TO FLASKS AND SONICATED FOR 20MINS. FLASKS WERE MADE UP WITH WATER: ACETONITRILE(50:50 V/V) AND LABELED AS STANDARD STOCK SOLUTION 1, 2 AND 3.

PREPARATION OF STANDARD WORKING SOLUTIONS (100% SOLUTION): 1ML FROM EACH STOCK SOLUTIONWAS PIPETTE OUT AND TAKEN INTO A 10ML VOLUMETRIC FLASK AND MADE UP WITH WATER:ACETONITRILE(50:50 V/V). (500PPM METFORMIN, 5PPM DAPAGLIFLOZIN&2.5PPMSAXAGLIPTIN).

PREPARATIONOFSAMPLESTOCKSOLUTIONS:5TABLETSWEREWEIGHEDANDCALCULATETHEAVERAGEWEIGHT OFEACHTABLETTHENTHEWEIGHTEQUIVALENTTO1TABLETWASTRANSFERREDINTOA100MLVOLUMETRICFLASK, 25ML OF DILUENT ADDED AND SONICATED FOR 50 MIN, FURTHER THE VOLUME MADE UP WITH DILUENT AND FILTERED.

PREPARATIONOFSAMPLEWORKINGSOLUTIONS(100%SOLUTION):FROMTHEFILTEREDSOLUTION0.5ML WAS PIPETTE OUT INTO A 10 ML VOLUMETRIC FLASK AND MADE UPTO 10ML WITH DILUENTS. (500PPM METFORMIN, 5PPM DAPAGLIFLOZIN&2.5PPMSAXAGLIPTIN)

4. **ASSAY:** QTERNMET XR (1000+10+5) THE LABEL CLAIM DAPAGLIFLOZIN 5MG METFORMIN 500MG SAXAGLIPTIN 2.5MG PER UNIT FORMULATION ASSAY WAS PERFORMED WITH THE ABOVE FORMULATION. AVERAGE % ASSAY FOR METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN. OBTAINED WAS 99.84%,99.69% AND 99.54%RESPECTIVELY.

DRUG	**AREA**	**LABELED AMOUNT(MG)**	**AMOUNT PRESENT(MG)**	**% ASSAY**

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METFORMIN,	3015691	500	500.63	99.84
SAXAGLIPTIN	302979	2.5	2.47	99.69
DAPAGLIFLOZIN	510717	5	4.95	99.54

TABLE-II-ASSAY CONDITIONS

VALIDATION

PARAMETER	**ACCEPTANCE CRITERIA**	**METFORMIN**	**DAPAGLIFLOZIN**	**SAXAGLIPTIN**
SYSTEM SUITABILITY PARAMETERS	% RSD = NOT BE MORE THAN 2%	0.8	0.6	1.1
PRECISION	RSD < 2%	1.1	1.1	1.7
LINEARITY	CORRELATION COEFFICIENT R^2 > 0.999	R^2 = 0.999	R^2 = 0.999	R^2 = 0.999
ACCURACY	RECOVERY 98-102% (INDIVIDUAL)	RECOVERY (50%) = 98.04%	RECOVERY (50%)= 99.47	RECOVERY (50%) = 100.53%
		RECOVERY (100%) =99.28	RECOVERY (100%) 101.07	RECOVERY (100%) =100.21 %
		RECOVERY (150%) =99.25	RECOVERY (150%)=101.42	RECOVERY (150%) =101.31
ROBUSTNESS	RECOVERY 98- 102%	COMPLIES	COMPLIES	COMPLIES
	FLOW RATE (-) 0.9ML/MIN	%RSD=1.2	%RSD=1.1	%RSD=1.3
	FLOW RATE (+) 1.1ML/MIN	%RSD=1.4	%RSD=1.1	%RSD=1.2
	MOBILE PHASE (-) 60B:40A	%RSD=1.1	%RSD=1.0	%RSD=0.9

