1.5 Review of Literature

Literature review is divided into two parts:

- Part I discloses the relevant patent and non-patent literature on Aripiprazole immediate release tablet and
- Part II on the Venlafaxine extended release capsule formulation.

1.5.1 Aripiprazole

**Amin, Alaa S. et al., -2014**, developed spectrophotometric methods for the assay of Aripiprazole in bulk drug and pharmaceutical formulation using N-bromosuccinimide and three dyes, methyl orange, amaranth and indigo carmine, as reagents. The methods were successfully applied to the assay of Aripiprazole in tablets preparations and the results were statistically compared with those of the reference method by applying Student's t-test and F-test.

**Goff, Donald C. et al., -2014**, describes maintenance treatment with long-acting injectable antipsychotics for schizophrenia. Long-acting injectable formulations of antipsychotics, which maintain therapeutic blood levels during the 2-4-week interval between injections. Long-acting injectable formulations are also available for 2 additional second-generation antipsychotics, Olanzapine and Aripiprazole.

**Haruka et al., -2014**, formulated an oral solid preparation that can be formulated in a simpler manner than conventional methods and the pharmaceutical composition exhibits high bioavailability and high dissolution even in persons having low stomach acid, and that can also ensure dissolution after being allowed to stand for a certain period of time.

**Hayes, Mark E. et al., -2014**, formulated a liposome composition containing sparingly soluble drugs that are used to treat life-threatening diseases. A preferred method of encapsulating a drug inside a liposome is by remote or active loading. Remote loading of a drug into liposomes containing a transmembrane electro-chemical gradient is initiated by co-mixing a liposome suspension with a solution of drug, whereby the neutral form of the compound freely enters the liposome and...
becomes electrostatically charged thereby preventing the reverse transfer out of the liposome.

**Hiraoka et al., -2014**, developed injectable high-drug-loading core-shell structure microspheres that release Aripiprazole over 2 month. The microparticles were prep'd by the oil-in-water emulsion solvent evaporation method and characterized. The theoretical drug loading in the particles was set to 80%. When prepared at fixed temperature conditions, all of the microparticles that were prepared with the 3 types of PLA were not spherical or smooth-surfaced. The dissolution profile of the microparticles showed a long release over 7 wk in vitro. The actual drug loading in the microspheres was 73-80%.

**Karavas et al., -2014**, prepared an orally dispersible formulation comprising Aripiprazole as the active ingredient and an effective amount of pharmaceutically acceptable water soluble and water insoluble diluents. Karavas et al. further discloses the process for the preparation of pharmaceutical composition of Aripiprazole.

**Luedecke et al., -2014**, described that second-generation antipsychotics (SGAs) are a mainstay in the treatment of patients with schizophrenia. Continuity in intake of the prescribed medication has been one of the greatest challenges in these patients. One option to improve medication adherence is to prescribe depot or long-acting injectable formulations (LAIs) of antipsychotics. Following risperidone, several other SGAs have been introduced as LAIs.

**Nethravani G. et al., - 2014**, formulated Aripiprazole liposomal suspensions with a view to surpass the Aripiprazole in the blood brain barrier and to increase the retention time in the brain for better therapy. Aripiprazole liposome was prepared by thin film hydration technique using rotary vacuum flash evaporator with phosphatidyl choline along with and without cholesterol in molecular weight ratios and determined the release profile of formulations.

**Rizwana et al., -2014**, formulated the Aripiprazole niosomal suspensions to target the drug to the brain surpassing the Blood brain barrier and to increase the retention time.
in the brain for better therapy. The niosomal suspensions containing Aripiprazole was formulated by thin film hydration technique using rotary vacuum flash evaporator with span 20, span 60, span 80 and varying ratios cholesterol in mol. wt. ratios. It is concluded that Aripiprazole niosomal suspension could act as better formulation for the effective management of psychotic disorders.

**Schwarz et al., -2014,** developed a drug delivery composition comprises a drug elution rate-controlling excipient comprising an elastomeric polymer defining a reservoir. The reservoir contains at least one discrete solid dosage form comprising at least one API and one or more non-polymeric sorption enhancers. The drug delivery composition is in an implantable dosage form.

**Shirley et al., -2014,** reviewed the use of Aripiprazole as maintenance treatment for adult patients with Schizophrenia. Recently, an intramuscular long-acting injectable (LAI) depot formulation of aripiprazole (Abilify Maintena) (aripiprazole LAI) has been approved for use as a treatment for schizophrenia in adults. The efficacy of aripiprazole LAI as a maintenance treatment for schizophrenia has been demonstrated in randomized clinical trials.

**Spanarello et al., -2014,** synthesized depot antipsychotics by esterification of the active drug to a long chain fatty acid and the synthesized compound is dissolved in a vegetable oil, with the exception of some molecules of new generation characterized by microcrystals technologies. The absorption rate constant is slower than the elimination rate constant and therefore, the depot antipsychotics exhibit 'flip-flop' kinetics where the time to steady-state is a function of the absorption rate, and the concentration at steady-state is a function of the elimination rate.

**Szoka, Francis C. et al., -2014,** discloses that sparingly water-soluble agents can be formulated as cyclodextrin complexes, and the water-soluble drug-cyclodextrin complexes dissociate when the complex is administered into patients. The dilution of the complex in the patient leads to the drug being released from the complex, so the drug is not effectively targeted. The present invention describes composition and
methods whereby cyclodextrin or polyanionic beta-cyclodextrin drug-complexes are mixed with a preformed liposome containing the amine salts of an acidic compound.

**Turncliff et al., -2014**, determined the relative bioavailability and safety of Aripiprazole lauroxil, following deltoid and gluteal administration in adult subjects with schizophrenia. The pharmacokinetics of aripiprazole following aripiprazole lauroxil was characterized by a steady rise in plasma concentrations (Tmax 44-50days), a broad peak, and prolonged exposure attributable to the dissolution of aripiprazole lauroxil and formation rate-limited elimination of aripiprazole (t1/2=15.4-19.2days).

**Wang et al., -2014**, discloses a long-acting injectable antipsychotic is one of the most effective methods for improving treatment adherence and decreasing rehospitalization rates in patients with schizophrenia. Only three second-generation antipsychotics were available in a long-acting injectable formulation (risperidone, paliperidone, and olanzapine). In this respect, the emergence of long-acting aripiprazole injection (ALAI), approved by the USFDA for the treatment of schizophrenia in 2013, is timely. ALAI is a lyophilized powder of aripiprazole, and the aripiprazole mol. is unmodified. The initial and target dosage of ALAI is 400 mg once monthly, but it could be reduced to 300 mg if adverse reactions occur with 400 mg.

**Yoo, Ha Na et al., -2014**, formulated a sustained-release lipid pre-concentration of cationic pharmacological active substance comprises liquid crystal formers, neutral phospholipids, liquid crystal hardeners, and anionic anchoring agents. The pre-concentration is a lipid liquid in a state without aqueous fluid, and can form liquid crystal on aqueous fluid. The sustained-release performance of the cationic pharmacological active substance is enhanced through ionic bonding of the anionic anchoring agent and the cationic pharmacological active substance.

**Abdelbary et al., -2013**, demonstrated effect of coprecipitation and nanomilling on crystallinity of aripiprazole and evaluate the in vitro dissolution rate (IDR). Aripiprazole compositions were prepared by physical mixing, coprecipitation and nanomilling using HPC, PVP K17 and pluronic F127. The particle size, solubility,
and drug crystallinity were studied. Aripiprazole pluronic compositions were compressed into tablets and dissolution rate was evaluated. The particle size of nanomilled composition was significantly smaller than that of the other composition. The saturation solubility of aripiprazole from nanoparticle (NP) and coprecipitate (CP) from PVP and Pluronic was comparable, however, NP of HPC containing composition showed higher solubility when compared to its CP composition. The crystallinity of aripiprazole decreased from physical mixture to coprecipitates and further in NPs. Aripiprazole tablets prepared from nanomilled powder dissolved >75% within 10 min compared with 17% and 20% for tablets prepared from physical mixture and coprecipitate powders, respectively.

