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Formulation and evaluation of Aripiprazole-IR tablets

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Abstract

Aripiprazole is used as anti-psychotic drug (in the form of immediate release tablet). This research work was conducted to study the disintegrants like starch (potato extract), PVA and corn starch usedfor 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 found that disintegrants like starch (potato extract), PVA and corn starch formulations have shown comparable results with innovator. There was no more significant impact on physical properties of the formulations by interchanging starch (potato extract), PVA 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 was concluded that formulation (f4) which contained corn starch as disintegrant showed similar dissolution profile with innovator.

Keywords: Aripiprazole, starch (potato extract), PVA, starch, direct compression

Full length article **Corresponding Author*, e-mail: lepakshi410@gmail.com

1. Introduction

Aripiprazole is a typical 3rd 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 within 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 23 min. 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

2.1. Materials

Aripiprazole (Hetero labs limited(unit-I)), Lactose monohydrate, ph. Eur (HMS Impalable), starch, USP/NP (potato extract), PVA, ph. Eur, corn starch, 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.

2.2. Methods

For the present study Aripiprazole is used as an anti-psychoyic 3rd generation drug. In current study, first time we have carried out preformulation studies.

2.2.1. Preformulation studies

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

2.2.2. API characterization

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

2.2.3. Drug-excipient compatibility studies

The compatibility studies provide the framework for the drugs combination with excipients in the fabrication of the dosage form. FT-IR Spectrophotometric analysis involved KBr pellet for measuring spectra [6,7].

2.2.4. Analytical method development

Analytical method development was studied for finding the purity of the drug [8]. It was carried out by UV method.

2.2.5. 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.

2.2.6. Formulation development and evaluation

For this study, 8 formulations were developed using different disintegrants. The following table shows the formulation development for the present study. After completion of the formulation development, the manufacturing of the tablets was done using direct compression method.

2.2.7. Evaluation parameters

The quality evaluation of the tablets was done using test including physical appearance, weight variation test, hardness, thickness, percentage friability, disintegration time, composition analysis by HPLC (high performance liquid chromatography) and dissolution.

2.2.8. HPLC analysis

Chemicals & Reagents used in the assay were orthophosphoric acid (AR grade), methanol (HPLC grade), acetonitrile (HPLC grade), and water (Milli-Q grade). The Chromatographic conditions were as follows: column: inertsil ODS-3V, 150×4.6mm; 5µm or equivalent; detection : UV, 215nm; flow rate : 1.5 mL/minute, column temp : 400 ˚C, injection volume : 10 µl and run time : 15 minutes.

Dissolution

Chemicals & reagents used for the dissolution included hydrochloric acid (AR grade), potassium chloride (AR grade), triethylamine (AR grade), orthophosphoric acid (AR grade), acetonitril (HPLC grade), methanol (HPLC grade), and water (HPLC grade).

Dissolution parameters were medium : pH 1.2 buffer; volume : 900 mL;apparatus : paddle Speed:60 rpm; temp : 37.0 ± 0.50 ˚C, sampling time: (a) for single point : 30mintues (b) for profile : 10, 20, 30 & 45 mintues.

Chromatographic conditions were column : inertsil ODS-3; 250×4.6 MM, 5µm or equilent; flow rate : 1.0 mL/minute; detection : UV, 215 nm; colum temperature : 400 ˚C; injection volume : 20µL; and 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 contained corn starch has shown better results than other formulations.

3. Results and discussions

3.1. 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 in 0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and purified water.

Pratical size analysis of API

Practicle size analysis of API has been shown in Table 3.

Drug-excipients compatability studies

Physical compatibility

The data of physical compatability has been shown in Table 4. There was not any type of color change or lumps were formed.

Analytical method development

The standard graph of Aripiprazole is shown in Table 5.

Precompression parameters results of granules

flow properties

The flow properties are shown in Table 4. 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 Fair Passable 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) was found to be within the range of standard sieves. All the granules were passed through sieve no. 16 easily and retained on sieve no. 20.

Formulation results

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. Tablets mean thickness were almost uniform in all formulations and were found to be in the range of 2.50 to 2.55 mm. The total weight of each formulation was not maintained constant, however, the weight variation of the tablet was within the limits of 0.5 %. All the tablets passed the pharmacopoeial specifications for the disintegration of uncoated tablets within 2.0-3.0. Formulations containing starch 1500 (lycotab-c) 5% shows rapid disintegration when compared with the other formulations. The disintegration time of F1 to F8 were found to have equivalent time with that of innovator product.

Assay by HPLC

The HPLC report having sample information @E/data/2020/february/aripiprazole 1.5.124 and sample information@E/data/2020/february/aripiprazole 1.5.14 are shown in Fig. 3 and Fig. 4.

Dissolution profile of aripiprazole tablets

The dissolution tablets of aripiprazole tablets are shown in Table 9 and 10.

