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The Review Article on – Analytical Method Development and Validation of Oral Anti-Diabetics Pharmaceutical Dosage form based on Recent Literature

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ABSTRACT:

The presented study's recent literature review of analytical method development and validation of oral antidiabetic drugs' chemical nature, and structure for diabetes mellitus (DM) is a disorder this is putting a growing burden on health carrier delivery internationally. Insulin secretagogues (Sulfonylureas), Fast-acting prandial insulin releasers ('Repaglinide, Nateglinide'), Insulin Sensitizers: Biguanides ('Metformin Phenformin'), Thiazolidinedione ('Pioglitazone, Rosiglitazone, Ciglitazone, Troglitazone'), Glucosidase inhibitors (Acarbose), New drug modalities: Incretins (Vildagliptin, Sitagliptin, Alogliptin, Teneligliptin, Saxagliptin'), SGLT-2 inhibitors ('Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin')

Analytical techniques play a decisive role by providing solutions like development. This paper could be a review and classification of the various analytical methods that are the foremost widely used in determining common provision issues. Pharmaceutical analysis plays an extremely outstanding conspicuous role in quality assurance, like internal control of bulk medication and pharmaceutical formulations. The fast increase in pharmaceutical industries and the production of drugs in numerous components of the globe has increased the demand for brand-new analytical techniques within the pharmaceutical industries. As an outcome, analytical methodology development has become the essential activity of study. Recent development in analytical ways has resulted from the advancement of analytical instruments.

KEYWORDS: Introduction of oral anti-diabetes drugs of all class, Pharmacology, Pharmacokinetics, Analytical Methods etc.

INTRODUCTION:

Type 2 diabetes mellitus (DM) is a disease characterized by the resource of insulin resistance and a progressive decline in pancreatic beta-mobile characteristics associated with growing hyperglycemia. Faulty beta-mobile characteristic occurs early and may be detected in people with impaired fasting and/or submit-prandial glucose tiers (the so-referred to as 'pre-diabetics'). The UK ability Diabetes (UKPD) [1-3] looks at indicates that by the time type 2 DM is recognized, people have already misplaced as much as 50% of their beta-cell traits. The decline in characteristic proceeds at 6% constant with yr, that is 20 times more than that explained through normal getting older.

This newsletter intends to gift a pinnacle-degree view of all the to-be-had oral antidiabetic tablets according to their unique classes, mechanisms of movement, and pharmacological profiles, and to assist physicians in making the correct choice for their patients. [4-6]

The literature review disclosed that a small wide variety of analytical methods square measure used for estimation of those oral anti-diabetics pills however there may be the development of an analytical techniques for the determination of Insulin secretagogues (Sulfonylureas), speedy-acting prandial insulin releasers ('Repaglinide, Nateglinide'), Insulin Sensitizers: Biguanides ('Metformin Phenformin'), Thiazolidinedione ('Pioglitazone, Rosiglitazone, Ciglitazone, Troglitazone'), Glucosidase inhibitors (Acarbose), New drug modalities: Incretins (Vildagliptin, Sitagliptin, Alogliptin, Teneligliptin, Saxagliptin'), SGLT-2 inhibitors ('Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin') this drug from its pharmaceutical dosage form. Because of the shortage of discovered liquid natural process ways for oral anti-diabetics drugs, this painting aimed to develop a reversed-section liquid natural process (RP-LC) technique that may be suitable for figuring out these oral anti-diabetics drugs from its pharmaceutical dosage type. The projected technique is simple, accurate, duplicatable, and suitable for the recurring determination of those oral anti-diabetics capsules from their pharmaceutical dose kind. [7-8]

Table: 01: Drug Profile:

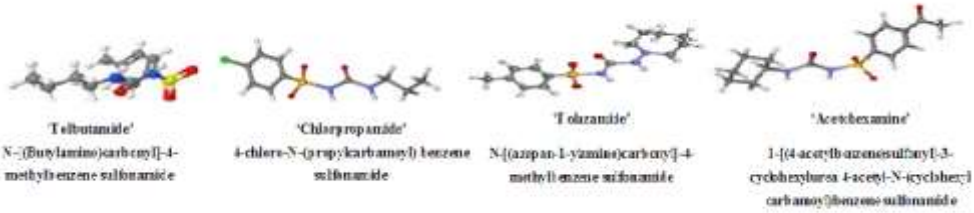
DRUG	Sulfonylureas
IUPAC Name	A central S-arylsulfonylurea structure with a p-substituent on the phenyl ring (R1) and various groups terminating the urea N′ end group (R2).

Chemical Formula	CH2N2O3S
Molecular Mass	244.2 g/mole
Melting Point	200— 203°C
Physical State	Solid
Solubility	Soluble in Water and Methanol
pKa	Azobenzene sulfonylurea 4.17 with a pK a of 4.76 readily dissolves in water at sufficiently high concentrations
t1/2	3 – 5 hrs.
Therapeutic Use	Used to reduce hyperglycemia in type2 diabetes mellitus.

Insulin secretagogues: Sulfonylureas –

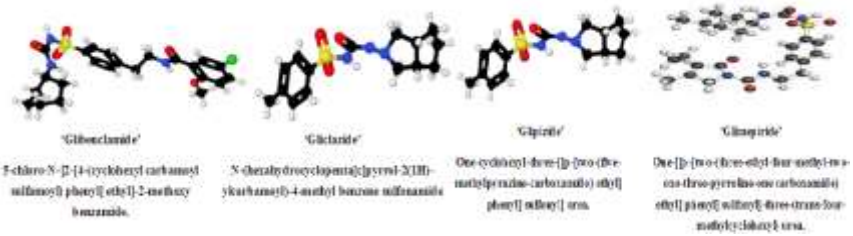
A) First generation Sulfonylureas – (‘Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamine.’)

Fig 01: Structure and chemical name of Insulin secretagogues-First generation-



B) Second generation Sulfonylureas-(‘Glibenclamide, Gliclazide, Glipizide, and Glimepiride’) the sulphonylureas (SUs):

Fig 02: Structure and chemical name of Insulin secretagogues-Second generation.



