2. LITERATURE REVIEW:

2.1 General Literature review from Journals for determination of Parkinson's disease:

Literature studies show various analytical methods reported for the estimation of Pramipexole drug substances of Parkinson's disease.

Parmar D. et al. (2008) \[8\] reported that it is very important to incorporate clinically relevant practicals into the undergraduate pharmacology practical (UGPP) curriculum. Various medical colleges in the state of Gujarat have included clinical practicals in their UGPP curriculum. Rai has recommended the inclusion of the 'P-drug' concept in the UGPP curriculum. The conference of experts on the rational use of drugs, convened by the World Health Organization in Nairobi in 1985, stated that: "Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, at the lowest cost to them and their community." This goal can be achieved by acquiring knowledge of the principles of rational drug usage during undergraduate training. This correspondence emphasizes the importance of this concept.

Biljana J. et al. (2007) \[9\] reported that Pramipexole is a dopamine D2-agonist/antiparkinsonian agent in which BI-II 546 CL, BI-II 751 and 2-amino benzothiazole are commonly found as impurities. Due to the lack of analytical data on pramipexole and its related substances in bulk drug and pharmaceuticals, we aim at the optimization and characterisation of the chromatographic behaviour of pramipexole and its related substances employing experimental design. The analysis was performed using a C18 column with mobile phases containing different ratios of acetonitrile and water phase (aqueous triethylamine/orthophosphoric acid). The detection was performed at 262 nm for pramipexole, BI-II 751 and 2-aminobenzthiazole and at 326 nm for BI-II 546 CL. To define the influence of chromatographic parameters on separation, a central composite design was chosen. The content of acetonitrile, TEA and pH of the water phase were identified as the factors with important influences on retention. Using an appropriate mathematical model, we were able to predict retention under different conditions.

Panditrao V. et al. (2011) \[10\] reported that a novel stability-indicating high-performance liquid chromatographic assay method was developed and validated for quantitative determination of pramipexole dihydrochloride in bulk drugs and in pharmaceutical dosage form in the presence of degradation products. An isocratic, reversed phase HPLC method was developed to separate the
drug from the degradation products, using an Ace5-C18 (250×4.6 mm, 5µm) advance chromatography column, and 10 mmol/L, ammonium acetate and acetonitrile (75:25 v/v) as a mobile phase. The detection was carried out at a wavelength of 260 nm. The pramipexole was subjected to stress conditions of hydrolysis (acid, base), oxidation, photolysis and thermal degradation. Degradation was observed for pramipexole in base, in acid and in 30% H2O2. The drug was found to be stable in the other stress conditions attempted. The degradation products were well resolved from the main peak. The percentage recovery of pramipexole was from (99.87 to 99.98%) in the pharmaceutical dosage form. The developed method was validated with respect to linearity, accuracy (recovery), precision, system suitability, specificity and robustness. The forced degradation studies prove the stability indicating power of the method.

Manjunath S. et al. (2011) [11] reported that three simple, sensitive and selective spectrophotometric methods have been developed and validated for the estimation of Pramipexole in bulk drug and pharmaceutical formulations. In Method A Pramipexole exhibits absorption maximum at 261.8 nm in ethanol, in Method B it shows a sharp peak at 249.4 nm in first order derivative spectrum with n=1 and Method C is based on calculation of area under curve (AUC) for analysis of Pramipexole in the wavelength range of 255-265 nm. The drug follows the Beer-Lambert's law in the concentration range of 9-45 µg/mL for the three methods. Results of the analysis were validated statistically and by recovery studies it was found to be satisfactory.

Humaira S, et al. (2010) [12] reported that a rapid, sensitive and selective method for the determination of Pramipexole in pure drug and in tablets was developed using gradient Ultra Fast Liquid Chromatography (UFLC). The devised method involved separation of Pramipexole (PRM) on a Reversed Phase Waters Symmetry Column and determination with UV detection at 260 nm. The standard curve was linear (R = 0.999) over the concentration range of 50–300µg /mL with a detection limit of 0.04 mg/ mL and a quantification limit of 0.16 mg/ mL. Intra-day and inter-day precision and accuracy of the method were established according to the current ICH guidelines. Intra-day and interlay of RSD values at three QC levels (100, 150 and 200 mg/ mL) were 0.02–0.05%, based on the peak area. The intra-day relative error (er) was between 0.01 and 0.2%. The developed method was successfully applied to the determination of PRM in tablets and the results were statistically compared with those obtained by a literature method. Accuracy evaluated by means of the spike recovery method, was the excellent with percent recovery in the range 97.7–
103.2 with precision in the range 1.6–2.2%. No interference was observed from the co-formulated substances. The method was economical in terms of the time taken and the amount of solvent used. **Wakode R. et al. (2010)** [13] reported that an oral monolithic osmotic system for highly water-soluble pramipexole dihydrochloride monohydrate has been developed and characterized. Monolithic osmotic system was developed using controlled porosity membrane, this system delivers drug in controlled manner for prolonged period of time. Controlled porosity osmotic membrane consists of cellulose acetate as coating polymer and water-soluble pore formers, which forms an in-situ microporous membrane after imbibing water, hence no laser drilling is required. Pore formation was controlled by varying concentration of pore forming agents to get controlled release of pramipexole for period of 24 hrs. Scanning electron microscopy was carried out to confirm the microporous structure. An optimized system was selected to study the effect of different concentration of coating polymer, osmotic agents, pH of dissolution media and effect of agitation on the release of drug. From in vitro release studies it was evident that drug release was independent of pH and agitation but highly dependent on concentration of pore forming agents used. Increasing concentration of cellulose acetate from 2% - 5% w/v drastically retarded drug release. Osmotic pressure generated was determined using 3D3 Freezing point osmometer and was found to be linear with drug release. The developed formulation gave desired once a day release of pramipexole without using laser drilling technique making it more patient compliance and cost effective.

