REVIEW OF LITERATURES

Lekha S et al., (2016) has reviewed hyperglycemia and hyperlipidemia are both risk factors for the development of various complications in patients with type 2 diabetes mellitus. Colesevelam Hydrochloride is a novel drug that can improve both hypercholesterolemia and hyperglycemia in such patients. It is an orally administered bile acid sequestrant with high capacity for binding bile acids. Colesevelam drug can offer potential new diabetes treatment along with other drugs.

Venkata VV et al., (2015) had estimated unbound bile acids in colesevelam HCL Tablets by using UHPLC Method. This method was developed for the quantitative determination of bile acids (glycocholic acid (GCA), glycochenodeoxycholic acid (GCDA) and taurodeoxycholic acid (TDCA)) in in-vitro bile acid-binding study of Welchol tablets. This method selective and capable for estimation of bile acids in the presence of placebo matrix. Hence, this developed method applied to in vitro bile acid-binding studies of colesevelam HCL tablets.

James RG III et al., (2014) discussed about safety and efficacy of colesevelam HCL in the treatment of Elderly patients. Colesevelam significantly reduces the cholesterol and hemoglobin AIC in patients with hypercholesterolemia and Type 2 diabetes mellitus (T2DM). The main purpose of this study was to evaluate the efficacy and safety/tolerability of colesevelam in older (≥65) and younger adults (<65). Hence, conducted post hoc analyses of pooled clinical trial data from seven phase II and III randomized, double-blind, placebo-controlled, primary hyperlipidemia and T2DM clinical trials. Adverse effects were similar between both subgroups. Hence, concluded that colesevelam appeared to be generally safe, well tolerated, and efficacious in older age group patients for primary hyperlipidemia and T2DM.

Swetha P et al., (2014) has developed a method for quantitative determination of ammonium content in omeprazole tablets by Ion Chromatography. The method was developed using suppressed conductivity detection with IonPac CS17 column (250*4.6mm*5µm) and mobile phase containing 1.5mM Methane sulfonic acid. The developed method was validated as per ICH guidelines. The LOD and LOQ values of Ammonium were 8ppm and 30ppm. The unknown peak and Ammonium peaks were well separated and resolution was more than 2.0.

Erwin A et al., (2013) has been used pulse electrochemical detection successfully for the analysis of tobramycin and similar antibiotics. The separation was achieved by using a discovery C-18 RP column (250mm*4.6mm, 5µm) and mobile phase containing sodium sulphate (35g/L), Sodium octanesulphonic acid (1g/L), tetrahydranfuran (14mL/L) and 0.2M
phosphate buffer  pH 3.0 (50mL/L). The limit of quantification was achieved 5ng. The linearity was examined in the range LOQ-60µg/mL and the coefficient of determination was 0.998. The proposed method is useful in quality control of tobramycin drug substances and drug products.

Venkata VV et al., (2013) An ion chromatography method has been developed to estimate free phosphate in in-vitro phosphate binding study of sevelam carbonate tablets. Sevelamer carbonate is a cross linked polymeric amine; it is the active ingredient in Renvela tablets. The method is selective and capable of detecting phosphate in the presence of placebo matrix. The Limit of quantification is 0.2mM for Phosphate. The developed method was applied to in-vitro phosphate binding studies of sevelam carbonate tablets.

Pavan KKSR et al., (2012) has been developed for determination of cyclopropylamine in nevirapine and Moxifloxacin HCl pharmaceutical substances. The separation was achieved Metrosep C4, 250*4.0mm, 5µm with conductometric detector and mobile phase consists of 5mM Hydrochloric acid containing 10% acetonitrile. The drug substance was subject to degrade process like hydrolysis, oxidation, photolytic, thermal and humidity degradation. This method was validated and LOD, LOQ values were 0.10µg/mL and 0.37µg/mL respectively. The recoveries of cyclopropylamine in both drug substances were 97.0 and 98.0% respectively.

Lokesh B et al., (2012) has reported for Ion Chromatography (IC) in the pharmaceutical Industry can be extended over wide range of analytes. IC with suppressed conductivity detection for cholinergic compounds has plays important role in the study of the stability profile of drug components. Most pharmaceuticals are administrated in the salt form (~ 56 %) compared to the free form (~ 44%). Cholride and sodium counter - ions remain the dominant salt forms for the manufacture of basic and acidic drugs respectively. Determination of wide range of chromophoric and non - chromophoric anionic and cationic pharmaceutical counter -ions can be done on IC and hence it becomes preferred technique for pharmaceuticals counter ion determination.

