REVIEW OF LITERATURE

Few researchers have published their research work on mentioned drugs. Available literature was reviewed and will be used to develop better analytical approach for antihistaminic drug considering preclinical biological matrices. Till date no research work on method validation of this drug has been conducted with precipitation method, to establish a comprehensive analytical and pre-clinical strategy. Few available bio-analytical research publications for diphenhydramine quantiation include:

- D. Lutz,e et.al. (1983), “Quantitative Determination of Diphenhydramine and Orphenadrine in Human Serum by Capillary Gas Chromatography”.
- Sanjeev Kumar et.al. (1998) in their publication “Simultaneous Determination of Diphenhydramine, Its N-Oxide Metabolite and Their Deuterium-labeled analogues in Ovine Plasma and Urine Using Liquid Chromatography/Electrospray Tandem Mass Spectrometry. The objective of this study was to develop and validate a liquid chromatographic/tandem mass spectrometric (LC/MS/MS) method for the simultaneous quantitation of DPHM, its N-oxide metabolite and their deuterium-labeled analogues in ovine plasma and urine. Samples spiked with the analytes and the internal standard, orphenadrine, were processed using liquid– liquid extraction. The extract was chromatographed on a propylamino LC column and MS/MS detection was performed in the positive ion electrospray mode using multiple reaction monitoring. The linear concentration ranges of the calibration curves for the N-oxides and the parent amines were (0.4 to 100.0 and 0.2 to 250.0 ng ml/1, respectively. In validation tests, the assay exhibited acceptable variability (±15% at analyte concentrations below 2.0 ng ml/1 and ±10% at all other concentrations) and bias (±15% at all concentrations), and the analytes were stable under a variety of sample handling conditions. Using this method, the labeled and unlabeled N-oxide metabolite was identified in fetal plasma after DPH administration. This method will be used further to examine the comparative metabolism of diphenhydramine to its N-oxide metabolite in the mother and the fetus.
- Imma Ferrer et.al. (2004) “EPA Method Agilent’s LC/MS/MS Solution for Pharmaceuticals and Personal Care Products in Water, Soil, Sediment and Biosolids by HPLC/MS/MS, Imma Ferrer et.al “Combination of LC/TOF-MS and LC/Ion Trap MS/MS for the Identification of Diphenhydramine in Sediment Samples, F. Estelle et.al...
H1-Antihistamines Current Status and Future Directions. Diphenhydramine (Benadryl) is a popular over-the-counter antihistaminic medication used for the treatment of allergies. After consumption, excretion, and subsequent discharge from wastewater treatment plants, it is possible that diphenhydramine will be found in environmental sediments due to its hydrophobicity (log P 3.27). This work describes a methodology for the first unequivocal determination of diphenhydramine bound to environmental sediments. The drug is removed from the sediments by accelerated solvent extraction and then analyzed by liquid chromatography with a time-of-flight mass spectrometer and an ion trap mass spectrometer. This combination of techniques provided unequivocal identification and confirmation of diphenhydramine in two sediment samples. The accurate mass measurements of the protonated molecules were m/z 256.1703 and 256.1696 compared to the calculated mass of m/z 256.1701, resulting in errors of 0.8 and 2.3 ppm. This mass accuracy was sufficient to verify the elemental composition of diphenhydramine in each sample. Furthermore, accurate mass measurements of the primary fragment ion were obtained. This work is the first application of time-of-flight mass spectrometry for the identification of diphenhydramine and shows the accumulation of an over-the-counter medication in aquatic sediments at five different locations.

- Vishnu D. Gupta (2006) Pharmaceutics Division University of Houston Houston, Texas “Chemical Stability of Diphenhydramine Hydrochloride from an Elixir and Lidocaine Hydrochloride from a Viscous Solution when Mixed Together”, The stability of diphenhydramine hydrochloride (from an elixir) and lidocaine hydrochloride (from a viscous solution) in a mixture (1:1) was studied using a stability-indicating high-performance liquid chromatographic assay method. The concentrations of the drugs were related directly to peak heights, and the percent relative standard deviations based on five injections were 1.4 for diphenhydramine and 1.3 for lidocaine. The products of hydrolysis from the both the drugs and a number of excipients present in the dosage forms did not interfere with the developed assay procedure. The mixture was stable for at least 21 days when stored in amber-colored bottles at room temperature. The pH value of the mixture remained constant, and the physical appearance did not change during the study period.
• Arun Kumar Mishra et.al. (2010), “Development and validation of UV spectrophotometric method for estimation of diphenhydramine hydrochloride in soft gelatin capsule. A simple, accurate, cost effective and reproducible spectrophotometric method has been developed for the estimation of Diphenhydramine Hydrochloride in soft gelatin capsule dosage form. For UV spectrophotometric method, maximum absorption was found at λmax 258nm. The percentage recovery of Diphenhydramine Hydrochloride ranged from (98.97 ± 0.2989) in capsule dosage form. The developed method was validated as per ICH guidelines with respect to linearity, accuracy (recovery), precision and specificity. Beers law was obeyed in the concentration range of 10-100 g/ml having line equation y = 0.016x - 0.018 with correlation coefficient of 0.9934. By treating the data statistically and by recovery study, results of study were validated.

• John M. Weiler, et.al., “Effects of Fexofenadine, Diphenhydramine, and Alcohol on Driving Performance: A Randomized, Placebo-Controlled Trial in the Iowa Driving Simulator”.

