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Review Article

An Overview Dextromethorphan

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ABSTRACT

Analytical methods development and validation play important roles in the discovery, development and Manufacture of pharmaceuticals. Method development is the process of proving that an analytical method is acceptable for use to measure the concentration of an API in a specific compounded dosage form which allow simplified procedures to be employed to verify that an analysis procedure, accurately and consistently will deliver a reliable measurement of an active ingredient in a compounded preparation. Liquid chromatography with UV detection has been found to be most studied for estimation of Dextromethorphan in bulk as well as pharmaceutical dosage forms, while hyphenated LCMS, LC- MS/MS methods reported for determination of Dextromethorphan and its metabolite in plasma and other biological fluids. Few chromatography approaches like HPTLC and Stability indicating HPLC, UPLC and HPTLC are also reported. Few simple UV -Spectrophotometric methods may be used for routine analysis of Dextromethorphan alone and in combination with other drugs. These compiled data may of use for research for further studies in analysis of Dextromethorphan.

INTRODUCTION

Dextromethorphan is a cough suppressant drug. It is generally sell as “over the counter drug”. It is generally prepared in the form of tablet, syrup, lozenges, spray etc type of dosage forms. Dextromethorphan does not have a significant affinity for the mu-opioid receptor activity typical of morphinan compounds and exerts its therapeutic effects through several other receptors. It is in the morphinan class of medications with sedative, dissociative and stimulant properties (at lower doses).[1] In its pure form, dextromethorphan occurs as a white powder. Dextromethorphan is also used recreationally. When exceeding approved dosages, dextromethorphan acts as a dissociative hallucinogen. It has multiple mechanisms of action, including actions as a nonselective

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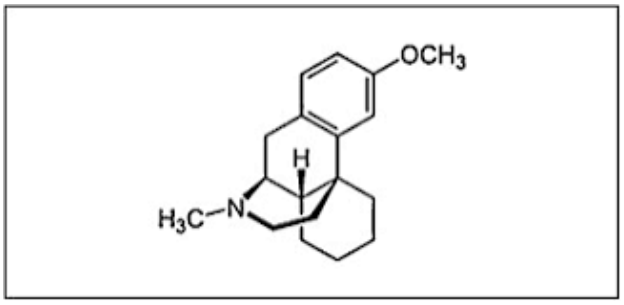
serotonin reuptake inhibitor and a sigma-1 receptor agonist. Dextromethorphan and its major metabolite, dextrorphan, also block the NMDA receptor at high doses, which produces effects similar to other dissociative anesthetics such as ketamine, nitrous oxide, and phencyclidine. It was patented in 1949 and approved for medical use in 1953.[2-5]



Structure of Dextromethorphan

Mechanism of Action:

Dextromethorphan is the d-isomer of the codeine analog, methorphan. Unlike the l-isomer, it has no analgesic or addictive properties and does not act through the opioid receptors. The exact mechanism for the antitussive effect by dextromethorphan remains unclear and is likely multifactorial. Dextromethorphan is known to be an *N*-methyl-d-aspartate (NMDA) receptor antagonist; however, dextromethorphan binding sites are not limited to the known distribution of NMDA receptors.

Dextromethorphan's main metabolite, dextrorphan, has NMDA receptor antagonist properties similar to ketamine and phencyclidine. This NMDA receptor antagonism is believed to result in a decreased reuptake of catecholamines. Dextromethorphan also inhibits the reuptake of serotonin. These properties make dextromethorphan have a high abuse and misuse potential.

Dextromethorphan is a common ingredient in over-the-counter cough and cold preparations, and is often combined with other agents including concurrent antihistamines, decongestants, analgesics, and ethanol. Patients may exhibit toxicity due to these congestants.[6]

Literature Survey:

01) The analysis was resolved by using a gradient mobile phase (Sodium salt of heptane sulphonic acid buffer solution and acetonitrile) at a flow rate of 1ml/min on an gradient consisting of Shimadzu LC 2010 HPLC system on variable wavelength UV detector using, Inertsil C8 (4.6 mm x 15 cm, 5 µm) column at a wavelength of 214 nm. The retention time were found to be Acetaminophen (5 min), Caffeine (6 min), Phenylephrine HCl (10 min), Dextromethorphan HBr (20 min). The percent recovery of Acetaminophen, Caffeine, Phenylephrine Hydrochloride and Dextromethorphan Hydrobromide were found to be in between 98% to 102%.[7]