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	MOBILE PHASE (+) 50B:50A	%RSD=1.9	%RSD=1.6	%RSD=1.9
	TEMPERATURE (-) 25°C	%RSD=1.7	%RSD=1.8	%RSD=1.7
	TEMPERATURE (+) 35°C	%RSD=1.5	%RSD=1.8	%RSD=1.7
LOD		4.50 µG/ML	0.10 µG/ML	0.02 µG/ML
LOQ		13.65 µG/ML	0.31 µG/ML	0.05 µG/ML

TABLE:III-VALIDATION RESULT DEGRADATION:

S.NO	DEGRADATION CONDITION	ANALYTE PEAK AREA	% AREA RECOVERY	% DRUG RECOVERY
1	ACID	2840763	94.38	5.62
2	ALKALI	2884216	95.83	4.17
3	OXIDATION	2908982	96.65	3.35
4	THERMAL	2940115	97.68	2.32
5	UV	2971856	98.74	1.26
6	WATER	2983638	99.13	0.87

TABLE III DEGRADATION DATA OFMETFORMIN.

S.NO	DEGRADATION CONDITION	ANALYTE PEAK AREA	% AREA RECOVERY	% DRUG RECOVERY
1	ACID	286701	94.44	5.56
2	ALKALI	290297	95.62	4.38
3	OXIDATION	292055	96.20	3.80

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4	THERMAL	295191	97.23	2.77
5	UV	298041	98.17	1.83
6	WATER	301933	99.46	0.54

TABLE IV DEGRADATION DATA OFSAXAGLIPTIN

S.NO	DEGRADATION CONDITION	ANALYTE PEAK AREA	% AREA RECOVERY	% DRUG RECOVERY
1	ACID	482220	94.23	5.77
2	ALKALI	487692	95.30	4.70
3	OXIDATION	491872	96.12	3.88
4	THERMAL	498894	97.49	2.51
5	UV	501661	98.03	1.97
6	WATER	507169	99.11	0.89

