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A REVIEW ON VARIOUS ANALYTICAL METHODS FOR ESTIMATION OF METOCLOPRAMIDE AN ANTIEMETIC DRUG

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ABSTRACT:

Metoclopramide Hydrochloride is used as Dopamine receptor antagonist, antiemetic, anti-sickness medicine. It's used to help stop you feeling or being sick (nausea or vomiting) includingafter radiotherapy or chemotherapy (treatment for cancer)sickness you may get with a migraine. Metoclopramide is recommended for adults with breakthrough or refractory chemotherapy induced nausea and vomiting (CINV) and for CINV prophylaxis in children. The drug regulatory agencies of Canada and the EU have revised the labeling of metoclopramide to contraindicate its use in children aged <1 year and to caution against its use in children aged <5 years and its duration of use beyond 5 days. It may provide symptomatic relief in dyspepsia and possibly in vertigo, reflux esophagitis and hiccups, but further controlled trials are needed to confirm the efficacy of metoclopramide in these proposed areas of use. It promotes gastric emptying prior to anesthesia. Its effects in healing gastric ulcer and preventing relapse of duodenal ulcer remain unproven.Various analytical methods such as High performance liquid chromatography (HPLC), Ultra performance liquid chromatography (UPLC), Mass spectrometric, Liquid chromatography-Mass spectroscopy (LC-MS) and UV-Spectrophotometric methods have been developed for the estimation of Metoclopramide as single and combinations with other drugs have been reported.

Keywords: Esophagitis, Anesthesia, UV-spectrophotometric methods, HPLC, HPTLC, UPLC, Antagonist, Antiemetic.

INTRODUCTION:

Metoclopramide is a medication used for stomach and esophageal problems. It is commonly used to treat and prevent nausea and vomiting, to help with emptying of the stomach in people with delayed stomach emptying, and to help with gastro esophageal reflux disease and migraine headaches. Metoclopramide reduces post-operative vomiting and radiation sickness, and ameliorates some types of drug-induced vomiting.[1]

It is thus rarely recommended that people take the medication for longer than twelve weeks. No evidence of harm has been found after being taken by many pregnant women. It belongs to the group of medications known as dopamine-receptor antagonists and works as a prokinetic.[2]

In 2012, metoclopramide was one of the top 100 most prescribed medications in the United States.[3]Metoclopramide assists radiological identification of lesions in the small intestine, facilitates duodenal intubation and small intestine biopsy, and eases emergency endoscopy in upper gastro-intestinal haemorrhage. It is available as a generic medication. It is on the World Health Organization's List of Essential Medicines. In 2020, it was the 352nd most commonly prescribed medication in the United States, with more than 600,000 prescriptions.[4]

Side effects: Focal dystonia, hypertension, hypotension, hyperprolactinaemia, galactorrhea, headache, and extrapyramidal effects such as oculogyric crisis, dizziness or fainting.(5)

UV-SPECTROSCOPIC METHODS:

Various UV spectroscopic methods have been reported for determination of metoclopramide in single and combined with other drugs.

VINAY WAMORKAR et al.,(6) 2011: Developed and validateda UV spectroscopic method for estimation of metoclopramide. The maximum wavelength (λ max) was found to be 272 nm. The linearity in the range of 2-20 µg/ml. all calibration curves shows a linear relationship between the absorbance and concentration with coefficient of correlation 0.998. The regression of curve was Y = 0.33x + 0.022. The precision of method was found to be good. The percentage recovery was found to be 100% ± SD. The optimized showed good reproducibility and recovery with standard deviation < 1 % and percent relative standard deviation less than 2 %, standard error in case of recovery studies are satisfactorily low and allow estimation metoclopramide in concentration range employed for this purpose in the assay of bulk drug and tablets. The sample solution was stable upto 36 hours.

Muhmmed Y.Basheer et al.,(7) 2017: Developed and validateda simple, specific, accurate and spectroscopicmethod for the estimation of Metoclopramide hydrochloride as well as parentral formulation.The maximum wavelength (λmax) was found to be 270 nm. Linearity range was 5µg/ml to 30µg/ml. Allcalibration curves showed a linear relationship between the absorbance and concentration withcorrelation-coefficient R2=0.9998. The precision of the method was found to be good. The recoverypercentages were found to be 101.77%, 100.27% and 101.23%. The method was found to be robust asthe RSD was 1.75%, and precise with RSD values of (0.869%, 1.17% and 0.925%) for therepeatability, intraday precision and interday precision, respectively. The LOD and LOQ are found tobe 0.34µg/ml and 1.031µg/ml, respectively. The proposed method will be suitable for analysis ofMetoclopramide in bulk as well as parentral pharmaceutical formulations for quality control purpose.