Comparison with innovator

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 45 mins. It was found that all the formulations met the limits (NLT 90 % in 30 min). 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 10 mg tablets were evaluated for accelerated stability studies at 20-25 ˚C/75 % RH condition. The stability details/results are presented as below. Storage Condition: 20-25 ˚C/75 % RH Pack: HDPE Container Storage Period: 1 month and 2 months.

The stability studies on aripiprazole IR tablets in HDPE container at 20-25 ˚C/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. 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 40 ± 2 ˚C/75 % RH and 2 months at 20-25 ˚C/60 % RH for aripiprazole IR tablets. No significant change was observed in the assay value of aripiprazole IR tablets, after a storage period of 1 month at 40 ± 2 ˚C/75 % RH and 2 months at 20-25 ˚C/60 % RH. 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 and 75 % RH for 1 month period and 2 months at 20-25 ˚C & 60 % RH.

Table 1: Formulation development of aripiprazole

Sr.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	69.44	71.44	70.44	67.44	64.44
3	Corn starch, USP/NP(potato extract)	-	-	-	10.0	8.0	9.0	12.0	15.0
4	Starch-1500	9.0	10.0	-	-	-	-	-	-
5	PVA	-	-	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

Table 2: 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

Table 3: Particle size analysis of API

Sr.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

Table 4: 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+microcrystalline	No Change	No Change
Aripiprazole+HPC	No Change	No Change
Aripiprazole+cornstarch	No Change	No Change
Aripiprazole+magnesium stearate	No Change	No Change

Table 5: Standard graphs of aripiprazole

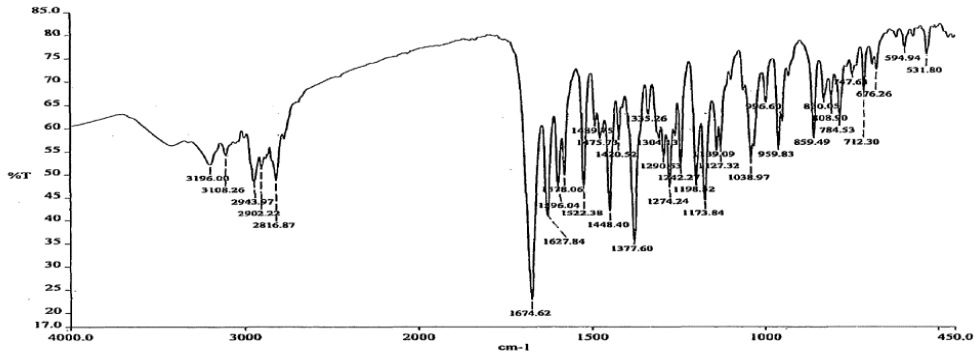

Figure 1: FTIR of Aripiprazole-API

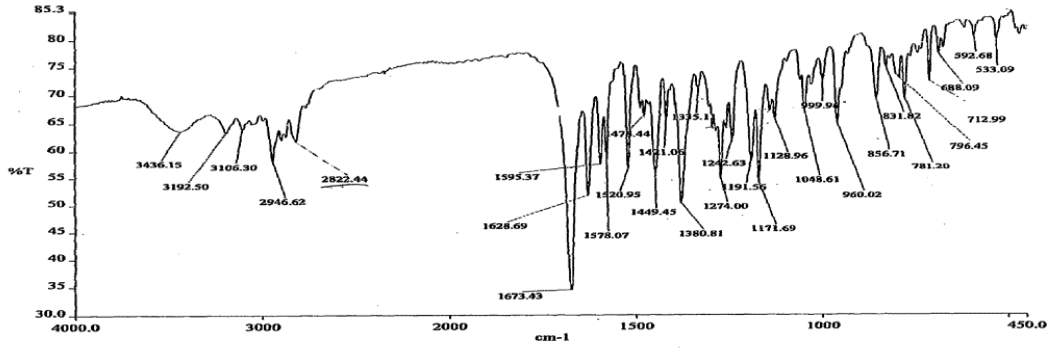

Figure 2: FTIR of formulation 4-Drug + Excipient

Table 6: Flow properties

Sr. 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	Tapdensity(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

