Research Article

Formulation Development and *In vitro* Dissolution Comparison of Aripiprazole IR Tablets with Innovator Product

Priyanka S. Arora*[1], Sanjay Shivnarayan Toshniwal[2]
*[1]Research Scholar, Department of Pharmacy, JJT University, Jhunjhunu, Rajasthan, India.
[2]Vidarbha Institute of Pharmacy, Washim (M.S.), India.
***Corresponding author's E-mail:** mepriya42@yahoo.co.in

Accepted on: 10-03-2014; **Finalized on:** 31-03-2014.

ABSTRACT

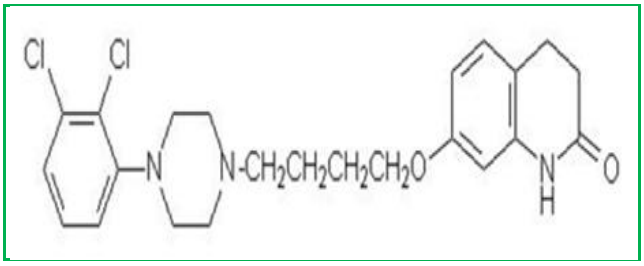
The main aim of the present study was to compare the differences in dissolution behavior of solid dosage forms between innovators (reference products) and their generic counterparts (tested products). Aripiprazole formulations were made with different concentration of binder (HPC, Corn starch) and without binder. Dissolution was carried out by pH 1.2 (hydro chloric acid) using USP-II apparatus. 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%. Aripiprazole immediate releases (IR) tablet without using binder was developed and the dissolution profile was same with innovator.

Keywords: Aripiprazole, Corn starch, Dissolution, Hydroxy propyl cellulose LH-21, USP-II Apparatus.

INTRODUCTION

Aripiprazole is a poorly soluble, poorly permeable Biopharmaceutics Classification System (BCS) Class IV compound. Aripiprazole has a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.[1]

Abilify (aripiprazole)[2] developed by Otsuka Pharmaceuticals, is an atypical antipsychotic that acts as a partial agonist at the dopamine (D2) receptors and an antagonist to the serotonin (5-HT2A) receptors. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical structure is:



The drug is available as a tablet, an orally disintegrating tablet (Abilify Discmelt), a non-refrigerated oral solution, and an intramuscular (IM) injection. ABILIFY Tablets are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths. Inactive ingredients include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake. With a slightly different mechanism of action some of the side effects experienced by the atypical antipsychotics – such as weight gain, QTc prolongation issues, and sedation – are exhibited to a lesser extent with Abilify.[2,3]

The above objective can be achieved by preparing an aripiprazole composition without using any binder, such composition when evaluated exhibit improved dissolution properties. Moreover, such composition also exhibit in vitro drug release profile that is equivalent to marketed aripiprazole formulation (Abilify®).[5, 6]

MATERIALS AND METHODS

Materials

Aripiprazole (Wockhardt Research Centre, Aurangabad). All reagents and chemicals were of analytical grade.

Method of preparation[7, 8]

Formulation optimization

Formulation development focused on evaluation of the high risk formulation variables as identified in the initial risk assessment. The development was conducted in two stages.

Procedure

- Co-sift aripiprazole and Lactose monohydrate (pharmatose 200M) in geometric proportions through #40 mesh. Co-sift Avicel PH 101 & HPC LH 21 through #40 mesh separately. FD&C Blue #2 Al lake & corn starch (unipure FL) are sifted through #120 mesh separately. All the three mixtures are sifted together through #40 mesh.
- Purified water is used as binder solution
- Step 1 materials were placed in 2 lit RMG and granulated with purified water
- Dry wet mass in FBD at 60±5°C for 45 minutes. Loss on Drying (LOD) was 1.36% at 105°C for 5 minutes in IR moisture analyzer.
- Sift dried granules through #20 mesh.

