Chapter 6: Summary and Conclusion

6. Summary and Conclusion

**Aripiprazole immediate release tablet**

The antipsychotic therapeutic market is threatened by exclusivity loss due to patent expirations. In year 2012, four out of the six largest selling antipsychotic drugs lost their patents. Thus, due to lesser side effects associated with Abilify, there is a need to develop a generic formulation for the same so as to provide the drug at a reasonable cost to the public.

Aripiprazole is a poorly soluble, poorly permeable Biopharmaceutics Classification System (BCS) Class IV compound. Since, Aripiprazole belongs to class IV comparing the dissolution with innovator becomes critical for getting a bioequivalent composition. Based on the solubility study, it was found that the Aripiprazole is highly soluble in dichloromethane, sparingly soluble in toluene & insoluble in methanol. Aripiprazole is available as ABILIFY® (aripiprazole) Tablets from Ostuka. ABILIFY Tablets are available in market in the strength of 2 mg, 5 mg, 10 mg, 15 mg, 20 mg & 30 mg.

The most common problem related to Aripiprazole therapy, that the atypical antipsychotic drugs have severe side effect related to CNS, cardiac disease and extrapiramedal side effects. Further, half life of atypical antipsychotic drugs are low and the bioavailability of most of the atypical antipsychotic drugs altered in the presence of food. The aqueous solubility of atypical antipsychotics is very low so that the bioavailabilities of atypical antipsychotic drugs are also low. Further, the stability of final finished dosages form from atypical antipsychotics is also low.

Aripiprazole is a newer antipsychohotic drug category whivch over come the existing problems in the atypicals antipshycotic drugs. Aripiprazole offers various advantages over previously reported atypical antipshychotic drug category like Aripiprazole is more effective and less side effect in comparison to the atypical antipsyhotics. Aripiprazole has long half life and the absorption is unaffected by food.
Keeping the same in mind the experiments were designed based on designs of experiments (DOE) taking into account the critical attributes that may affect the dissolution of the drug. The drug excipients profile compatibility studies were performed. The formulation development and dissolution profile were determined by using two different particle size of Aripiprazole and D(0.9) of NMT 30µm or less was selected.

Development of Aripiprazole Tablets was started with wet granulation as tablet manufacturing process with 2 mg, 5mg, 10mg tablets are essentially proportionally similar i.e the total tablet weight is the same with the only change being the amount of drug with a corresponding change in the amount of lactose and the presence of a different colorant respectively for each strength. The other strengths 15mg, 20 mg, 30 tablets are dose proportional to 10mg strength with corresponding change in the colorant for each strength.

Wet granulation was selected as the granulation method due to the low dose of Aripiprazole. Due to low solubility of aripiprazole, aripiprazole is milled to improve its bioavailability. The milled drug substance has poor flow characteristics and is cohesive. Thus, wet granulation is performed prior to compression to achieve tablet content uniformity. The tablet manufacturing process started with initially 2 mg, 5mg, and 10mg tablets of Aripiprazole.

Prototype formulations were compressed and evaluated for physical parameters and drug release and based on the results obtained further prototype formulations were developed until the in-vitro release of the test pharmaceutical composition was found comparable to the innovator formulation of same strength. The quality target product profile (QTPP) was defined based on the drug substance property, characterization of the RLD product, and consideration of the RLD label and intended patient population.

The excipients similar to those listed in the pack insert of the innovator RLD product were chosen. The formulation optimization investigated the impact of Aripiprazole and levels of intragranular lactose, microcrystalline cellulose, corn starch (unipure FL) and L HPC LH-21 on drug product CQAs. The second DOE studied the levels of
process parameters on drug product CQAs. The formulation composition was finalized based on the knowledge gained from these two DOE studies.

It was observed that percentage drug release from the pharmaceutical composition comprising binder was less compared to the formulations devoid of any binder. The drug release of aripiprazole with hydroxy propyl cellulose as binder was 82% and with corn starch 86% compare with innovator drug release was less. Without binder the drug release was same with that of innovator abilify that is 99%. It was also observed that particle size of the API that Aripiprazole has profound impact on % drug release from the formulation. As the particle size of Aripiprazole increased, percentage drug release from the formulation decreased.