Table 7: Characteristics of optimized formulation

Sr. 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

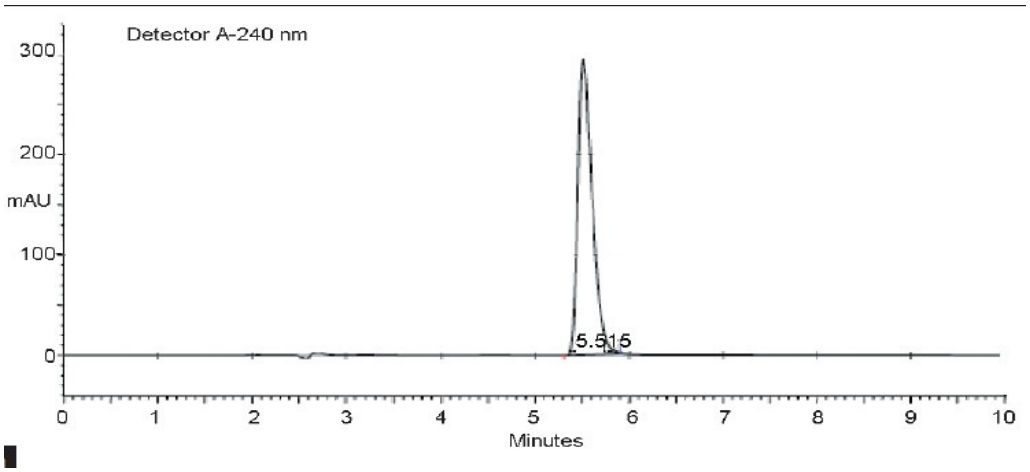

Figure 3: Standard peak table information@E/data/2020/february/aripiprazole 1.5.14

Table 8: PD A multi 240 nm

Peak	Name	Ret. Time	Theoretical plates	Tailing factor
1	Aripiprazole	5.151	3000	1.12

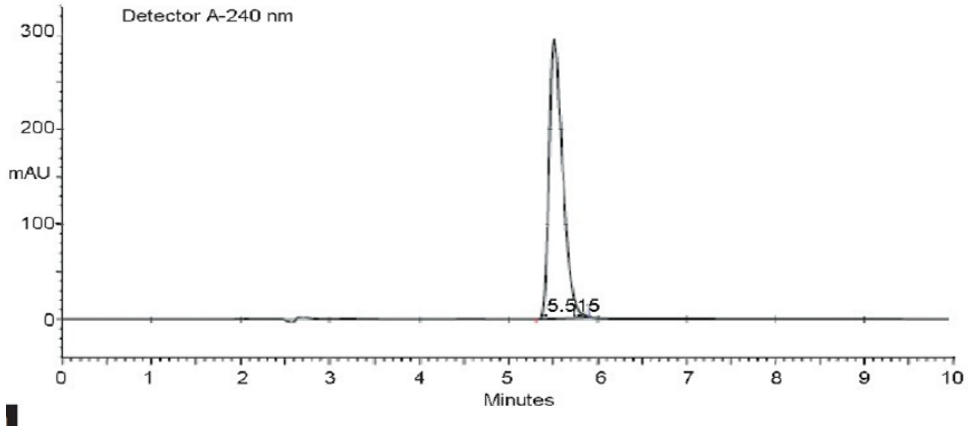

Figure 4: Sample peak table information @E/data/2020/february/Aripiprazole 1.5.14

Table 9: PD A multi 240nm

Peak	Name	Retention Time	Area	Area
1	Aripiprazole	5.151	8877654	100%
Total	-	-	8877654	-

Table 10: 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

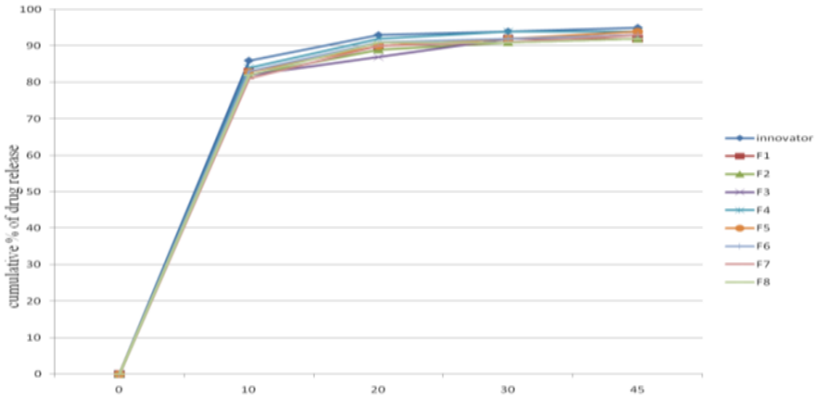

Figure 5: Dissolution profile of Innovator, F1-F8 batches

Table 9: Summary of Accelerated Stability Studies

Sr. 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 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 was done [Table 2, 3 and 4]. The drug and excipient blends were subjected to compatibility studies [Table 5]. From the FT-IR reports, it was found that there was no incompatibility [Figure 1 and 2]. Physical compatibility is also tested by subjecting the blend to various storage conditions and it was found that the blend was 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. It is concluded that F4 is better and similar to innovator product. Because other formulations have low drug release profile on dissolution compared to innovator product [Figure 5]. The F4 formulation has been subjected to stability studies according to ICH guidelines. This formulation is found to be stable for 2 months.

Conclusions

The present study concluded that aripiprazole 10 mg tablets can be formulated and developed by using direct compression technique. In order to obtain best optimized product, 8 different formulations were developed. Different physical properties of developed formulations were comparable with the reference product. But higher percentage of drug release was observed when the formulation contained starch (potato extract) as compared with formulations contained starch and PVA. The formulation F4 has shown drug release NLT 94 % in 45 min in accordance with the USP dissolution criteria for IR aripiprazole tablet formulation. The obtained results suggested that formulation with corn starch showed similar dissolution profile with innovator drug.

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