CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com Review Article

OVERVIEWS ON ANALYTICAL METHODS OF ANAGLIPTIN AND METFORMIN HYDROCHOLRIDE

Khushbu S. Patel, Dr.Sejal G. Patel and Dr. Richa Dayaramani
Department of Pharmaceutical Assurance, Sankalchand Patel University,
Visanagar, Gujarat, India.

Article Received: October 2021 **Accepted:**October 2021 **Published:** November 2021

Abstract:
Antidiabetic drugs used in diabetes to treat diabetes mellitus by lowering the glucose level in the blood. Antidiabetic drugs mainly classify in oral hypoglycemic agent and insulin preparation. Where Anagliptin and Metformin HCl both drugs are oral hypoglycemic agents. In the Anagliptin is Dipeptidyl peptidase-4 inhibitors is also known as gliptins class and Metformin belong to bigunide, combination of Anagliptin and Metformin HCl give interactive effect and also homeostasis model assessment of Beta-index. Many Analytical Methods developed for single Metformin HCl & Anagliptin. Metformin is official in IP, BP, USP, and other methods like….UV, SPECTROPHOTOMETRIC, RP-HPLC, LC-MS,MS/MS are also developed. Anagliptin is not official in any pharmacopeia but ELISA, NMR, UV, LC/MS are developed. In combination of Anagliptin and Metformin HCl for first order derivative UV method is developed.

Key Words: *Analytical Methods, Anagliptin, Metformin HCl*

Corresponding author:
Khushbu S. Patel*,
Sankalchand Patel University
Visnagar,Gujarat,India
Email Id: khooshbupatel304@gmail.com
Mobile No: 91+7383511625

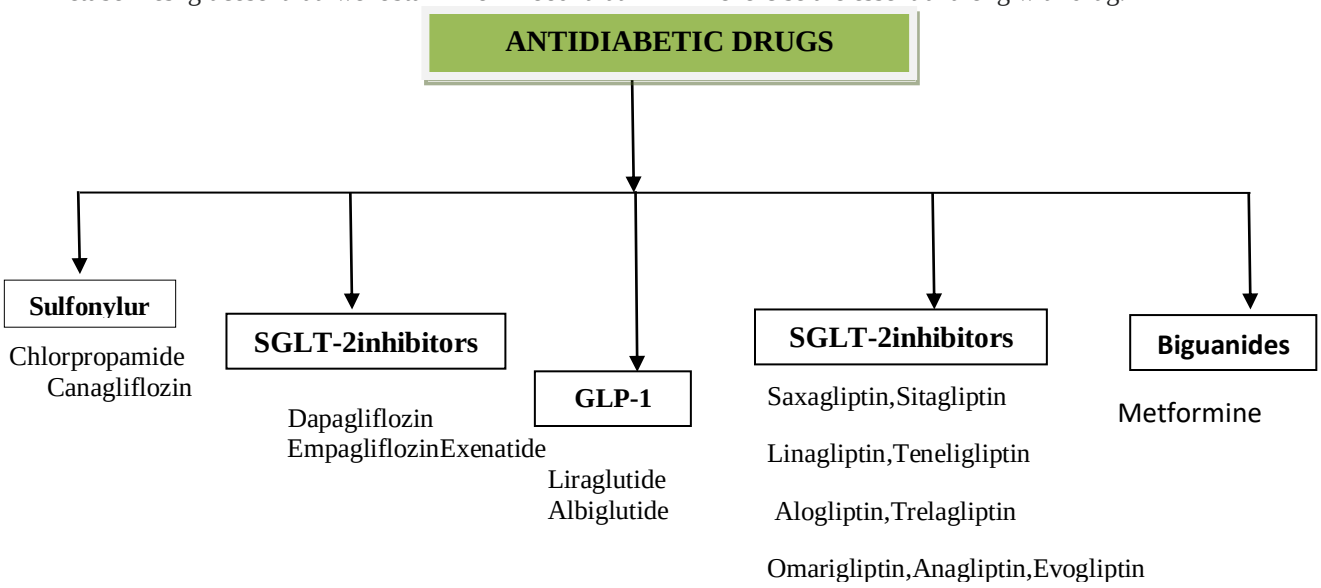
QR code

Please cite this article in press Khushbu S. Patelet al, ***Overviews on Analytical Methods of Anagliptin and Metformin Hydrocholride,*** *Indo Am. J. P. Sci, 2021; 08(11).*