Four formulation optimization trials and eight process optimization trials were conducted. The formulation optimization trials were conducted to optimize the formulation and the process optimization trials were done to optimist the various process parameters during the wet granulation process. It was found that the % Quantity of water in granulation showed a significant impact on tablet dissolution at 30 mins.

On the basis of forced degradation data it is found that the N oxide impurity, Dimer impurity and Dehydro Aripiprazole impurities are increasing during the storage of finished dosages form. Dimer and dehydro Aripiprazole impurity are process impurities. The intragranular L HPC LH 21, % MCC in MCC/Lactose ratio and corn starch showed a insignificant impact on tablet dissolution at 30 mins and content uniformity.

Because no curvature effects were observed for any of the responses studied, and the main effects and interaction effects were identified using a half factorial DOE, further studies to optimize the intragranular excipients were unnecessary.

Based on the results it is observed that % quantity of water does not have any adverse effect on the formulation. This may be due to the drug property, as the drug substance belongs to BCS class IV wetting of drug substance is required for complete
dissolution. So as per the results of design of experiments (DOE) for % quantity of water is significant factor for dissolution. Because no curvature effects were observed for any other responses studied, and the main effects and interaction effects were identified using a full factorial DOE, further studies to optimize the process parameters were unnecessary. The DOE models were used to establish acceptable ranges for process variables.

All the impurities Aripiprazole Quinoline (Related compound A), Aripiprazole related compound B, DCCP (Related compound C), 3-chloro Aripiprazole, Dehydro Aripiprazole (Related compound G), Dimer impurity (Related compound D), Chlorobutoxy carbostyril (Related compound E) are process impurity. N-oxide is degradant impurity is monitored during stability. Product was found to be stable in HDPE bottle pack with 3g Sil. Canister and Alu Alu blister pack.

Aripiprazole immediate releases (IR) tablet so developed without using binder achieved comparable in-vitro dissolution profile and are found to be bioequivalent that of the reference listed drug. The Aripiprazole immediate release tablets provide a cheaper alternative to the innovator product.

The dissolution medium used for the determination of % drug release from immediate release product, the dissolution medium having pH low was selected because the drug absorption was at upper intestine. Dissolution was carried out with recommended dissolution procedure the FDA: 900 mL of pH1.2 USP buffer (Hydrochloric acid) using USP apparatus 2 at 60 rpm. Further pH 4.5 and pH 6.8 buffers were evaluated using USP apparatus 2 at 60 rpm. Because of poor solubility & dissolution profile of test product in pH 6.8 buffer, 0.5% SLS was added to the media. Then it was found to be similar to the RLD tablets.

The dissolution method selected for development of product uses 900 mL of pH1.2 USP buffer (Hydrochloric acid) in a dissolution apparatus equipped with paddles (speed 60 rpm) and maintained at a temperature of 37°C, followed by HPLC determination. Additionally, this method is capable of detecting dissolution changes in the drug product caused by deliberately varying the drug substance (DS) particle
size distribution (PSD). If dissolution is done in the absence of sodium lauryl sulfate the release was found to be only 3%.

Invitro dissolution and in vivo performance was carried out to know relation and the dissolution test was performed on the three prototypes and the RLD using FDA-recommended dissolution method. The data indicated that particle size is the major parameter for the in vitro dissolution performance. A dissolution rate of not less than (NLT) 80% in 30 min in pH 1.2 USP buffer (Hydrochloric acid) was set as target for pharmaceutical development studies based on dissolution rate as observed for the innovator.

The final batches were subjected to bioequivalence study. The results of the PK study indicated that a drug substance particle size distribution with a D (0.9) of 23.76µ (NMT 30µ) or less showed similar performance based on test to reference ratio calculations for AUC and C\text{max}. In the fasting study 2 individuals were outlyers. After removing these two individuals the BE acceptance criteria were achieved. As per the package insert there is no effect of food on the bioequivalency of the product.