Pharmacology: Sulfonylureas first and second technology (‘Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamine.’) (Glibenclamide, Gliclazide, Glipizide, and Glimepiride) the sulphonylureas (SUs) have been, initially, advanced in the Twenties and have grown to be crucial in the control of type 2 DM. The sulfonylureas lower blood glucose thru a boom inside the secretion of insulin from the pancreatic beta cells. Their number one mechanism of action is to shut ATP-sensitive ok-channels in the beta-mobile plasma membrane, and so initiate a sequence of activities that outcomes in insulin release. The mechanism of motion entails a direct secretory impact on the pancreatic islet beta-cells. Adenosine triphosphate (ATP) - touchy potassium channels of the beta-cells play an essential function inside the launch of insulin and encompass two components: a pore and a regulatory subunit (SUR-1). The sulphonylureas act to enhance the sensitivity of the beta-cell to glucose and, even as positive to the transmembrane sulphonylureas receptor (SUR-1), mediate the very last of the potassium-sensitive ATP channels at the cell membrane. Cellular efflux of potassium is reduced and membrane depolarization takes place. Calcium influx is mediated via the hollow of voltage-based Ca2+ channels that sell the discharge of pre-long-established insulin granules which lie simply adjacent to the plasma membrane. [9]

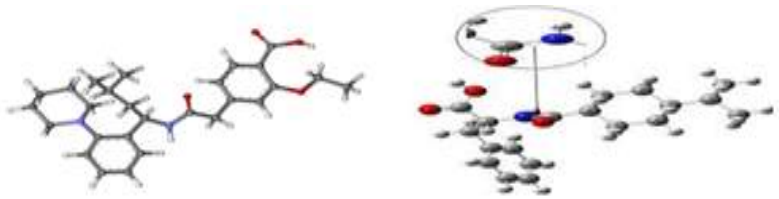
Sulphonylureas decorate the so-known first section of insulin secretion whereby the insulin-containing granules close to the plasma membrane are released in addition to the so-known as 2nd phase of insulin launch a couple of minutes later whilst more excellent insulin granules are translocated from the cytoplasm to the beta-cell membrane and launched by ATP-established exocytosis.[10] Hypoglycemia can occur because those capsules potentiate the release of insulin even if glucose concentrations are beneath the everyday threshold for glucose-stimulated insulin launch (<5 mmol/l).[11-12]

Pharmacokinetics: Sulphonylureas are well absorbed after oral administration and reach peak plasma concentrations within 2 - four hours food ingestion appears to have little or no effect on their efficacy, however, it's far despite the fact that it suggested that they be taken a minimum of 15 - 20 mins earlier than a meal.

Glibenclamide is considered an intermediate-acting drug (12 - 24 hours) with lively metabolites of which about 50% are eliminated by way of the liver. Gliclazide additionally has a duration of motion of 12 - 24 hours, however, as much as 65% of active metabolites are excreted especially by the kidneys.[12] Glimepiride has a length of action of approximately 24 hours and is removed with the aid of the liver.[13]

Fast-acting prandial insulin releasers (‘Repaglinide, Nateglinide’):

Fig 03: Structure and chemical name of Fast-acting prandial insulin releasers.



'Repaglinide' (S)-2-Ethoxy-4-(1-[2-{piperidin-1-yl}phenyl]-3-Methylbutylcarbamoylmethyl) benzoic acid)

'Nateglinide' (2R)-2-({[Trans-4-(1-methylethyl)cyclohexyl] carbonyl} amino)-3-phenylpropanoic acid

Pharmacology: In the natural history of type 2 diabetes, a blunted reaction of the primary section of glucose-inspired insulin launch has been determined. An initial surge of insulin is important to suppress hepatic gluconeogenesis inside the postprandial length. If this mechanism fails, the postprandial effect of the first phase of insulin secretion, but the effect on the second phase is not sustained. [14-23]

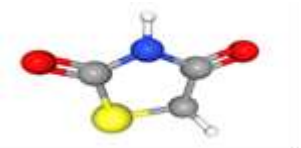
Pharmacokinetics: Repaglinide pharmacokinetic profile shows that it is rapidly absorbed after oral intake and can reach peak concentrations within 1 hour (t½ =0.6 hours). The duration of action is 4 - 5 hours; the drug is metabolized by the liver and excreted in both feces and urine. [24] Nateglinide has t½ = 1.5 hours and a duration of action of 5 - 6 hours. In contrast to repaglinide, this drug has active metabolites. Excretion is in bile and urine. [24-25]

Insulin Sensitizers:

Table: 02: Drug Profile:

DRUG	Biguanides	Thiazolidinedione
IUPAC Name	Imidodicarbonimidic Diamide	1,3-thiazolidine-2,4-dione
Chemical Formula	$C_2H_7N_5$	C3H3NO2S
Molecular Mass	101.113 g·mol^{-1}	117.13 g/mole
Melting Point	136°C	125-127 °C
Physical State	Solid	Solid
Solubility	Dissolves in water to give highly basic solution.	sparingly soluble in a variety of common organic solvents including water, MeOH, EtOH, DMSO and Et2O
pKa	3.07, 13.25	Strongest Acidic), 7.36
t1/2	10 – 11 Hrs	3 – 5 hrs.
Therapeutic Use	Antihyperglycemic agents	Used to reduce hyperglycemia in type2 diabetes mellitus.

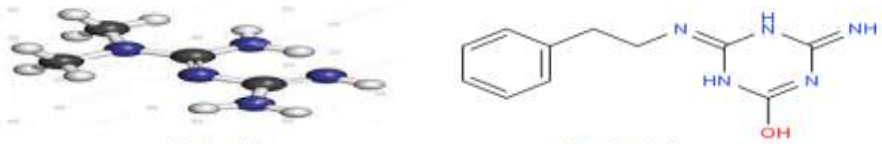
Biguanides



Thiazolidinedione

Biguanides ('Metformin, Phenformin'):

Fig 04: Structure and chemical name of Biguanides ('Metformin, Phenformin'):



'Metformin' (1, 1-Dimethylbiguanide hydrochloride)'

'Phenformin' 2-(N-phenethylcarbamimidoyl)guanidine

Pharmacology: Metformin has been available since the 1950s. Its historic roots and origin can be traced back to the guanidine-rich Galega officinalis (goat's rue or French lilac) which has traditionally been used in Europe to treat diabetes. Metformin has a variety of clinical actions that extend beyond just the glucose-lowering effects such as weight reduction, improving lipid profiles, and vascular effects, which includes improving endothelial function, as well as decreasing PAI-1 levels. [26-28] the molecular mechanisms of action have not as yet been clearly established. However, it is thought that insulin sensitivity is improved and mediated via modification of post-receptor signaling in the insulin pathway. A protein, adenosine 5'-monophosphate protein kinase, has been identified as a possible target of Metformin. [29- 30]

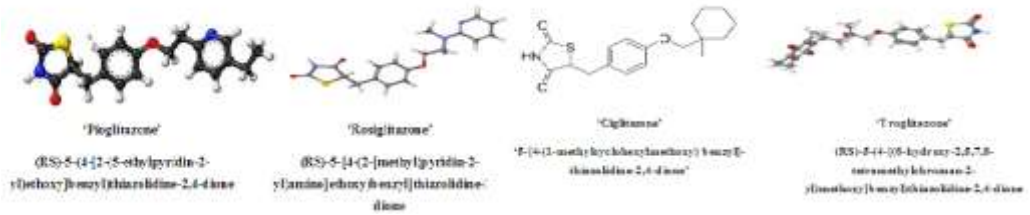
Pharmacokinetics: Metformin is fast absorbed and completely removed inside the urine via tubular secretion. Consequently, its miles prudent to keep away from this drug in sufferers with impaired renal characteristics. Metformin needs to be discontinued prior to contrast studies, e.g. angiographic

evaluations because it has been implicated in the development of comparison-precipitated nephropathy. The iodinated contrast media compete with Metformin for tubular secretion, and caution is important if the management of competing substances is needed. In view that Metformin isn't bound to plasma proteins and isn't always metabolized; it no longer intervenes with co-administered medicine. In patients with the everyday renal feature, the plasma t½ is 2 - 5 hours, with 90% of the dosage eliminated within 12 hours. Biguanides are generally taken into consideration as the medication of choice in obese type 2 diabetics. Metformin can be used in aggregate with another magnificence of oral antidiabetic drug or with insulin. Metformin is likewise used within the treatment of polycystic ovarian syndrome (PCOS) to enhance insulin sensitivity and decrease circulating androgen degrees. It also improves ovulation and menstrual cyclicity.