INTRODUCTION:

Diabetes mellitus

Diabetes mellitus is a metabolic disease that causes high blood sugar in the blood.Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time.Pancreas secrets hormone called insulin which metabolizes glucose that we obtain from food that converts into energy. In people with type-II diabetes mellitus either pancreas does not produce enough insulin or pancreas produces insulin but cells don't use it this is also called insulin resistance.When a cell becomes insulin resistance, it requires more insulin to convert glucose into energy and it leads to hyperglycaemia or raised blood sugar.For the treatment of diabetes mellitus type II proper diet and exercise are essential along with drug.



DPP-IV inhibitors

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are new class of oral diabetes drugs. Gliptins, also known as DPP-IV, are commonly used for patient with type-II diabetes who hasn't reacted well to sulphonylureas and metformin.Dipeptidyl peptidase-IV inhibitors can help with weight loss and blood glucose control, but they've also been linked to an increased risk of pancreatitis.

They work by blocking the action of DPP-IV, an enzyme which destroys incretins (a group of gastrointestinal hormones).Incretins aids in the stimulation of insulin production when it is required (e.g., after eating) and the reduction of glucagon production by the liver when it is not required (e.g., during digestion).

They also decrease appetite &delay digestion. So, by defending incretins from damage, DPP-IV inhibitor helps tocontrol blood glucose levels.[3]They do not cause hypoglycaemia unless they are combined with other therapies that cause hypoglycaemia.[4,6]After metformin and sulphonylureas, DPP-IV inhibitors can be used as a second or third-line treatment for patients with type-II diabetes, as asubstitute to thiazolidinediones.[3,4]

Example of DDP-IV inhibiors are Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin, Omarigliptin, Evogliptin.

History of Anagliptin:

- Anagliptin, which is marketed as Beskoa or Suiny, is a Dipeptidyl peptidase-IV (DPP-4) inhibitor which was **approved in September 2012** and **launched in November 2012 in Japan** for the treatment of Type II diabetes.
- The drug was co-developed by three Japanese companies; Kowa, Sanwa Kagaku and JW pharmaceutical.

Mechanism of Action:

Anagliptin is an orally active, antidiabetic drug that works by inhibiting the enzyme Dipeptidyl peptidase-4 (DPP-4).In response to food intake, endocrine cells in the gastrointestinal tract release incretin hormones, **GLP-1(Glucagon like peptide)** and GIP, to stimulateinsulin secretion. Normally, DPP-4 degrades the incretin hormones within a few minutes of their release, thereby playing a key role in regulating the duration of incretin hormone function. Anagliptin, like Sitagliptin, is a non-substrate-like inhibitor of DPP-4. By blocking DPP-

4 enzymatic activity, Anagliptin increases the half-life of incretin hormones, which in turn stimulates increased secretion of insulin by pancreatic β-cells and reduces secretion of glucagon by pancreatic α-cells. Collectively, these functions lower blood glucose levels. Since incretin are only released by the small intestine after eating, DPP-4 inhibitors typically do not induce hypoglycaemia.