**Scope of the present work**

There are large sizes of population suffering from schizophrenia of mental disorder. According to the WHO schizophrenia affects about 7 per 1,000 of the adult population, mostly in the 15–35 year age group (WHO, 2010). Due to this reason the size of market for schizophrenia is consistently increasing. It is expected that by 2021, the market is forecast to grow to $6.9bn, at a CAGR (compound annual growth rate) of 3.3% [Daniel Chancellor, 2012].

The branded approved Abilify price is about 20mg tablet (90 tablet) - $2089.86, about $23.22 per tablet. Whereas the generic drug cost is much cheaper than the branded drugs. The generic drug cost of Abilify is about 20mg (90 Tablet)- $224.57; about $2.495 per tablet. Based on the about discussion it is cleared that the generic drug is more than 10 times cheaper than the branded drug.
Further, the antipsychotic therapeutic market is threatened by exclusivity loss due to patent expirations. In year 2012, four out of the six largest selling antipsychotic drugs lost their patents. Due to loss of patent protection, it is golden opportunity for generic industries to enter in the antipsychotic market without any obstruction.

Further, Aripiprazole is a novel atypical antipsychotic drug. Aripiprazole is selected for the immediate release formulation because it has more effective than other antipsychotic and lesser side effects associated with this. Further its absorption unaffected by food, long half life, low solubility and low permeability makes Aripiprazole as a best drug of choice.

Based on the above discussion, there is a need to develop a generic formulation for the Aripiprazole in the immediate release dosages form, so as to provide the drug at a reasonable cost to the public.

**Limitation of the immediate release Aripiprazole Tablet**

Aripiprazole is a novel atypical antipsychotic drug. As the cost of per dose of generic drug is almost 10 times cheaper than the branded drug, there is a need of a generic formulation for the Aripiprazole in the immediate release dosages form, so as to provide the drug at a reasonable cost to the public. But the main limitation associated with the formulation of generic is the patent protection of Aripiprazole formulation. Aripiprazole is patent protected by 6 orange book listed patents till Mar 25, 2023.

Most of the atypical antipsychotic drugs have severe side effect related to CNS and cardiac disease. Further, conventional antipsychotics are commonly associated with distressing adverse effects such as extrapyramidal side-effects. So that dose of Aripiprazole and frequency of Aripiprazole administration is most important factor of the Aripiprazole immediate release formulation. As discussed above due to low water solubility the bioavailability of most of the atypical antipsychotic drugs altered in the presence of food.
The orange book listed patents of Abilify (Aripiprazole) is 5006528 (Apr 20, 2015*PED); 7053092 (Jan 28, 2022); 8017615 (Dec. 16, 2014*PED); 8580796 (Mar. 25, 2023*PED); 8642600 (Jul 28, 2022*PED); and 8642760 (Mar 25, 2023*PED).

Further Aripiprazole has low water solubility hence it has low bioavailability. The low solubility and hence low bioavailability is the barrier step during the formulation of immediate release dosages form. During the process increasing the water solubility is challenging task. Due to low water solubility, its bioavailability is also low. So that Aripiprazole is subjected into solubility enhancing techniques before formulation.

Half life of atypical antipsychotic drugs is high so that it is suitable for the immediate release formulation. The stability of final finished dosages form of antipsychotic drugs is another limiting factor for the formulation of immediate release Aripiprazole formulation.

**Recommendation during formulating Aripiprazole Immediate release Tablet**

As discussed above, the antipsychotic drugs are low water solubility and low bioavailability, so that the Aripiprazole is subjected to solubility enhancing techniques for enhancing the solubility of Aripiprazole so that the bioavailability can be also increased. For formulation development, dissolution profile using two different particle size of Aripiprazole was evaluated and D (0.9) of NMT 30µm or less was selected in the present formulation and it is difficult to getting a bioequivalent composition with innovator.

The half life of antipsychotics is high so that the immediate release formulation of antipsychotics can be formulated to avoid CNS and extrapyramidal side effect. Further Aripiprazole is a biopharmaceutical classification system (BCS) class IV drug (low solubility and low permeability); so that it is a challenging task for a formulation scientist to make a bioavailable dosage form of such type of drugs.

