ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

EFFECT OF NATURAL AND SYNTHETIC SUPER DISINTEGRANTS USED IN THE DEVELOPMENT OF ARIPIPRAZOLE FAST DISSOLVING TABLETS

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ARTICLE INFO

Key words:
Fast dissolving tablets, Aripiprazole, Super disintegrants, Direct compression, disintegration, dissolution and wetting time.

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Aripiprazole is a atypical antipsychotic medication used for treatment of schizophrenia. It has also recently received FDA approval for the treatment of acute manic and mixed episodes associated with bipolar disorder. Fast dissolving tablets [FDTS] are novel types of tablets that dissolve/disintegrate/disperse in saliva within few seconds without water. The demand of fast dissolving tablets has been growing especially for pediatric and geriatric patients because of swallowing difficulties. The objective of present study is to formulate and evaluate fast dissolving tablets of Aripiprazole employing two [natural and synthetic] super disintegrants namely Hibiscus rosa sinensis [natural] and Croscarmellose sodium [synthetic]. The FDTs were prepared by direct compression method and were evaluated for drug content, hardness, friability, disintegration time, wetting time, moisture absorption and dissolution rate. Aripiprazole FDTs prepared employing hibiscus rosa sinensis mucilage and croscarmellose sodium disintegrated rapidly within 21 – 28 sec at 5% concentration. The wetting time of these FDTs were in the range of 5 sec in case of hibiscus rosa sinensis mucilage at 5% conc. and 8 sec in case of croscarmellose sodium at 5% conc. Among the two super disintegrants tested, hibiscus rosa sinensis gave rapid disintegration and dissolution of the FDTs prepared. The increasing order of dissolution rate [K_1] observed with the hibiscus rosa sinensis mucilage compared to croscarmellose sodium. Aripiprazole FDTs formulated employing hibiscus rosa sinensis mucilage and croscarmellose sodium gave rapid dissolution, fulfilling the corresponding official dissolution rate test specification prescribed in pharmacopoeias. The natural super disintegrant i.e., hibiscus rosa sinensis at 5% concentration gave better dissolution compared to croscarmellose sodium at 5% concentration. **Novelty of the work:** Fast Dissolving Tablets of Aripiprazole were prepared by employing different concentrations [2,4,5%] of Hibiscus rosa sinensis and Croscarmellose sodium as super disintegrants.A total of 6 formulations were prepared i.e., 3 in each case.

INTRODUCTION

Oral route is the most preferred route for administration of various drugs because it is regarded as the safest, most convenient and economical route. Fast Dissolving Tablets [FDTs] are novel types of tablets that dissolve/disintegrate/disperse in saliva within few seconds without water. Fast dissolving drug delivery systems [FDDDS] are a new generation of formulations which Combine the advantages of both liquid and conventional tablet formulations and at the same time, offer added advantages over the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. Currently these tablets are available in the market for treating many disease conditions like hypertension,

migraine, dysphasia, nausea, vomiting, parkinson's disease, schizophrenia and pediatric emergency.

Advantages of FDTs:

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who cannot swallow and who refuse to swallow such as pediatrics, geriatrics and psychiatric patients.
- Patient's compliance for disabled, bedridden patients and for travelling people who donot have ready access to water.
- Good mouth feel property of FDTs helps to change the basic view of medication as 'bitter pill', particularly for pediatric patients due to improved taste of bitter drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pre-gastric area i.e., mouth, pharynx and oesophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.

In the present study,FDTs of Aripiprazole were prepared using different concentrations of natural and synthetic super disintegrants [2,4,5% concentrations].

MATERIALS AND METHODS

Chemicals required for the formulation include

Aripiprazole, Croscarmellose sodium, PVP K-30, Talc, Magnesium stearate, Mannitol, Spray dried Microcrystalline cellulose, Aerosil, Sodium saccharin, Lemon flavor.

Estimation of Aripiprazole

A U.V Spectrophotometric method based on the measurement of absorbance at 249nm in methanol was used for estimation of Aripiprazole. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration of 2-10µg/ml. Low RSD values ensured reproducibility of the method. When the standard solution was repeatedly assayed, the Regression value was found to be 0.9999.

