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# Formulation and Evaluation of Aripiprazole-IR Tablets by Direct Compression Method

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**Abstract:** ***Aripiprazole used as anti-psychotic drug therapy in the form of immediate release tablet. This paper represents the disintegrants like starch, pre-gelatinated starch and corn starch which were used as suitable disintegrants for drug release. The investigation of drug release profile in the formulation of immediate release tablet with manufacturing includes the use of Direct compression processes. In this work the Characteristic study of drug release from immediate release tablets by taking 8 different formulations. It was obtained that disintegrants like starch, pre-gelatinated starch and corn starch formulations were shown comparable results with innovator.There was no more significant impact on physical properties of the formulations by interchanging starch, pre-gelatinated starch and corn starch. But higher percentage of drug release was observed when the formulation contained corn starh(f4) compared to other formulations. From this study it concluded that formulation(f4) which contained corn starch as disintegrant showed similar dissolution profile with innovator.***

**Keywords:** Aripiprazole, starch, pregelatinated starch, starch, direct compression

## 1. Introduction

Aripiprazole is an atypical III generation antipsychotic and antidepressant used in the treatment of schizophrenia, bipolar disorder, and clinical depression. It was approved by the US Food and Drug Administration (FDA) for schizophrenia . Aripiprazole is also a partial agonist at the 5-HT1A receptor and like the other atypical antipsychotics displays an antagonist profile at the 5HT2A receptor. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and ease of manufacturing; however in many cases immediate onset of action is required than conventional therapy.

To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after administration. Immediate release (IR) tablets are a better choice for drugs which need to elicit their action in a short duration. In contrast to conventional tablets IR tablets are intended to disintegrate in the stomach in less than three minutes and must release 85% or more of stated amount of drug with in 30 min. Anti psychotics are used to treat schizophrenia. Immediate release tablet/disintegrating tablets are a perfect fit to take dose of an antipsychotic easily. IR formulation of an antipsychotics drug can have several advantages like quick onset of action, increased bioavailability, reduced dose, minimal side effects etc; over conventional tablets. Immediate release tablets (IR) have received ever-increasing demand during the last decade and the field has become a rapidly growing area in the pharmaceutical industry. Upon administration, these tablets were easily disintegrate and the drug will be released in 23min. The main objective of this work is to formulate an immediate release oral solid dosage form of aripiprazole which is considered to be stable and pharmaceutically equivalent to that of the reference [marketed] product for the treatment of schizophrenia disease. To achieve this goal various trials are to be taken and evaluated with respect to the various quality parameters such as dissolution and related studies. The objectives of the present study are to design, optimize and evaluate immediate release tablets of antipsychotic drug.

## 2. Materials and Methods

### Materials

Aripiprazole (Hetero labs limited(unit-I)), Lactose monohydrate, ph.Eur (HMS Impalable, starch, USP/NP (extra white maize),Starch1500,Pregelatinised Starch, ph. Eur (Extra white maize),Cellulose, microcrystalline, ph.eur (Avicel PH101) Hydroxypropyl cellulose, ph.Eur(Klucel EXF), Cellulose microcrystalline, Ph.eur(avicel PH 112), Magnesium stearate, Ph.Eur.All other reagents and chemicals were of analytical grade.

### Methods

For the following study we are taken Aripiprazole which is an antipsychoyic third generation drug. In this study first we did preformulation studies.

### Preformulation Studies

In this preformulation studies we studied about the API characterization, Drug - Excipient Compatibility Studies, Analytical Method Development and Pre-compression parameters.

**API Characterization:** It is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, melting point, particle size and compatibility.

**Drug - Excipient Compatibility Studies:** The compatibility studies provide the framework for the drugs combination with excipients in the fabrication of the dosage form. Basically two methods were followed. Here we followed FT-IR Spectrophotometric Method. It is performed by KBr pellet method [6,7].

**Analytical Method Development:** Analytical method development is studied for knowing about the purity of the

drug [8]. It is carried out by two methods. HPLC or U.V. Here we are followed U.V method.