**Narendra Kumar R. et al. (2011)** [14] reported that an isocratic stability indicating liquid chromatographic method has been developed and validated for the determination of Pramipexole in bulk drug and its pharmaceutical dosage forms. Separation of the drug with degradation products was achieved using Prontosil,C18, 150 x 4.6mm, 5µm column as stationary phase and pH 3.0 (±0.05) buffer: Acetonitrile (72:28,v/v) as mobile phase at a flow rate of 1.0 mL/min. UV detection was performed at 264 nm. The method is linear over the range of 0.96 – 89.7 µg/mL. The percent recovery of drug in dosage forms was ranged from 100 to 102.2. The method is simple, rapid, precise, selective and stability indicating and can be used for the assay in quality control and stability studies samples.

**Vinodhini C. et al. (2011)** [15] reported that Two simple and sensitive spectrophotometric methods in ultraviolet and visible region were developed for the estimation of Pramipexole dihydrochloride
monohydrate in pharmaceutical dosage forms. Method I was based on Pramipexole dihydrochloride monohydrate showing absorption maximum at 265nm in methanol. Method II was based on reaction of Pramipexole dihydrochloride monohydrate with ferric nitrate under acidic condition to yield a yellowish green color. This color has a characteristics light absorption in the visible region with the absorption maximum at 435nm. Method I and II obeyed Beer’s law in the concentration range of 10 - 80µg/ml and 5 – 25µg/ml respectively. The result of analysis has been validated statistically and by recovery studies. These methods are successfully employed for the determination of Pramipexole dihydrochloride monohydrate in various pharmaceutical preparations.

Gurupadayya B. et al. (2009) reported that two simple, sensitive, accurate and economic methods A and B have been developed for the quantitative estimation of pramipexole dihydrochloride drug and its formulations (Tablets). Method A is based on the diazotization of primary amine group of pramipexole with sodium nitrate and hydrochloric acid followed by coupling with N-(1-naphthyl) ethylene diamine hydrochloride (BM Reagent) to form a colored chromogen with a characteristic absorption maximum at 616 nm.. Method B is based on the reaction of the drug in methanolic solution with paradimethylaminobenzaldehyde (PDAB) in acidic condition producing Schiff’s base having a 8 at 474.5nm. Beer’s law is obeyed in concentrations ranging from 4-20 µg/ml for method max A and 50-150 µg/ml for method B. The results obtained with the proposed methods are in good agreement with labeled amounts when the marketed pharmaceutical formulations are analyzed. The results of analysis have been validated statistically and by recovery studies.

Wakode R. et al. (2010) reported that once a day push pull osmotic tablets containing pramipexole as an antiparkinson’s agent were developed and evaluated for in vivo efficacy. Push pull osmotic tablets are bilayered tablets consisting of pull layer (drug layer) and push layer (polymer layer) coated with semipermeable cellulose acetate membrane containing water leaching pore forming agents. To determine the in vivo efficacy of formulation, symptoms of Parkinson’s disease were induced in male Wistar rats using reserpine 5mg/kg, (i.p) and induction of disease was confirmed with the help of in vivo tests. Striatal dopamine content was decreased from 12 ng/gm of tissue in normal control to 0.6 ng/gm in disease induced rats. Dopamine content was found to increase to 6ng/gm after intragastric administration of push pull osmotic tablet and even the motility in rats was improved. Various pharmacokinetic parameters were estimated and the
studies revealed that the developed formulation maintained plasma levels of pramipexole for a period of 24 hrs. Malenović A. et al. (2011) reported that a previously optimized method for HPLC analysis of pramipexole and its impurities was subjected to method validation in accordance with official regulations. The optimized chromatographic conditions were as follows: mobile phase acetonitrile-water phase [15 + 85, v/v, water phase contained 1 triethylamine (TEA), pH adjusted to 7.0 with orthophosphoric acid]; detection at 262 nm for pramipexole, BI-II 751 xx, BI-II 786 BS, BI-II 820 BS, and 2-aminobenzothiazole and at 326 nm for BI-II 546 CL; column temperature, 25°C; and flow rate, 1 mL/min. Acetonitrile and TEA content, pH of the water phase, flow rate, column temperature, and column type were factors studied in robustness testing. According to the experimental plan defined by a Plackett-Burman design, five dummy variables were added in order to have 12 factors. As output, resolution factor was chosen. Robustness was assessed by graphical (half-normal probability plots and Pareto charts) and statistical (t-test) methods. Also, nonsignificance intervals for significant factors were estimated, and limits for the system suitability test were determined. Finally, linearity, accuracy, and precision of the proposed HPLC method were defined. LOD and LOQ values for analyzed impurities were determined. The method was completely defined by these experiments.

The parent guideline on drug stability testing Q1A (R2) issued by International Conference on Harmonization (ICH) stipulates stress studies to be carried out on a drug in order to establish the drug's inherent stability characteristics. The parent guideline on validation of analytical procedure Q2A (R1) issued by International Conference on Harmonization (ICH) guideline provided the guidance for method validation procedure to prove the method is qualify and fit for use to regular analysis. On base of validation characteristics complies the method will be suitable for regular uses.