Preparation of Hibiscus rosa sinensis mucilage: The fresh leaves of Hibiscus rosa sinensis Linn were collected, washed with water to remove the dirt and debris. Washed leaves were dried and powdered. The powdered leaves were soaked in water for 5-6 hours, boiled for 30 min, and kept aside for 1 hour for complete release of the mucilage into water. The material was squeezed from an eight fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in an oven at a temperature of >50°C, collected, dried, powdered and passed through sieve 80 and stored for use in dessicator.

Precompression studies of blends:

Angle of Repose: Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula,

θ = Tan-1(h / r)

Where, θ = angle of repose, r=radius of the pile, h=height of the pile

Bulk density: Bulk density is defined as mass of the powder divided by the bulk volume. Apparent bulk density (*b) was determined by pouring the blend in to graduated cylinder. The bulk volume (V*) and the weight of the powder (M) was determined. The bulk density was calculated using the formula: *b =M/V*

Tapped density: The measuring cylinder containing a known mass of blend was tapped for a fixed time (100tappings). The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula

*t =M/Vt

Carr's index: Carr's index = (Tapped density - Bulk density)/Tapped density × 100.

The compressibility index (CI) and the Hausner's ratios (HR) were determined from the bulk and tapped densities according to the relationships.

Hausner's ratio: It is the ratio of tapped density to bulk density. This is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner's ratio = *t/*d

*t =Tapped density *d=Bulk density.

Preparation of Aripiprazole FDTs: Fast dissolving tablets of Aripiprazole were prepared by direct compression method, employing various superdisintegrants as per the formulae. All the materials were passed through sieve (# 60) separately to ensure better mixing. Superdisintegrants were used separately in different proportions as shown in Table:1.All the ingredients were weighed and mixed in geometrical order and the blends were transferred into a closed polyethylene bag. The blends were compressed into 150 mg tablets using RIMEK tablet punching machine employing 9mm flat punches compressed in to tablets of 150 mg.

Evaluation of Fast Dissolving Tablets prepared

Uniformity of Weight: The weights were determined by using Shimadzu balance (Model ATY 224).Weight control is based on a sample of 20 tablets.

Tablet Hardness: The hardness of prepared tablets were determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Tablet Friability:

The friability of the tablets were measured in a Roche friabilator using the formula

Friability = [(Initial weight- Final weight) / (Initial weight)] x 100%

Drug Content of Aripiprazole FDTs:

Weighed tablets (5) were powdered using a mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of Aripiprazole was taken into 100 ml volumetric flask, dissolved in methanol and the solution was filtered through whatman filter paper no.41. The filtrate was collected and suitably diluted with methanol. The drug content was determined at 219nm.

Disintegration test: Disintegration time of the tablets was determined using single unit disintegration test apparatus employing water as test fluid.

Wetting Time: The wetting time of the tablets was measured as follows. Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. 10 ml of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water Absorption Ratio: A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

$R = 100 \times (Wa - Wb)/Wa$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption.

Dissolution Rate Study on Aripiprazole FDTs: Dissolution rate of aripiprazole tablets prepared was studied in 0.1 N HCl (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DISSO 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a pipette at different time intervals and assayed for aripiprazole at 249 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made forthe amount of drug present in the samples withdrawn. Each dissolution experiment is run in triplicate (n=3).

RESULTS AND DISCUSSION

Table:1 Formulae for Fast Dissolving Tablets of Aripiprazole

Ingredient (mg / tablet)	Formulation					
	AF1	AF2	AF3	AF4	AF5	AF6
Aripiprazole	10	10	10	10	10	10
Hibiscus rosa sinensis mucilage	3	6	7.5	-	-	-
Croscarmellose sodium	-	-	-	3	6	7.5
PVP K-30	4	4	4	4	4	4
Spray dried microcrystalline cellulose	20	20	20	20	20	20
Mannitol	105	102	100.5	105	102	100.5
Talc	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2
Sodium saccharin	1	1	1	1	1	1
Lemon flavour	1	1	1	1	1	1
Total weight	150	150	150	150	150	150

Table: 2 Pre compression parameters of blends of Aripiprazole

Parameters	Formulation Batches					
	AF1	AF2	AF3	AF4	AF5	AF6
Angle of repose	26.56	29.24	27.92	28.5	20.21	23.45
Bulk density (g/ml)	0.317	0.357	0.436	0.385	0.362	0.350
Tapped density(g/ml)	0.54	0.491	0.65	0.491	0.481	0.491
Carr's index	41.2	27.3	32.9	28.71	24.74	28.71
Hausner's ratio	1.19	1.24	1.20	1.24	1.26	1.24