**Pre-compression parameters:** Before going to formulation we need to study pre compression parameters like Angle of Repose, Bulk density, Tapped density, Compressibility index, Hausner ratio and Sieve analysis. Then we went for the formulation development…

**Formulation Development and Evaluation:** For this study we developed 8 formulations by using different disintegrants. The following table shown the formulation development for the present study.

**Table I:** Formulation development of aripiprazole

| S.No | Ingredients(mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Aripiprazole, IH | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2 | Lactose monohydrate, USP/NF(HMSimpalpable) | 69.44 | 69.44 | 69.44 | 68.4 | 71.40 | 70.44 | 67.44 | 64.44 |
| 3 | Corn starch, USP/NP(extra white maize) | - | - | - | 10.0 | 8.0 | 9.0 | 12.0 | 15.0 |
| 4 | Starch-1500 | 9.0 | 10.0 | - | - | - | - | - | - |
| 5 | Pregelatinised Starch | - | - | 10.0 | - | - | - | - | - |
| 6 | Microcrystalline cellulose, USP/NF(avicel ph101) | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 | 8.5 |
| 7 | Ferric oxide, USP/NF(sicovit red 30E172) | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 |
| 8 | Hydroxypropyl cellulose, USP/NF | 2.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| 9 | Magnesium stearate, USP | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |

After completion of the formulation development we did the manufacturing of the tablets. For the preparation of the tablets we are selected direct compression method. After completion of compression of the tablets we need to study the evaluation parameters of the prepared tablets.

**Evaluation Parameters:** The following test were done for the evaluation of the tablets.like Physical appearance, Weight variation test, Hardness, Thickness, Percentage Friability, Disintegration time, Assay by HPLC and Dissolution.

**Assay by HPLC:**

Chemicals & Reagents used in the assay:

Orthophosphoric acid : AR grade
Methanol : HPLC grade
Acetonitrile : HPLC grade
Water : Milli-Q grade

The Chromatographic Conditions are..

(i) Column:inertsil ODS-3V, 150×4.6mm; 5µm or equivalent.
(ii) Detection:UV, 215nm.
(iii) Flow rate : 1.5mL/minute.
(iv) Column temp : 400c.
(v) Injection volume : 10µl.
(vi) Run time:15 minutes.

**Dissolution:**

Chemicals & reagents used for the dissolution

(i) Hydrochloric acid : AR grade.
(ii) Potassium chloride : AR grade.
(iii) Triethylamine : AR grade.
(iv) Orthophosphoric acid : AR grade.
(v) Acetonitrile : HPLC grade.
(vi) Methanol : HPLC grade
(vii) Water : HPLC grade

Dissolution parameters are….

(i) Medium : pH 1.2 buffer.
(ii) Volume : 900 ml.
(iii) Apparatus : paddle. Speed:60rpm.
(iv) Temp : 37.0 ± 0.50c

Sampling time:

(i) For single point : 30mintues.
(ii) For profile : 10, 20, 30, & 45 minutes.

Chromatographic conditions are…

(i) Column: inertsil ODS-3 ;250 X 4.6 MM,5µm or equilent
(ii) Flow rate : 1.0mL/minute.
(iii) Detection : UV, 215nm.
(iv) Colum temperature : 400c.
(v) Injection volume : 20µL.
(vi) Run time : 10 minutes.

After completion of the in-vitro evaluation, tablets were subjected to the Accelerated stability studies. Finally we concluded that formulation 4 which contain corn starch shown better results than other formulations.

## 3. Results

**Pre-Formulation Studies:**

**API Characterization:**

Appearance: Aripiprazole is a white to half weight crystalline solid. Based on the above inferences the drug ARIPIPRAZOLE was determined to be practically soluble in0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, Purified water. Solubility: Based on the below inferences the drug ARIPIPRAZOLE was determined to be practically soluble in0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, Purified water.