Dudhane N.P. et al.,(8) 2010: Developed and validatedsimultaneousestimation of metoclopramide hydrochloride and paracetamol in combined dosage form by UV Spectrophotometricmethod. Method I, Absorbance Ratiomethod, Method II and correction Method III, For development of Method I, wavelengths selected were243.0 nm and 273.5 nm for estimation of metoclopramide hydrochloride (MET) and paracetamol (PAR)respectively while for Method II, 243.0 nm λmax for paracetamol, 262.0 nm Isoabsorptive point of Par and Met and309.0 nm for correction method. The two drugs follow Beer-Lambert's law over the concentration range of 4-16µg/mL for MET and 4-16 µg/mL for PAR. The % estimation of the drugs was found near to 100 % representing theaccuracy of the three methods. The recovery of the MET and PAR were found near to 100 %. The proposed methods can be successfully applied for the determination ofmetoclopramide hydrochloride and paracetamol in combined dosage form.

Muhammad Suleman Imtiaz et al.,(9) 2022: Developed a drug-in-adhesive-type transdermal patch formulation of metoclopramide HCl, In vitro permeation profiles and parameters were obtained by using the skin of hairless albino Wistar rats. The influence of drug content on the rate of permeation was investigated, and patch formulation was optimized based on Q_{12}, flux, and lag time. The effect of permeation enhancers (EO and PG) on the permeation rate of metoclopramide HCl was also studied. The skin irritation study was performed to observe the hypersensitivity against the patch component. The transdermal patch formulation containing 10% w/w metoclopramide HCl was capable of effectively delivering metoclopramide HCl for systemic effect without any skin irritation. It has Q_{12} of 3.892 ± 0.0043 mg/cm^2, flux rate of 0.2501 mg/cm^2 h, and the coefficient of

permeability of 6.25E−02 cm/h with a lag time of 0.442 h. The stability data revealed that the optimized patch formulation could be stored at 4 °C in the refrigerator with a shelf life of 3.53 months. This newly developed metoclopramide transdermal DIA patch is an effective alternative to oral delivery with desirable antiemetic activity.

Nief Rahman Ahmed et al.,[10] 2019: Developed and validateda simple precise method for the estimation of metoclopramide. HCL in pharmaceutical preparations and environmentalwastewater samples, which shows maximum absorbance at 310 nm in distilled water. Beer's law was obeyed in therange of 2-25 µ g/ ml, with molar absorptivity of 1.25X104 L.mol-1.cm-1, relative standard deviation of the methodwas less than 1.8%, and accuracy (average recovery %) was 100 ± 1.0. The method was successfully applied to theestimation of metoclopramide.

HPLC METHODS:

Nancy Kahaliet al.,[11] 2018: Developed a simple precise method for the estimation of this method and the column efficiency (theoreticalplate) after extraction of metoclopramide from PVP K30-Metoclopramide (3:1 w/w) solid dispersion (SD). The values of limit of detection (LOD) and limit of quantitation (LOQ) for the metoclopramide baseas obtained are, 0.052µg/mL and 0.159µg/mL respectively. The linearity was found in the range of 2-20µg/mL; performance of column remained satisfactory throughout the analysis, N = 4927-2434. The percentage recoveryof pure and extracted metoclopramide ranges from 103-105% and 86-120% approximately. The results collectivelydemonstrate that the proposed method is selective. Clear isolation of metoclopramide from SD is achieved withoutany solid state interference.

Mohamed Walash et al.,[12]2013 Developed a simple precise method for the simultaneous determination of metoclopramide hydrochloride (MCA) and pyridoxine hydrochloride (PDX). The column was (250 × 4.6 mm, 5 µm particle size) using a mobile phase methanol:0.02 M phosphate buffer mixture (45:55, v/v) of pH 3.0. The mobile phase was pumped at a flow rate of 1 mL/min with fluorescence detection at 308/374 nm. The linearity concentration ranges of 0.004–0.20 and 0.05–1.0 µg/mL for MCA and PDX, respectively, with limits of detection of 0.9 and 11.2 µg/mL. Average % recoveries of 100.31 ± 1.19 and 99.63 ± 1.27 for MCA and PDX, respectively. To developed method was further applied to the determination of MCA in human plasma with mean % recovery of 101.00 ± 7.00.