Table:3 Physical parameters of Fast Dissolving Tablets of Aripiprazole prepared

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration time (min-sec)	Drug content (mg/tablet)	Wetting time (Sec)	Water absorption ratio (%)
AF1	3.5	0.40	1 -30	97.25	30	50.94
AF2	3.5	0.45	1-12	99.25	15	53.70
AF3	3.0	0.34	0-21	100.4	5	96.64
AF4	3.5	0.48	1- 20	97.70	40	46.13
AF5	3.5	0.34	1-15	98.42	30	63.08
AF6	3.5	0.68	0-28	99.89	8	74.97

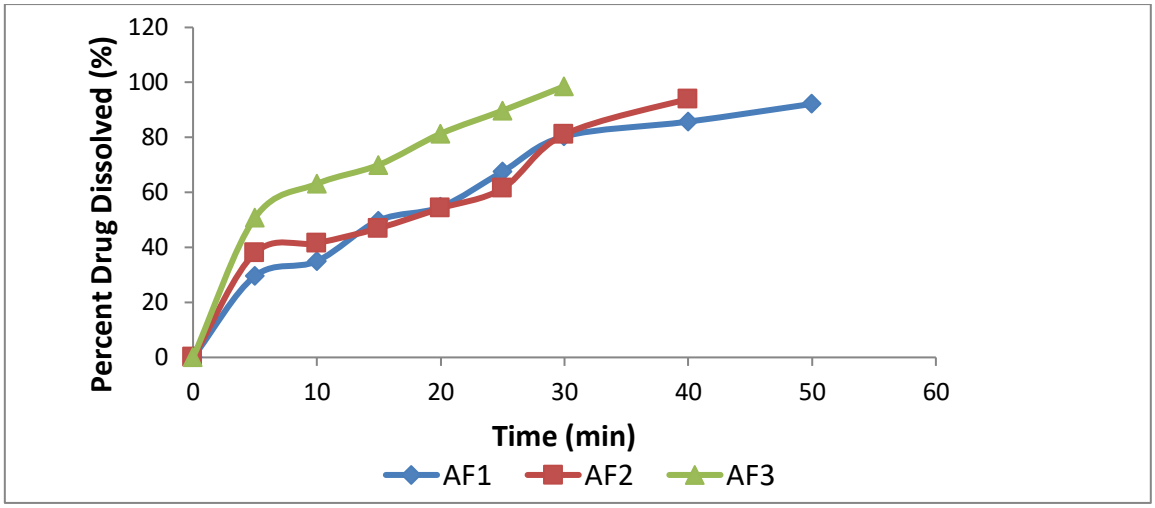

Fig:1 Dissolution Profiles of Aripiprazole Fast Dissolving Tablets prepared employing Hibiscus rosa sinensis mucilage as a super disintegrant [2,4,5%]

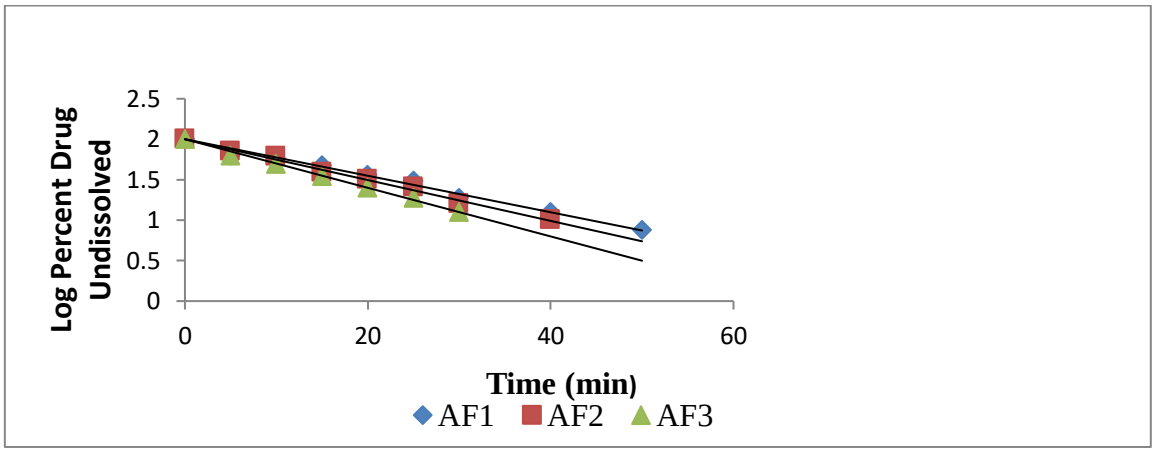

Fig:2 First order Dissolution plots of Aripiprazole Fast Dissolving Tablets prepared employing Hibiscus rosa sinensis as a super disintegrant [2,4,5%]