ICH guidelines Q3A (R2) and Q3B (R2) provide information on the classification of impurities, reporting identification and qualification thresholds of impurities.

Kumar MN et al., (2011) has been developed for the simultaneous assay of Ibandronate sodium drug substance and its impurities. The separation was achieved on Allsep anion column 150*4.6mm, 7µm with conductometric detector and mobile phase is 1 %( v/v) formic acid and acetone 98:2%. The drug substance was subject to degrade process like hydrolysis,
oxidation, photolytic, thermal and humidity degradation. The remarkable degradation was achieved under oxidative process. This method was validated and LOD, LOQ for impurities were in the range of 0.36-0.80 µg/mL and 1.00-2.40µg/mL respectively. For Ibandronate LOD and LOQ were 38µg/mL and 113 µg/mL respectively. The recovery studies for impurities and Ibandronate were in the range of 99-103.1.

Kaleemullah T et al., (2011) has been developed a simple and sensitive ion chromatographic method for the determination of sodium citrate and formic acid in penicillin class of drugs. The separation was achieved with Hamilton PRP-X 300 (250*4mm*7µm) column with conductometric detection. The linearity ranges for sodium citrate and formic acid were 10.8-64.7µg/mL and 1.5-15.0µg/mL respectively. The limit of detection and quantification for sodium citrate and formic acid were 1.2µg/mL and 0.4µg/mL respectively.

Podolska M et al., (2011) has developed a method for determination of sodium metabisulfite in parenteral formulations containing tartrate ions. A satisfactory separation of SO3 2- and SO4 2- was achieved by the proposed HPIC method with 15 mM NaHCO3/0.6 mM Na2CO3 mobile phase and columns with various packing materials. The limit of detection for SO3 2- and SO4 2- were 3 µg/mL and 1 µg/mL, respectively.

Dennis J et al., (2011) reviewed IC applications for the determination of active and inactive ingredients, excipients, degradation products, and impurities relevant to pharmaceutical analyses and thus serves as a resource for investigators looking for insights into the use of IC methodology in this field of applications. Ion chromatography has developed and served into an important analytical methodology in a number of diverse applications and industries, including pharmaceuticals.

Brunetti L et al., (2010) has evaluated the safety and efficacy of colesevelam hydrochloride for the treatment of hypercholesterolemia and type 2 diabetes mellitus. The study reveals the efficacy of colesevelam in monotherapy and combination with HMG-CoA reductase inhibitors and also with other lipid lowering therapies. In type 2 diabetes mellitus trials, colesevelam was evaluated in combination with metformin, sulfonylureas, insulin, and rosiglitazone and sitagliptin. It has been proved that colesevelam monotherapy effectively reduces low-density lipoprotein cholesterol (LDL-C) and also have great affectivity in reduction of hemoglobin A1c in patients with type 2 diabetes mellitus. In addition the
combination of colesvelam with other lipid-lowering therapies further reduces LDL-C.

Lakshmana SP et al., (2010) reviewed characterization and control of impurities in pharmaceutical substances and products. The control of pharmaceutical impurities in the pharmaceutical industry is an important task to the formulator. The International Conferences on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities in pharmaceutical drug substance as well as drug product. This article provides the valuable information about the impurities types and its classification, various techniques of isolation for the determination, qualification of impurities and critical factors to be considered while preparations of the bulk drugs.

Gowrisankar D et al., (2010) has demonstrated validation and Calibration of Analytical Instruments. The regular performance verification of analytical instruments is made to ensure that the instruments to be used are suitable for its intended application. All equipments used in the production should be properly validated and calibrated. This producer ensures that minimizes the risk of contamination and cross contamination. Hence, Validation and Calibration is very important for analytical instruments.

Richard K et al., (2010) determined choline and its analogs by using Ion chromatography in various matrices such as prescription and non-prescription medications, milk and infant formula, vitamins, mineral formulations. The method demonstrated that a cation RFIC system can determine methacholine, acetylcholine, β-methylcholine with high precision, high recovery, and excellent reproducibility.

Pavan KKSR et al., (2010) has developed, optimized and validated ion chromatographic method for the determination of Monomethylamine (MMA) in various drug substances. Tadalafil drug substance was chosen for this study and LOD, LOQ values were 0.09µg/ml and 0.30µg/ml respectively. The average accuracy was 101.6%. The present study was discussed a different methodologies for determination of MMA in different pharmaceutical drug substances.