As we all know that the conventional antipsychotics are commonly associated with distressing adverse effects such as extrapyramidal side-effects. Aripiprazole is more efficacious at treating positive symptoms and the risk of EPS and
hyperprolactinaemia. Further antipsychotic has severe CNS and Heart side effect associated with this so that the tighter control on the strength of dose and frequency of administration of dose is required.

For further process development the dry granulation or melt granulation process can be used for the formulation of immediate release composition of Aripiprazole. In the present formulation wet granulation techniques is used due to low dose of Aripiprazole.
Venlafaxine Extended release Capsule

There are many drug categories, which are used in the treatment of MDD. The therapeutic drug category includes tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOIs), Selective serotonin reuptake inhibitors (SSRIs), and Atypical antidepressants. But these therapeutic drug categories have many problems related to therapy i.e. the SNRI category of drugs required multiple daily dosing so that the side effect associated with the SNRI therapy was very high. The solubility of this class of drug is low so that the bioavailability is also low. One more problem associated with the SNRI therapy that the drugs are unstable for a long duration after formulation.

Venlafaxine as compared to Aripiprazole was a highly soluble drug and thus controlling the drug release from the formulation was a challenging task. Venlafaxine and ODV attain steady state concentrations within 3 days after oral multiple dose therapy. They exhibit linear release kinetics over the dose range of about 75 -450 mg/day. Half-life is about 5.0±2.0 and about 11.0±2.0 hours, respectively.

The innovators product in capsules dosages form contains venlafaxine HCl equivalent to strength of 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive pharmaceutical ingredients consist of cellulose, EC, gelatin, HPMC, iron oxide, and titanium dioxide. Administration of Effexor XR generally resulted in lower maximum plasma concentration (Cmax) (150 ng/mL for venlafaxine HCl and 260 ng/mL for O-desmethylvenlafaxine) and later time to achieve maximum plasma concentration (Tmax) (5.5 hours for venlafaxine HCl and 9 hours for O-desmethylvenlafaxine) than for Effexor (IR) [Effexor- 2014].

Process of selection of excipients has been based on the design and fabrication of the extended release dosage form, their compatibility with drug substance and their intended functions, so that the in-vivo and in-vitro performance of the proposed formulation is comparable to that of the reference product.
Compatibility screening of a number of commonly used excipients was performed at the early pre-formulation stage of development to obtain information regarding potential incompatibilities between Venlafaxine Hydrochloride and excipients. The drug along with different excipients was mixed, sealed in clear glass vials with LDPE stoppers and charged into stability chambers at 40°C± 2 °C/ 75 % ± 5% RH and 25°C± 2°C/ 60% ± 5% RH.

The Venlafaxine ER capsule filled with venlafaxine spheroids were made using extrusion spheronization technique. The drug release from the spheroids was controlled by applying a coating comprising ethylcellulose as rate controlling polymer. The coated pellets were then encapsulated in the hard gelatin capsules.

Spheroids were prepared by the extrusion and spheronization technique. Spheroids were coated with extended release coating composition comprising ethyl cellulose and triethyl citrate. The spheroids were coated with extended release coating composition comprising ethyl cellulose and Triethyl citrate followed by another coating using Acryl EZE MP 93018508 white dispersion and coated pellets encapsulated in hard gelatin capsule shells. A suitable binder is required for desired strength of spheroids. Drug release profile was slow compared to reference product in all the three media’s.

The effect of coating weight build up was studied at 1.82% and 2.4%w/w levels using spheroids with 7%w/w extended release coating I. Drug release in 6.87 pH phosphate buffer, 900ml, type I, 100 rpm was studied.