Bothra et al., -2013, discloses a stable pharmaceutical composition comprising aripiprazole, crospovidone having peroxide content of <80 ppm, advantageously <50 ppm, and other suitable pharmaceutically acceptable excipients, and its use in the treatment of various mental disorders. Thus, a tablet composition contained aripiprazole 10.00, mannitol 78.45, Polypladone Ultra-10 8.50, red iron oxide 0.05, and calcium stearate 3.00%.

Rao et al., -2013, studies the effect of three different viscosity grades on the in vitro dissolution profile of Aripiprazole controlled release tablets. The release rate of 5 to 6 mg%/h was targeted and the effect of the polymers on drug release over 24 h was evaluated at the total polymer level between 30% and 45%. The DOE experiments have shown that when the combination of polymer is used, the total polymer concentration should be in a narrow range of 32.4% wt./wt. to 37.5% wt./wt. in order to achieve the target dissolution profile.

Wen et al., -2013, determined the clinical efficacy and safety of Aripiprazole with magnesium valproate sustained-release tablets (MVST) in mental disorder due to brain trauma (MDBT). Aripiprazole plus MVST takes effect more quickly, has an evident effect, higher safety and better compliance compared with single Aripiprazole in mental disorder due to brain trauma.
Zheng et al., -2013, discloses the preparation method for a composition comprising the following steps: dissolving aripiprazole in an acidic solution having an acidifier to obtain a medicament having acidic solution; then, performing a wet granulation on or preparing a suspension with the obtained medicament having acidic solution, an alkalizer, and an excipient to obtain the aripiprazole medicament formulation; the excipient comprising an antioxidant. The aripiprazole medicament formulation obtained through the preparation method has a significantly reduced amount of related substances, great solubility, great stability, high bioavailability, reduced individual differences, and enhanced wettability and content uniformity of medicaments.

Dastagiri et al., -2012, prepared a wet granulated solid oral pharmaceutical composition of Aripiprazole tablet suitable for oral dispersible which deliver an optimum concentration of drug at desired reaction site at specific time comparable to the references product with better stability, high production feasibility, and excellent patient compatibility.

Hemanth et al., -2012, developed a stable solid dosage form comprising aripiprazole, tablet diluent and/or tablet binder prepared by wet granulation using organic solvent as granulating liquid. This patent application discusses the problems associated with aqueous wet granulation technique in the preparation of aripiprazole formulation. The inventors have developed a non-aqueous wet granulation technique using organic solvents as granulating liquids.

Liu et al., -2012, discloses that the use of non-metal, dual carboxyl group organic acids such as succinic acid, fumaric acid to improve the stability of the atypical antipsychotic drug. The patent therefore, discloses pharmaceutical dosage form comprising an atypical antipsychotic drug and an organic acid.

Lulla et al., -2012, discussed the problems to develop and formulate sensitive product like Aripiprazole solid dosage form, keeping into consideration the reduction in the conversion of the polymorphic forms and prevention of interparticle collision thereby leading to criticalities in the development and manufacture of the product. Objective was to provide a stable formulation of Aripiprazole by means of an improved process.
for manufacturing Aripiprazole solid dosage form so as to avoid manufacturing deformities. Specification further, discloses an improved process of manufacturing Aripiprazole solid dosage form comprising i) wet granulating the active ingredient with pharmaceutically acceptable excipients comprising diluents and/or disintegrants with binder; ii) drying the granules at temperatures less than about 70°C; iii) sieving the granules and lubricating the granules with lubricants; iv) compressing the granules to form tablet.

*Mihajlovic et al., - 2012*, studied the strategies to increase drug solubility by inclusion of the APIs in cyclodextrins. The objective was to study the possibility of aripiprazole solubility improvement by inclusion in (2-hydroxy) propyl-β-cyclodextrin (HPBCD) and simultaneous manipulation of pH of the medium and addition of polyvinylpyrrolidone.

*Nguyen Thanh-Tam, -2012*, discloses a method for preparing an oral lyophilizate composition comprising: a) forming a liquid phase by using homogenising agent having tensioactive properties, said liquid phase comprising at least an active pharmaceutical ingredient, a filler and/or a binding agent and a solvent, b) lyophilizing said liquid phase to form the oral lyophilizate composition.

*Xu et al., -2012*, studied the nanosuspensions using nanoprecipitation/homogenization method based on acid-base neutralization, wherein the nanosuspensions expressively augmented the solubility as well as the release profile of aripiprazole due to the reduced size of aripiprazole.

*Choy et al., -2011*, intensively studied for developing a formulation of aripiprazole, which is needed to treat psychiatric illness, is administered more easily and thus drug-administration compliance is increased, and shows high bioavailability through a rapid dissolution rate. As a result, they surprisingly found that a hybrid obtained by incorporating aripiprazole between the layers of bentonite, which is a pharmaceutical excipient used as a thickener or an inorganic carrier, and then coating with AEA (polyvinyl acetal-diethyl amino-acetate) polymer, which is a gastric coating, blocks
the bitter taste of ursodeoxycholic acid and simultaneously shows an improved dissolution rate and high bioavailability.

**Jingyi et al., -2011**, discloses an ODT of aripiprazole microcrystallites composition comprising microcrystallites of the aripiprazole lactose composition, a filling agent, a disintegrating agent, a flavor correction agent and a lubricating agent, with particle size less than 30µm. Further, it discloses a preparation method comprising the following steps: uniformly mixing all components and then directly tabletting or performing wet-granulation tabletting. The microcrystallites obtained have following advantages: higher dissolution rate, the crystal form of the composition is not transformed, uniformity of content of the ODT is higher, and the hardness is 5-8kg, disintegration time limit is less than 30 seconds.

**Toksoz et al., -2011**, formulated a pharmaceutical formulation, characterized by comprising Aripiprazole monohydrate and super disintegrant and disintegrant mixture. The present invention more particularly relates to a formulation of Aripiprazole monohydrate, in which the latter has high solubility, high dissolution rate, and therefore high bioavailability.

**Toksoez et al., -2011**, discloses that aripiprazole is used in many formulations. It is also possible to develop various formulations with the salts and polymorphs of aripiprazole. Whilst it is possible to develop various formulations with aripiprazole monohydrate, for instance, the solubility and dissolution rate of aripiprazole monohydrate are quite low. This fact brings about a significant problem with respect to the formulations developed. Therefore, the bioavailability of formulations made with aripiprazole monohydrate remains quite low. The aim of the invention was to obtain a formulation of aripiprazole with high stability and bioavailability.

**Dreyer et al., -2010**, developed an oral formulation containing morphologically stabilized amorphous aripiprazole which has enhanced dissolution abilities. When exposed to moisture, the conventional anhydrous forms of aripiprazole absorb water and convert to hydrous forms such as the monohydrate. The hydrous form has the drawback of being less soluble than the anhydrous forms.
Ettema et al., -2010, discusses the stability problem associated with Type I aripiprazole which is hydrated/hygroscopic in nature. The inventors have developed a process of producing Type II tablets by wet granulation using aqueous solvents containing unmilled aripiprazole Type II having a particle size distribution not greater than 50 microns, one or more polyol fillers, one or more binders, one or more disintegrants and a lubricant. This method discloses a drying temperature of 70°C.

Hiraoka et al., -2010, discloses a process for making an aripiprazole suspension, wherein the process includes: mixing bulk aripiprazole with vehicle followed by pulverization and again subjecting the resultant suspension to second pulverization to form final suspension.

Jie et al., -2010, provides a high bioavailability of the oral pharmaceutical composition containing aripiprazole Type I crystal 1-50mg, characterized in that the average particle diameter of aripiprazole Type I crystal is not more than 50um, preferably not more than 35um. The dissolution of aripiprazole in microcrystalline solid oral pharmaceutical composition is significantly improved, especially in the tablets compositions, wherein the diluent is lactose and microcrystalline cellulose, and its content is 80-95% (tablet weight), together with other pharmaceutical excipients, especially effect, can improve the bioavailability and efficacy of aripiprazole preparation.

Reddy et al., -2010, discloses method and results of impurity profiling analysis of aripiprazole in its final dosage form using LC-MS.