**Table II:** Solubility of Aripiprazole

| Solvent | Mg/ml | Approax volume of solvent in ml/gm of solute | Solubility Criteria |
|---|---|---|---|
| 0.1 N Hcl | 0.0670 | 14925.37 | Practically insoluble |
| pH 4.5 acetate buffer | 0.0686 | 14577.25948 | Practically insoluble |
| pH 6.8 phosphate buffer | 0.0051 | 196078.4314 | Practically insoluble |
| Purified water | 0.0005 | 2000000 | Practically insoluble |

**Pratical size Analysis of API:**

**Table III:** Partical size Analysis of API

| S.NO | Sieve no. | Cumulative % retention |
|---|---|---|
| 1 | 40 | 4 |
| 2 | 60 | 12.6 |
| 3 | 80 | 18.8 |
| 4 | 100 | 23.2 |
| 5 | 120 | 29.4 |
| | RECEIVER | 100 |

**Drug-Excipients Compatability Studies:**
**Physical Compatibility:**

**Table IV:** Physical Compatibility Results

| Material | Sample Status After 1 month, kept at Accelerated 40°C±2°C/75% RH ±5% RH | Sample Status After 1 month, kept at 25°C ± 2°C /60%RH ± 5% RH |
|---|---|---|
| Aripiprazole+microcrystallin | No Change | No Change |
| Aripiprazole+HPC | No Change | No Change |
| Aripiprazole+cornstarch | No Change | No Change |
| Aripiprazole+magnesiumstearate | No Change | No Change |

## 4. Results

**Above study states that there was not any type of color change or lumps were formed.**
**Analytical method development:**

