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AN OVERVIEW- DIFFERENT ANALYTICAL TECHNIQUES FOR THE ESTIMATION OF TENELIGLIPTIN AND METFORMIN IN PHARMACEUTICAL DOSAGE FORM

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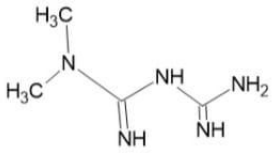
ABSTRACT
Teneligliptin and metformin are pharmaceutical drugs used for the treatment of type-2 diabetes mellitus. This review is based on estimation of Teneligliptin and its combination with Metformin. Various analytical methods has been carried out for its estimation like UV, RP-HPLC, Stability indicating HPLC, liquid chromatography, HPTLC, UPLC, UFLC, RP-UHPLC, LC-MS/MS. The UV estimation has been carried out in three different spectroscopic methods like simultaneous equation, absorbance ratio and first derivative (zero crossing) spectroscopic methods. An accurate precise and reproducible HPLC method was developed for the quantitative estimation of Metformin and Teneligliptin simultaneously in tablet dosage form. Ultra fast liquid chromatographic (RP-UFLC) is a fast, reliable and cost effective method. The present review will be used for research and study purpose regarding Metformin and Teneligliptin.

KEYWORDS: Teneligliptin, metformin, UV Spectrophotometry, RP-HPLC, Liquid chromatography.

INTRODUCTION
Diabetes mellitus is the metabolic illness common over the worldwide and continuous increase in risk due to change in lifestyle and reduce of physical activity of human being. The diabetes term was firstly described by ancient Egyptian about 3000 years ago. Later on ancient Indian observed sweetness of urine and blood and rediscovered by Thomas Willis in 1675 and designated the word mellitus that is mean honey sweet. In 1776 Dobson confirmed the unnecessary sugar in blood and also in urine. During 1936 the distinction among the type1 and type 2 Diabetes was cleared. Diabetes mainly categorized in Type1and Type 2 and Gestational diabetes. The Type1 diabetes is an auto immune disorder in which the destruction of Beta cells of pancreas occurs. In Type2 diabetes, the body becomes resistant to insulin and result into impairment in the production of insulin.[1]

Metformin hydrochloride "Fig-1" chemically N, N dimethylimidodicarbonimidic diamide hydrochloride is an Antidiabetic agent which acts by decreasing intestinal absorption of glucose reducing hepatic glucose production and increasing sensitivity. Metformin is an orally administered drug used to lower blood glucose concentration in patients with non insulin dependent diabetes mellitus(NIDDM).[2]



METFORMIN

Fig 2: Structure of Metformin.

Teneligliptin "Fig. 2" is chemically described as {(2s,4s)-4-[4-(3-methyl -1 phenyl-1H-pyrazole -5-yl) piperazine -1 –yl] pyrrolidin-2-yl}(1,3-thiazolidin- 3-yl) Methanone hemipentahydrobromide hydrate is a dipeptidyl peptidase inhibitor. Teneligliptin slows the inactivation of incretin hormones thereby increasing blood stream concentration and reducing pasting and postprandial glucose concentration in a glucose dependent manner in patients with Type 2 diabetes mellitus.[3] This review is based on collective information regarding various analytical methods and its validation of Teneligliptn and Metformin in combination and single dosage form. It provides precise information about various instruments like HPLC, UV, HPTLC, Liquid Chromatography, UPLC, UFLC, RP-UHPLC, LC-MS/MS.

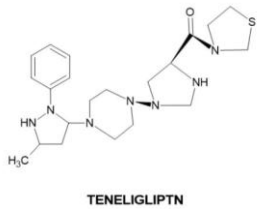


Fig 2: Structure of Teneligliptin.

ANALYTICAL METHODS

Review survey demonstrated that there are several analytical methods have been accounted for Metformin and Teneligliptin evaluation in bulk, pharmaceutical preparation and in biological fluids, involving high performance liquid chromatography, high performance thin layer chromatography, UV spectroscopy, UPLC, UFLC, liquid chromatography, RP-UHPLC and hyphenated technique like LC-MS/MS.

Spectrophotometric Methods

Now –a-days UV spectrophotometry technique is broadly used in the pharmaceutical industry due to its straight forwardness and fast investigation. Till the date lots of spectroscopic methods have been evaluated for this drug. This review consists of eight papers describing UV spectroscopic methods in both combination and single form of Teneligliptin and Metformin. The below table consists of UV spectrophotometry for teneligliptin and Metformin. The different UV methods were shown in table -1.

Table 1: Represent UV spectrophotometry in different methods.