Sheth Rakesh, et al., -2010, developed a stable, solid oral pharmaceutical composition comprising aripiprazole, manufactured by wet granulation, wherein intragranular stage is devoid of diluent. They also provided a process of manufacturing stable, solid oral pharmaceutical composition of aripiprazole by wet granulation.
Wang et al., -2010, discloses tablet containing aripiprazole composition crystallite 4-15, filling 75-85, disintegrant 1-10, and lubricant 0-2. The mass ratio of aripiprazole and lactose in crystallite is 1:(1-5), and the average particle size is 5-15 µm. The preparation method consists of mixing aripiprazole composition crystallite with filling, adding other materials, mixing, and tableting. The inventive tablet has hardness of 5-8 kg, disintegrating time limit < 0 s and improved dissolution rate.

Banbale et al., -2009, discloses a process of producing aripiprazole formulation by wet granulation by using an organic solvent as granulating liquid.

Nerurkar et al., -2009, discloses that an inclusion complex of aripiprazole in a substituted β-cyclodextrin. The inclusion results in more water-solubility of aripiprazole which may be formulated as an injectable delivering aripiprazole to the muscular site with surprisingly reduced irritation as compared to uncomplexed aripiprazole.

Prasade et al., -2009, discloses ODT compositions of antipsychotic agents. Precisely the invention relates to ODT compositions of aripiprazole. This patent application further, discloses an orally disintegrating tablet compositions of aripiprazole comprising at least 70% w/w of one or more water-soluble or swellable diluent, 0.5 to 10% w/w of disintegrant, 0.05 to 2% w/w of sweetening agent, 0.5 to 3% w/w of lubricant, wherein the composition is free of silicates or stabilizers.

Sheth R. et al., -2009, discloses to stable, solid oral pharmaceutical composition comprising aripiprazole manufactured by wet granulation, wherein intragranular stage is devoid of diluent. The patent further discloses processes for the making of said composition of aripiprazole. Formulations of tablets containing 30mg of aripiprazole are disclosed.

Liu et al., -2008, discloses a formulation that comprises aripiprazole along with succinic acid, fumaric acid or a mixture of both to increase the solubility of the drug.
Uslu Abdullah, et al., -2008, discloses that the anhydrous aripiprazole crystals have high hygroscopic property. The hydrous form has less BA and less solubility than the anhydrous forms of aripiprazole. In addition, usage of the hydrous aripiprazole crystals in the production of medicine manufacture causes breakdown in production processes and increases the procurement costs. Additionally, the shelf-life of the high hygroscopic aripiprazole crystals could be significantly decreased. The inventor has developed a method of making high-hygroscopic anhydrous aripiprazole tablets comprising, a filler consisting of mannitol, isomalt and sorbitol, a disintegrant consisting of crosspovidone, crosscarmellose sodium and sodium starch glycollate, a pharmaceutical acceptable binder and a pharmaceutical acceptable lubricant, prepared by aqueous wet granulation method.

Bertelsen P. et. al., -2007, discloses a benzidimazole tablet formulation with good shelf life stability and release profile. Process for formulation includes dry compression of enteric coating of benzimidazole, wherein the benzimidazole is stabilized by an alkaline substance in the tablet.

Deng et al., -2007, discloses compositions containing aripiprazole type I crystallite with mean particle diameter no more than 50 µm 1-50 mg, and pharmaceutically acceptable adjuvant such as diluent, disintegrating agent, adhesive and lubricant.

Guo et al., -2007, discloses a stable crystal form I of aripiprazole is prepared by (1) dissolving aripiprazole in Ethyl acetate-ethanol system or Ethyl acetate-ethanol-other organic solvent system under refluxing; (2) cooling rapidly under stirring to crystallize; and (3) drying at 30-120°C for 2-50 h. The crystal form I has also low hygroscopicity (not more than 0.3% after 24 h of storage at 60°C and humidity of 100%).

Hrakovsky et al., -2007, provides a process of manufacturing an aripiprazole composition containing diluent, disintegrant, binder; and alternatively adding lubricant to the blend; followed by dry compression. The process can additionally include milling the slug or compact into an granulates, addition of lubricant, and dry compressing the granulate into a tablet.


Hrakovsky et al., -2007, discloses a process of producing tablets of anhydrous aripiprazole Type-I, Type-II, or Form II, wherein d(0.9) is ≥300µm; by wet granulation. The method involves blending aripiprazole, diluent, binder, and water to obtain a wet granulate; drying the same at >70ºC; followed by grinding, with the condition that the wet granulate is not grinded prior to drying. The process can additionally include adding lubricanting agent to the dried milled granulate; and the dried milled granulate after compressing to form tablets.

Jenkins et al., -2007, discloses compositions comprising aripiprazole, with particle size of >2000nm. The compositions comprise particles of a nanoparticulate aripiprazole, and surface stabilizer adsorbed on surface of aripiprazole particles. Such nanoparticles may be in phase such as crystalline, amorphous, semi-crystalline, semi-amorphous, or mixtures thereof.

Keck PE JR et al., -2007, studies a 26-wk, double-blind, placebo-controlled relapse prevention study of Aripiprazole was designed a priori with a prospective, 74-wk, double-blind, placebo-controlled extension phase. Efficacy and tolerability of Aripiprazole for relapse prevention in bipolar I disorder was, therefore, evaluated for 100 wk. Over a 100-wk treatment period, Aripiprazole monotherapy was effective for relapse prevention in patients who were initially stabilized on Aripiprazole for 6 consecutive weeks, and it maintained a good safety and tolerability profile.

Roy et al., -2007, provides an orally disintegrating composition comprising (a) Aripiprazole or its salts or solvate thereof, (b) sugar alcohol and pharmaceutically acceptable carrier and process for preparing it. The present application further provides an oral compound comprising (a) aripiprazole or its salts or solvate thereof, (b) sugar alcohol and a carrier and process for preparing it. Thus, a formulation contained aripiprazole 5, Eudragit EPO 3.0, Perlitol SD200 50.0 mg/tablet, and EtOH qs.

Roy et al.,- 2007, discloses that aripiprazole is highly desirable to design formulations and processes which suit aripiprazole active substance without imposing any
restrictions on the particle size and yet administering therapeutically effective amount of aripiprazole to desired absorption site in an absorbable form. The specification claims oral formulations for Aripiprazole or its salts/solvates, having improved solubility. The formulations are in the form of oral dosage forms such as pellets, microtablets, tablets, granules and capsules etc. The invention further relates to various processes of improving solubility of Aripiprazole.

Stritzke et al.,-2007, discloses mophologically stabilized amorphous aripiprazole and process for producing the same.

Wilding and Pendleton, et al., -2007, disclose a formulation for the CR of aripiprazole. It comprises a direct compression tablet containing aripiprazole 20, Methocel K4M 35, Avicel PH-200 44, and sodium stearyl fumarate 1%.

Zalit et al., -2007, discloses a process for making a pharmaceutical formulation of a drug, having low aqueous solubility e.g. aripiprazole, the process comprising (A) fixing the drug in a strong matrix comprising partially amorphous sugar to obtain a sugar-drug matrix; and (B) milling, preferably intensely, the sugar-drug matrix to obtain a milled sugar-drug matrix as the pharmaceutical formulation. The fixing step, i.e., step (A), of the above process of the invention is performed by heating a mixture of the drug, optionally pre-mixed or pre-granulated with at least one inactive excipient, and the at least one at least partially amorphous sugar followed by cooling. Alternatively, the fixing step of the above process of the invention is performed by heating a mixture of the drug, optionally pre-mixed or pre-granulated with inactive excipient, and at least one sugar followed by cooling, wherein the at least one sugar is converted to the at least one at least partially amorphous sugar. Preferably, the heating is accompanied with mixing of the drug and the sugar.

Bhushan et al., -2006, an oral composition comprising (a) aripiprazole or its salts or solvate thereof, (b) sugar alcohol and a carrier and process for preparing it. Thus, a formulation contained aripiprazole 5, Eudragit EPO 3.0, Perlitol SD200, 50.0 mg/tablet, and ethyl alcohol.
Ettema et al., -2006, discloses that crystalline Type II aripiprazole forms pharmaceutical tablet compositions having improved stability in comparison to the commercially available aripiprazole tablet, which presumably contains Type I. The invention discloses a tablet formulation, comprising 1 to 50 mg of aripiprazole Type II and pharmaceutically acceptable excipients. The excipients generally include (a) one or more polyol fillers, such as lactose, sorbitol, mannitol, etc.; (b) one or more binders, such as MCC, HPC, PVP, starch, etc.; (c) one or more disintegranting agent, such as crosspovidone, SSG, crosscarmelose sodium, etc.; and (d) a lubricant, such as magnesium stearate. Generally the aripiprazole is unmilled and typically has a particle size of > 40µ. In terms of particle size distribution, the d (90) is not <50µ.