**Table V:** Standard Graph of Aripiprazole

**FTIR-Reports:**

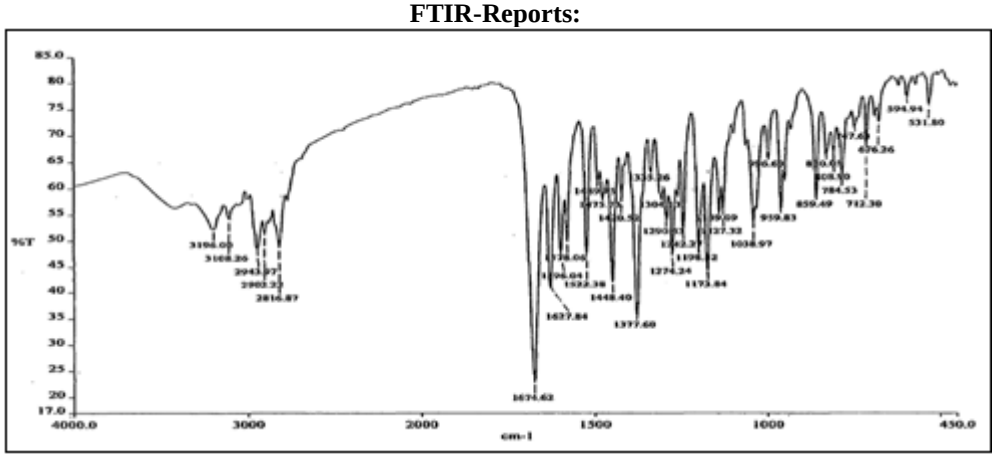


**Figure 1:** FTIR of Aripiprazole- API

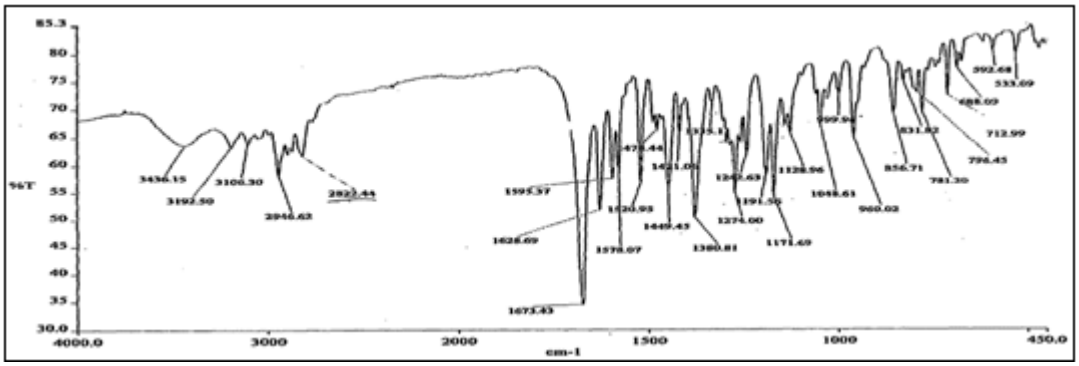


**Figure 2:** FTIR of Formulation 8-Drug+ Excipient

**Precompression Parameters Results of Granules:**
**Flow properties:**

**Table VI:** Flow properties

| S.No | Blend characterization data | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Parameters | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 1 | Bulkdensity (gm/ml) | 0.5912 | 0.5913 | 0.5918 | 0.5915 | 0.5912 | 0.5915 | 0.5912 | 0.5915 |
| 2 | Tapped density(gm/ml) | 0.7422 | 0.7425 | 0.7424 | 0.7425 | 0.7422 | 0.7425 | 0.7422 | 0.7425 |
| 3 | Compressibility Index (%) | 20.334 | 20.334 | 20.334 | 20.336 | 20.334 | 20.336 | 20.334 | 20.336 |
| 4 | Angle of repose | 25.590 | 25.590 | 25.590 | 25.594 | 25.590 | 25.594 | 25.590 | 25.594 |
| 5 | Haursner ratio | 1.25541 | 1.2557 | 1.2544 | 1.2552 | 1.2554 | 1.2552 | 1.2554 | 1.2552 |

The formulated granules were characterized with respect to Angle of repose, bulk density and tapped density. Angle of repose of API was found to be 250-260, thus indicating that the flow properties were Excellent.Hausner's ratio was more than 1.25 for all the batches indicating Fair Passable flow properties.Compressibility index was 20%-21% for all the batches indicating FairPassable flow properties.

**Sieve Analysis:** All the Granules were tested for particle size by sieve analysis using mechanical sieve shaker. The size of granules (841-1190µm) is found to be within the range of standard sieves. All the granules are passed through sieve no.16 easily and retained on sieve no.20.

**Formulation-Results:**

**Table VII:** Characteristics of Optimized Formulation:

| S.No | Formulation code | Hardness of tablet (KP) | Thickness of tablet(mm) | Friability(%) | Average wt(mg) | Disintegration time(min) |
|---|---|---|---|---|---|---|
| 1 | F1 | 4.52 | 2.50 | 0.063 | 95 | 2.5 |
| 2 | F2 | 4.55 | 2.52 | 0.070 | 95.5 | 1.5 |
| 3 | F3 | 4.32 | 2.50 | 0.052 | 95.2 | 2 |
| 4 | F4 | 4.20 | 2.50 | 0.055 | 95 | 2.2 |
| 5 | F5 | 4.10 | 2.53 | 0.059 | 95.2 | 2.5 |
| 6 | F6 | 4.25 | 2.55 | 0.066 | 95 | 2.8 |
| 7 | F7 | 4.2 | 2.52 | 0.063 | 95.2 | 3.5 |
| 8 | F8 | 4.2 | 2.52 | 0.070 | 95 | 3.8 |

1) Hardness of each formulation was analysed for formulations F1 to F8 and all formulations were found to have good hardness. So they were taken for further studies to measure hardness of tablets of each batch range between 4.2 to 4.5 kp.
2) Tablets mean thickness were almost uniform in all formulations and were found to be in the range of 2.50to 2.55 mm.
3) The total weight of each formulation was not maintained constant however the weight variation of the tablet was within the limits of 0.5% .iv)All the tablets passed the pharmacopoeial specifications for the disintegration of uncoated tablets within 2.0-3.0. Formulations containing starch1500 (lycotab-c) 5% shows rapid disintegration when compared with the other formulations. The disintegration time of F1to F8 were found to have equivalent time with that of innovator product.