S.no	Compounds	Methods	Wavelength	Solvent	Author
1.	TEN + MET	Dual wavelength UV	236nm & 238nm	Methanol	Shivlal[4]
2.	TEN +MET	UV spectroscopy	243nm & 233.0nm	Water	Leena ajay Sawaikar[5]
3.	TEN +MET	UV spectroscopy three methods	237nm & 246nm	Methanol	Sen[6]
4.	TEN+ MET	UV-Visible Spectroscopy	230nm & 245nm	Water	Parul Bisht[7]
5.	TEN	UV spectroscopy	267.2nm	Dimethyl Sulphoxide	Kshirsagar, S.A [8]
6.	TEN	UV spectroscopy	244nm	Water	Nita Yadav[9]
7.	MET	UV spectroscopy (three methods)	233nm	Sodium Hydroxide	Reatul Karim[10]
8.	MET+ REM	UV Derivative spectroscopy	252.2nm & 233.0nm	Water	Mahesh Attimarad[11]
9.	MET+GLIM	UV Spectroscopy in three methods	236nm & 228nm	water	Audumbar Digambar Mali[12]

Kshirsagar SA *et al*., Prostated UV spectrophotometry for the determination of Teneligliptin hydrobromide hydrate (THH) in API and pharmaceutical dosage form has been developed and validated. In this method solution of Teneligliptin hydrobromide (THH) were prepared in Dimethyl Sulphoxide (DMSO). Teneligliptin Hydrobromide Hydrate (THH) standard solution was scanned in the UV range (400-200 nm) in a 1 cm quartz cell in a double bean UV spectrophotometer. The standard solution of THH was showed maximum absorption at wavelength 267.2nm. The method obeys Beer's law in the concentration range from 20-100µg/ml. The correlation coefficient was found to be 0.999 and the regression of the curve was found Y=0.012×+0.058 with excellent recovery 102 – 104%. Limit of detection and limit of quantification were found to be 4.1987µg/ml and 12.7233µg/ml respectively.

Magesh Attimarad *et al.,* Reported Metformin and Remogliflozin in three different UV spectrophotometry methods has been developed and validated. The first method was established using First derivative absorption spectroscopic method by determining the peak amplitude at 233.0 nm for REM and 252.2 nm for Metformin, a zero crossing of one of the component. The second and third methods based on the peak amplitude difference and first-order derivative absorption of the ratio spectra developed by the manipulation of scanned UV spectra. REM and MET showed good linearity in the series of 1-20µg ml^{-1} and 2.5-35µg ml^{-1}, respectively, by all the three methods with on excellent correlation coefficient ($r^2 \geq 0.998$).

Audumbar digambar Mali *et al.,* Reported Metformin and Glimepiride in two different UV methods in bulk and pharmaceutical dosage form has been developed and validated. Method A is absorbance maxima method, which is based on measurement of absorption at maxima wavelength of 236 nm and 228 nm for Metformin HCl and Glimepiride respectively. Method B is area under curve (AUC), in the wavelength in the range of 217-247 nm for Metformin HCl and 213-239 nm for Glimepiride. Linearity for detector response was absorbed in the concentration range of 5-25µg/ml for Glimepiride the accuracy of the methods was assessed by recovery studies and was found to be 100.23% and 99.67% Metformin HCl and Glimepiride respectively.

Nita Yadav *et al.,* Reported Teneligliptin by UV - Spectrophotometric methods followed by distilled water. Here three methods were used for quantitative estimation of teneligliptin in tablet dosage from. Quantitative estimation of pure drug solution was done at λ max of 244 nm for method I. For measurement of response in

method π peak minima of 266.4 nm was selected. Wavelength range of 238.6-247.8 nm was selected for calculating area in area under the curve method. The % assay of the formulation by the three methods was in the range of 100.17-100.74. Graph was linear in the range of 5-70 µg/ml for zero order derivative technique. Good correlation between response and concentration was found as the value of regression coefficient (r^2) was 0.999. The accuracy of the drug was ranged in between 98.54-101.80 for all ultraviolet-spectrophotometric methods and was in acceptable range.

Shivlal *et al.,* Prostated UV spectrophotometric method for estimation of Teneligliptin Hydrobromide hydrate and Metformin Hydrochloride in tablet dosage form has been developed. Dual wavelength method is based on selection of wavelength, where one drug shows equal absorbance (or difference between absorbance is zero) and other drug shows some response. The wavelengths were selected for determination of Teneligliptin 236 nm and 230.5 nm. Whereas wavelengths selected for the determination of Metformin were 238 nm and 249 nm. Methanol was taken as solvent. Regression analysis of Beer's law plots showed good correlation in concentration range 5-25µg/ml for Teneligliptin and 2-10 µg/ml for Metformin.