Contra indications include the presence of underlying impairment of renal function, conditions predisposing to hypoxia or reduced perfusion because of the increased risk of lactic acidosis, liver disease, and alcohol abuse and, a history of a previous episode of lactic acidosis. Contraindications include the presence of underlying impairment of renal function, conditions predisposing to hypoxia or reduced perfusion because of the improved danger of lactic acidosis, liver disorder, alcohol abuse, and a history of a previous episode of lactic acidosis reported in the literature. Abdominal discomfort and diarrhea are the most frequent side effects. Vitamin B_{12}deficiency owing to decreased GIT absorption can occur. [31-35]

Thiazolidinedione ('Pioglitazone, Rosiglitazone, Ciglitazone, Troglitazone'):

Fig 05: Structure and chemical name of Thiazolidinedione:



Pharmacology: With the introduction of this new class of drugsin1997, the world has watched the peroxisome proliferator-activated receptor (PPAR)–η agonists with anticipation. The net effect of these drugs results from the stimulation of a nuclear PPAR-η that regulates the transcription of genes increase in insulin sensitivity. Troglitazone, the fore runner drug, was withdrawn in 2000 following reports of fatal hepatotoxicity, and the future of Rosiglitazone currently hangs in the balance, owing to a possible increased risk of myocardial infarction and cardiovascular-related deaths. [36-40]

Thiazolidinedione (TZDs) mediate their function through binding to the PPAR-η receptor that is expressed predominantly in adipocytes. It is expressed to ales serextentin muscle and liver tissue. The Binding of the PPAR-η receptor in turn mediates binding to their tonic-X receptor (RXR-receptor). This hetero dimmer then binds to a nuclear response element which then witches on gene transcription. Many of the genes

That are activated play a central role in carbohydrate and lipid metabolism.TZDs, like Metformin, require the presence of insulin to mediate a blood glucose-lowering effect. Interestingly, thiazolidinedione also suppresses the expression of TNF-α by adipocytes.

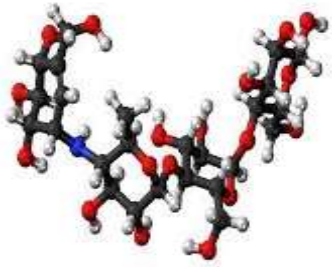
Pharmacokinetics: The pharmacokinetics of these drugs indicates that both Rosiglitazone and Pioglitazone are rapidly absorbed after a meal, reaching peak concentrations within 1-2 hours. Both drugs undergo hepatic metabolism, with Rosiglitazone excreted mainly in urine and Pioglitazone in bile. Although Rosiglitazone and Pioglitazone are metabolized by CYP2C8 and CYP3A4 respectively, no major drug interactions have been reported. This class of drug can be used as monotherapy in obese as well as non-obese patients who have failed other conservative measures. TZDs can be used in combination with Metformin and sulphonylureas their use is not recommended in this condition, since these drugs display gene activity that may be harmfully nearly pregnancy. Another complication related to the use of this class of drug is that of TZD induced low formation osteoporosis. Already in 2006, evidence of increased fracture risk with Rosiglitazone emerged as the data of the ADOPT trial were published. [41-42] these trial data reported an increased fracture risk inwomenbutnotinmen.Significantbonelosswithanincreasedfracturerisk only became the use in aggregate with insulin is illegitimate in Europe because of the increased risk of weight gain inside the form of adipogenesis and fluid retention. The usage of TZDs has been contraindicated in acute liver ailment thanks to the increased hazard of hepatotoxicity. Seeing that they lower hepatic glucose output, the priority exists that they may probably aggravate hypoglycemia.

Ciglitazone (INN) is a thiazolidinedione. Developed by Takeda Pharmaceuticals in the early 1980s, it is considered the prototypical compound for the thiazolidinedione class. Ciglitazone become never been used as a remedy, but it sparked interest in the results of thiazolidinedione. Several analogs have later developed, a number of which—inclusive of Troglitazone—made it to the market. Ciglitazone drastically decreases VEGF manufacturing by way of the use of human granulosa cells in vitro take a look at and can doubtlessly be applied in ovarian hyperstimulation syndrome. Ciglitazone is a first-rate and selective PPARγ ligand. It binds to the PPARγ ligand-binding area with an EC50 of 3.0 μM. Ciglitazone is active in vivo as an anti-hyperglycemic agent in the ob/ob murine version. [6] Inhibits HUVEC differentiation and angiogenesis and also stimulates adipogenesis and reduces osteoblastogenesis in human mesenchymal stem cells. [43-49]

Glucosidase inhibitors (Acarbose):

Table: 03: Drug Profile:

DRUG	Acarbose
IUPAC Name	"O-4,6-dideoxy-4-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl] amino]-α-d-glcopyranosyl-(1 → 4)-O-α-d-glcopyranosyl (1 → 4)-d-glucose (8)"
Chemical Formula	C25H43NO18
Molecular Mass	645.6 g/mole
Melting Point	165–170 °C
Physical State	Solid
Solubility	soluble in water
pKa	5.1
t1/2	3 – 5 hrs.
Therapeutic Use	Used to reduce hyperglycemia in type2 diabetes mellitus.



Pharmacology: Acarbose turned into the primary glucosidase inhibitor and was introduced to the market in the early 1990s. This magnificence of the drug has the advantage of decreasing postprandial hyperglycemia without associated weight gain. Its usage is at gift hampered with the aid of unfortunate gastrointestinal side consequences in spite of an awesome safety document. The α-glucosidase inhibitors inhibit the activity of the glucosidase enzymes which might be present inside the brush border of enterocytes within the intestinal villi. Disaccharide and oligosaccharide cleavage is prevented with a net decrease in intestinal carbohydrate absorption. Typical, α -glucosidase inhibitors reduce postprandial insulin concentrations via the attenuated rise in postprandial glucose levels much less than 2% of the drug is absorbed.