• Akram M. et.al published (2010) “Spectrophotometric determination of diphenhydramine hydrochloride in pharmaceutical preparations and biological fluids via ion-pair formation”. A simple, sensitive and accurate spectrophotometric method has been described for the assay of diphenhydramine hydrochloride (DPH) in raw material and in biological samples. The method is based on extraction of DPH into dichloromethane as ion-pair complexes with patent blue (PB), eriochrome black T (EBT), methyl orange (MO) and bromocresol purple (BCP) in acidic medium. The coloured species exhibited absorption maxima at 632, 514, 428 and 414 nm for PB, EBT, MO and BCP, with molar absorptivity values of 1.32 · 105, 2.36 · 104, 3.68 · 104 and 3.07 · 104 l mol1 cm1, respectively. The reaction conditions were optimized to obtain the maximum colour intensity. Beer’s law was obeyed with a good correlation coefficient (0.9982–0.9993) in the concentration ranges 0.5–3, 2.0–16, 2.0–10 and 1.0–10 lg ml1 for PB, EBT, MO and BCP methods, respectively.

• Dantu Durga Rao et.al (2011), published “Development and Validation of an UPLC Method for Rapid Determination of Ibuprofen and Diphenhydramine Citrate in the Presence of Impurities in Combined Dosage Form”. A novel, stability-indicating gradient reverse-phase ultraperformance liquid chromatographic method was developed for the
simultaneous determination of ibuprofen and diphenhydramine citrate in the presence of degradation products and process related impurities in combined dosage form. The method was developed using C18 column with mobile phase containing a gradient mixture of solvent A and B. The eluted compounds were monitored at 220 nm. Ibuprofen and diphenhydramine citrate were subjected to the stress condition of oxidative, acid, base, hydrolytic, thermal, and photolytic degradation. Major unknown impurity formed under oxidative degradation was identified using LC–MS–MS study. The developed method was validated as per ICH guidelines with respect to specificity, linearity, limit of detection, limit of quantitation, accuracy, precision and robustness. The described method was linear over the range of 0.20–6.00 g/mL (r > 0.998) for Ibuprofen and 0.084–1.14 g/mL for diphenhydramine citrate (r > 0.998). The limit of detection results were ranged from 0.200–0.320 g/mL for ibuprofen impurities and 0.084–0.099 g/mL for diphenhydramine citrate impurities. The limit of quantitation results were ranged from 0.440 to 0.880 g/mL for ibuprofen impurities and 0.258 to 0.372 g/mL for diphenhydramine citrate impurities. The recovery of ibuprofen impurities were ranged from 98.1% to 100.5% and the recovery of diphenhydramine citrate impurities were ranged from 97.5% to 102.1%.

Z. K. Ge et al. (2011) published “Simultaneous determination of ibuprofen and diphenhydramine HCl in orally disintegrating tablets and its dissolution by reversed-phase high performance liquid chromatography (RP-HPLC)”. Reversed-phase high performance liquid chromatography (RP-HPLC) methods were established for the simultaneous determination of ibuprofen (IBU) and diphenhydramine HCl (DPH) in orally disintegrating tablets (ODTs) and its dissolution in this work. The separation was performed on a Shim-pack VP-ODS C18 (150 × 4.6 mm, 5 μm) column. The mobile phases of determination and dissolution were a mixture of 0.05 mol/L potassium dihydrogen phosphate buffer (containing 0.2% triethylamine and 0.2% glacial acetic acid)-acetonitrile (54:46, v/v) and a mixture of 0.05 mol/L potassium dihydrogen phosphate buffer-acetonitrile-triethylamine (60:40:0.2), respectively. The mobile phase was delivered at a flow rate of 1.0 ml/min, and the detection was carried out at 263 nm
under the column temperature of 30°C and the injection volume of 20 μl. The linear ranges of determination were 100 to 1000 μg/ml with the correlation coefficient of 0.9996 for IBU and 7.5 to 120 μg/ml with the correlation coefficient of 0.9998 for DPH. The average recoveries (n = 9) were 98.52% (relative standard deviation (RSD) = 0.22%) for IBU and 99.07% (RSD = 0.87%) for DPH, respectively. The linear ranges of dissolution were 50 to 800 μg/ml with the correlation coefficient of 0.9999 for IBU and 5 to 80 μg/ml with the correlation coefficient of 0.9999 for DPH; the dissolution both exceeded 80% of the labeled at 10 min. The results showed that the proposed methods were simple, sensitive, accurate and specific. To evaluate its potential application value, IBU and DPH in compound ODTs were simultaneously detected using this approach, and satisfied results were obtained.

- Nouruddin W et.al (2013) “Simultaneous determination of paracetamol and diphenhydramine hydrochloride mixture in the presence of their degradation products”. New accurate, selective, sensitive and precise methods were developed and validated for determination of paracetamol and diphenhydramine hydrochloride in the presence of P-amino phenol, the hydrolytic degrade and the most potential impurity of paracetamol and the N oxide degradation product of diphenhydramine in bulk form and in pharmaceutical formulation. Method A uses double divisor second derivative of ratio spectrophotometric technique, at 304nm for paracetamol and 256.4nm for diphenhydramine hydrochloride. Method B utilizes Principle Component Regression (PCR) and Partial Least Squares (PLS) chemometric techniques for quantification of the four components using a UV spectrum range of 210-350 nm. The proposed methods were successfully applied to the analysis of the mentioned drugs either in bulk powder or in pharmaceutical formulation without interference from other dosage form additives, and the results were statistically compared with the pharmacopoeial method.