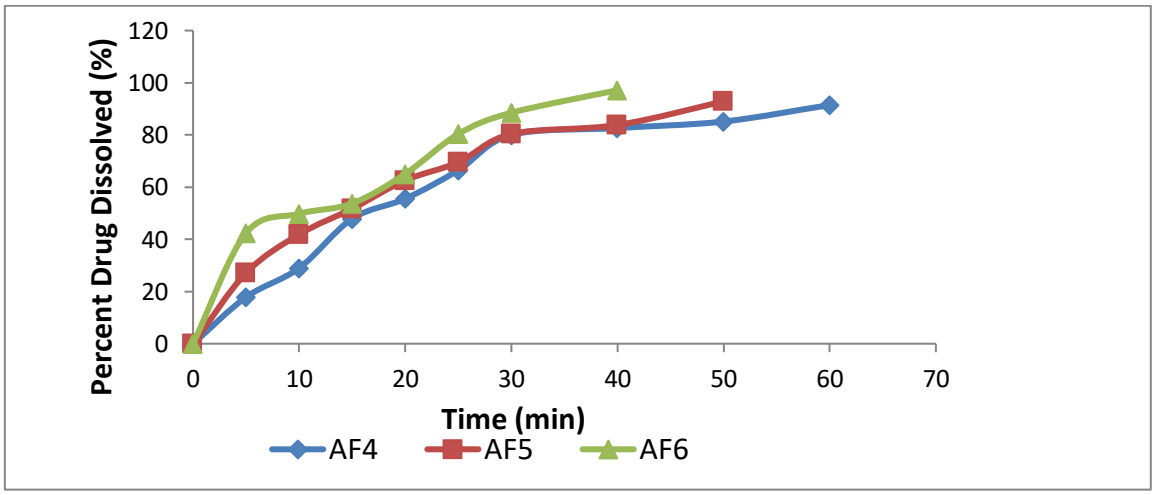

Fig:3 Dissolution profiles of Aripiprazole Fast Dissolving Tablets prepared employing Croscarmellose sodium as super disintegrant [2,4,5%]

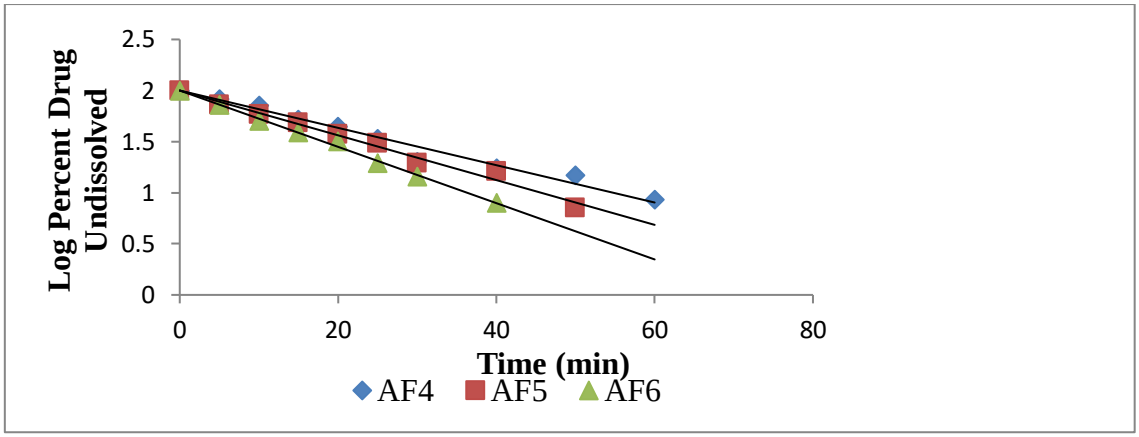

Fig:4 First order Dissolution plots of Aripiprazole Fast Dissolving Tablets prepared employing Croscarmellose sodium as a super disintegrant [2,4,5%]