Harold B et al., (2007) has reviewed colesvelam HCl’s pharmacology, lipid and glucose efficacy, safety/tolerability, and its clinical use. Colesevelam HCl is a bile acid sequestrant (BAS) and for the purpose of improving tolerability and reducing potential drug interactions compared to older BAS. BAS are known to reduce cholesterol and glucose levels, and to reduce atherosclerotic coronary heart disease (CHD) risk as monotherapy, and in combination with other lipid-altering drug therapies. Colesevelam HCl has specifically been shown to reduce total and low-density lipoprotein (LDL) cholesterol levels, and has been approved as a cholesterol-lowering drug since year 2000. colesvelam HCl will be the first LDL-C lowering
medication also indicated for the glycemic treatment of T2DM, which may significantly help T2DM patients achieve both their LDL-C and HbA1C goals, if approved by US Food and Drug Administration.

Davidson MH et al., (2007) reviewed the use of colesevelam in the treatment of dyslipidemia. Bile acid sequestrant drugs are used to lower LDL-C levels. Two major bile acid sequestrants present are colestyramine resin and colestipol which have been used since 1980s. These have been proven effective and safe as non systemic approaches to reduce cholesterol level. However these drugs have issues related to palatability and gastrointestinal side effects. Hence, these sequestrants have limited use for reduction of Cholesterol. Colesevelam HCL is a non absorbed lipid lowering agent. It can use in monotherapy or in combination with an HMG-CoA reductase inhibitor to reduce lower LDL-C in patients.

Willy RGB et al., (2005) has developed a method for simultaneous determination of ephedrine, pseudoephedrine and norephedrine. A mixture of 2mM HNO3 and 2% (v/v) acetonitrile was used as an eluent. The three ephedrine compounds were separated and linear ranges for ephedrine, pseudoephedrine and norephedrine were 0.08-50 µg/mL, 0.08-40 µg/mL, and 0.06-40 µg/mL respectively. The detection limits were 0.03µg/mL for ephedrine, pseudoephedrine, and 0.02µg/mL for norephedrine. The method has been applied successfully to determination of these sympathomimetics in pharmaceutical products and in Ephedra herbs.

Joachim W et al., (2004) has mentioned that Ion -exchange chromatography is used for the separation of both inorganic and organic anions and cations. Separation of anions is carried out with quaternary ammonium groups attached to the polymer and suffocated, carboxyl or phosphonate groups are used as ion exchange site for the separation of cations. Ion pair chromatography is suited for the seperation of surface active anions and cations, sulfur compound, amines and transition metal complexes. The analysis of amines is an application area of great significance of recent application development. Increasing number of application of aliphatic amines, gradient techniques have become increasingly important in cation exchange chromatography. The Mobile phase Ion chromatography (MPIC) describes a method which combines the major elements of Reverse Phase Ion chromatography with suppressed conductivity detection. The primary advantage of ion -pair chromatography over ion -exchange chromatography is its great flexibility, which allows the chromatographic conditions to be adjusted for a given separation problem.

Rainer S et al., (2001) has reported for the determination of quaternary alkyl ammonium
compounds in the pharmaceutical product Welchol. The analytical technique developed is by Capillary Electrophoresis. The method has been validated and comparative study was made with the existing Ion chromatographic technique with suppressed conductivity detector. The current development of analytical method is done by Indirect UV detection and buffers were used based on creatinine as visualization reagent with different inorganic and organic acids like Phosphoric, sulphuric, formic, acetic, oxalic and citric acid. The selectivity of ten quaternary ammonium compounds was studied based on type of buffer systems applied. The selectivity changes are observed for the di- and trivalent analytes. The influence / effect of the solvents like acetonitrile, methanol, 1, 4-dioxane and tetrahydrofuran was investigated for the selectivity parameter. The limit of quantification of 0.01% w/w of each impurity in the active substance was achieved.

**Wolfgang B et al., (2001)** reported structural elucidation of unknown by-products (mostly quaternary ammonium compounds) in a new-cholesterol reducing drug by combination of Suppressed and non-suppressed Cation-exchange chromatography with electrospray ionization mass spectroscopy. In this technique the mobile phase employed involves 200mM formic acid and 60% (v/v) Acetonitrile. By non-suppressed mode process separation and detection of 8 unknown compounds were possible. Among the separation evolved three most prominent compounds were selected for structural elucidation utilizing collision induced dissociation experiment. In a series of experiments the fragmentation behavior was investigated at different voltages finally leading to structure proposals.