Brown et al., -2005, discloses a pharmaceutical composition comprises Aripiprazole and a carrier and is administered in a bolus injection resulting in an extended release profile similar to that obtained by the injection of a poly (lactide-co-glycolide) microsphere formulation containing the active agent. Pharmacological beneficial extended-release formulations without the complexities associated with the manufacturing microspheres can be prepared. Thus, an injection vehicle comprised an aqueous diluent containing 3% CM-Cellulose (low viscosity), 0.1% Tween-20 in 0.9% NaCl and water.

Kostanski et al., -2005, discloses a controlled release sterile freeze-dried Aripiprazole formulation is provided which is formed of Aripiprazole of a desired mean particle size and which upon constitution with water forms an injectable suspension. A method for preparing the controlled release freeze-dried Aripiprazole formulation, and a method for treating schizophrenia employing the above formulation are also provided. Aripiprazole injectable depot formulation was administered intramuscular to patients diagnosed with chronic, stable schizophrenia or schizoaffective disorder. In all cases Aripiprazole plasma levels showed a fast onset of release and sustained release for at least 30 days.

Nerurkar et al., -2004, discloses an Aripiprazole formulation is provided which includes the antipsychotic agent Aripiprazole in the form of an inclusion complex in a β-cyclodextrin, preferably, sulfobutyl ether β-cyclodextrin (SBECD), which in the
form of an injectable produces reversible, generally minimal-to-mild irritation at the intramuscular injection site. A method for minimizing or reducing irritation caused by Aripiprazole at an intramuscular injection site and a method for treating schizophrenia employing the above formulation are also provided.

Kothari et al., -2002, discloses a flash-melt dosage form including a drug such as aripiprazole a dispersing agent selected from calcium silicate, magnesium trisilicate or silicic acid; a superdisintegrant, and a binder.
1.5. 2 Venlafaxine

Cui et al., -2014, discloses a method for preparing Venlafaxine hydrochloride sustained-release pellets. The method comprises the steps of: centrifugal granulation of microcrystalline cellulose, regulation of slurry spray speed and powder supply speed till material is flocculate, keeping flocculate, controlling powder/slurry ratio to preparing microcrystalline cellulose blank pill cores, pulverizing raw medicines, mixing with MCC and HPMC (3cp) proportionally, performing powder lamination using MCC blank pill cores as mother cores, water as humectants, HPMC and TEC proportionally to obtain coating liquid, coating, and aging to obtain the final product.

Davidson et al., -2014, performed two randomized, double-blind studies conducted with adult outpatients treated with flexible doses of venlafaxine extended release (ER) 37.5 to 300 mg/day or placebo. Analyses were conducted for the overall population and sep. for the individual treatment groups. In total, pretreatment resilience predicted a post treatment response. For the overall population, all versions of the CD-RISC predicted CAPS-SX17 change scores and remission after controlling for variables such as treatment group and baseline symptom severity.

Khanfar, M. et al., -2014, prepared sustained release tablets of Venlafaxine HCl. Different liquisolid formulations, liquid vehicles, drug concentration in the liquid medication and different ratios of carrier to coating material (R) were prepared. The prepared powders were characterized for possible interactions between drug and excipients using differential scanning calorimetry, X-ray, Fourier transform IR analysis and SEM.

Gupta, Pravin et al., -2014, prepared and evaluated the Venlafaxine hydrochloride Microspheres by Ionotropic Gelation method. SEM confirmed cracks on the surface of calcium-alginate microspheres and due to these cracks low drug content and entrapment efficiency was observed. With the increase in the concentration of pectin, a higher no. of free carboxylic groups of pectin was able to interact with Ca++ counter-ions and thus increases the drug entrapment.
Jain et al., -2014, studied the effect of pH of the drug solution, time and initial drug concentration on drug loading capacity. The adsorption isotherm was fitted by the Langmuir model and follows the pseudo-second-order kinetics. The synthesized Mt-VF complexes were characterized by XRD, FTIR, TGA, DSC etc. VF was found to be intercalated in the Mt layers. The release profile of the VF and Mt-VF complex in simulated gastric and intestinal fluids has been discussed.

Joffe, Hadine et al., -2014, determined the efficacy and tolerability of low-dose oral 17β-estradiol and low-dose venlafaxine extended release in alleviating vasomotor symptoms (VMS). DESIGN, SETTING, AND PARTICIPANTS In total, 339 perimenopausal and postmenopausal women with at least 2 bothersome VMS per day (mean, 8.1 per day) were recruited from the community to MsFLASH. Low-dose oral estradiol and venlafaxine are effective treatments for VMS in women during midlife. While the efficacy of low-dose estradiol may be slightly superior to that of venlafaxine, the difference is small and of uncertain clinical relevance.

Li, Zhaoming et al., -2014, prepared an alcohol-tolerant venlafaxine hydrochloride sustained-release pellet. The sustained-release pellet contains venlafaxine hydrochloride-containing pill core, a separator and a sustained-release coat layer. The sustained-release film-forming material is mixed coating material selected from Et cellulose and polysaccharides. The alcohol tolerance is that it avoids the quick release of venlafaxine hydrochloride sustained-release pellet in alcohol-containing medium or after drinking, and the sustained-release effect is unchanged.

Liu, Feng et al., -2014, prepared venlafaxine hydrochloride sustained-release capsule contains sustained-release pellets, and the sustained-release pellet is composed of pellet core and sustained-release coating. The pellet core contains venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropylmethyl cellulose. The prepared venlafaxine hydrochloride sustained-release capsule has stable release, no organic solvent residues, and high safety, and is environment-friendly.

Nidadavolu et al., -2014, developed and characterize once daily sustained release pellets of highly water soluble drug Venlafaxine Hydrochloride, which is an
antidepressant of serotonin nor-epinephrine reuptake inhibitor (SNRI). Compatibility studies by FTIR spectroscopy observed Venlafaxine HCl was compatible with all the excipients used. These pellets were prepared in three stages. In drug loading stage, drug was loaded on non-pareil sugar spheres by using Mannitol, Microcrystalline powder (MCCP) as diluents and PVP K30 as binder. The concentration of Venlafaxine HCl was kept constant.

**Patel, Sachin R. *et al.*, -2014**, formulated and evaluated floating microspheres of highly water soluble drug venalfaxine HCl, using cellulose acetate and eudragit RS100 polymers. The microspheres were prepared by solvent evaporation method. The prepared microsphere showed good drug loading capacity and floating ability. The particle size was ranged between 50 µm to 200 µm depends on the drug polymer ratio. The SEM study revealed that microspheres were good spherical geometry and uniform size. The in vitro release studies were performed in 900 mL of 0.1N HCl for 12 h using USP XXIV dissolution apparatus.

**Sanap, S. A *et al.*, -2014**, discussed about formulation design and evaluation of novel sustained release gastro-retentive tablet of venlafaxine hydrochloride. To overcome the multiple doses at short intervals of time due to short biol. half-life and poor bioavailability of venlafaxine, it was formulated into gastroretentive floating tablets, employing a new floating polymer tamarind kernel gum and known polymers HPMC-K4M. The tablets were evaluated for thickness, weight variation, hardness, friability, drug content; in vitro buoyancy test, in vitro drug release and Fourier transform IR (FT-IR) spectroscopy, DSC.

**Wei *et al.*, -2014**, discloses a composite structural material and pharmaceutical composition comprising same, the use of the composite structural material in preparing a sustained release preparation, and a pharmaceutical composition preparation method; the composite structural material comprises a hydrophobic structural material and a hydrophilic structural material; the proportion of the hydrophobic structural material to the hydrophilic structural material ranges from 1:0.01 to 1:5, preferably 1:0.05 to 1:4, more preferably 1:0.1 to 1:3, and most preferably 1:0.4 to 1:2, such as 1:0.4 to 1:1.3.
Wu, Yan et al., -2014, discloses a method of investigation of drug release behaviour of venlafaxine hydrochloride sustained-release pellets. Venlafaxine hydrochloride pellets were prepared by extrusion-spheronization technology coated by the fluidized bed and filled into capsules. The preparation technology of venlafaxine hydrochloride pellets using extrusion-spheronization method was simple and productive.