TABLE V DEGRADATION DATA OF DAPAGLIFLOZIN

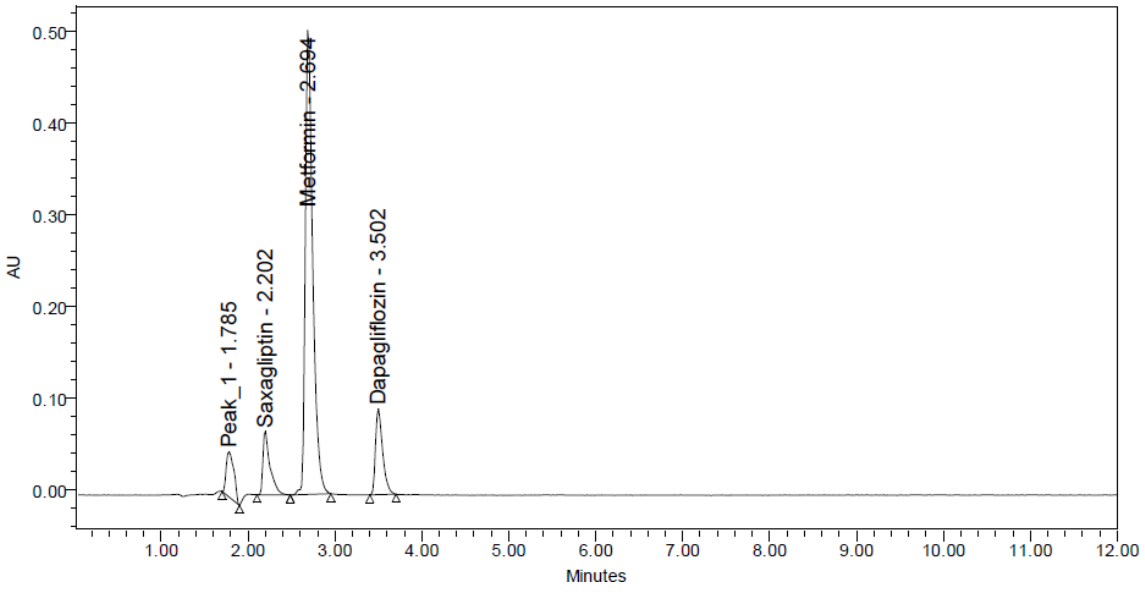

FIG I ACID DEGRADATION CHROMATOGRAM OF METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN

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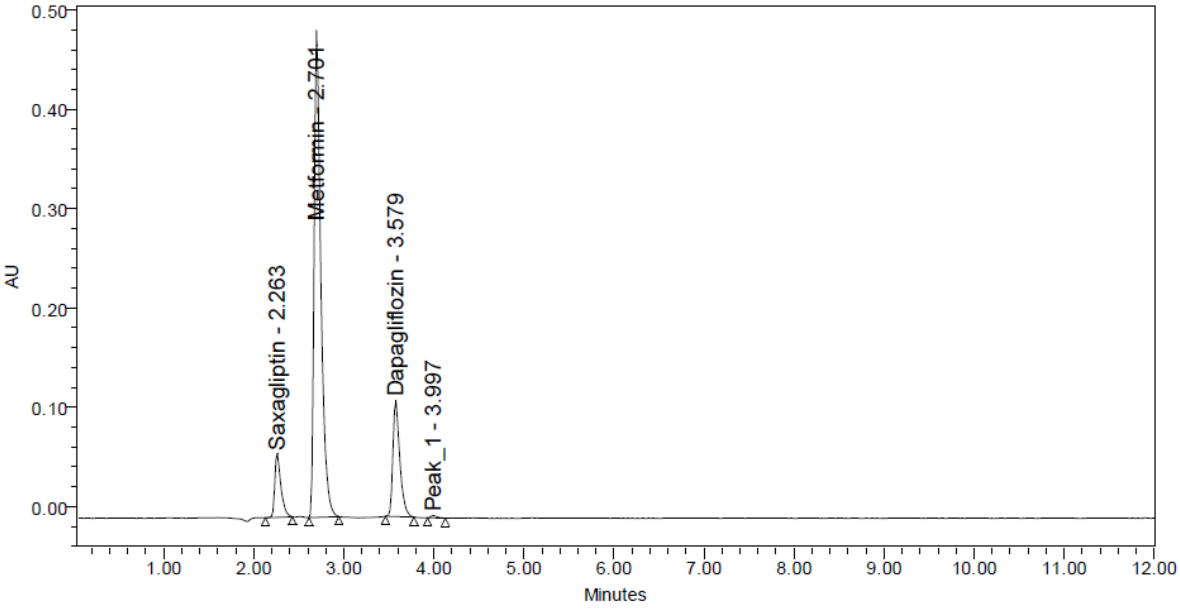