Pharmacokinetics: It's far broken down by means of intestinal amylases and positive intestinal microorganisms. Some degradation products are taken up and subsequently eliminated within the urine. The drug needs to be desirous about the primary chewing of meals delays gastric emptying reduces food consumption and allows weight reduction. Using those tablets is contraindicated in pregnancy and breastfeeding. Efficacy measures show that postprandial glucose levels may be lowered by means of 1 - 4 mmol/l. A median decrease in HbA1C of 0.5 - 1.0% can be predicted. Side outcomes consist of flatulence, stomach discomfort, and diarrhea, but tolerance to the aspect effects fast develops. Hypoglycemia can occur most effectively if used together with sulphonylureas or insulin.

New drug modalities: Incretins (Vildagliptin, Sitagliptin, Alogliptin, Teneligliptin, Saxagliptin'):

Table: 04: Drug Profile:

DRUG	Incretins
IUPAC Name	glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1)
Chemical Formula	C226H338N60O66S
Molecular Mass	4984g/mole
Melting Point	208 - 212 °C
Physical State	Solid
Solubility	soluble in water
pKa	5.1
t1/2	3 – 5 hrs.
Therapeutic Use	Used to reduce hyperglycemia in type2 diabetes mellitus.

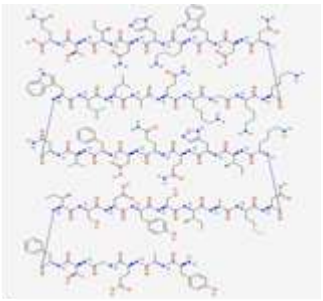


Fig 06: Structure and chemical name of New drug modalities-Incretins.

'Vildagliptin' 'Sitagliptin'

'Alogliptin'

2-({6-[(3R)-3-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile

'Teneligliptin'

[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl]-3-thiazolidinyl-methanone, hydrobromide hydrate

'Saxagliptin'

(1S,3S,5S)-2-[(2S)-2-amino-2-[(5S,7R)-3-hydroxy-1-adamantyl]acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile

The small intestine secretes glucagon-like peptide-1 (GLP-1) as well as glucose-dependent insulin tropic polypeptide (GIP, previously called a gastric inhibitory peptide) in response to food intake. These hormones stimulate insulin secretion, insulin gene expression, and pancreatic beta-cell growth. Furthermore, they mediate the incretin effect which augments insulin secretion following oral administration of glucose. The GLP-1 molecule is subject to rapid degradation by the DPP-IV (dipeptidyl peptidase) enzyme. Patients with type 2 diabetes have greatly impaired or absent incretin-mediated insulin secretion due to a decrease in the level of GLP-1 which leads to a decrease in the glucose-dependent secretion of insulin by the pancreatic beta-cells. [49, 50]Several therapeutic strategies are currently undergoing clinical trials, namely:

- DPP-IV enzyme inhibitors (Vildagliptin, Sitagliptin).

'Vildagliptin': This drug is taken in oral format a once-daily dosage. Inhibition of dipeptidyl peptidase-IV (DDP-IV) stimulates insulin secretion in a glucose-dependent fashion, minimizing possible hypoglycemic side effects. Inhibition of DDP-IV is dose-dependent. Recent data suggest restorative effects on pancreatic islet cells, thereby fueling thehopethattheDDP-IVinhibitorscouldpotentiallysloworreversethecourseofbeta-cellfailure. [53-55]

"Sitagliptin" This medicine is also a DDP- IV asset and can be used as monotherapy in Type 2 diabetes or in combination with Metformin, the SUs, or the TZDs if the being authority no longer provides acceptable glycemic control. It has not yet been studied in combination with insulin. Sitagliptin is taken orally and has been shown to reduce HbA1C situations by0.6- 1.

"Alogliptin" After eating a sensible diet and exercising constantly, people who nonetheless have high blood sugar are specified the drug" Alogliptin." It works by adding the quantum of insulin that your body produces. The hormone that regulates blood sugar situations is insulin. It's judicious to gain an Alogliptin with a tradition.

"Teneligliptin" Teneligliptin is a lately created oral dipeptidyl peptidase 4 assets that's used to treat type 2 diabetes mellitus (T2DM) in grown-ups together with a healthy diet and exercise.

"Saxagliptin" Saxagliptin is used to treat high blood sugar (glucose) situations in people with type 2 diabetes when they follow the correct diet and exercise authority.

SGLT- 2 inhibitors –'Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin'.

Table: 05: Drug Profile:

DRUG	SGLT-2 inhibitors
IUPAC Name	Sodium-glucose cotransporter-2
Chemical Formula	C22H19O5
Molecular Mass	363 g/mole
Melting Point	103- 109 °C
Physical State	Solid
Solubility	soluble in water
pKa	12.57
t1/2	8 – 16 hrs.
Therapeutic Use	Used to reduce hyperglycemia in type 2 diabetes mellitus.

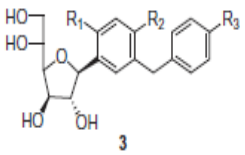


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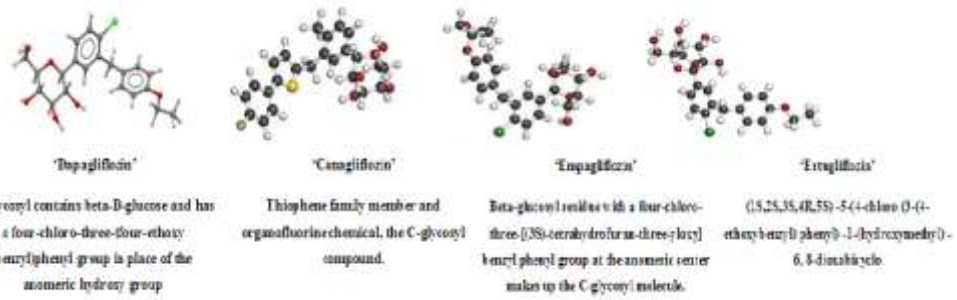
Fig 07: Structure and chemical name ofSGLT-2 inhibitors.



Pharmacology: In individuals with type 2 diabetes, the use of SGLT2 inhibitors, a class of prescription medications, along with dietary restrictions and exercise programmers, may be allowed by the FDA. The SGLT2 inhibitor class of medications consists of Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin. The FDA has approved the use of Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin for treating type 2 diabetes mellitus (DM) in individual patients in order to enhance blood sugar control in conjunction with diet and exercise.

Pharmacokinetics: The four retailers all work to lower the renal threshold for glucose (RTG), increase urine glucose excretion, and inhibit sodium-glucose transport protein 2 (SGLT2) proteins expressed inside the renal proximal convoluted tubules. This curiosity will emphasize the mechanism of motion, the profile of adverse events, and other crucial

Analytical methods for estimation of oral anti-diabetic's drugs:

Table: 06: Estimation of oral anti-diabetic's drugs by HPLC: High-performance liquid activity (or high liquid activity, HPLC) could be a specific type of chromatography usually employed in organic chemistry and analysis to separate, identify, and quantify the active compounds.