Zhang, Kang et al., -2014, discloses a pharmaceutical preparation of venlafaxine hydrochloride sustained-release composition. The preparation is composed of venlafaxine hydrochloride sustained-release pellets and sustained-release coating layer adhered on its outer layer to make drug be stably released within 24 h, keep stable blood drug concentration, reduce medication times and improve medication safety and patient's compliance. The diluent is microcrystalline cellulose, lactose, dextrin; the adhesive is hydroxypropyl cellulose. The blocker is Et cellulose 100FP, 100P, N-100. The pore-forming agent is povidone, PEG, PVA, SDS.

Zhang, Shuo et al., -2014, discloses a sustained-release capsule, which comprises sustained-release content and a capsule shell. The sustained-release content comprises drug-loaded sucrose micropill cores and sustained-release layers. The drug-loaded sucrose micropill core contains venlafaxine hydrochloride 120-180, blank sucrose micropill core 50-60, and hydroxypropyl Me cellulose-E5 1-1.5. The sustained-release capsule has the advantages of convenient administration, high compliance, low adverse reaction, stable blood concentration and good therapeutic effect.

Bagdiya et al., -2013, also developed Venlafaxine HCl ER pellets by extrusion spheronization technique using blend of hydrophobic low melting wax and hydrophilic polymers as rate controlling agent. Single layer or double layer coating was used to make ER pellets of Venlafaxine HCl. This process avoids layering or film coating.

Butani, Shital Bhavin et al., -2013, developed a triple layer sustained release tablets of venlafaxine HCl using xanthan gum or polyethylene oxide. The venlafaxine HCl
150 mg sustained release tablets were prepared by wet granulation technique where drug was incorporated in middle layer with part of polymer. The barrier layers were composed of remaining polymer and other excipients. The granules and tablets were characterized. Optimized batches were also tested for drug release at different pH and in presence of ethanol, for kinetics of drug release and for water uptake/swelling.

**Hao et al., 2013,** discussed the discuss control effect of venlafaxine sustained-release tablets on 92 patients with depression. 92 patients with depression were divided into two groups, one as comparison group and the other group as observation group, the comparison group was treated with fluoxetine hydrochloride, the observation group was treated with venlafaxine sustained-release tablets, after 2 month, clinical effects were compared. The venlafaxine sustained-release tablets have good effect for treating depression, with low side effect, and treatment effect is better than fluoxetine.

**Liu, Yan-mei et al., 2013,** discloses the pharmacokinetics and bioequivalence parameter of venlafaxine hydrochloride extended-release capsules in healthy volunteers. Twenty-eight Chinese healthy male volunteers were randomly administered a single and multiple 150 mg oral dose of the test and ref. capsules. The 90% confidence intervals (CI) of $p_{\text{max}}$ and $\text{AUC}$ of venlafaxin and O-desmethylvenlafaxine for the test preparation after single and multiple oral doses were all within the bioequivalence criteria. The two imported venlafaxine hydrochloride extended-release capsules were considered bioequivalent in human.

**Parekh et al., -2013,** prepared Extended released pellets containing venlafaxine hcl using an extrusion-spherization technique. Amtount of Microcrystalline cellulose Avicel pH101, Hypromellose 15 cps and Eudragit NE 30D were taken as the formulation variables for optimizing to keep round shape of pellets and percentage release of drug. The pellets were evaluated for Physical characterization, Assay, Sizing, SEM, In-vitro drug release and Binder's concentration tends to very effective pellets shape and size. Percentage release of drug tended to very non-linear with polymer type and percentage of coating on the pellets.
Peng et al., 2013, determine the clinical effect and safety of venlafaxine sustained release and domestic escitalopram for depression. 64 depression patients in the hospital from Jan. 2011 - Jan. 2012 were randomly divided into a control group and an observation group with 32 cases in each group. The control group was treated with venlafaxine sustained release with initial dose of 50 mg/times, and then 150-225 mg/d according to the patient condition. The domestic escitalopram had good effect on treatment of depression with high safety.

Rani, B. S. et al., 2013, studied the formulation and evaluation of mucoadhesive buccal patches of venlafaxine hydrochloride. Venlafaxine HCL patches were fabricated by using sodium alginate with various polymers such as CMC, HPMC E15LV in various proportions using solvent casting technique. Buccal patches were evaluated by different parameters such as thickness, weight uniformity, content uniformity, swelling index, surface pH, moisture up take study, moisture absorbance study, folding endurance and in-vitro drug release study and FTIR studies.

Rong et al., 2013, determined the efficacy and safety of venlafaxine sustained-release tablets vs. paroxetine in depression without psychotic symptoms. Eighty-four depression patients without psychotic symptoms were randomly assigned to two groups of 42 ones each, observation group took orally venlafaxine sustained-release tablets and control group did paroxetine for 8 week. Both venlafaxine sustained-release tablets and paroxetine have an evident effect in depression, higher safety and better compliance, but the former takes effect more rapidly and deserves to be clinically spread and utilized.

Sailaja et al., 2013, prepared matrix tablets of Venlafaxine Hcl employing olibanum gum and to evaluate its application in sustained release (SR). Matrix tablets each containing 37.5 mg of Venlafaxine Hcl were formulated employing olibanum gum polymer in different proportions of drug and polymer and the tablets were evaluated for various tabletting properties. Venlafaxine Hcl release from the formulated tablets was slow spread over 24 h and depended on percent polymer in the tablet.
Thorat et al., -2013, prepared sustained Release Dosage Form (SRDF) of Venlafaxine HCl. It was formulated to matrix tablet by direct compression method using Carbopol 971P and Et cellulose as sustaining polymers. The effects of polymers concentration on drug release profile were investigated. Concentration of Carbopol 971P and Et cellulose are selected as independent variables and % Cumulative release of drug for 3 and 24 h (Q3,Q24) were selected as dependent variables. Formulating sustained release matrix tablets of Venlafaxine for 24 Hrs creates new hope for patient as improving patient compliance and decreasing frequency of administration.

Tiwari et al., -2013, developed and optimize oral controlled-release formulations for highly water soluble model drug Venlafaxine hydrochloride using a combination of hot-melt subcoatings based coating polymer and aqueous polymer coating. Hot melt subcoating was achieved by centrifugal granulator. For the polymer coating, Acrylate-based (Eudragit RS 30D and Eudragit NE 30D), were used. In this study, the release profile of pellets was found to be optimum at a 4% level of hot melt subcoating and 15 % level of Eudragit NE30D polymer coating combination, consequently meeting the desired responses.

Venkata Ratnam G. et al., -2013, formulated and evaluated the Venlafaxine sustained release capsules. Venlafaxine is having disadvantage of less biological half life of about 5 h due to extensive hepatic first pass metabolism. It is further discloses that the development of a sustained release dosage form of venlafaxine in the form of capsules to be taken once daily. The polymers such as Et cellulose (10, 20, 50 cps), Hydroxypropyl methylcellulose phthalate, were used as coating polymers which helps in providing sustained release.

Wang et al., -2013, discloses a Venlafaxine HCl sustained-release capsule wherein the pellet comprises a pill core, an isolation layer coated outside the pill core, and a CR layer coated outside the isolation layer. Core of the pill is made of Venlafaxine HCl 30-60, filler 30-80, sustained release framework material 1-20, and binder 1-10 weight%. The invention thoroughly solves the problems of potential safety hazard and high equipment requirement in existing method adopting organic solvent including dichloromethane and ethanol as solvent.
Wang, Yihua et al., 2013, prepared venlafaxine hydrochloride unilocal osmotic pump controlled-release tablet, which is composed of a tablet core and an insoluble semipermeable membrane having one or more pore canals. The tablet core is composed of (by parts): venlafaxine hydrochloride 75, hydroxypropyl Me cellulose 10-60, osmotic pressure promoter 2-20, filler 0-200, agglomerant 2-10, and lubricant 1-5. The semipermeable membrane is composed of cellulose acetate and pore-forming agent, and the pore canals on the semipermeable membrane are formed via mech. perforation or laser perforation. The venlafaxine hydrochloride unilocal osmotic pump controlled-release tablet accomplishes zero-order release of venlafaxine hydrochloride, and guarantees good controlled-release effect.