FIG II BASE DEGRADATION CHROMATOGRAM OF METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN

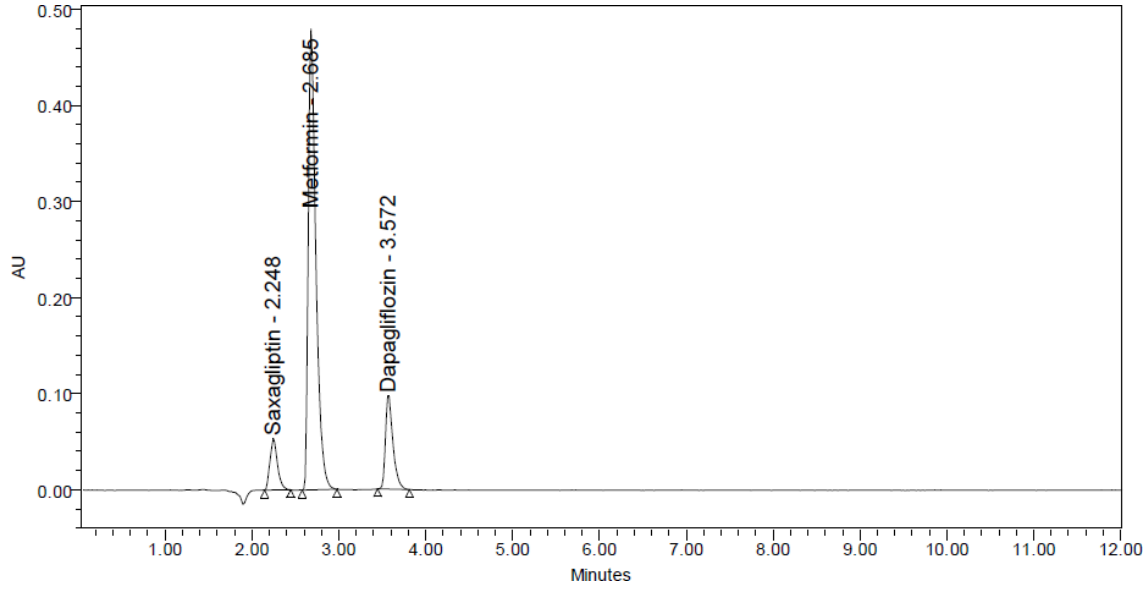

FIG III PEROXIDE DEGRADATION CHROMATOGRAM OF METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN

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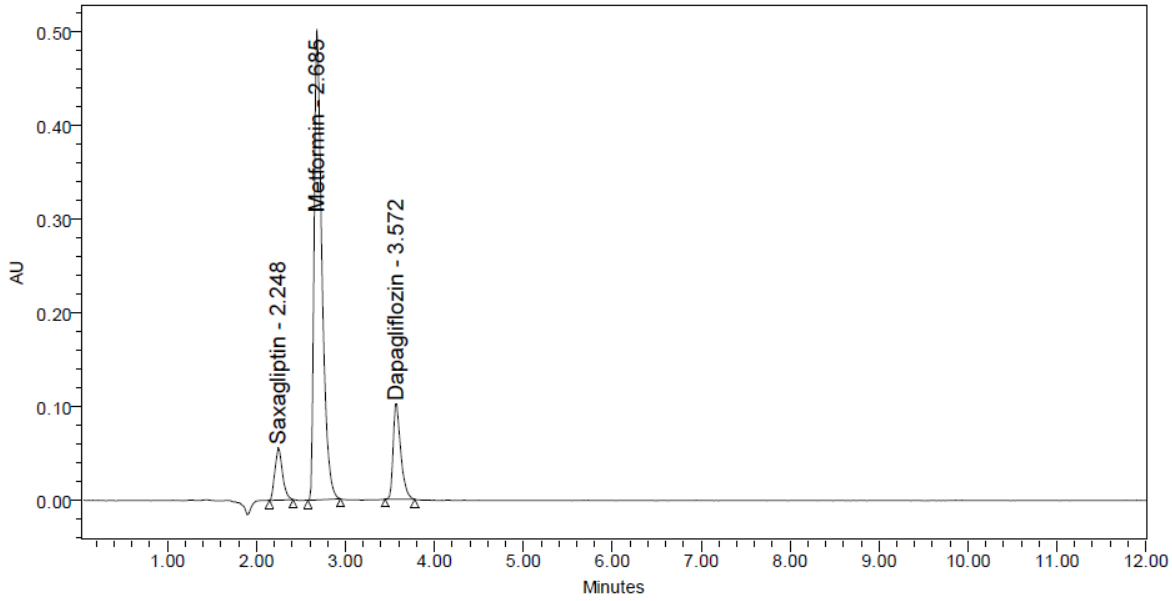