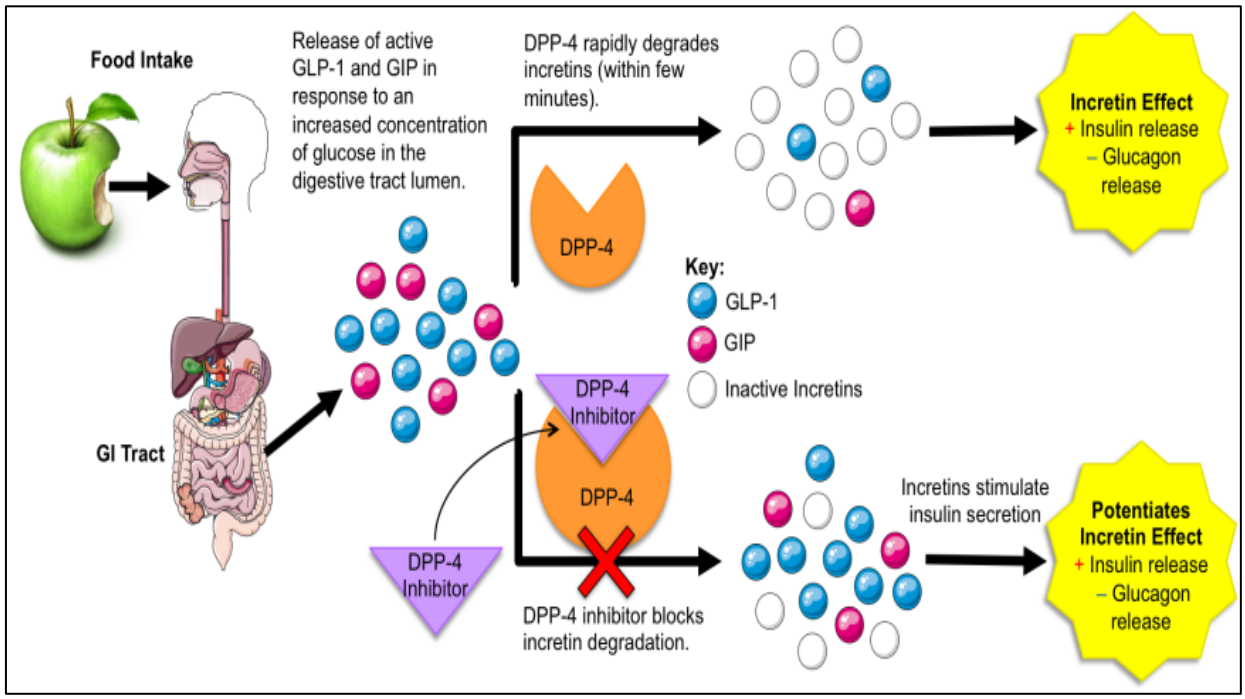
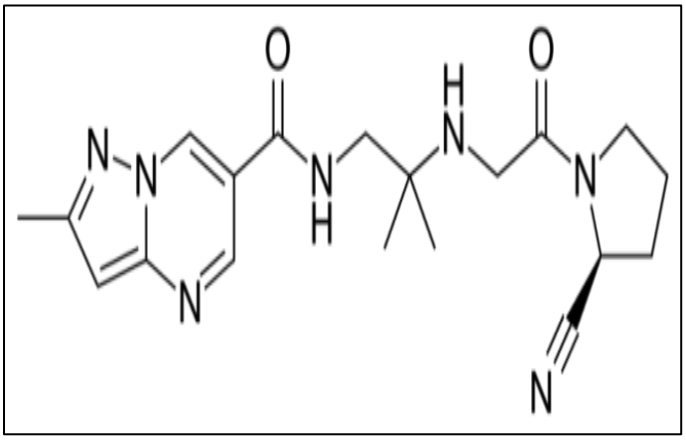


Figure-Mechanism of Action of DPP-4

Chemistry of Anagliptin is N-[2-[2-[(2S)-2-Cyanopyrrolidin-1-yl]-2-oxoethyl] amino]-2-methylpropyl]-2-methyl pyrazolo [1, 5-a] pyrimidine-6-carboxamide. Anagliptin is under investigation for the treatment of LDL Cholesterol, Coronary Disease, Diabetes Mellitus, Glycosylated Haemoglobin, and Dipeptidyl-Peptidase 4 Inhibitors. Its Chemical Formula is $C_{19}H_{25}N_7O_2$.Whichis freely soluble in water, slightly soluble in Ethanol, Methanol. It is novel molecular weight 383.45 gm/mol. Anagliptin always storage at cool and protect from moisture. The Partition co-efficient value (log P) is -0.54. While Dissociate constant (pKa) is 6.99 and melting point is 120-125°C.



Chemical structure of Anagliptin

Pharmacology

Pharmacokinetic:

Absorbed in 1.8 hours that mean fraction of dose> 73% so that metabolite by hepatic CYP3A4 &CYP2C8 4.1% drug is excreted in urine during the pharmacokinetic activity is decrease blood glucose level by in present specific functional group as pyrazolopyrimidine derivative is inhibit DPP-4 inhibitor enzyme.

Dosing:

The usual dose of Anagliptin is 200 mg daily, and increases in the dose up to 400 mg daily have been approved in cases in which the blood glucose–lowering effect is insufficient.