Zhang et al., 2013, discloses venlafaxine sustained-release capsule contains sustained-release pellets. The sustained-release pellet comprises (by weight parts), from inside to outside, a hollow pellet core 10-20, an insulating layer 5-15, a drug-containing layer 10-50 and sustained-release protective layer 10-60. The insulating layer comprises adhesive and filling agent. The drug-containing layer comprises adhesive and venlafaxine. The protective layer comprises filling agent and adhesive. The isolating layer isolates the pellet core, decreases osmotic pressure inside the sustained-release capsule, and reduces releasing speed of drug. The adhesive is used in the drug-containing layer and sustained-release protective layer to seal the venlafaxine in sustained-release material and decrease solubleness of the pellets.

Zhu et al., 2013, compared clinical efficacy and safety of escitalopram and venlafaxine in the treatment of elderly anxiety disorders. 60 elderly patients with anxiety disorders were randomly divided into group for escitalopram treatment and group for venlafaxine treatment. Escitalopram group had effective rate of 70.00%, total effective rate of 96.67%, and venlafaxine group had effective rate of 63.33%, total effective rate of 93.33%, respectively, while the difference had no statistically significance (P> 0.05).

Aniket, Ladani et al., 2012, developed a triple layered matrix sustained release tablets of highly water soluble Venlafaxine hydrochloride using natural gum (Xanthan
gum) and Hydroxypropyl Me cellulose K-100M and formulation was optimized using 32 factorial design. The method adopted for preparation was hybrid wet granulation barrier layer technology, using Xanthan gum and HPMC K 100M as rate controlling ingredient in the middle sandwich layer and Xanthan gum in the barrier layers. The dissolution studies were performed in 900 mL of distilled water at 100 rpm using the USP XXIII basket apparatus up to 24 h. The triple layered tablets give the release pattern similar to that of ref. product.

Jiang et al., -2012, discloses Venlafaxine HCl film-controlled sustained-release pellet capsule contains a sustained-release coating film using Kollicoat-SR30D as film-forming material, a pellet core containing low-substituted HPC having high expansibility, and MCC. The pellet core contains low-substituted HPC 10-40 weight%. The sustained-release coating film contains Kollicoat-SR30D, tri-Et citrate, and talc powder, preferably at a weight ratio of 30:1:4. Preferably, the coating weight gain is 21-39%. The pellet core expands when encountering water, so that the sustained-release coating film has reduced thickness, enlarged pore size, and improved permeability.

Krishnarajan et al., -2012, demonstrated the effect of polymers on release profile of Venlafaxine HCl pellets. SR capsules of Venlafaxine HCl were prepared by using the pelletization process by drug layering on inert sugar pellets by using sucrose and Hypermellose 606 as a binder. Preparation of Venlafaxine HCl pellets has been done by two stages namely loading of drug and coating of dosages form. Loading of drug in pellets has been done by coating pan method. The coated pellets were filled in capsules size no. 2.

Kumar et al., -2012, perform formulation and evaluation of multi-unit pellet system of Venlafaxine HCl. Venlafaxine ER pellets prepared by extrusion spheronization technique, coating them with mixture of rate controlling polymers ethyl cellulose and different grades of HPMC using Wurster process to achieve the desired dissolution pattern and compressing the pellets into tablets. The disso profile of Venlafaxine hydrochloride ER tablets were compared with that of Innovator (VENLAR).
Li *et al.*, -2012, prepared Venlafaxine HCl sustained-release (SR) capsules by extrusion-spheronization method, wherein MCC was used as the filling substance, water was used as the binder, and Kollicoat SR 30D was used as the sustained-release material. Pellets of venlafaxine HCl were formulated by extrusion-spheronization technology, and venlafaxine HCl SR pellets were prepared by fluidized bed coating technology. With the drug release result as an indicator, the coating weight gain was investigated. The surface of pellets was smooth and had good roundness. When the coating weight was between 24%-28%, the in vitro release behavior of homemade venlafaxine HCl SR capsules was consistent with the original research product.

Lin *et al.*, -2012, discloses sustained-release capsule comprising a capsule shell and sustained-release pellets. The pellet comprises a pellet core, an isolating layer, and a SR layer. Core of the pellet contains Venlafaxine HCl and adjuvant. The coating layer contains a plasticizer, and a pore forming agent. The SR layer is formed with Ethylcellulose water dispersion as coating liquid. The manufacturing method thereof extruding and balling to obtain the pellet core, coating in fluidized bed, drying, and encapsulating.

Liu, Yang *et al.*, -2012, prepared different venlafaxine hydrochloride sustained-release products and to elucidate the influence of composition of the coating film on the in vitro drug release profiles and in vivo pharmacokinetics. Pellets were prepared by a standardized process of extrusion/spheronization. Many efforts have been made to tailor drug release rate by choosing different coating materials, different percent of pore forming components and coating wt. variation to achieve a desired sustained-release effect. The dissolution studies were performed and data were analyzed in terms of cumulative release as a function of time.

Liu *et al.*, -2012, prepared SR Venlafaxine HCl pellets by extrusion/spheronization technique. Pellets were coated with EC (10 CPS) or Eudragit NE30D. SEM micrographs revealed morphological variations of the pellet coating surface which were related to in vitro drug release profiles.
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**Liu et al.,** 2012, demonstrated the influence the composition of coating film on the release of drugs from different Venlafaxine HCl SR products. Pellets were prepared by extrusion/spheronization. A selected fraction size (0.8-1.0 mm diameter) of pellets of each formulation was coated with Eudragit NE30D or ethylcellulose (10 cps) and evaluated for its dissolution and PK studies.

**Prasanthi, B. et al., (2012),** investigated the influence of sodium Carboxy methyl cellulose (blanose) on the initial burst release from a hydroxypropylmethylcellulose (methocel) matrix formulation containing Venlafaxine hydrochloride. The predominant release mechanism varied with matrix composition and drug release was controlled by both diffusion and relaxation, with predominance of the latter mechanism mainly in the mixture of the 2 cellulose ethers formulation. A reduction in the initial burst effect, a commonly observed phenomenon with highly soluble drugs and hydrophilic matrixes, was achieved.

**Remya et al., -2012 and 2012a,** developed SR pellets of Venlafaxine HCl by Wruster technique which released the drug to the period of 20hr. various polymers like MCC-101, HPMC-E6, EC 7cps were used in the preparation of granules or pellets by wurster coating.

**Seetharaman and Nallaperumal, et al., -2012,** prepared a conventional single layer matrix tablet. Matrix system based on swellable polymer HPMC was selected for increasing the time of drug release.

**Tripathi et al., -2012,** studied the effect of water uptake on particle size distribution of core pellets of Venlafaxine HCl prepared by extrusion-spheronization technique. Water was selected as a wetting agent and three formulations containing 15%, 35%, 45% water were prepared and performed and same drug concentration (100%). The effect of percentage of water uptake was determined by particle size distribution method. The sphericity, particle size, properties of pellets was affected by the water uptake.
Udayakumar et al., -2012, formulated a sustained release matrix tablets by adopting wet granulation method using Hydroxy Propyl Methyl cellulose (HPMC), Hydrogenated castor oil (HCO) and Ethyl cellulose (EC) as retarding materials at different concentration. The sustained release formulations of Venlafaxine were formulated to reduce dosing frequency due to its low biol. half life and also improving patient compliance. All the formulations were assayed for its drug content and in vitro release followed by in vivo drug release for the best among these formulations.

Zhang et al., -2012, prepared venlafaxine HCl sustained release capsules. Venlafaxine HCl pellet was prepared by extrusion-spheronization equipment, and then the pellet was coated and filled into capsule. The pellets prepared by extrusion-spheronization equipment had a perfect sphericity and high yield. The release of prepared venlafaxine HCl sustained-release capsules was consistent with imported Venlafaxine HCl Capsules. The preparation technology of Venlafaxine HCl pellet with extrusion-spheronization method was simple; the pellets had good quality and high yield. The satisfactory release was obtained by coating with ethylcellulose.