Farhad Ullah et al.,[13] 2017: Developed and validated for simultaneous determination of the methotrexate and metoclopramide samples using sparfloxacin as internal standard. The analytes were separated on a Kromasil 100-5C18 RP (250 × 4.6 mm, 5 µm) column, methanol, and 0.05% trifloroacetic acid (36:64 v/v) as mobile phase with a flow rate of 1 mL/min, detection wavelength of 290 nm, and column oven temperature at 40°C. Both the analytes were extracted from physiological fluids using methanol and 10% perchloric acid (50:50 v/v). The method was linear over the concentration range of 0.025–1.0 µg/mL for methotrexate and 0.030–1.0 µg/mL for metoclopramide. The % recovery from human plasma was 98.57 and 96.74% for MTX and MCP, respectively, while from aqueous humor and vitreous humor was 95.84 and 98.51% for MTX. The developed method was applied for *in vitro* release of MTX from polymeric nanoparticles and can be applied for analysis of pharmaceutical and biological samples containing both the drugs.

Mahasen A. Radwan et al.,[14] 2006: Developed a method for determination of metoclopramide employing reversed phase high performance liquid chromatography with UV detection at 270 nm. The separation was performed on a Novapak C_{18}, column 4 µm (3.9 × 150 mm). Acetonitrile (18%) in 0.02 M ammonium acetate containing 0.1% triethylamine was used as the mobile phase and the run time was 7 min. Tramadol was used as the internal standard. The mean retention times of metoclopramide and tramadol were 3.4 and 4.6 min, respectively. Linear response ($r > 0.997$) was observed over the range of 0.025–5 µg/ml of metoclopramide. There was no significant difference ($p < 0.05$) between inter- and intra-day studies for metoclopramide. The mean relative standard deviations (%RSD) of the results of within-day precision and accuracy of the drug were < 10%. The half-life was 2.09 ± 0.39 h with an apparent clearance of 2.45 ± 0.70 (L/h)/kg in rat.

Nagwa H.Foda et al.,[15] 2006: Developed a, specific method for the estimation of Metoclopramide by Reversed-phase chromatography and their mobile phase was acetate buffer and acetonitrile, (75% v/v) and detection at 273nm. The six Metoclopramide tablets were containing 100.5% and 0.889% respectively. The regression analyses of three standard plots in the concentration range of 0.5 – 7 mcg/mL obtained on three different days gave a correlation coefficient > 0.996 and the coefficient of variation of the slopes < 1%. The assay was precise within day and between days as indicated by ANOVA test. The recoveries from 10 replicate tablets of three different commercial Metoclopramide was 98.7, 100.8 and 100.3% of the label amount and their coefficients of variation were 1.16, 1.76 and 1.6%.

T. G. Venkateshwaran et al.,[16] 2006: Developed a method for the assay of a metoclopramide and ondansetron mixture in 0.9% sodium chloride injection. The deactivated octylsilane column at ambient temperature and a mobile phase was 77:23 v/v 0.01 M phosphate buffer, pH 4-acetonitrile at a flow rate of 1.0 mL/min with detection of analytes at 273 nm. The separation is achieved within 15–20 min with sensitivity in the μg/mL range for each analyte. The method showed linearity for metoclopramide and ondansetron in the 12.5–50 and 5–20 μ/mL ranges, respectively. Accuracy and precision were in the 1–2% and 0.3–1.3% ranges, respectively, for both drugs. The limits of detection for metoclopramide and ondansetron were 49 and 20 μg/mL, respectively, based on a signal to noise ratio of 3 and a 20 μL injection.

OTHER ANALYTICAL METHODS:

Miao Yan, Huan-De Li et al.,[17] 2010: Developed an LC–MS method for the determination of metoclopramide in human plasma. Sample preparation involved extraction with ethyl acetate. Chromatographic separation was performed on a Thermo Hypersil-Hypurity C_{18} (150 mm × 2.1 mm, 5 μm) the mobile phase consisting of 40 mM ammonium acetate–methanol–acetonitrile. A single-quadrupole mass spectrometer with an electrospray interface was operated in the selected-ion monitoring mode to detect the $[M+H]^+$ ions at *m/z* 300 for metoclopramide and at *m/z* 384 for the internal standard (prazosin). The method was validated over 0.78–50.00 μg mL^{-1} for metoclopramide. The recovery was 67.8–83.1%, and the limit of quantitation (LOQ) detection was 0.78 μg mL^{-1} for metoclopramide. The intra- and inter-day precision of the method at three concentrations was 5.0–13.6% with accuracy of 99.2–104.0%. The method was successfully applied to bioequivalence studies of metoclopramide hydrochloride tablets.