Contraindication

If people with any disease condition the risk of heart failure, decrease blood sugar level With Anagliptin**.**

Therapeutic Indication:

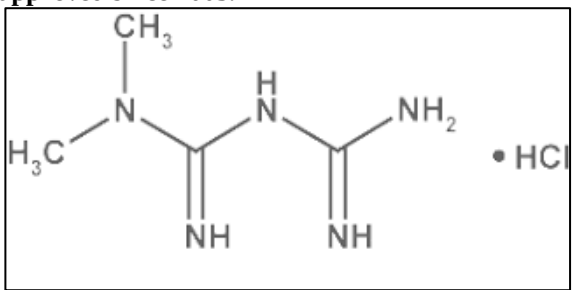
for the treatment of type-II diabetes mellitus as an adjunct to Exercise & diet to increase glycaemic control, if used as a monotherapy or in combination with Metformin.

Side effect

- gastrointestinal problems – including nausea, diarrhoea and stomach pain
- flu-like symptoms – headache, runny nose, sore throat
- skin reactions – painful skin followed by a red or purple rash

Metformin Hydrochloride:

Metformin hydrochloride drug is used to treat diabetes mellitus. It is decreasing the amount of glucose released into the bloodstream from a liver & decreases the body's use of glucose. It also calls Glucophage. Metformin hydrochloride is **CDSCO approved since 2005.**



Chemical Structure of Metformin HCl

- **Official methods of Metformin Hydrochloride**
  1. **Metformin Hydrochloride in IP 2014-** HPLC mobile phase:0.087%w/v of sodium pentanesulphate and 0.12%w/v of NaCl adjusted to pH 3.5 using 1%v/v solution of orthophosphoric acid detection wavelength :233 nm, Retention Time:2.9 min.
  2. **Metformin Hydrochloride in BP 2015-** HPLC mobile phase: Ammonium phosphate buffer pH 3 wavelength: 218 nm, Retention Time: 2.3 min.
  3. **Metformin Hydrochloride in USP NF 2015-** HPLC Mobile phase: Ammonium phosphate buffer pH 3, Detection wavelength: 233 nm, Retention, Time: 2.5 min.

- **Reported Methods of Metformin Hydrochloride**

1. **Spectrophotometric Method for analysis of Metformin Hydrochloride in Bulk & tablet formulation:** UV Detection Wavelength – 570 nm, Percentage recovery ranged: 97-100% Linearity Range: 8-18 µg/ml.
2. **Method development and Validation of Metformin Hydrochloride in Tablet dosage form by beer's law:** UV-Detection wavelength-233 nm, Percentage Recovery range – 98-100% linearity range: 8-13 µg/ml.
3. **Development & Validation of RP-HPLC Method for the determination of Metformin HCl in Pharmaceutical dosage Forms**: HPLC Column – C18, 250mm × 4.6mm, Mobile Phase – Buffer Ph 3.0 with ammonium Dihydrogen phosphate, Flow rate -1.0mL/min at 218nm, Recovery Range-99.22-100.11%.
4. **HPLC Method for Estimation of Metformin Hydrochloride in Formulated Microspheres and Tablet Dosage Form**: HPLC Column-Phenomenex C_{18} Column, Mobile Phase – ACN: Phosphate buffer (65:35) pH 5.75 with O-phosphoric acid, Linearity Range – 0-25 µg/ml.
5. **Analytical Method Development and Validation of Metformin Hydrochloride by Using RP-HPLC with ICH Guidelines**: RP-HPLC Column – C_{18} [4.6×250mm] Mobile Phase: Phosphate Buffer pH 3 & Methanol (30:70).
6. **Quantitative Determination of Metformin HCl in Tablet Formulation Containing Croscarmellose Sodium as Disintegrate By HPLC & UV Spectophotometry:** UV wave Length 232nm HPLC Column – C_{18} (300mm×3.9mm),Mobile Phase – Buffer (1-heptane sulphonic acid) and ACN (90:10v/v), Flow rate-1mL/min, Detection Wavelength: 218nm.
7. **Spectrophotometric Quantitation of Metformin in Bulk Drug and Pharmaceutical Formulation Using Multivariate Technique-** Spectrophotometric method Linearity Range-1-

10µg/ml, Correlation Coefficient -0.997, %Recovery- 102.50±0.063, LOD-0.082 µg/ml, LOQ- 0.25µg/ml.