Akelesh et al., -2011, discloses SR formulation of Venlafaxine HCl pellets. Among the various composition prepared, composition no. 10 coated with EC N-50 4.5%, HPMC 15%, Steric acid 5%, was found be satisfactory.

Guan et al., -2011, compares the stability of Venlafaxine HCl SR pellets formulated by double polymer coatings and hot melt subcoating combined with Eudragit NE30D outercoating. The uncoated venlafaxine pellets, containing 45% (weight/weight) VEN, 45% (weight/weight) microcrystalline cellulose (PH101), 10% (weight/weight) stearic acid and 0.5% (weight/weight) Carbopol974, were prepared by extrusion-spheronization. Satisfactory release profiles were obtained when venlafaxine pellets were prepared by 4% EC sub coating combined with 4% Eudragit NE30D outercoating and 8% hot-melt sub coating combined with 6% Eudragit NE30D outercoating, respectively.

Jiang and Wang H. et al., -2011, discloses pellet comprising main drug, sustained-release material, and hydrophobic matrix with weight ratio of 1-50%. The
hydrophobic matrix is wax or fatty acid and its ester or PEG or organic acid. The sustained-release material is hydrophilic skeleton material or erosive skeleton material. The method comprises putting main drug, SR material and hydrophobic matrix in a wet mixing granulator, spraying adhesive, preparing soft material, extruding and rounding, and drying.

Ma et al., -2011, discloses Venlafaxine HCl SR capsule comprises a hollow capsule and SR pellets. SR pellets are composed of pellet cores and SR coatings. Pellet cores are composed of Venlafaxine HCl, microcrystalline cellulose cellulose, gaseous silicon dioxide, Tween-80 and HPMC. SR coatings are composed of polyacrylic resin, talc powder, polyethylene glycol and sodium dodecyl sulfate. The title preparation method comprises the steps of: mixing Venlafaxine HCl, MCC and gaseous silicon dioxide, adding mixed aqueous solution of tween-80 and HPMC, granulating, balling, drying to obtain pellet cores, dissolving polyethylene glycol and sodium dodecyl sulfate in water, adding polyacrylic resin and talcum powder to obtain sustained-release coating liquid, coating pellet cores to obtain sustained-release pellets, and packaging pellets in hollow capsules. The prepared capsule has smooth release, and long sustained-release time of 24 h.

Madat et al., -2011, studied critical composition parameters which affect the release of drug from CR composition of Venlafaxine HCl. The conc^n of Ethylcellulose (X1), conc^n of hydroxy propyl methyl cellulose (X2) and viscosity grade of hydroxy propyl methyl cellulose (X3), were optimized using a 3^3 Box-Behnken design. The selected dependent variables were the cumulative percentage of Venlafaxine HCl dissolved after 2 (Y1), 6 (Y2) and 12 h (Y3). Release profile of CR pellets of the optimized composition exhibited nearly same as predicted values.

Bhushan et al., -2010, prepare modified release pharmaceutical composition of Venlafaxine HCl. A formulation contained Venlafaxine HCl 45.05, low-substituted hydroxypropyl cellulose 42.34, and hydroxypropyl methyl cellulose 2.70% by weight. The coating component comprised ethyl cellulose 8.92 and hydroxypropyl methyl cellulose 0.99 by weight. Venlafaxine HCl and low-substituted hydroxypropyl
cellulose were mixed and hydroxypropyl methyl cellulose was dissolved in a suitable solvent to make a binder solution.

Ashwini R. et al., -2009, designed sustained release matrix tablets of venlafaxine hydrochloride using ion exchange resin with the incorporation of hydrophilic and hydrophobic polymer combinations. Venlafaxine HCl was loaded onto Indion 244 by batch method and then resinate were wet granulated with ethyl cellulose and blended with hydroxypropylmethylcellulose and compressed. Compressed matrices exhibited the anomalous release mechanism, as the value of release rate exponent (n) varied between 0.8109 and 0.8719, resulting in regulated and complete release until 20 h.

Jiang et al., -2009, discloses venlafaxine sustained released pellet capsule is composed of skeleton sustained-release pills core, and sustained-release coating film. The skeleton sustained-release pills core is composed of main medicine 1-40 wt%, bulking agent 20-80 wt%, adhesives 1-50 wt%, skeleton sustained-release material 1-50 wt% and balanced adjuvants. The preparation method comprises mixing Venlafaxine HCl with microcrystalline cellulose and other adjuvants together, processing soft material with polyacrylic resin NE30D, processing pill core, drying, coating polyacrylic resin NE30D and polyethylene glycol to obtain pellet, and packaging the pellet in capsules.

Zhang and Tan K. et al., -2009, discloses a method of preparation of venlafaxine sustained-release formulation. It comprises the steps of dispersing venlafaxine and binder into isopropanol to form a suspension, spraying the suspension onto the sugar spheres to form the drug pellets, making aqueous suspension of talc and well mixing it with a polyacrylic resin water-dispersion, and then, spraying the talc-polyacrylic resin suspension onto the drug pellets to form said micropellet formulation with a slow-release coating.

Bhalekar M R et al., -2008, prepared a sustained release drug delivery system of Venlafaxine hydrochloride by using a wax matrix system. The effects of bees wax and carnauba wax on drug release profile was investigated. A 3(2) full factorial design was applied to systemically optimize the drug release profile. The response
surfaces and contour plots for each response parameter are presented for further interpretation of the results.

**Tian et al., -2008,** prepared SR pellets of such drugs which has water solubility is high by combination of wax matrixes and double-layer coatings. The pellets were made by wet mass extrusion spheronization technique and then coated in fluidized bed coater.

**Ding et al., -2007,** discloses preparation of Venlafaxine HCl sustained-release pellets. At first, the drug substance was microencapsulated into an ethylcellulose solution to prepare fast-release (FR) pellets by a centrifugal granulator; then, the FR pellets were used as the core and microencapsulated into aqueous dispersed coating materials made of Eudragit NE 30D to prepare sustained-release (SR) pellets; next, the FR pellets and SR pellets were mixed in ratio of 1:2 to make the final SR pellets. The effects of coating thicknesses on the SR parameters were analyzed. The results showed that the optimal SR behavior in vitro of the SR pellets mixed from FR pellets and SR pellets in a ratio of 1:2 was selected when the amount of coating materials was 20% of total weight. It was concluded that the Venlafaxine HCl sustained-release pellets provided rather good sustained-release efficiency.

**Heinick G. W. et al., -2007,** discloses a method of optimizing a dissolution profile for a selected active agent dosage form, comprises combining a first amount of a first ensemble of pulsed-release pellets having a first dissolution profile with a first T50 and a second amount of a second ensemble of pulsed-release pellets having a second dissolution profile with a second T50 to produce a combination ensemble of pellets having a combination dissolution profile of a combination slope, wherein the combination slope corresponds to a single phase release, and wherein the combination slope is >10% lower than the slope of the first dissolution profile and >10% lower than the slope of the second dissolution profile, the core composition layer comprising the active agent, and a pulsed-release coating disposed on the core composition layer.

**Odidi and Odidi, et al., -2007,** studied on drug delivery compositions, extruded spheroids comprising active pharmaceutical ingredient, extrusion-spheronization aid,
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superdisintegrant, glidant, lubricant, and oil. The spheroids comprise at least one active pharmaceutical ingredient; at least one extrusion-spheronization aid; at least one superdisintegrant; and at least one glidant, at least one lubricant, and/or at least one oil. In a further aspect, a drug delivery component that comprises coated spheroids that have inert spheroids and at least one coating for the spheroids. The coating comprises at least one active pharmaceutical ingredient and at least one superdisintegrant.

Patel et al., -2007, discloses an once a day modified release capsule comprising non-pareil seeds as core coated with venlafaxine HCl, Na alginate, talc, and titanium mixture; which is further seal coated with Na alginate, talc, and titanium mixture; and final functional coating containing Kollicoat SR30D, propylene glycol, and talc.