HPLC Methods

Several HPLC methods have been reported for the estimation of teneligliptin and metformin in bulk and pharmaceutical dosage form. Summary of the reported HPLC methods were shown in table -2.

Srinivas rao S *et al.,* Prostated reverse phase -HPLC methods for simultaneous estimation of bulk and pharmaceutical dosage form. Separation of Teneligliptin and Metformin HCl was successfully achieved by using column like thermo, C_{18}, 250×4.6mm, 5µm or equivalent in an isocratic mode utilizing 0.1M KH_2 PO_4: Methanol (60:40) at a flow rate of 1.0ml / min and eluate was monitored at 280nm with a retention time of 4.421 and 3.421 minutes for teneligliptin and metformin HCl respectively. The method was validated ad their response was found to be linear in the drug concentration range of 50µg/ml to 150µg/ml for teneligliptin and 50µg/ml to 150µg/ml for metformin HCl. The values of the correlation coefficient were found to 0.999 for HCl. The LOD and LOQ for teneligliptin were found to be 0.2725 and 0.9085 respectively.

Table 2: Represent for reported HPLC method.

Compounds	Methods	Wave Length(nm)	Mobile Phase	Flow rate (ml/min)	Retention time (min)	Author name
TEN +MET	RP-HPLC	280	KH_2PO_4 : MeOH	1.0	4.4, 3.4	Srinivas rao.S[13]
MET + TEN	RP-HPLC	235	MeOH : Water	0.7	2.1, 7.6	Deepak Patil[3]
TEN+ MET	Stability indicating	240	Buffer : ACN	1.0	-	Ramesh Dhani[14]
MET+ TEN	Stability indicating	220	Phosphate buffer : ACN	0.8	2.13, 2.94	Chowdary.K.P.R[15]
MET+TEN	Stability indicating	254	ACN: Buffer: MeOH	1.0	2.84, 2.07	Rajani Vetapalem[16]
MET+TEN	RP-HPLC	240	Phosphate buffer: ACN	1.0	3.60,5.14	Prem kumar Bichala[17]
MET	RP-HPLC	233.0	ACN: Phosphate Buffer	1.0	2.30	Mousumi Kar[18]
MET+ERT	Stability indicating	220	ACN: Buffer	1.0	2.22, 2.95	Bhawani Sunkara[19]
TEN	RP-HPLC	235	MeOH: ACN	1.0	-	Chandana.M[20]

Deepak Patil *et al.,* Prostated high performance liquid chromatography for quantitative estimation of Metformin and Teneligliptin simultaneously in tablet dosage forms. Younglin (S.K.) gradient system UV Detector and C_8 (Agilent) column with 250mm×4.6mm i.d and 5µm particle size. Methanol:water0.05%OPA (50:50) was used as the mobile phase for the method. The detection wavelength was 245nm×4.6nm i.d and 5µm particle size. Methanol: water 0.05%OPS (50:50) was used as the mobile phase for the method. Teneligliptin were found to be 2.1min and 7.6min. The method was validated according to the ICH guidelines.

Ramesh Dhani *et al.,* Reported Stability indicating RP-HPLC method for estimation of Metformin and Teneligliptin in pharmaceutical dosage form has been developed and validated. Chromatogram was run through ODS2 C_{18} (4.6×200nm, 10.0µm) Column. Mobile phase containing Buffer : Acetonitrile (50: 50% v/v) was pumped through column at a flow rate of 1.0 ml /min. Temperature was maintained at ambient. Optimized wavelength for Metformin and Teneligliptin was 240nm.

Rajani Vetapalem *et al.,* Reported Stability indicating RP-HPLC for Teneliglptin and Metformin. The analysis was performed with a Kromasil C_{18} column (250×4.6mm, 5µm) at 30ºC using buffer : Acetonitrile : Methanol (65:25:10,V/V/V) as Mobile phase. The detection carried out with a flow rate of 1.0ml/min at

254nm. The retention time of Teneligliptin and Metformin was 2.842 min and 2.017min, respectively.

Chandana M *et al.,* Reported Reverse Phase-HPLC method for Teneligliptin in bulk and pharmaceutical dosage form. Separation was achieved with a Zodiac C_{18} column (250×4.6mm) I.D., 5µm particle size, Methanol :Acetonitrile (90:10) V/V as mobile phase at a flow rate of 1.0ml/min, p^H 5.2 adjust with 0.10% Orthophosphoric acid and the column temperature was maintained at 25ºC. UV Detection was performed at 235nm and sample temperature was maintained at 5ºC with a run time of 10min.