Sr. no	Drug name	Description	Reference
01.	Repaglinide	1. Mobile phase: Methanol-0.2% Heptane Sulphonate Sodium (70:30 V/V) 2. Flow rate: l.0ml/min 3. Detection: 287 nrn 4. Retention Time: 14.21min 5. Limit of detection: 0.14µg/ml 6. Limit of quantification: 0.47 µg/ml 7. Linearity range:1-10 µg/ml 8. Calibration curve: 1-10 µg/ml(r2=0.9997) 9. Percentage recovery: -99.58-100.45 ± 0.386-0.931. % 10. Thermo C18 column (250 x 4.6 x 5µ particle size).	52
02.	Nateglinide	1. Mobile phase: acetonitrile: phosphate buffer pH-5.5,70:30%v/v 2. Flow rate: l.0ml/min 3. Detection: 210 nrn 4. Retention Time: 4.47 min 5. Limit of detection: 0.523 µg/ml 6. Limit of quantification: 1.743 µg/ml 7. Linearity range:0.5-200 µg/ml 8. Calibration curve: 0.5-200 µg/ml (r2=0.9997) 9. Percentage recovery: 100.19±0.0672 % 10.Hypersil ODS C18, 4.6mm x 250mm, 5µm	53
03.	Metformin	1. Mobile phase: of phosphate buffer (Ph4.0): Acetonitrile: methanol (30:60:10) 2. Flow rate: l.0ml/min 3. Detection: 221 nrn 4. Retention Time: 2.25min 5. Limit of detection: 2.18µg/ml 6. Limit of quantification: 8.52µg/ml 7. Linearity range: 60.-140 µg/ml 8. Calibration curve: 0.5-200 µg/ml (r2=0.999) 9. Percentage recovery: 99.59-101.36% 10.Inertsil C18-ODS 3V (250×4.6 mm, 5 µm)	54

04.	Phenformin	1. Mobile phase: acetonitrile and 0.01M di-potassium hydrogen phosphate buffer in ratio of 75:25 and adjusting pH 7.0 with orthophosphoric 2. Flow rate: l.0ml/min 3. Detection: 237 nm 4. Retention Time: 11.06 min 5. Limit of detection: 2 ng/mL 6. Limit of quantification: 4.5 ng/mL 7. Linearity range: 1-32 ng/mL 8. Calibration curve: 1-32 ng/mL (r2=0.99) 9. Percentage recovery: 97.19±0.0472 % 10. Grace vyadyec genesis CN (150 × 4.6 mm, 4 µm) column.	55
05.	Pioglitazone	1. Mobile phase: acetonitrile: phosphate buffer, (50:50 v/v) 2. Flow rate: l.0ml/min 3. Detection: 267 nm 4. Retention Time: 8.08 min 5. Linearity range:11.82 ppm to 35.46 ppm 6. Calibration curve: 11.82 ppm to 35.46 ppm (r2=0.99987) 7. C18 column (300 mm × 3.9 mm, 5 µm, particle size)	56
06.	Rosiglitazone	1. Mobile phase: 0.01 M dibasic potassium hydrogen phosphate (pH 6.5) and acetonitrile (65:35, v.v) 2. Flow rate: 2.0ml/min. 3. Detection: 247 nm. 4. Retention Time: 6.5 min. 5. Limit of detection: 5.0 ng/ml. 6. Limit of quantification: 2.5 ng/ml. 7. Linearity range:5-800 ng/ml 8. Calibration curve: 5-800 ng/ml (r2=0.9988) 9. Percentage recovery: -99.11-100.62% 10. (8 x 100 mm 4-µm) Nova-Pak C18 cartridge preceded by a Guard Pak pre-column module with Nova-Pak C18 4-µm insert.	57
07.	Troglitazone	1. Mobile phase: (50 mM aqueous NaH2PO4, pH 4.0): acetonitrile: methanol, (35:50:15, v: v: v) 2. Flow rate: l.0ml/min 3. Detection: 225 nm 4. Retention Time: 14.21min 5. Limit of detection: 0.050 µg/ml 6. Limit of quantification: 0.20 µg/ml 7. Linearity range:50 to 150% 8. Calibration curve: 200pg/ml(r2=0.9999) 9. Percentage recovery: 100.2% 10.YMC ODS-A, 120 A, (4.6_150 mm, 5 mm) column	58
08	Acarbose	1. Mobile phase: acetonitrile–0.007 M phosphate buffer (pH 6.7) (750: 250, v/v) 2. Flow rate: 2.0ml/min 3. Detection: 210 nm 4. Retention Time: 7.5 – 8.0 min 5. Linearity range:2.5–20 mg/mL 6. Calibration curve: 2.5–20 mg/mL (r2=0.9995) 7. Percentage recovery: 99.02 and 97.80% 8. Lichrospher®–100–NH2, 5 µm, 250 × 4.6 mm i.d. column	59
09	Vildagliptin	1. Mobile phase: Methanol and Ammonium hydroxide (25%), Orthophosphoric acid (85%) 2. Flow rate: l.0ml/min 3. Detection: 2l0 nm 4. Retention Time: 6.0 min 5. Limit of detection: 1.47pg/ml 6. Limit of quantification: 4.90pg/ml 7. Linearity range: 50 – 200pg/ml 8. Calibration curve: 50 – 200pg/ml (r2=0.9997)	60

		9. Percentage recovery: -99.11-100.62% 10. Column (150mmxd.6mm, 5pm).	
10.	Sitagliptin	1. Mobile phase: 0.01M KH2PO4: Methanol in the ratio of50:50 % v/v and the pH 2.5 adjusted with 0.2% orthophosphoric acid. 2. Flow rate: 0.7ml/min 3. Detection: 267 nm 4. Retention Time: 3.124 ± 0.016 min 5. Limit of detection: 0.6 µg/ml 6. Limit of quantification: 1.9 µg/ml 7. Linearity range: 5- 30µg/ml 8. Calibration curve: 5- 30µg/ml (r2=0.999) 9. Percentage recovery: 99.84 ± 0.251 10.Zorbax Eclipse XDB C18 (150×4.6 mm, 5µ)	61
11.	Alogliptin	1. Mobile phase: a mixture of Phosphate Buffer: Acetonitrile = 60:40 (pH-2.9) 2. Flow rate: l.0ml/min 3. Detection: 237 nm 4. Retention Time: 6.0 min 5. Limit of detection: 0.02 µg/ml 6. Limit of quantification: 0.06 µg/ml 7. Linearity range: 0.0 – 60 µg/ml 8. Calibration curve: 0.0 – 60 µg/ml (r2=0.9956) 9. Percentage recovery: 99.24 %. 10.Phenomenex Luna C18, 100A, 5µm, 250mmx4.6mm	62
12.	Teneligliptin	1. Mobile phase: Methanol: Phosphate buffer pH:3 [70:30 (v/v)] 2. Flow rate: 0.8 ml/min 3. Detection: 246 nm 4. Retention Time: 3.8 min 5. Limit of detection: 0.109 µg/ml 6. Limit of quantification: 0.3350 µg/ml 7. Linearity range:10 – 50 µg/ml 8. Calibration curve: 10 - 50 µg/ml (r2=0.9968) 9. Percentage recovery: 99.57% 10. Cosmosil C18 (250mm x 4.6ID,Particle size: 5 micron)	63
13.	Saxagliptin	1. Mobile phase:0.05 M KH2PO4 buffer (pH 4.5): Methanol: Acetonitrile (60:20:20 %v/v) 2. Flow rate: 0.6 ml/min 3. Detection: 220 nm 4. Retention Time: 6.92 min 5. Limit of detection: 0.029 µg/mL 6. Limit of quantification: 0.096 µg/mL, 7. Linearity range: 0.2 – 1.2 µg/mL 8. Calibration curve: 0.2 – 1.2 µg/mL (r2=0.998) 9. Percentage recovery: 100.54 ± 1.061% 10.C18 G (250 × 4.6 mm; 5 µm particle size) column	64
14	Dapagliflozin	1. Mobile phase: consisted of Methanol and Water (80:20, v/v). 2. Flow rate: 1.0 ml/min 3. Detection: 235 nm 4. Retention Time: 4.42 min 5. Limit of detection: 2.98 µg/mL 6. Limit of quantification: 2.98 µg/mL, 7. Linearity range: 50 – 90 µg/mL 8. Calibration curve: 50 – 90 µg/mL (r2=0.998) 9. Percentage recovery: 99.98% 10. Inspire (4.6 x 150mm, 5µm)5micro column with isocratic flow	65