Bang et al., -2006, discloses sustained-release pellet composition comprises: (1) a core 1.4-1.7 weight parts, (2) a first release adjusting layer containing Venlafaxine HCl 1 weight parts and at least one of cetostearyl alcohol, polyvinylacetate aqueous dispersion, dimethylaminoethyl methacrylate-neutral methacrylic acid copolymer, hydroxypropyl methylcellulose, and methylcellulose 0.02-0.9 weight parts, (3) a second release adjusting layer selected from ethylcellulose and ethylcellulose aqueous dispersion 0.2-4 weight parts, and (4) a third release adjusting layer selected from ethylcellulose aqueous dispersion and polyvinylacetate aqueous dispersion 0.25-1.3 weight parts. By adjusting the release of medicine via the three release adjusting layer, dissolution rate can be uniformly and stably adjusted. Because the whole process for manufacturing the pellet composition is executed in a single machine, manufacturing process is simplified, and manufacturing time is shortened. The obtained pellets have uniform particle size distribution and medicine content.

Bhushan et al., -2006, discloses extended release oral pharmaceutical compositions of Venlafaxine HCl containing specific polymethacrylate content and processes for preparing the same have been disclosed. Total polymethacrylate content is from around 5%-15% of total composition with ratio of polymethacrylate to Venlafaxine HCl from about 1:1 to about 1:10. These compositions comprise of pellets made up of cores and coating. Venlafaxine HCl can be in the cores or in the form of layer
deposited on inert cores. These compositions show in vitro release profile similar to that of marketed compositions of Venlafaxine HCl and with peak plasma concentration which is substantially sustained over a period of from about 4 h to about 8 h.

Valducci et al., -2005, discloses a CR composition comprising an inert core, on which the venlafaxine-HCl, is uniformly layered, which is further coated with a layer of a hardening agent and a lipophilic agent.

Doshi et al., -2004, discloses SR coated pellets prepared as follows: (i) a core containing venlafaxine-HCl 169.70 mg, microcrystalline cellulose 199.0 mg, HPMC K 4M 1.85 mg, (ii) a wax coating containing cetostearyl alcohol 9.26 mg, and a polymer (sustained release) coating containing Eudragit NE 30D 56.97 mg and talc 28.49 mg. The resulting coated pellets were sieved so as to obtain a desired pellet size range of between 0.85 mm and 1.75 mm and filled into hard gelatin capsules.

Fekete et al., -2004, discloses to pellets containing Venlafaxine HCl and a process for the preparation thereof. The pellets according to the invention are nearly spherical in shape and comprise pharmaceutically active Venlafaxine HCl in an amt. of at most 80% by weight, furthermore 10 to 60% by weight of sodium chloride and/or potassium chloride, 10 to 60% by weight of microcrystalline cellulose and optionally other pharmaceutically acceptable excipients and/or pelletization promoting additives. Said pellets are particularly suitable to be coated with a layer ensuring a controlled release of the active ingredient.

Gassert M. et al., -2004, discloses microtablets comprising about 0.1-99.9 weight% of venlafaxine, about 0.1-20 weight% of a lubricant, and optionally one or more excipients, having a tablet size of about 1 mm to about 4 mm, and a tablet weight of 1 to 50 mg are described. The microtablets prevent or minimize leaching of the highly water-soluble venlafaxine during an aqueous coating process, and provide a more uniform release rate, as compared to conventional venlafaxine compositions. For example, venlafaxine extended-release microtablets were prepared comprising (i) a tablet core containing venlafaxine HCl 40%, lactose 38.3%, Copovidone 20%, fumed
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silica 0.2%, and Magnesium Stearate 1.5%, and (ii) tablet coating containing Eudragit NE 30D (30% aqueous dispersion) 11%, and talc 4.7%. Microtablets prepared were packed into hard gelatin capsules, each capsule containing 49 of the microtablets. Capsules containing the microtablets display a uniform dissolution or release rate of venlafaxine HCl.

**Geena M. et al., -2004,** discloses sustained-release pellets containing Venlafaxine HCl are provided to maintain the therapeutic blood concentration of a drug for 24 h, prevent side-effects of the drug by changing blood concentration of the drug, and simplify the production step of the sustained release pellets by removing a globule core-producing process. The sustained-release pellets contains a globule core consisting of sugar sphere, a drug layer containing Venlafaxine HCl and hydroxypropylcellulose, and a release-controlling membrane layer containing hydroxypropylcellulose and ethylcellulose in a weight ratio of 1:21 to 1:37. The sustained-release capsules contain a therapeutically effective amt. of the sustained-release pellets.

**Odidi and Odidi et al., -2004,** discloses use of transition coating and transition coating composition to control and or target the release of drug and a method of preparing controlled release systems utilizing these components. Tablets containing venlafaxine-HCl tablets were coated with an aqueous dispersion composed of Ethylcellulose plasticized with di-Bu sebacate.

**Dixit et al., -2003,** discloses a CR formulation of venlafaxine that comprises an immediate-release (IR) pellet and an extended-release (ER) pellet. IR pellets comprised Venlafaxine HCl 60%, sugar sphere 35%, and Ethylcellulose5%. ER pellets were prepared using 63.38% of the above IR pellets coated with a coating composition comprising talc 4.58%, magnesium stearate 4.58%, Tween 80 0.05% and Eudragit NE 30D 27.41%. The IR pellets and ER pellets were encapsulated.

**Escoi et al., -2003,** discloses solid pharmaceutical compositions comprising venlafaxine. Tablets were prepared containing venlafaxine base 30.00 mg, silicified
microcrystalline cellulose 15.00 mg, dicalcium phosphate 44.10 mg, and magnesium stearate 0.90 mg.

Heinicke et al., -2003, discloses a process of producing a multiparticulate dosage form using rotary granulation with polyethylene oxide as a binder. The core composition layer comprises a drug and a polyethylene oxide as binder. For example, oral dosage contained spheroids coated with Venlafaxine HCl, Eudragit EPO, di-Bu sebacate.

Kumar et al., -2003, discloses modified-release multiple unit systems, and methods of preparing these systems, which can be filled into capsule or compressed into tablets or sachets without affecting the desired release characteristics of the pharmaceutical active ingredients incorporated within the systems. Each unit includes at least one core having an outer surface, a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, one or more rate controlling polymers, and one or more active pharmaceutical ingredients. The coating layer includes one or both the active pharmaceutical ingredients and the rate controlling polymers. The tablet may further include an outer layer on the outer surface of the unit which includes a material that is one or both of elastic and compressible. The material may be a wax material, such as polyethylene glycol (PEG). For example, modified-release multiple units (pellets) were prepared containing (i) non-pariel seed 65 mg, as an inert core, (ii) venlafaxine-HCl 171.0 mg, magnesium stearate 13.5 mg, colloidal silica 19.7 mg, hydroxypropyl methylcellulose 13.5 mg, and water, as a drug layer, (iii) Ethylcellulose93 mg, hydroxypropyl methylcellulose 24 mg, triacetin 1% of total polymer, mg as a rate controlling layer, and (iv) polyethylene glycol (PEG) 6000, as a wax layer. Pellets 473 mg, silicified microcrystalline cellulose288 mg, PEG 6000 71 mg, Crospovidone 102 mg, and magnesium cellulose were compressed into sustained-release tablets.

Oosterbaan et al., -2003, discloses low water soluble salts of venlafaxine such as venlafaxine maleate. ER hydrogel tablets were prepared by direct compression of venlafaxine hydrogen maleate 3.125 parts, HPMC 53.125 parts, microcrystalline cellulose12.0 parts, Emcompress 5.0 parts, and magnesium stearate 1.250 parts.
**Petereit et al., -2003,** discloses a method for producing a tablets, pellets as drug-containing matrix, whereby the tablets, pellets and/or active ingredient-containing matrix contain a pharmaceutical active ingredient and a copolymer serving as a coating agent and/or binding agent, and optionally contain a core and pharmaceutically common additives.

**Makhija, Sapna N. et al., -2002,** discloses that the venlafaxine is a unique antidepressant that differs structurally from other currently available antidepressants. Sustained release tablets of venlafaxine to be taken once daily were formulated with venlafaxine hydrochloride equivalent to 75 mg of venlafaxine base. Matrix system based on swellable as well as non-swellable polymers was selected for sustaining the drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. These were evaluated for appearance, wt. variation, thickness, hardness, friability, drug content and in vitro drug release at selected time intervals.

**Jeary et al., -2000,** discloses a multiparticulate CR formulation of selective serotonin reuptake inhibitor (SSRI) drugs for oral administration. The composition contains SSRI particles coated with rate-controlling polymer.