- **Reported Methods for combination of Metformin Hydrochloride with other drugs.**

1. **Simple HPLC method has been developed and validated for simultaneous determination of gliclazide and Metformin Hydrochloride In bulk and applied on marketed Metformin & gliclazide products :** Mobile Phase-BufferpH3.5: Acetonitrile(45:55)Using Alltima CN(250mm×4.6mm×5µ),Linearity Range-1.25-150µg/ml for gliclazide & 2.5-150 µg/ml for Metformin, UV wavelength-227nm.
2. **Developing single analytical method for estimation of individual drug from a multidrug composition is a very challenging task By RP-HPLC method for separation and estimation of Metformin,Glimipride & Pioglitazone:** Inertsil ODS-3V (250mm×4.6mm,5µm) column; Mobile Phase –Acetonitrile: tetrahydrofuran:Buffer at pH5;Flow rate- 1.7mL/min;UV-wavelength-228nm.
3. **To study stability indicating RP-HPLC method for the simultaneous estimation of Ertugliflozin pidolate and Metformin HCl:** Column-Kromasil C18 (150mm×4.6mm;5µm); Mobile Phase- buffer (pH2.7)0.1%ortho-phosphoric acid: Acetonitrile (65:35); Flow rate-1ml/min.
4. **Stability indicating RP-HPLC method for simultaneous estimation of Tengliptin and Metformin in Bulk and Tablet Dosage form**: Column-Kromasil C18 (250×4.6mm, 5µm); Mobile phase Acetonitril: methanol: Buffer (25:10:65v/v/v); Detection Wavelength-254nm; UV detection wavelength-254nm; Flow rate-1ml/min.
5. **To develop RP-HPLC method for simultaneous quantitative estimation of Metformin hydrochloride and Neteglinide in tablet and validate as per ICH guidelines:** Column –Inertsil C18-ODS 3V (250×4.6mm,5µm); Mobile Phase-Buffer(pH4): Acetonitrile: Methanol (30:60:10); Flow rate-1ml/min;detection Wavelegth-221nm.

- **Official methods for Estimation of Anagliptin**

Anagliptin drug is not official in any pharmacopoeia.

- **Reported methods for estimation of Anagliptin**

1. **A gradient-specific stability indicating HPLC method was developed and validated for the determination of Anagliptin in Laboratory mixtures**: RP-chromatography LC-20AD Pump, using C18 Column with detection wavelength 247nm;Using two Mobile phase 1.Buffer(pH5):Methanol:Acetonitrile(90:5:5);2.Buffer(pH5):Methanol:Acetonitrie(50:25:25);flow rate-1ml/min.. Anagliptin- UV spectroscopy detection wavelength: 246nm; Correlation co-efficient: 0.999 Mean%Recovery-98.18-99398%; Linearity Range-3-15µg/mL.
2. A case study combination of GI, Miglitol, DPP-4 inhibitor & Anagliptin was effective in reducing glucose fluctuation and stabilizing postrandial blood glucose levels in three of the four patients.
3. . The application of quantitative 1Hours NMR for determination of Anagliptin: Operating condition-400MHz in DMSO at 25C with tetra methane silane as the internal standard. Chemical shift in ppm.
4. Anagliptin: LC/MS Injection –Water 2690; Detection Wavelength-PDA detector Operating 210-400nm.
5. ELISA method for estimation of Anagliptin in Sold phase extraction disc plates with 0.02ml or 0.005ml urine Vehicle -0.5%Methyl cellulose in rat after 1 hrs. Mixed with 50mg/ml EDTA Determined by Histamine enzyme-linked immunosorbent assay kit.
6. Anagliptin-LC/MS/MS Sample collect into sodium-heparinized tube centrifuged 4°C at 1500g for 15 min for plasma storage of sample-20°CMass spectroscopy-Tandem Technique.

Reported Methods for Combination of Anagliptin with Metformin Hydrochloride

Anagliptin and Metformin HCl: UV Spectroscopy First Order Derivative wavelength-233nm for Metformin and 247nm for Anagliptin; concentration-5-25µg/ml and 1-5 µg/ml; Solvent-Distilled water**.**

CONCLUSION:

The review article carried out an overview about an Anagliptin and Metformin. Anagliptin is DPP-4 inhibitor which is used in diabetes mellitus.and also use in anti-atherosclerosis drug when it targets arterial inflammation DPP4 inhibitor is modern class of drug that retain incretin hormones while increasing postprandial insulin secretion. So thatover all article only one single method was developed on Anagliptin.