Spheroids are encapsulated in hard gelatin capsule shells. Extrusion and spheronization technique was used to prepare the spheroids. These spheroids are coated with ethyl cellulose as release controlling polymer and Triethyl citrate as plasticizer. Ethyl cellulose forms an insoluble and semi permeable membrane coating and the release of drug from the pellets coated with ethyl cellulose polymer could be by diffusion mechanism. Encapsulation of the coated pellets is done using hard gelatin capsules.
During the manufacturing of spheroids, it was observed that more fines were generated during the extrusion spheronization, which is not suitable for large scale production of the formulation. Accordingly batches were optimized using different types of binder and coating composition. Pellets with milled Venlafaxine hydrochloride provides uniform distribution of pellets compared to unmilled Venlafaxine hydrochloride. Hence milled Venlafaxine hydrochloride could be used for fabrication of batches.

Effect of the binder and percentage coating was studied. The drug release of venlafaxine using Povidone K30 as binder, Ethyl cellulose and Acryl-EZE MP 93018508 white as release control polymers was compared with innovator’s drug release and was found to be equivalent. From the results, it was concluded that use Povidone K30 as binder during extrusion spheronization process results on generation of less fines, thus increases the yield of the product. Also, the formulation containing dual coating of Ethyl cellulose and Acryl-EZE MP 93018508 on the spheroids containing Povidone K30 as binder showed the dissolution profile identical to that of the Reference Product Effexor XR. The developed pellets offer better control on the release of Venlafaxine.

The formulation of 75mg, 150mg venlafaxine hydrochloride capsules compared with the reference listed drug Effexor of different strengths like 75mg and 150mg in different medias like pH 6.8 phosphate, pH 4.5 acetate and HCl (0.1N) and water. The scale-up batches were found to be similar to the innovator’s drug release profile.

The drug profile was compared in various medias like pH 6.8 phosphate, pH 4.5 acetate and HCl (0.1N). The different strengths were compared like 150mg, 75mg and respectively. The in-vitro dissolution studies were performed to evaluate the release of the drug venlafaxine from the coated spheroids contained in capsule at 6.8 pH using phosphate buffer. The in-vitro drug release profile of the test compositions was compared with Reference Product Effexor XR®. The results obtained showed that the test formulations had higher percentage release of venlafaxine in initial time period. Therefore, a better control on the release was desired.
Two packs, viz. blister pack and bulk (container) pack are intended to be used for commercial and repackaging respectively. Blister pack consisting of 196mm white opaque PVD coated PVC film (0.25mm) and 192mm plain lidding aluminium foil (0.025mm) of 2x14 capsules is proposed. The inherent protective property of PVDC coated PVC film from moisture and other environmental factors makes it suitable for capsule blister packing. The PVC layer will be in contact with capsules while PVDC layer in contact with environment.

The bulk pack for repackaging at UK site is proposed based on stability data of bulk replica pack. The proposed bulk pack size for 75mg strength is 12,000 capsules and for 150 mg strength is 10,000 capsules. The bulk capsules are first packaged in low density polyethylene bag with polypropylene strap seal. The bag is then kept in triple laminated sachet with two silica gel bags on the top and thermo-sealed. The thermo-sealed triple laminated bag is then kept in HDPE container. Microbiological testing is conducted on test batches, and is also a part of stability protocol; the results are satisfactory. This test will be performed on first three validation batches and thereafter on every 10th batch or annually whichever is sooner.

All the sample batches were tested and analysed for critical control parameters as well as the analytical parameters such as the assay and content uniformity and were found to comply within the limits. The values for all the tests fall within the acceptance criteria and specifications.

The present formulations provide alternative, economic, industrially scalable extended release formulations of Venlafaxine having comparable in-vitro dissolution profile with that of the respective Innovator products. The formulations are easy to manufacture and does not require costly excipients. The optimized formulations were found to be stable. More such alternative formulations need to be developed to offer patients medicine at affordable price.
Scope of the present work

According to WHO, worldwide around 350M people affected by depression. Multiple drug classes exist for the treatment of major depressive disorder (MDD). Newer classes of medications are usually the first line of treatment. There are four categories of drugs which can be used in the treatment of MDD they are tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAOIs); selective serotonin reuptake inhibitors (SSRIs); and atypical antidepressants.