15.	Canagliflozin	1. Mobile phase: composition of Ammonium acetate buffer (pH-4.5) and Acetonitrile in the ratio of 30:70% v/v. 2. Flow rate: 1.0 ml/min 3. Detection: 252 nm 4. Retention Time: 4.5min 5. Limit of detection: 0.01 µg/mL 6. Limit of quantification: 0.04 µg/mL, 7. Linearity range:5 – 30 µg/mL 8. Calibration curve: 5 – 30 µg/mL(r2=0.9995) 9. Percentage recovery: 99.70 – 100.1 % 10.nonpolar Inertsil ODS-3 (250 × 4.6 mm, 5µ) column	66
16.	Empagliflozin	1. Mobile phase:(pH 4.8) consisted of 0.1%trifluoroacetic acid solution and acetonitrile (70:30 v/v) 2. Flow rate: 1.0 ml/min 3. Detection: 252 nm 4. Retention Time: 4.5 min 5. Limit of detection: 0.01 µg/mL 6. Limit of quantification: 0.04 µg/mL, 7. Linearity range:0.025-30 µg/mL 8. Calibration curve: 0.025-30 µg/mL (r2=0.999) 9. Percentage recovery: 98.0 to 100.13%. 10.C18 column	67
17.	Ertugliflozin	1. Mobile phase: consisted of Buffer (Potassium di hydrogen Ortho Phosphate): Acetonitrile (70:30 V/V) 2. Flow rate: 1.0 ml/min 3. Detection: 240 nm 4. Retention Time: 3.18min 5. Limit of detection: 0.43 µg/mL 6. Limit of quantification: 1.31 µg/mL, 7. Linearity range:3.75- 22.5µg/mL 8. Calibration curve: 3.75- 22.5µg/mL(r2=0.9992) 9. Percentage recovery: 99.18- 99.13%. 10.Std Agilent column (150×4.6, 5 µm)	68

VALIDATION PARAMETER:

Validation is a fundamental part of any good analytical practice. Method for a specific test is suitable for its intended use to judge the quality, reliability, and consistency of analytical results the method validation is used validation is the process used to confirm that the analytical procedure employed. For method validation USP has published the specific guidelines defines eight steps for validation:

1. Accuracy:
2. Precision
3. Specificity
4. Linearity
5. Range
6. Detection limit
7. Quantitation limit
8. Robustness
9. Ruggedness
10. Sensitivity
11. Repeatability
12. Reproducibility

CONCLUSION:

The oral anti-diabetic drug .it is approved by USFDA. The above study gives the analytical methods for analysis of oral anti-diabetic drug in bulk and tablet dosage form. Literature survey reveals that various methods are reported for the development and validation of various drugs. at present review illustrates various analytical approaches exercised for the evaluation of oral anti-diabetic drug numerous investigations had perform including HPLC in bulk, and pharmaceutical dosage form. These methods are reported for the development and validation of various drugs. Analysis of drug plays a significant role during formulation to identify the drug and its metabolites.

RESULT AND DISCUSSION:

The presented study's recent literature review of oral anti-diabetic drug their chemical nature, structure for Type 2 diabetes mellitus (DM) is a disorder this is putting a growing burden on health carrier delivery internationally. Therefore, it has to turn out to be more and more crucial that physicians who deal with such patients have an excellent understanding of antidiabetic capsules which might be currently to be had or will come onto the marketplace.

This review geared toward specializing in frequent analytical strategies according for the assay of oral anti-diabetic drug. A broad vary of techniques is out there for the estimation of oral anti-diabetic drug and [type- II antidiabetic drugs] in biological samples, and pharmaceutical indefinite quantity type. The analysis of revealed information unconcealed that chemical analysis strategies are the straightforward and economical strategies for estimation of oral anti-diabetic drug in pharmaceutical formulation. For analysis of oral anti-diabetic drug, and type- II antidiabetic medicine, HPLC provides correct results and low price compared to advance detection techniques. HPLC with personal organizer detection was extensively used for the event of stability-indicating assay strategies for separation and quantification of oral anti-diabetic drug within the presence of degradation product. This survey conjointly highlights the combined techniques that incorporate the economical separation of metabolites of oral anti-diabetic drug persecution HPLC sensitive detection has become an imperative tool for quantification of oral anti-diabetic drug in biological fluids and pharmacokinetic studies

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REFERENCES:

[1]UK Prospective Diabetes Study Group: Intensive blood glucose control with sulfonyl urea's or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes(UKPDS33).Lancet1998;52:837-853.

[2]AmericanDiabetesAssociation;EuropeanAssociationfortheStudyofDiabetes;InternationalFederationofClinicalChemistryandLaboratory;International DiabetesFederationMedicine.Consensusstatementontheworldwidestandardizationoftheha1cmeasurement.Diabetologia2007;50(10):2042-2043.

[3]AmericanAssociationofClinicalEndocrinologistsMedicalGuidelinesforclinicalpracticeforthemanagementofdiabetesmellitus.EndoPract2007;13(suppl 1):1-68.KrentzA,BaileyC.Oralantidiabeticdrugs–currentroleinType 2 diabetesmellitus. *Drugs*2005; 65(3):385-411.

[4]Aguilar- Bryan L, Nichols C G, Wechsler S W, *etal*. Cloning the β-cell high-affinity sulphonylureas receptor: a regulator of insulin secretion.Science1995; 268: 423-426.