Ziya Bayraket al.,[18] 2014: Developed a simple, selective and rapid LC–MS method has been developed and validated for the sensitive determination of metoclopramide in rabbit blood, ex vivo permeation studies. LC–MS analysis was performed isocratically on a Zorbax SB-C_{18} column with a mobile phase consisting of methanol:ammonium acetate buffer (pH 3.0) 75:25 (v/v) at a flow rate of 0.70 mL min^{-1}. The assay was linear over the concentration range of 1.25–200 pg μL^{-1} with a limit of detection of 0.077 pg μL^{-1} for standard solutions and 2.5–200 pg μL^{-1} with a limit of detection of 0.42 pg μL^{-1} for serum samples. Metoclopramide was extracted from rabbit blood by liquid–liquid extraction using ether as the extraction solvent. The reproducibility of the method was found to be between 0.96 and 1.98 % (RSD) values. Moreover, for the stability of metoclopramide, the effect of temperature, UV light, H_2O_2, HCl and NaOH were also investigated.

Kouko HAMAMOTOet al.,[19]2013: Developed anassay method using LC/ESI-MS/MS for simultaneous determination of MCP in cattle plasma was developed and validated. Chromatographic separation was carried out using a multimode column (2 × 150 mm, 3 μm) with gradient elution (0.05% formic acid/methanol with 0.05% formic acid). MCP and levosulpiride (internal standard) were analyzed in the precursor/product ion pair of m/z 300.1/226.9 and 342.0/112.0, respectively. Linear calibration curves were obtained in the range of 2.5–500 μg/mL(R^2>0.999) with a lower limit of quantification of 0.05 μg/m*l*. Mean recoveries were 96–103%, and the coefficient of variation was less than 6.5%. Plasma MCP concentrations after intravenous administration at 0.4 mg/kg to 12 cattle were determined by the LC-MS/MS method.

Suman.Avula.K. Naveen Babu et al.,[20]2011: Developed asimple, specific, accurate and precise reverse phase HPLC method was developed and validated for the estimation of Metoclopramide.Zodiac C-18, 5μm column having 250 x 4.6mm internal diameter in isocratic mode with mobile phasecontaining Acetonitrile:1%TEA 50:50 (/v/v) was used. The flow rate was 1.0ml/min and effluents were monitored at 250nm. The retention time for Metoclopramide was 2.565 min. Limit of detection and limit of quantification were found to be 0.03ppm and

0.099ppm respectively andrecovery of Metoclopramide from tablet formulation was found to be 8.73%. This method wassuccessfully applied for the quantitative determination of Metoclopramide in tablet formulation.

Aqeel A.Fatmi et al.,[21] 2008: Developed a simple precise method for Metoclopramidesample extracted in methanol and injected on a reverse phase C_{18} column with a mobile phase of 0.15M ammonium acetate and acetonitrile (80:20) with detection at 268 nm. The method was highly reproducible with average assay recovery of 104.7 2 1.1%.

Prathyusha Sowjanyaet al.,[22]2013: Developed a simple precise method for the estimation of Metoclopramide. The chromatographic separation was achieved using a Waters X-terra RP18 (150 × 4.6 mm), 3.5 µm particle size column using the mobile phase consisting of solvent-A 30 mM monobasic sodium phosphate and 2.3 mM of pentane-1-sulphonic acid sodium salt (pH 3.0 buffer) and solvent-B (Acetonitrile). A flow rate of 1.2 mL/min and UV detector at 273 nm was used.

CONCLUSION:

Metoclopramide Hydrochloride is used as Dopamine receptor antagonist, antiemetic, anti-sickness medicine. It's used to help stop you feeling of nausea or vomiting after radiotherapy or chemotherapy (treatment for cancer)sickness you may get with a migraine.Various analytical methods such as High performance liquid chromatography, Ultra performance liquid chromatography, Mass spectrometry, Liquid chromatography-Mass spectroscopy and UV-Spectrophotometric methods have been discussed for the estimation of Metoclopramide in this review article for easy verification for the researchers.

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