**Assay by HPLC:**
**HPLC Report**
**Sample information@E/data/2020/jan3/aripiprazole 1.5.124**

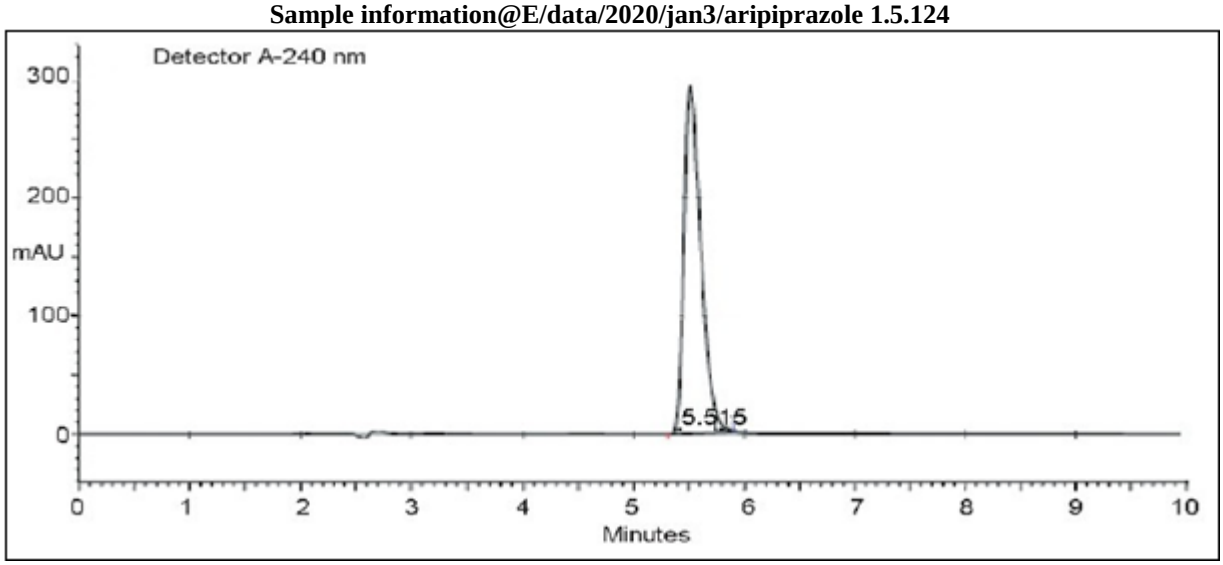


**Figure 3:** Standard Peak Table information@E/data/2020 jan3/aripiprazole 1.5.14

**Table VIII:** PD A multi 240nm

| Peak | Name | Ret.time | Theoretical plates | Tailing factor |
|---|---|---|---|---|
| 1 | Aripiprazole | 5.151 | 3000 | 1.12 |