02) A chemical hydrolysis method was optimized using a chemometric approach. Three factors (acid concentration, hydrolysis time and temperature) were selected and simultaneously varied to study their effect on conjugated DOR hydrolysis. Hydrolysis conditions that maximize DOR release without significant degradation of both DEM and DOR were chosen and results were compared to those obtained by enzymatic method using -glucuronidase. An HPLC method with fluorescence detection was developed for the simultaneous quantitation of DEM, DOR and levallorphan, used as an internal standard. Separation was performed on a phenyl analytical column (150 mm × 4.6 mm i.d., 5µm) with a mobile phase consisting of 18% acetonitrile and 50 mM phosphoric acid (pH 3). The overall analytical procedure was validated and showed good performances in terms of selectivity, linearity, sensitivity, precision and accuracy. And, this assay was used to determine DEM/DOR molar ratios in fibromyalgia patients for the purpose of determining phenotype status for the CYP2D6[8]

03) gas chromatography-mass spectrometry confirmation method for the detection of

dextromethorphan and its major metabolite dextrorphan in urine and oral fluid is described. For the screening assay, the intraday precision was less than 8% for urine and less than 5% for oral fluid. The interday precision was less than 10% for both drugs in urine and oral fluid. For the confirmatory procedure, both inter- and intraday precision was less than 5% for both matrices. The detection limit for both methods was 1 ng/mL. The quantifying ions chosen from the full scan mass spectra were m/z 271 for dextromethorphan, m/z 329 for dextrorphan, and m/z 332 for tri-deuterated dextrorphan-d3. A high recovery yield (> 93%) from the Quantisal TM oral fluid collection device was achieved, and the drugs were stable in the collection device for at least 10 days at room temperature. The extracted drugs from both matrices were stable for at least 48 h while kept at room temperature. Both screening and confirmatory procedures were applied to authentic urine and oral fluid specimens obtained from volunteers following therapeutic ingestion of dextromethorphan. [9]

04) reverse phase high performance liquid chromatographic method was developed for the simultaneous estimation of bromhexine hydrochloride, chlorpheniramine maleate, dextromethorphan hydrobromide and guaiphenesin in their tablet dosage form. The chromatographic conditions were standardised using a Chromatopak C18 (25 cm × 4.6 mm i.d. × 5µm) with UV detection at 265 nm, and the mobile phase consisted of methanol:acetonitrile:0.025 M phosphate buffer (50:25:25, v/v/v). The retention times of bromhexine hydrochloride, chlorpheniramine maleate, dextromethorphan hydrobromide and guaiphenesin were 16.254 min, 12.219 min, 6.156 min and 9.432 min, respectively. The calibration curves were linear with correlation coefficients of 0.9987, 0.9988, 0.9981 and 0.9981 over a concentration range of 4.0–24.0 µg/ml for bromhexine hydrochloride, 5.0–30.0 µg/ml for chlorpheniramine maleate, and 10.0–60.0 µg/ml for both dextromethorphan hydrobromide and guaiphenesin, respectively. [10]

05) The chromatographic separation was performed using Phenomenex Luna C8 Column (250 mm x 4.6 mm, 5 µm particle size). Mobile phase composed of buffer and acetonitrile and a flow rate of 1 ml/minute is monitored with injection volume of 20 µl. Detection was carried out at 229 nm. The method was validated as per ICH guidelines. The retention time for Brompheniramine maleate, Dextromethorphan HBr and Phenylephrine HCl are observed as 12.6, 13.6 and 3.3 minutes respectively. Linearity range was observed in concentration of 10 – 30 µg/ml for Brompheniramine maleate, 50 – 150 µg/ml for Dextromethorphan HBr and 25 – 75 µg/ml for Phenylephrine HCl. The percentage recoveries of Brompheniramine maleate, Dextromethorphan HBr and Phenylephrine HCl are 101.16%, 100.27 and 100.26% respectively. The correlation coefficients for all the components are close to 1. [11]

06) A more sensitive and accurate high-performance liquid chromatography/electrospray ionization tandem mass spectrometry (HPLC-ESI-MS) method has been developed and validated simultaneously for analysis of three analytes. The method is sensitive, enough for the study of analyte pharmacokinetics and metabolic pathways of drugs. The current method includes a simple reversed-phase Liquid chromatography–mass spectrometry (LC-MS) assay in determining the plasma concentrations of dextromethorphan, dextrorphan, and midazolam. Analytes were extracted simply via liquid-liquid extraction with methyl-tert-butyl ether (MTBE). Separation and analysis were done through an Eclipse XDB® C-8 (150 x 2.1 mm, 3.5 µm particle size, Agilent, Wilmington, DE, USA) analytical column. Analytes were eluted using a mobile phase gradient with good separation and peak shape

within 10 min. Using a small sample volume as low as 50 µL of plasma, assay sensitivity was found to be lower limit of quantitation (LLOQ) as low as 0.5 ngmL−1 and the linearity range of 0.5 to 500 ngmL−1 has been achieved for each compound. The limit of quantitation (LOQ) is 0.5 ngmL−1. The Intra- and inter-day precision was less than 4.0 and 7.0%, respectively. The within and between day accuracies were between 94.3 and 111.4% with a mean of 101.5%.[12]