[5]Pratley R, Weyer C. The role of impaired insulin secretion in the pathogenesis of type II diabetes mellitus.Diabetologia2001; 44:929-945.

[6]Rydberg T, Jönsson A, Rode M, Melander A. Hypoglycemic activity of Glyburide (Glibenclamide) metabolites in humans.DiabetesCare1994;17:1026-1030.

[7]Shorr R I, Ray W A, Daugherty J R, etal. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas.ArchInternMed1997; 157:1681-1686.

[8]Bressler R, Johnson D G. Pharmacological regulation of blood glucose levels in noninsulin dependent diabetes mellitus.ArchInternMed1997; 157:836-848.

[9]Jönsson A, Rydberg Y, Ekberg G, etal. Slow elimination of Glyburide in NIDDM subjects.DiabetesCare1994; 17:142-145.

[10] Jönsson A, Rydberg T, Sterner G, Melander A. Pharmacokinetics of Glibenclamide and its metabolites in diabetic patients with impaired renal function. Eur J Clin Pharmacol1998; 53(6):429-435.

[11] Tessier D, Dawson K, Tétrault JP, Bravo G, Meneilly GS. Glibenclamide vs. gliclazide in Type 2 diabetesoftheelderly.DiabetMed1994; 11(10):974-980.

[12] Langtry H D, Balfour J A. Glimepiride .Are view of it sues in the management of type diabetes mellitus. Drugs1998; 55(4):563-584.

[13] Nathan D M, Buse J B, Davidson M B, *etal*. Management of hyperglycemia in Type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: Update regarding the thiazolidinedione. Diabetologia2008; 51(1):8-11.

[14] De Fronzo R A. Pharmacologic therapy for Type 2 diabetes mellitus. Ann Intern Med 2000; 133(1):73-74.

[15] Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after directangioplastyforacutemyocardialinfarction.JAmCollCardiol1999;33(1):119-124.

[16] Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between sulfonylurea drugs and mortality in Type 2 diabetes mellitus: apopulation-basedcohortstudy.CMAJ2006; 174(2):169-174.

[17] Bell D S. Do sulfonylurea drugs increase the risk of cardia cevents? CMAJ2006; 174(2):185-186. Wilson S H, Kennedy F P, Garrat K N. Optimization of the management of patients with coronary artery disease and Type 2 diabetes mellitus.DrugsAging2001;18:325-333.

[18] Inzucchi S E. Oral antihyperglycemic therapy for Type 2 diabetes: scientific review. JAMA2002; 287(3):360-372.

[19] Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs asadd-ontreatmentstoMetforminin Type 2 diabetes:ameta-analysis.DiabetesResClinPract2008;79(2):196-203.

Chounta A, Zouridakis S, Ellinas C, *etal*. Cholestatic liver injury after glimepiride therapy. J Hepatol 2005; 42(6):944-946.

[20] Fuhlendorff J, Rorsman P, Kofod H, *etal*. Stimulation of insulin release by repaglinide and Glibenclamide involves both common and distinct processes.Diabetes1998; 47(3):345-351.

[21] Dunn C, Faulds D. Nateglinide .Drugs2000; 60:607-615.

[22] Gribble FM, Manley SE, Levy JC. Randomized dose ranging study of the reduction offasting and postprandial glucose in Type 2 diabetes by Nateglinide (A-4166). DiabetesCare2001; 24(7):1221-1225.

[23] Moses R G, Gomis R, Frandsen K B, Schlienger J L, Dedov I. Flexible meal-related do sing with repaglinide facilitates glycemic control in therapy-naïve Type 2 diabetes.DiabetesCare2001;24(1):11-15.

[24] Moses R, Slobodniuk R, Boyages S, *etal*. Effect of repaglinide addition to Metformin mono therapy on glycemic controlling patients with Type 2 diabetes. Diabetes Care1999; 22(1):119-124.

[25] Hawley S A, Gadalla A E, Olsen G S, Hardie D G. The antidiabetic drug Metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism.Diabetes2002; 51(8):2420-2425.

[26] Shaw R J, Lamia K A, Vasquez D, *etal*. The kinase LKB1 mediatesglucosehomeostasisinliverandtherapeuticeffectsofMetformin.Science2005; 310(5754):1642-1646.

[27] Klip A, LeiterLA.CellularmechanismofactionofMetformin.DiabetesCare1990; 13(6):696-704.

[28] NestlerJE.Metforminforthetreatmentofpolycysticovariansyndrome.NEnglJMed 2008; 358(1):47-54.

[29] Roiwan J A, Hague W M, Gao W, Battin M R, Moore P. Metformin versus insulin for the treatment of gestational diabetes. N Engl JMed2008; 358:2003-2015.

[30] Varughese G I, Tahrani A, Scarpello J H. The long and short of Metformin-related vitamin B12deficiency.ArchInternMed2007; 167(7):729-730.

[31] Diamond GA, Bax L, Kaul S. Uncertain effects of Rosiglitazone on the risk for myocardial infarction and cardio vascular death .Ann Intern Med 2007;147(8):578-581.

[32] Dormandy J A, Charbonne l B, Eckland D J, *etal*. Secondary prevention of macrovascular events in patients with Type 2 diabetes in the Proactive Study (Prospective pioglitazone Clinical Trial in Macrovascular Events): a randomized control trial. *Lancet*2005; 366:1279-1289.

[33] Stafylas P C, Sarafidis P A, Lasaridis A N. The controversial effects of thiazolidinedione on cardiovascular morbidity and mortality.*IntJCardiol*2008; 4 Aug.

[34] Nesto R W, Bell D, Bonow, etal. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003; 108:2941-2948.

[35] Erdmann E, Wilcox R G. Weighing up the cardio vascular benefits of thiazolidinedione therapy: the impact of increased risk of heart failure. Eur Heart J 2008; 29(1):12-20.

[36] Patel C, Wyne K C, Mc Guire D K. Thiazolidinedione, peripheral oedema and congestive cardiac failure: What is the evidence? DiabVascDisRes2005; 2(2):61-66.

[37] Kahn S E, Zinman B, Lachin J M. Rosiglitazone-associated fractures in type 2diabetes: an analysis from ADOPT. *Diabetes Care* 2008, 31(5):845-851.

[38] Takeda Pharmaceutical Co. Observation of an increased incidence of fractures in female patients who receive long – term treatment with ACTOS (pioglitazone HCL) tablets for Type 2 diabetes mellitus (LettertoHealthCareProviders).http://www.fda.gov/medwatch/safety/2007/Actosmar0807.pdf.(Accesse19March2007).

[39] Sottile V, Seuwen K, Kneisse l M. Enhanced marrow adipogenesis and bone resorption in estrogen-deprived rats treated with the PPAR-gamma agonist BRL40653 (Rosiglitazone). Calcified Tissue International 2004; 75(4):329-337.

[40] Reid D M, Hughes R A, Laan RFJM, *etal* .Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized control trial. *J Bone Miner Res* 2000:15(6):1006-1013.