Chowdary KPR *et al.,* Reported New Stability Indicating RP-HPLC Method for Simultaneous Estimation of Metformin Hydrochloride and Teneligliptin Hydrobromide. The method involves separation on YMC C_{18} column (150mm x 4.6mm x5µm). The optimized mobile phase consists of Phosphate buffer (p^H 3) and Acetonitrile (80:20V/V) with a flow rate of 0.8ml/min and UV detection at 220mn. Retention time was 2.138min (Metformin Hydrochloride), 2.943min (Teneligliptin). Linearity range was 9.98-600ug/ml (Metformin Hydrochloride), 0.51-24ug/ml (Teneligliptin). Accuracy was in the range of 99.41-100.74% for both drugs. Precision was 0.8% and 0.9% for Metformin Hydrochloride and Teneligliptin.

HPTLC reported methods

Mehul Patel *et al.,* Reported High Performance Thin Layer Chromatography for Teneligliptin hydrobromide and Metformin hydrochloride in bulk and pharmaceutical formulation. HPTLC system equipped Camag Linomat V, TLC Scanner IV, Twin Trough chamber, Dual – wavelength UV cabinet, and win CATS software V1.4.7 were used during the study. Separation of analyte was achieved using a pre coated silica gel G60 F254 aluminum sheets 10×10cm^2, with the thickness of 0.2mm as stationary phase and mobile phase comprising of Methanol : Ammonium Sulphate (0.5%W/V): Triethylamine (9:2.7:0.5V/V/V). The detection wavelength was set at 237 nm. The R_f value of the TH and MH was 0.63 and 0.19, respectively.[21]

Abinaya N Reported HPTLC method Teneligliptin Hydrobromide Hydrate and Glimepiride in bulk and tablet dosage form has been developed and validated. HPTLC method was developed on Merck TLC Aluminum sheets of Silica gel 60 F_{222} using Toluene: Methanol: Triethylamine (1:3:1 V/V/V) as mobile phase. Quantitation was achieved with ultra violet detection at 246nm and R_f value was found to be 0.48 and 0.60 for Glimepiride and Teneligliptin Hydrobromide Hydrate respectively.[22]

Susheel JV *et al.,* Reported HPTLC for Metformin and Rosiglitazone in combined tablet dosage form. The HPTLC separation was carried out on Aluminium packed silica gel 60F254 layers using Methanoltetrahydrofuron – ammonia, 8:3:1.5 (V/V/V), as the mobile phase. Quantification was achieved with UV detection at 262 nm.[23]

RP-UFLC reported methods

Maruthi R *et al.,* Reported RP-UFLC method for the simultaneous estimation of Teneligliptin and Metformin has been developed and validated. The chromatographic conditions were using C_{18} Phenomenex Kinetex (250mm×4.6mm i.e., µm practicle size) column in gradient elution mode. The mobile phase consisting of methanol, acetonitrile and potassium dihydrogen orthophosphate adjusted to P^H 4.6 using orthophosphoric acid (40:20:40) with a flow rate of 1.0 ml/min injection volume 10µl and the eluent was detected at 250 nm. PDA detector was used. The retention time of Teneligliptin and Metformin were found to be 5.2 min and 2.5min respectively.[24]

Chandan RS. *et al.,* Prostated for the determination of Teneligliptin by Ultra-Fast Liquid Chromatography method. The approximate flowing rate was 1.0ml/min for the Phenomenex Kinetex column C_{18} (250mm×4.6mm. 5µ) with Methanol and Acetontrile (60:40 V/V) as a portable stream. A PDA detector at 246nm was used to tack the eluent. Teneligliptin elutes at 4.938 minutes of the processing period. The proposed method has a linearity of 10 to50µg/ml concentration range; the calibration diagram is continuous and 0.9942 percent for the correlations variable (r^2). For the suggested procedure, both LOD and LOQ are measured as 0.097 and 1.023µg/ml, respectively.[25]

LIQUID CHROMAROGRAPHY

Sunkara Mrunal Chaitanya *et al.,* Reported liquid chromatography method for the estimation Metformin and Teneligliptin has been developed and validated. Shimadzu Model CBM-20A/20 Alite, Ultrafast liquid chromatographic system with C_8 Phenomenex column (250mm×4.6mm i.d., 5µm particle size) and PDA detector was used for the simultaneous determination of Metformin and Teneligliptin. A mixture of methanol and formic acid was used as mobile phase with a flow rate 0.5 ml/min (UV detection at 210nm). Metformin and Teneligliptin have shown linear regression equations, y =159069.66x-139280.39 (r^2 = 0.9998) and y = 4863932.73x-12592.06 (r^2 = 0.9999). The LOD and LOQ are found to be 0.7631µg/ml and 2.3147µg/ml for Metformin and 0.0029µg/ml and 0.0084µg/ml for Teneligliptin respectively.[26]