- Dried granules & Avicel PH112 (#40 mesh) were mixed in Double Cone Blender for 5 min at 24rpm.
- Lubricate the step 6 material with Magnesium stearate (Hyqual) (#40 mesh) in Double Cone Blender for 3 minutes at 24 rpm.
- The lubricated blend is taken for compression using 8.1x4.6mm, pillow shape (modified rectangular) punches with W on one side & 706 other side. The procedure has been same for the all formulations with binder and devoid of binder.

Stage	Binder addition	Time (Sec)	Impeller	Chopper
Dry mix	---	300	150	off
Binder addition	141 mL	63	150	off
Kneading 1	---	120	150	off

Formulation 1 and 2

Aripiprazole tablet compositions were disclosed in Table 1 containing hydroxy propyl Cellulose as binder.

The dissolution characteristics of the prepared formulations 1 and 2 in 900 ml of pH 1.2 USP buffer (hydrochloric acid) using USP apparatus II are mentioned in Table 5.

Formulation 3, 4 and 5

Aripiprazole tablet compositions were disclosed in Table 2 containing corn starch as binder.

The dissolution characteristics of the prepared formulations 3, 4 and 5 in 900 ml of pH 1.2 USP buffer (hydrochloric acid) using USP apparatus II are mentioned as below table 6.

Formulation 6 and 7

Aripiprazole tablet compositions were disclosed in Table 3 containing hydroxy propyl cellulose as binder.

The dissolution characteristics of the prepared formulations as per example 6 and 7 in 900 ml of pH 1.2 USP buffer (hydrochloric acid) using USP apparatus II are mentioned in table 7.

Formulation 8

Aripiprazole tablet composition was made devoid of binder.

The dissolution characteristics of the prepared formulation as per example 8 in 900 ml of pH 1.2 USP buffer (hydrochloric acid) using USP apparatus II is mentioned in table 8.

RESULTS AND DISCUSSION

The tablets were prepared using hydroxy propyl cellulose as binder with concentrations and dissolution was carried out using pH 1.2 buffer and USP apparatus II. The release of drug was found to be 85% at 45 min.

Table 1: Optimized formula using Hydroxy propyl cellulose

Ingredients	F1 % w/w	F2 % w/w
Intragranular		
Aripiprazole	10	10
Lactose monohydrate	62.18	62.18
Microcrystalline cellulose	7.05	6.05
Corn starch	8.00	9.00
L-HPC	5.00	5.00
Red iron oxide	0.02	0.02
Binder		
Hydroxy propyl cellulose	2.00	1.00
Water	q.s.	q.s.
Extragranular		
Microcrystalline cellulose	5.00	5.00
Magnesium stearate	0.75	0.75

Table 2: Optimized formula using Corn starch

Ingredients	F3 % w/w	F4 % w/w	F5 % w/w
Intragranular			
Aripiprazole	15	15	15
Lactose monohydrate	57.10	57.10	55.25
Microcrystalline cellulose	7.05	7.05	7.05
Corn starch	9.00	9.75	9.75
L-HPC	5.00	5.00	5.00
Yellow iron oxide	0.10	0.20	0.20
Binder			
Corn starch	**1.00**	**0.25**	**2.00**
Water	q.s.	q.s.	q.s.
Extragranular			
Microcrystalline cellulose	5.00	5.00	5.00
Magnesium stearate	0.75	0.75	0.75

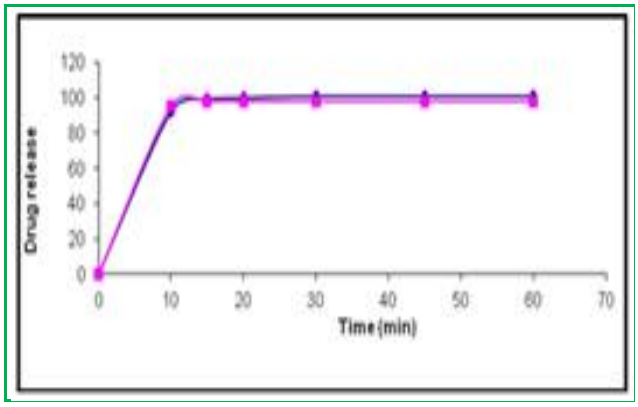


Figure 1: Comparison of without Binder and abilify

Table 3: Optimized formula using Hydroxy propyl cellulose

Ingredients	F6 % w/w	F7 % w/w
Intragranular		
Aripiprazole	10	10
Lactose monohydrate	59.98	59.98
Microcrystalline cellulose	-	10.00
Corn starch	7.75	7.75
Red iron oxide	0.02	0.02
Binder		
Hydroxy propyl cellulose	**1.5**	**1.5**
Water	q.s.	q.s.
Extragranular		
Microcrystalline cellulose	10.00	-
Corn starch	10.00	10.00
Magnesium stearate	0.75	0.75