FIG IV THERMAL DEGRADATION CHROMATOGRAM OF METFORMIN, DAPAGLIFLOZIN & SAXAGLIPTIN

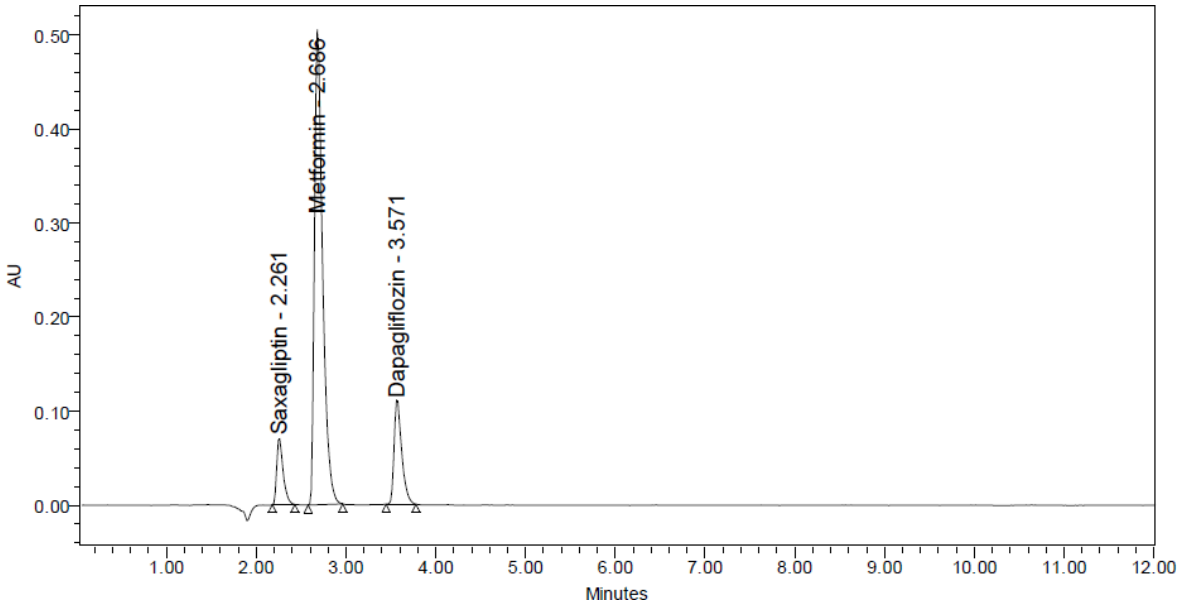

FIG V UV DEGRADATION CHROMATOGRAM OF METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN

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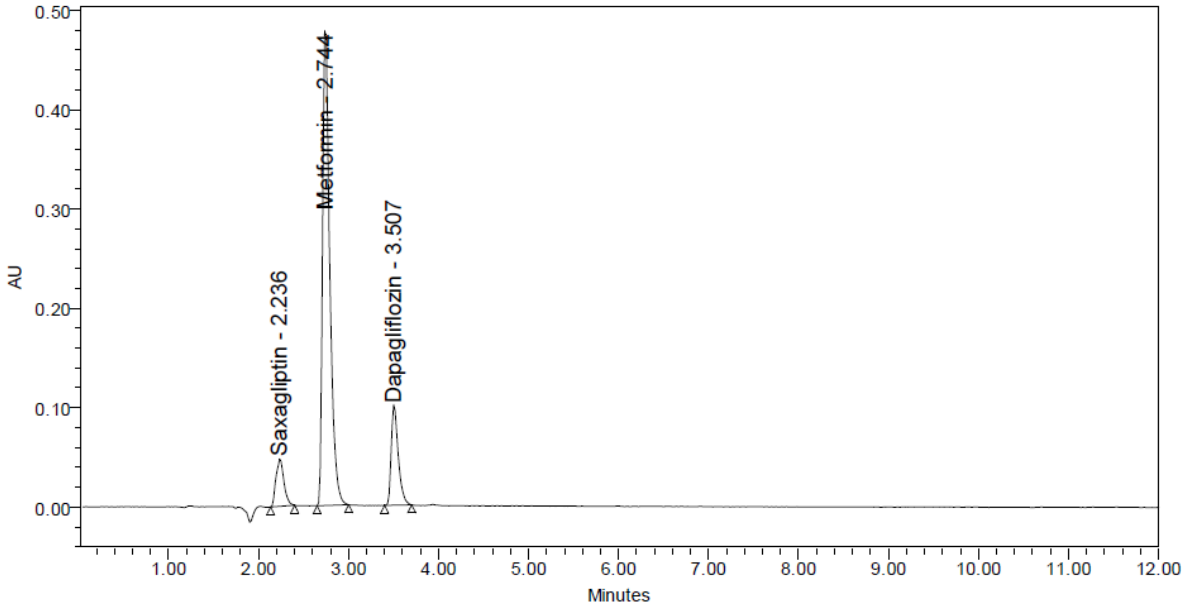