UPLC reported method

Sridevi.P *et al.,* Prostated Ultra Performance Liquid Chromatography method for the simultaneous estimation of Teneligliptin hydrochloride and Metformin hydrochloride in bulk and tablet dosage form. The method was carried out using Endoversil column (2.1×50 mm, 1.8 mm) with mobile phase consisting of 0.1%V/V ortho-phosphoric acid:acetonitrile (80:20) under isocratic mode with an injection volume 1µl and at flow rate

0.3ml/min and both the analytes were monitored at 221nm. Stress conditions were performed by subjecting the individual analytes to the hydrolysis (acidic, basic), oxidation photolytic and thermal stress conditions. The retention times of Metformin hydrochloride and Teneligliptin hydrobromide were 0.443 and 0.694 min, respectively.[27]

RP-UHPLC reported methods

Patel.V *et al.,* Prostated Ultra High Performance Liquid Chromatography method for the simultaneous estimation of Metformin and Teneligliptin in fixed dose Combination. The analysis was performed on Agilent symmetry Analytical column Eclipse plus C_{18} (150mm×4.6mm, 5µm) Ultra Performance liquid chromatography-Diode Array Detectors (UHPLC-DAD), while the detection was performed on 233nm using Diode Array Detectors. Buffer and acetonitrile (65:35V/V) were the Mobile phase, run at a flow rate of 0.7ml/min for Isocratic solution. The buffer used in the mobile phase contained 50mM Potassium Dihydrogen Phosphate.[28]

David Paul *et al.,* Reported UHPLC-QTOF-MS Method for the Quantification of Metformin and Teneligliptin in Rat Plasma. Chromatographic separation were carried out on acquity UPLC HSS Cyano column (100 mm x 2.1 mm, 1.8 µm) using gradient mobile phase system consisting of 0.1% formic acid and acetonitrile at a flow rate of 0.4 ml/min, within a run time of 6 min. Protein precipitation method was used as sample preparation approach. Detection of target ions $[M+H]^+$ at m/z 130.1085 for MET, m/z 427.2277 for TEN and m/z 409.1623 for IS was performed at positive ion electrospray ionization mode. Linearity was assessed in the range of 0.98–1000 ng/ml for both MET and TEN.[29]

LC-MS/MS reported method

Priyanka A Shah *et al.,* Prostated LC-MS/MS method for the Simultaneous determination of Metformin and Teneligliptin in human plasma using hydrophilic reaction. The mechanism of retention of analytes was studied by varying the proportion of organic diluent, buffer strength, pH of the mobile phase and temperature. The results showed a mixed-mode mechanism comprising of hydrophilic (partition) and electrostatic interaction (ion exchange) for MET and essentially hydrophilic for TEN. The linear calibration curves were established in the concentration range of 1.0-1000 ng/ml for MET and 0.50-750 ng/ml for TEN.[30]

CONCULSION

The present review revealed that there is a broad range of numerous investigations has been performed for Metformin and Teneligliptin. Various analytical methods has been reported for Metformin and Teneligliptin like UV, RP-HPLC, Stability indicating HPLC, Liquid Chromatography, HPTIC, UFLC, UPLC, RP-UHPLC, LC-MS/MS. It Consists of UV Spectroscopic methods in different wavelengths, and HPLC methods using different mobile phases. This analytical review may be used for future research purposes based on Information regarding Metformin and Teneligliptin. UV, HPLC was found to be most deliberate for detection of Metformin and teneligliptin. This review will be helpful for further analytical method development and validation for Metformin and Teneligliptin combination bulk and in pharmaceutical dosage forms.

ABBREVIATION

TEN- Teneligliptin, MET- metformin, REM – Remogloflozin, GLIM-Glimepiride, RP-HPLC-Reverse Phase -High Performance Liquid Chromatography, HPTLC-High Performance Thin Layer Chromatography, RP-UFLC-Reverse Phase-Ultra Fluid Liquid Chromatography, UPLC-Ultra Performance Liquid Chromatography, RP-UHPLC-Reverse Phase-Ultra High Performance Liquid Chromatography, DAD-Diode Array Detector, MeOH- Methanol, ACN- Acetonitrile, nm-Nanometer, µl- Microlitre.

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