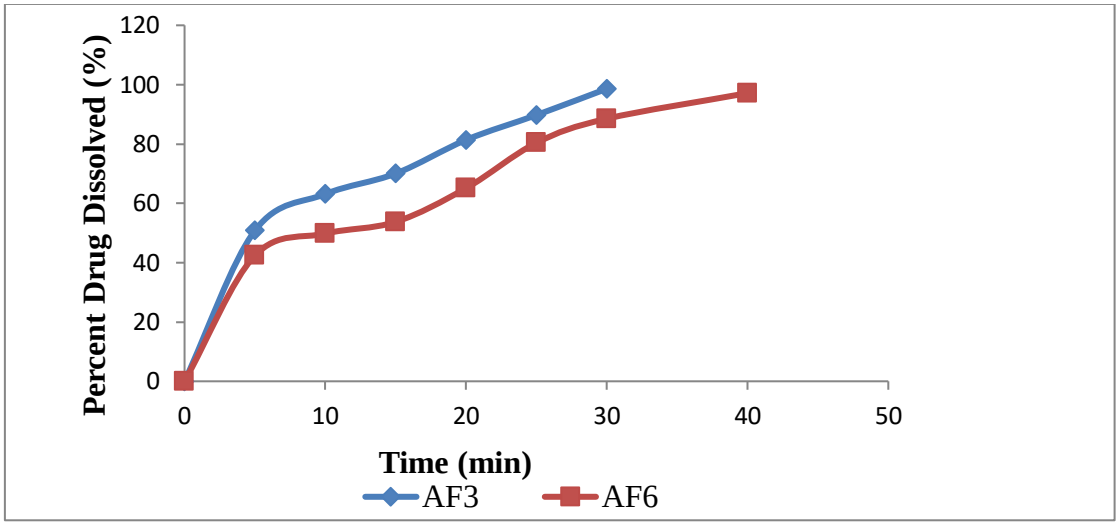

Fig:5 Dissolution profiles of Aripiprazole Fast Dissolving Tablets prepared employing Hibiscus rosa sinensis mucilage and Croscarmellose sodium as a super disintegrant at 5% concentration

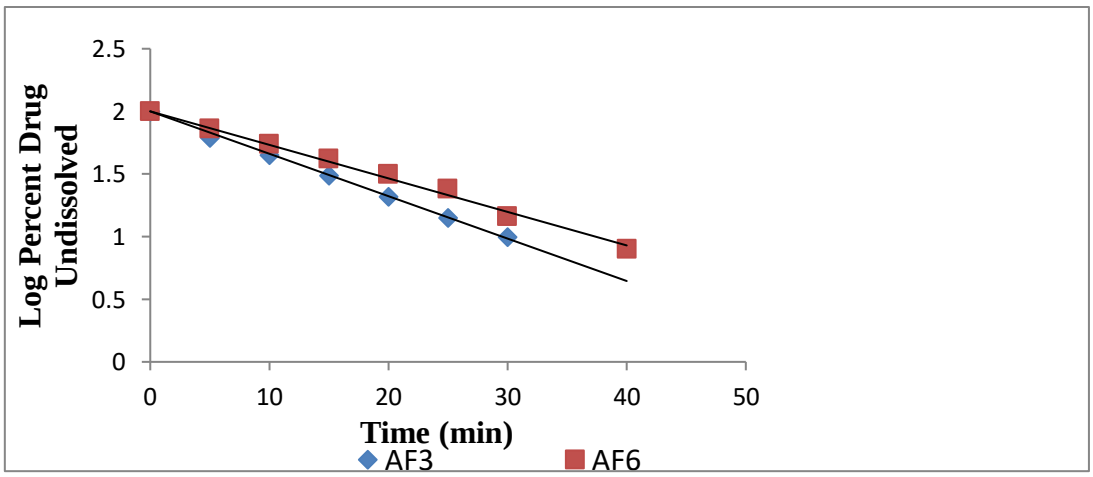

Fig:6 First order Dissolution plots of Aripiprazole Fast Dissolution Tablets prepared employing Hibiscus rosa sinensis and Croscarmellose sodium as a super disintegrant at 5% concentration