According to Datamonitor report published in 2011 there were 32,240,000 cases of MDD in grownups aged 18 and over in the worlds 7 major markets, and this number is expected to increase to 33,379,000 by 2020, at an 0.4% of average annual growth rate. Five major European Union markets are France, Germany, Italy, Spain, and the UK.

Further, Datamonitor epidemiologists estimate that the number of cases in the five major EU markets will grow from 10,638,000 in 2011 to 10,737,000 in 2021. Multiple drug classes exist for the treatment of MDD. Newer classes of medications are usually the first line of treatment. Most antidepressants have similar rates of efficacy overall and time to onset of effectiveness, but differ in terms of side-effect profiles.

Effexor XR is an ER capsule of venlafaxine HCl for once in a day oral administration. Release of drug is dependent on the coating membrane on the spheroids. Capsules contain venlafaxine HCl equivalent to strength of 37.5 mg, 75 mg, or 150 mg Venlafaxine which are about $1.56 per dose whereas the cost of generic drug is about $0.65 per dose. So that the generic drug is almost 10 times cheaper than branded innovator formulation. As per the pharmaceutical industry, based on the market size and market potential of Effexor (Venlafaxine) is most important drugs for the generic launch.

There are five orange book listed patents for Effexor (Venlafaxine HCl) out of which two are already expired and remaining three going to be expired in 2017. Thus, there
was a need of development of an ER dosages form of SNRI category of drugs, which eliminates or minimizes variation in blood level (peak and trough) following administration of multiple IR dosage forms and provides in a single dose, a therapeutic blood serum level over a twenty four hour period. So that it is great opportunity for the generic pharmaceutical industry to formulate the generic version of Effexor due to large market size and great potential for growth in generic market.

The composition is particularly useful for providing required therapeutic effects of Venlafaxine, by providing appreciable release in both acidic and basic pH environments and thus being absorbed throughout the gastro-intestinal tract (GIT).

**Limitation of formulation comprising Venlafaxine HCl Extended Release Capsule**

Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of 5-HT and NE reuptake and weak inhibitors of dopamine reuptake which is used in the treatment of major depressive disorder (MDD); generalized anxiety disorder (GAD); social anxiety disorder; and panic disorder. Venlafaxine and ODV exhibit linear release kinetics over the dose range of about 75 -450 mg/day. Half-life is about 5.0±2.0 and about 11.0±2.0 hours, respectively.

There are five orange book listed patents for Venlafaxine 5916923 (Dec 28, 2013); 6274171 (Sep 20, 2017); 6403120 (Sep 20, 2017); 6419958(Sep 20, 2017); and 6444708 (Dec 28, 2013). Two of the orange book listed patents are already expired and remaining three is going to be expired in 2017.

Venlafaxine is highly water soluble drug with a water solubility of 572mg/ml (Hydrochloride salt). The rapid dissolution of venlafaxine due to higher water solubility of drug leads to quick increase in plasma concentration of the active drug shortly after administration leading to side effects. Due to rapid increase and decrease in the blood levels followed by the administration of immediate release dosage form, patients experienced nausea.
Due to higher solubility in water, dose dumping phenomenon is very common in the Venlafaxine formulation. The sudden release of all the drugs in body leads to increase drug concentration in blood plasma. So that during the formulation of Venlafaxine extended release formulation, the tighter control in the release mechanism is most important.

**Recommendation based on the present work**
Venlafaxine is a weakly basic drug having relatively good solubility at gastric pH and poor solubility at intestinal pH. Venlafaxine is weakly basic drug, therefore the drug has an appreciable release in stomach i.e. acidic pH environment but relatively less release in the intestine i.e. basic pH environment. Thus, formulating Venlafaxine or salts thereof into an extended release dosage form that overcomes the solubility issues of Venlafaxine in the GIT, presents a number of challenges to a formulation scientist.

Hence, there was a need to for improved compositions providing extended release dosage form that overcomes the solubility issues of desvenlafaxine in the GIT and provide a sustained drug release over the desired period of time to achieve the desired concentration of Venlafaxine in the blood.