Table 4: Optimized formula without using binder

Ingredients	% w/w
Aripiprazole	10.00
Lactose monohydrate	62.18
Microcrystalline cellulose	7.05
Corn starch	10.00
L-Hydroxypropyl cellulose	5.00
Iron Oxide Red	0.02
Purified water	q.s.
Microcrystalline cellulose	5.00
Magnesium stearate	0.75

Table 5: % Drug release with Hydroxy propyl cellulose

Time points	F1	F2
15	82	81
30	83	83
45	85	85

Table 6: % drug release with corn starch as binder

Time points	F3	F4	F5
15	78	85	90
30	80	86	91
45	81	85	92

Table 7: % Drug release with Hydroxy propyl cellulose

Time points	F 6	F7
15	73	81
30	80	85
45	83	85

Table 8: Comparison study of % drug release

Time (min)	Innovator Abilify®	Wockhardt PS (100)-49-177A
10	92	95
15	99	98
20	100	98
30	101	98
45	101	98
60	101	98

The tablets were prepared using corn starch as binder with concentrations and dissolution was carried out using pH 1.2 buffer and USP apparatus II. The release of drug was found to be 81 with 0.5%corn starch, 85 with 1.5% of corn starch and 92%release with 2% corn starch at 45 min was observed.

Formulation made without binder and the release studies carried out same like with above and release of drug was same was observed with innovator drug.

Drug release of both the drugs innovator abilify and wockhardt was compared the release was same with innovator 98% drug release without binder was observed. The release comparison was showed in Fig 4.

CONCLUSION

Aripiprazole immediate releases (IR) tablet without using binder was developed and the dissolution profile was same with innovator.

Acknowledgment: This work was supported by and conducted at Wockhardt Research Centre. Authors thank Dr. Yatendra Kumar and Dr. Mandar Kodgule for their guidance, contribution, and timely help in concluding the work.

REFERENCES

1. USFDA approved label of ABILIFY: Accessed on 8, Feb. 2013, form http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21436_Abilify_lbl.pdf
2. Alyssia Klein, Schizophrenia epidemiology: Data monitor Healthcare, Mar 25, 2011.
3. Frances R Frankenburg, Schizophrenia, Retrieved on February 8, 2013, from http://emedicine.medscape.com/article/288259-overview#aw2aab6b2b3.
4. Selten JP, Cantor-Graae E, Kahn RS, Migration and schizophrenia, Curr Opin Psychiatry, 20(2), 2007, 111-115.
5. Bourque F, van der Ven E, Malla A, A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants, Psychol Med, May 2011; 41(5):897-910.
6. Kirkbride J, Coid JW, Morgan C, Translating the epidemiology of psychosis into public mental health:

evidence, challenges and future prospects, J Public Ment Health, 9(2), Jun 2010, 4-14.

7. Mihajlovic T, Kachrimanis K, Graovac A, Djuric Z, Ibric S, Improvement of Aripiprazole solubility by complexation with (2-hydroxy)propyl-β-cyclodextrin using spray drying technique, AAPS Pharmaceutical Science and Technology, 13(2), Jun 2012, 623-631.

8. Ayman EK, Oral Absorption, Intestinal Metabolism and Human Oral Bioavailability. Accessed on Feb. 8, 2013 from http://www.intechopen.com/books/topics-on-drug-metabolism/oral-absorption-intestinal-metabolism-and-human-oral-bioavailability.

Source of Support: Nil, **Conflict of Interest:** None.