07) Separation of Guaifenesin and Dextromethorphan was done by THERMO, C18, 250X4.6mm, 5µm or equivalent in an isocratic mode utilizing 0.1M KH2PO4: Methanol (60:40) at a flow rate of 1.0ml/min and eluate was monitored at 280nm, with a retention time of 3.259 and 4.164 minutes for Guaifenesin and Dextromethorphan respectively. The method was validated and their response were found to be linear in the drug concentration range of 50µg/ml to150 µg/ml for Guaifenesin and 50µg/ml to150 µg/ml for Dextromethorphan. The values of the correlation coefficient were found to 0.999 for Guaifenesin and 1for Dextromethorphan. respectively. The LOD and LOQ for Guaifenesin were found to be 0.597 and 1.991 respectively. The LOD and LOQ for Dextromethorphan were found to be 0.1072 and 0.3572 respectively. This method was found to be good percentage recovery for were found to be 99 and 100 respectively indicates that the proposed method is highly accurate. The specificity of the method shows good correlation between retention times of standard with the sample so, the method specifically determines the analyte in the sample without interference from excipients of tablet dosage forms.[13]

08) reverse phase high performance liquid chromatographic (RP-HPLC) method for simultaneous estimation of Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride of Chlorpheniramine Maleate in Cough syrup. The first method of three drugs which involves absorbance measurement at 265 nm. Linearity was obtained in the range of 5-15 µg/ml, 2.5-7.5 µg/ml and 1-3 µg/ml respectively. Good Chromatographic separation was achieved isocratically at 35ºC ± 0.5 ºC on Partisil 10 SCX column (250 × 4.6 mm i.d.) with a mobile phase composed of Buffer: Methanol the ratio of 40:60 % V/V at flow rate of 1.0ml/min. The retention time of Phenylephrine Hydrochloride, Dextromethorphan Hydrobromide, and Chlorpheniramine Maleate retention time was found to be 5.0 min, 8.0 min., and 13.0min respectively. The correlation coefficient for calibration curve of all three peaks was found to be 0.9999. [14]

09) The chromatographic conditions were standardized using Phenomenex Luna C18 (250 mm × 4.6 mm i.d., 5 µm particle size) with UV detection at 258 nm and mobile phase consisting of methanol: 0.05 M phosphate buffer pH 3.0 (60 : 40 v/v). Mobile phase was delivered at the flow rate of 1.3 mL/ min and separation was completed within 8 min. The retention times of guaiphenesin, dextromethorphan hydrobromide and bromhexine hydrochloride were 3.1 min, 4.1 min and 6.8 min respectively. Calibration curves were linear with correlation coefficient 0.998. 0.999 and 0.999 over a concentration range of 50-250, 5-25 and 1-6 µg/mL for guaiphenesin, dextromethorphan hydrobromide and bromhexine hydrochloride respectively. Recoveries were between 97.04-100.15, 101.92-104.67 and 102.01-102.55 respectively.[15]

10) high performance liquid chromatograhic (HPLC) methods were developed and validated for quantitative analysis of CYP2D6-mediated dextromethorphan O-demethylation and CYP3A4-mediated testosterone 6µ-hydroxylation. Both the assays showed a good linearity in the substrate concentration range of 0.05 – 20.0 µM and 0.01 – 100.0 µM with limit of detection (LOD)

of 0.01 µM and 0.001 µM for CYP2D6 and CYP3A4, respectively. The intra- and inter-day precisions were from 7.21% to 12.22% and 3.09% to 14.60% for CYP2D6; and from 4.77% to 9.19% and 3.65% to 11.84% for CYP3A4. Assay accuracy for CYP2D6 ranged from 85.3% to 104.9% over dextrorphan concentrations of 0.05-5.0 µM; and that of CYP3A4 was 105.1% to 109.6% at hydroxytestosterone concentrations of 0.01-50 µM. Enzyme kinetic parameters obtained (Km and Vmax) using the two assays were within reported ranges. Thus, the assays were able to serve as activity markers in the assessment of pharmacokinetic drug interaction and metabolism mediated by CYP2D6 and CYP3A4. [16]

CONCLUSION

The analytical method validation is essential for analytical method development and tested extensively for specificity, linearity, accuracy, precision, range, detection limit, quantization limit, and robustness. In summary, analytical method development and validation allows to confirm that an accurate and reliable potency measurement of a pharmaceutical preparation can be performed. Most of the drugs in multi component dosage forms can be analyzed by HPLC method because of the several advantages like rapidity, specificity, accuracy, precision and ease of automation in this method. HPLC methods development and validation play important roles in new discovery, development, manufacture of pharmaceutical drugs and various other studies related to humans and animals. An analytical procedure is developed to test a defined characteristic of the drug substance or drug product against established acceptance criteria for that characteristic. This review gives information regarding various stages involved in development and validation of HPLC method.

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