**HPLC Report**
**Sample information@E/data/2020 jan3/aripiprazole 1.5.14**

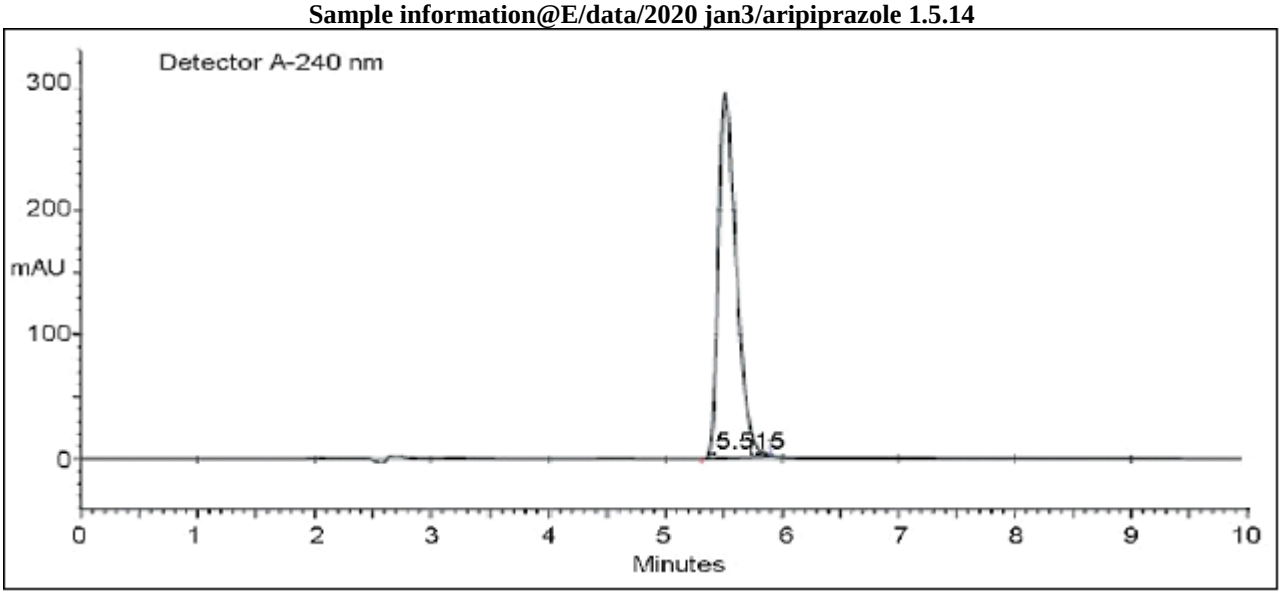


**Figure 4:** Sample peak table information @E/data/2020 jan3/Aripiprazole 1.5.14

**Table IX:** PD A multi 240nm

| Peak | Name | Ret.time | Area | Area |
|---|---|---|---|---|
| 1 | Aripiprazole | 5.151 | 8877654 | 100% |
| Total | | | 8877654 | |

Dissolution Profile of Aripiprazole Tablets:

**able X:** Dissolution profile of Aripiprazole Formulations

| BATCH | Cumulative % of Drug release- Time (min) | | | | |
|---|---|---|---|---|---|
| | 0 | 10 | 20 | 30 | 45 |
| INNOVATOR | 0 | 86 | 93 | 94 | 95 |
| F1 | 0 | 83 | 90 | 92 | 92 |
| F2 | 0 | 82 | 89 | 91 | 92 |
| F3 | 0 | 82 | 87 | 92 | 93 |
| F4 | 0 | 84 | 92 | 94 | 94 |
| F5 | 0 | 83 | 90 | 92 | 94 |
| F6 | 0 | 83 | 91 | 92 | 93 |
| F7 | 0 | 81 | 90 | 91 | 93 |
| F8 | 0 | 82 | 91 | 91 | 92 |