Table:4 Dissolution parameters of prepared Aripiprazole Fast Dissolving Tablets

Formulation	P_{30} (min)	T_{50} (min)	DE_{30} (%)	Dissolution rate K_1 (min^{-1})	Official dissolution rate specification
AF1	80.39	16	54.76	0.0506	NLT 80 % of stated amount in 30 min (USP)
AF2	81.14	15	55.34	0.0557	
AF3	98.61	5	67.38	0.0921	
AF4	80.02	18	42.54	0.0485	
AF5	80.37	16	49.31	0.0514	
AF6	89.74	11	64.28	0.0875	

DISCUSSION

Aripiprazole FDTs were formulated employing two superdisintegrants namely Natural superdisintegrant-Hibiscus rosa sinensis mucilage and Synthetic superdisintegrant- Croscarmellose sodium. In each case three different concentrations of superdisintegrant (2, 4, 5%) were used. The prepared blends were studied for precompression parameters and the angle of repose of the powder blend of Aripiprazole was in the range of 23.45 to 29.24 showing that the powder blend was free flowing and can be used for direct compression. Bulk density was between 0.317 to 0.436 g/cm3 and Tapped density was between 0.481 and 0.650 g/cm3. Hausner's ratio was between 1.19 and 1.26 Cars index was between 27.3 and 41.2%. All the formulations showed good blend properties for direct compression and hence tablets were prepared by direct compression technology. The tablets were prepared by direct compression method as per the formulae given in Table 1 and evaluated for various physical parameters and dissolution rate. The physical parameters of the Aripiprazole FDTs prepared are given in Table 3. The hardness of the tablets was in the range 3.0-3.5 kg/cm^2. Percent weight loss in the friability test was less than 0.70 % in all the cases. Drug content of the tablets prepared was within 100±3 % of the labelled claim. All the FDTs prepared disintegrated within 1 min 30 sec. Among the two Super Disintegrates tested Hibiscus rosa sinensis mucilage gave rapid disintegration of the tablets.

CONCLUSIONS

The objective of the present study is to formulate and evaluate fast dissolving tablets (FDTs) of Aripiprazole employing superdisintegrants. Direct compression technique was tried for the preparation of FDTs of Aripiprazole. Two superdisintegrants namely i) Hibiscus rosa sinensis mucilage and ii) Croscarmellose sodium were employed for formulation of fast dissolving tablets. In each case three concentrations of superdisintegrant (2, 4 and 5 %) were used in the formulation of fast dissolving tablets. All the fast dissolving tablets prepared were evaluated for drug content, hardness, friability, disintegration time, wetting time, moisture absorption and dissolution rate.

From the results obtained the following conclusions are drawn.

1. All the FDTs prepared disintegrated within 1 min 30 sec.
2. Among the two superdisintegrants tested, Hibiscus rosa sinensis mucilage gave rapid disintegration of the tablets.
3. FDTs formulated employing 5% Hibiscus rosa sinensis (AF3) and 5 % Croscarmellose sodium (AF6) disintegrated within 21 and 28 sec and the wetting time of these tablets was 5

and 8 sec respectively. Water absorption ratio (%) of these tablets was 96.64 % and 74.97 respectively.

4. All the FDTs prepared gave rapid dissolution of Aripiprazole. Compared to all Concentrations of super disintegrants (2,4 and 5 %), 5 % concentration in case of both Hibiscus rosa sinensis mucilage (98% in 30 min) and Croscarmellose sodium (97% in 40 min) gave rapid dissolution. In comparison to 5% Croscarmellose sodium, Hibiscus rosasinensismucilage at 5 % concentration gave rapid dissolution. The dissolution rate of Aripiprazole was increased as the concentration of superdisintegrant was increased in each case.

5. At 5 % concentration the increasing order of dissolution rate (K_1) observed with two super disintegrants was Hibiscus rosa sinensis mucilage (AF3) > Croscarmellose sodium (AF6).

6. FDTs formulated employing Hibiscus rosa sinensis mucilage and Croscarmellose sodium 5 % concentration gave more than 90 % dissolution in 30 min fulfilling the official dissolution rate specification of Aripiprazole tablets.

7. FDTs formulated using 5% Hibiscus rosa sinensis mucilage (AF 3) and 5 % Croscarmellose sodium (AF 6) gave rapid and higher dissolution of Aripiprazole.

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