**Aldrigde MA et al., (2001)** reviewed the pharmacology and its related adverse effects of colesevelam hydrochloride. Colesevelam Hydrochloride alone or in combination with an HMG-CoA reductase inhibitor is effective in reduction of total and LDL Cholesterol. Colesevelam is formulated as an oral solid dosage form due to which palatability problems aroused with the formulation developed when bounded with bile acid-binding resins which have to be eliminated. Colesevelam appears to be more cost-effective than older brand formulation of bile acid resins.

**Alan RJ et al., (2001)** has reported the catalytic effect of quaternary ammonium salts in the basic liquid: liquid two phase alkylation of amines is somewhat unexpected in view of the low acidity of most amines (pKa> 30). In general the rate of reeducation by the ammonium salts are slower than those attained under normal conditions with the lithium salts, but the use of a non-etheral solvent can be an advantage. Quaternary ammonium aluminum hydrides reduce ketone and amides effectively to alcohols and amines.
Davidson MH et al., (1999) has compared colesevelam HCL properties with bile acid sequestrants, with placebo for its efficacy, effects on laboratory and clinical safety parameters along with adverse effects. For this study, administered placebo or colesevelam at 4 doses (1.5, 2.25, 3.0 or 3.75 g/d) for 6 weeks with morning and evening meals to men and women with hypercholesterolemia. After 6 weeks of treatment, samples were collected for complete patient profiling like serum chemistry, vitamins level, coagulation studies, and hematological studies. Finally concluded that colesevelam is an effective for lowering low-density lipoprotein cholesterol concentrations in persons with moderate hypercholesterolemia. Mark L et al., (1999) developed method for determination of choline in infant formula by ion chromatography with suppressed conductivity detection. Choline and alkali/alkaline earth metals were separated on a high resolution cation exchange column. Samples were digested with 1M hydrochloric acid, filtered, diluted and injected into the chromatographic system. This method accurately determined choline in powered, concentrated, and ready-to-feed infant formulas.

Masami S et al., (1998) has developed method for separation and determination of alkyl quaternary ammonium compounds by using hydrophilic polymer packing column (Shodex Asahipak GF-310 HQ) and a water-acetonitrile mixture containing 4,4’-bipyridyl and hydrochloric acid used as a mobile phase. The mobile composition is to depress hydrophobic adsorption of the quaternary ammonium compounds and increase sensitivity of the conductivity detection with a micro membrane suppressor. The stationary phase (Shodex Asahipak GF-310 HQ) showed moderate retention and high resolution for the cationic surfactants like Dodecyltrimethylammonium, cetyltrimethylammonium, tetradecyldimethylbenzylammonium and stearyltrimethy lammonium. This method quantified analyte compounds at 0.1nmol level.

Micheel AP et al., (1998) has been developed method for monitoring topiramate degradation in drug substance and drug products by quantifying sulfamate and sulphate ions. The chromatographic system consists of a sodium hydroxide gradient (2-25mM) and an anion exchange HPLC column and an anion suppressor. This method enhances the sample preparation efficiency and throughput. The method has been validated for analysis of degraded and non degraded topiramate drug substance and drug product.

Cullum DC et al., (1994) has reported in Acid the quaternary ammonium group is not hydrolyzed by acids, but ester or amide groups in the alkyl chain may be hydrolyzed. In
alkali conversion to olefin and tertiary amine or pyridine take place. Gravimetric methods were favored at one time, but have largely gone out of fashion because they have mostly been found to be not very quantitative and they take longer time. Ion chromatography as proposed by Small et al. uses a suppressor column after the separation column which reduces the conductivity of the eluent and enables the sample ions to be detected. 

Anthony JW et al., (1992) has been elaborated for the separation of quaternary ammonium surfactants by using normal phase high pressure liquid chromatography technique. The separation was achieved on a bonded polyphenol silica gel column with gradient elution and evaporative light-scattering (ELS) detection. The proposed method has been applied to the quantitative determination of amine.

Williams PA et al., (1990) has reported that the late 1970's the term Ion Chromatography (IC) came into common usage. Traditionally the technique involved an Ion exchange separation followed by conductivity detection. Chemically Suppressed Ion Chromatography (CSIC) is used in a variety of applications.

Its principle role is assisting in the characterization of organic compounds of pharmaceutical interest; this involves elemental analysis, trace analysis and studies of counter ions. It appears that the reaction of metal ions with the colloidal suspension of the allylamine intercalation compound provokes an irreversible delimitation. When metal ions were equilibrated with the polyamine intercalation compounds, the extraction capacities were less than 20% of the theoretical.