REFERENCES:

1] Shah S and Maheshwari D. First order derivative spectrophotometric method for simultaneous estimation of anagliptin and metformin HCl in bulk and synthetic mixture. J of Globle Trend in Pharmaceutical Sciences 2015; 6(3): 2925-29.

2] Bhatti P and Panchal H. Stability indicating chromatographic method development and

validation for the simultaneous estimation of metformin HCl & anagliptin in its synthetic mixture by HPLC. World J of Pharma Research 2017; 6(11): 956-73.

3] Majithia R and Shah J.Development and validation of analytical method for estimation of Anagliptin tablet dosage form by UV Spectrophotometric method. International J of Pharmacy and Technologies 2015; 6: 7765-71.

4] Patil A and Shiekhedkar A. development and validation of five simple UV-Spectrophotometry methods for estimation of Anagliptin in bulk and in-house tablets. Research Gate 2016; 7(2): 127-131.

5] Pandya C and Rajput S. Stress degradation studies of anagliptin, development of validated stability indicating method, degradation kinetics study, identification and isolation of degradation products. Article in Chromatographia 2018; 1-21.

6] Brain S and Sigalapalli D. LC/MS/MS Characterization, molecular docking and in silico toxicity prediction studies on degradation products of Anagliptin. J of Pharma and Biomedical Analysis 2018; 159:92-99.

7] Arayne MS and Sultana N: Spectrophotometric Quantitation of Metformin in Bulk Drug and Pharmaceutical Formulation Using Multivariate Technique.Indian Journal Pharmaceutical Science2009; 71:331-335.

8] Umapathi P and Ayyappan J: Quantitative Determination of metformin hydrochloride in tablet formulation containing croscarmellose sodium as disintegrant by HPLC and UV spectrophotometry. Tropical Journal of Pharmaceutical Research 2012; 11 (1): 107-16.

9] Zhang W and Zhao H: Determination of Metformin in rat plasma by HILIC-MS/MS combined with Tecan automation and direct injection. Biomedical chromatography 2011.

10] Mubeen G and Khalikha N: Spectrophotometric Method for Estimation of Metformin Hydrochloride. International Journal Chemical Techanical Research 2010; 2: 1330-1331.

11] Reddy C and Mubeen G: HPTLC method for estimation of metformin hydrochloride. Biomed. & Pharmacol. Journal 2008; 1(2): 445-48.

12] Indian Pharmacopoeia, India: Government of India Ministry of health & family welfare and Published by Indian Pharmacopoeia Commission, Vol. II, 2014: 503, 728.

13] British Pharmacopoeia, London: Medicine & Healthcare Products Regulatory Agency, Vol. II, 2010: 3813-14.

14] United States Pharmacopoeia 30, National Formulary 25, Rockville: United States Pharmacopoeia Convention, Vol. II, 2010: 1092-93.

15] ICH Harmonized Tripartite Guideline, ICH Q2 (R1); Text & Methodology; October-1994.

16] Tripathi KD: Essential of Medical Pharmacology. Jaypee Brother Mesical Publishers Ltd, Sixth Edition 2008.

17] Ahuja S. and Scypinski S. 2001 Handbook of Modern Pharmaceutical Analysis.Academic Press, Second Edition; London: 356-367.

18] Sharma BK 2011: Instrumental Method of Chemical Analysis. Goel Publishing Housing, Krishna Prakashan Ltd, 27th edition: 68-175.

19] Mohan H: Textbook of Pathophysiology. Medical publishers Pvt Limited, Sixth Edition 2005.

20] Rang H. and Dale M: Range & Dale Pharmacology. Elsevier Publication Seventh Edition 2012.

21] https://go.drugbank.com/drugs/DB00331[Accessed 11 October 2021].

22] "Metformin Hydrochloride Compound" [Accessed 07 August 2021].

23] https://pubchem.ncbi.nlm.nih.gov/compound/44513473 [Accessed 21 July 2021].

24] https://www.sciencedirect.com/topics/medicine-and-dentistry/anagliptin [Accessed 21 July 2021].

25] https://www.diabetes.co.uk/diabetes-medication/dpp-4-inhibitors.html [Accessed 11 November 2021]