FIG VI WATER DEGRADATION CHROMATOGRAM OF METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN

RESULTS AND DISCUSSION:

PARAMETERS		METFORMIN.	SAXAGLIPTIN	DAPAGLIFLOZIN	LIMIT
LINEARITY RANGE (µG/ML)		125-750µG/ML	0.625-3.75µG/ML	1.25-7.5 µG/ML	R< 1
REGRESSIONCOEFFICIENT		0.999	0.999	0.999	
SLOPE(M)		5934	119948	101914	
INTERCEPT(C)		13728	2393.4	5013	
REGRESSION EQUATION (Y=MX+C)		Y = 5934X + 13728	Y = 119948X + 2393.4	Y = 101914X + 5013	
ASSAY (% MEAN ASSAY)		99.84%	99.69%	99.54%	90-110%
SPECIFICITY		SPECIFIC	SPECIFIC	SPECIFIC	NO INTERFERENCE OF ANY PEAK
SYSTEM PRECISION %RSD		1.1	1.7	1.1	NMT 2.0%
METHOD PRECISION %RSD		0.8	1.1	0.6	NMT 2.0%
ACCURACY % RECOVERY		98.94%	100.35%	100.13%	98-102%
LOD		4.50/ML	0.02µG/ML	0.10µG/ML	NMT 3 µG/ML
LOQ		13.65G/ML	0.05µG/ML	0.31µG/ML	NMT 10µG/ML
ROBUSTNESS	FM	1.2	1.3	1.1	%RSD NMT 2.0
	FP	1.4	1.2	1.1	
	MM	1.1	0.9	1.0	
	MP	1.9	1.9	1.6	

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	TM	1.7	1.7	1.8	
	TP	1.5	1.7	1.8	

CONCLUSION:

A SIMPLE, ACCURATE, PRECISE METHOD WAS DEVELOPED FOR THE SIMULTANEOUS ESTIMATION OF THE METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZININ TABLET DOSAGE FORM. RETENTION TIME OF SAXAGLIPTIN, METFORMIN AND DAPAGLIFLOZIN WERE FOUND TO BE 2.253MIN, 2.701MIN AND 3.598MIN. %RSD OF SYSTEM PRECISION FOR METFORMIN, SAXAGLIPTIN AND DAPAGLIFLOZIN WERE AND FOUND TO BE 1.1, 1.7 AND

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CONFLICTS OF INTREST:

THE AUTHORS ARE NOT HAVING ANY CONFLITS OF INTREST. ALL AUTHORS ARE CONTRIBUTED EQUALLY AND WRITING THE RESEARCH PAPER.

ACKNOWLEDGEMENT: THE AUTHORS ARE VERY MUCH THANKFUL TO THE MANAGEMENT, PRINICIPAL AND STUDENTS OF NIRMALA COLLEGE OF PHARMACY, ATMAKUR, MANGALAGIRI, GUNTUR, AP

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