[41] Semple R K, Krishna K .PPAR-η and humanmetabolicdisease.JClinInvest2006; 116:581-586.

Chiasson J L .Prevention of Type 2 diabetes: factor fiction? Expert Opin Pharma co ther2007; 8(18):3147-3158.

[42] Chiasson J L. Acarbose for the prevention of diabetes, hypertension, and cardio vascular disease in subjects with impaired glucose tolerance: The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) Trial. Endocr Pract 2006; 12(suppl1):25-30.

[43] Inzucchi S E, Mc Guire D K. New drugs for the treatment of diabetes: part II: Incretin-based therapy and beyond. Circulation 2008; 117(4):574-584.

[44] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptoragonists and dipeptidyl peptidase-4 inhibitors in Type 2 diabetes. Lancet 2006; 368(9548):1696-1705.

[45] Todd J F, Bloom S R. Incretins and other peptides in the treatment of diabetes. Diabet Med 2007; 24:223-232.

[46] Vilsbøll T, Brock B, Perrild H, *etal*. Liraglutide, a once-daily human GLP-1analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycemia in patients with Type 2 diabetes mellitus. Diabet Med 2008; 25(2):152-156.

[47] Idris I, Donnely R. DDP-IV inhibitors: a major new class of oral anti-diabetic drug. DiabetesObesMetab2007; 9:153-156

[48] Rosenstock J, Fitchet M. Vildagliptin: clinical trials programme in mono therapy and combination therapy for Type 2 diabetes. Int J Clin Pract 2008; supp l159:15-23.

[49] Ahrén B, Foley J E. The islet enhancer Vildagliptin: mechanisms of improved glucose metabolism. Int J Clin Pract 2008; suppl159:8-14.

[50] Kruger D F, Gloster M A. Pramlintide for the treatment of insulin-requiring diabetes mellitus. Drugs 2004; 63(13):1419-1432.

[51] Van De Koppel S, Choe H M, Sweet B V. Managed care perspective on three new agents for Type 2 diabetes. J Manag Care Pharm 2008; 14(4):363-380.

[52] Manal M. Fouad* Noha S. Rashed. Development and Validation of Chromatographic and Spectroscopic methods forestimation of Repaglinide and Metformin HCL in combined dosage Form: A Review, 5(3):1844-48. (2014)

[53] K.Srinivasa Rao, K.Srinivas.Development and validation of anHPLCmethod for the analysis ofNateglinide in pharmaceutical dosage forms.ACAIJ, 7(7) 2008 [462-465]

[54]Prasanthi Chengalva*, Angala Parameswari S., Aruna G.Development and Validation of RP-HPLC Method for Metformin Hydrochloride and Nateglinide In Bulk and Combined Dosage Form.Vol 8, Issue 4, 2016.

[55] Rutvik H Pandya*, Rajeshwari Rathod and Dilip G. Maheswari. Bioanalytical Method Development and Validation for Simultaneous Determination of Linagliptin and Metformin Drugs in Human Plasma by RP-HPLC Method. Pharmacophore 2014, Vol. 5 (2), 202-218.

[56]Meenaxi M. Maste, Nikhil S. Gawas, and Utkarsh Shashtri, Poonam Shelar.RP-HPLC Method Development and Validation for Pioglitazone in Bulk and MarketedFormulation.Der Pharma Chemical,2021, 13(6): 6-15

[57]Ahmed Yusuf, Syed N. Alvi and Muhammad M. Hammami.Development and Validation of RP-HPLC Method for the determination of Rosiglitazone in human plasma.Volume 4, Issue 03, 231-242.

[58]John Lambropoulos a, Akio B. Bergholdt.Method development and validation for the HPLC potency

assay of troglitazone tablets.J. Pharm. Biomed. Anal. 24 (2000) 251–258.

[59]Azam Sadat Montazeria, b, Ali Mohammadib, *, Noushin Adibc, and Ali Naeemyb.Development and Validation of a Stability-Indicating HPLC Methodfor the Determination of Acarbose in Pharmaceutical Dosage Forms.Journal of Analytical Chemistry Vol. 73 No. 9 2018.

[60]Aparajita Malakar, Bishwajit Bokshi, Dilruba Nasrin. Development and Validation of RP-HPLC Method for Estimation of Vildagliptin from Tablet Dosage Form), International Journal of Pharmaceutical and Life Sciences. Volume, Issue1, Serial 2:August2012.

[61]R. Lavanya*, Md. Yunoos.Development and Validation of RP-HPLC method for theestimation of Sitagliptin Phosphate in Bulk and its Tablet DosageForm.Journal of Advanced Pharmacy Education & Research Oct-Dec 2013 Vol 3 Issue 4 475 – 479.

[62]Snigdha Dhamireddy, Dr. Sanjeev Kumar Subudhi,Veeramalla Swetha, Kallepelli Shirisha, Cheripelli Srinija, N.Sneha Sadashiv.RP-HPLC Method Development and Validation of Alogliptin Tablet Dosage Form.JARMPS-ISSN-2455-6998

[63]Dr. Pradnya Lokhande.Analytical Method Development and Validation ofTeneligliptin by using RP-HPLC with ICH Guidelines.Volume – 3, Issue – 3, 2019 Page: 259 – 262.

[64]P. B. N. Prasad1, K. Satyanaryana, G. Krishnamohan.Development and Validation of a Method for Simultaneous Determination of Metformin and Saxagliptin in a Formulation by RP-HPLC.American Journal of

Analytical Chemistry, 6, 841-850.

[65]Asmita V. Gaikwad, Ashwini S. Gawade, Hupparage Vrushabh B., Shubhrajit Mantry, Aditya Kale, Jaydeep Kale.Method Development and Validation of Dapagliflozin by RP-HPLC.Journal of Pharmaceutical Negative Results ¦ Volume 13 ¦ Special Issue 6 ¦ 2022 4316– 4334

[66]Darshan Bhatt, Padmini Thatavarthi, B. Rajkamal.Analytical Method Development and Validation for the Estimation of Canagliflozin in Bulk and Formulation by RP- HPLC.Int. J. Pharm. Sci. Drug Res. 2018; 10(3): 139-143.

[67]Anas M. Hanif1, Rabia Bushra, Nahlah Elkudssiah Ismail, Rahila Bano, Saima Abedin, Shazia Alam, Maqsood Ahmed Khan4 and Hafiz Muhammad Arif.Empagliflozin: HPLC based analytical method development andapplication to pharmaceutical raw material and dosage form.Pak. J. Pharm. Sci., Vol.34, No.3 (Suppl), May 2021, pp.1081-1087.

[68]P. Venkateswara Rao, A. Lakshmana Rao, and S.V.U.M Prasad.A New Stability Indicating RP-HPLC Method for Simultaneous Estimation of Ertugliflozin and Sitagliptin In Bulk and Pharmaceutical Dosage Form Its Validation as Per ICH Guidelines.Indo Am. J. P. Sci, 2018; 05(04).