**Comparision with Innovator:**

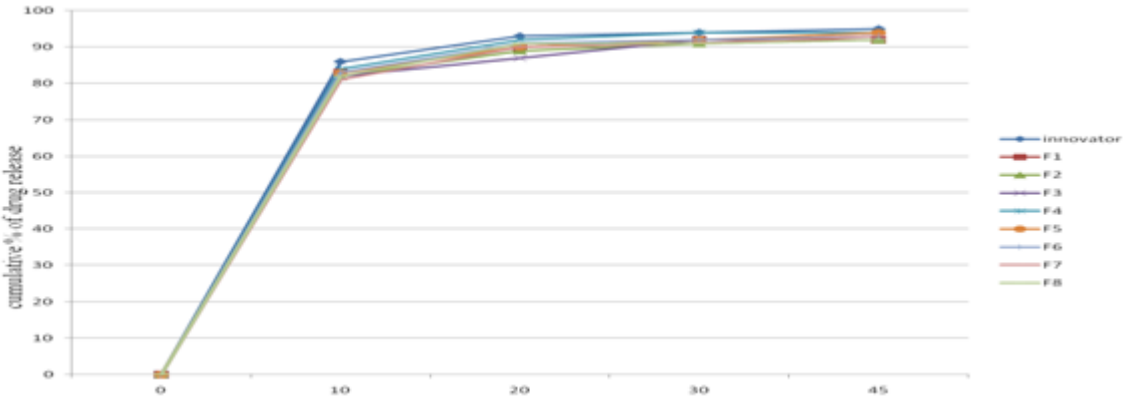


**Figure 5:** Dissolution profile of Innovator, F1-F8batches

Invitro dissolution studies of formulations F1-F8 were carried out PH 1.2 buffer medium and percentage of drug release was calculated. All the formulations were kept for 45mins. It was found that all the formulations met the limits( NLT 90% in 30min ).The dissolution profile of each formulation was compared with that of the innovator product and found the formulation F4 had approximate values of percentage drug release with that of innovator. Accelerated Stability Studies: Aripiprazole 10mg tablets were evaluated for accelerated stability studies at 20-250C / 75 % RH condition. The stability details / results are presented as below Storage Condition: 20-250C / 75 % RH Pack: HDPE Container Storage Period: 1 month and 2 months.

**Table XI:** Summary of Accelerated Stability Studies

| S.No | Test | Specifications | Initial | After 1 month | After 2 months |
|---|---|---|---|---|---|
| 1 | Description | Light pink to pink,modified rectangular, bevel edged binconvex tablets | Complies | Complies | Complies |
| 2 | Identification | The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay. | Complies | Complies | Complies |
| 3 | Dissolution | NLT 75% release after 30min | 94% | 93.8% | 93.7% |
| 4 | Related Substances (%) | NMT 0.30%w/w | Complies | Complies | Complies |
| 5 | Assay (By HPLC) | NLT 9.0 percent and NMT 11.0 percent | 10.5% | 10% | 9.5% |

The stability studies on aripiprazole IR tablets in HDPE container at 20-250C / 60 % RH for 2 months were conducted as per ICH protocol. After the specified time period (1 month and 2 months), the samples were unloaded from the stability chambers and were tested for any physical or chemical changes. Also the tests for dissolution and assay were conducted to assess the stability of product. The results for dissolution and assay are summarised below.

Dissolution: No significant change was observed in the percentage drug dissolved after a storage period of 1 month at 4o±20C / 75 % RH and 2 months at 20-250C / 60 % RH for aripiprazole IR tablets.
Assay: No significant change was observed in the assay value of aripiprazole IR tablets, after a storage period of 1 month at 40±20C / 75 % RH and 2 months at 20-250C / 60 % RH.

Inference: From the above data it was evident that there was no significant change in the physical and chemical parameters of aripiprazole IR tablets during the stability studies conducted at 40±2°C & 75%RH for1 month period and 2 months at 20-25°C & 60%RH.

## 5. Discussion

The prepared tablets were checked for assay as per IP specifications. All the formulations passed the test and the percentage of active ingredient ranges from 96 to 99.8%. In preformulation study API characterization is done[Table2,3,4], drug and excipient blends are subjected to compatibility studies[Table5]. From the FT-IR reports, it is found that there is no incompatibility [Fig 1, 2]. Physical compatibility is also tested by subjecting the blend to various storage conditions and it is found that the blend is stable. The blend was compressed into tablets and were analysed for the parameters such as average weight, disintegration, friability, thickness and hardness. All formulations shows satisfactory values compared to innovator product But the dissolution profile of F4 have equivalent profile that of innovator as compared to other formulations and concluded that F4 is better and similar to innovator product. Because other formulations have low drug release profile on dissolution compared to innovator product[Fig 5]. The F4 formulation has been subjected to stability studies according to ICH guidelines. This formulation is found to be stable for 2months.

## 6. Conclusion

The present study concluded that aripiprazole 100mg tablets have been formulated and developed by using Direct compression technique. In order to obtain best optimised product, 8 different formulations were developed. For 8 formulations the different physical properties showed best comparable with reference product. But higher percentage of drug release was observed when the formulation contained corn starch when compared with formulations contained starch and Pregelatinised starch. The formulation F4 has shown drug release NLT 94% in 45min accordance with the USP dissolution criteria for IR aripiprazole tablet formulation. The results suggest that formulation with corn starch showed similar dissolution profile with innovator drug.

## 7. Acknowledgements

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