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

FORMULATION AND *IN VITRO* EVALUATION OF ORAL DISINTEGRATING TABLETS OF ARIPIPRAZOLE

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ARTICLE INFO

Key words:

Aripiprazole, oral disintegrating tablets, anti-psychotic drug, preformulation

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

ABSTRACT

Orally Disintegrating Tablets (ODTs) have the unique property of disintegrating in the mouth in seconds without chewing and the need of water which is advantageous mainly for paediatric, geriatrics, mentally challenged, bed ridden, uncooperative patients and patients having difficulty in swallowing tablets. The present study was carried out for enhancement of dissolution rate of aripiprazole fast dissolving tablets using super disintegrants commonly used as an atypical anti-psychotic drug. The prepared formulations were evaluated for pre and post compression studies. All formulations were found to be within limits. *In vitro* drug released studies revealed that, formulations prepared with HPMC 6cps showed good in concentration of 8 mg at 30 min. Formulations prepared with Croscarmellose sodium showed good drug release in the concentration of 8 mg at 15 min. Among 8 formulations F8 was considered as optimized formulation. Optimized formulation compared with F9 formulations which contain combination of super disintegrants. F9 formulation was showed maximum drug release at 20 min. Among those all formulations F8 was shown maximum drug release at 15 min i.e., 98.26%. It was considered as optimized formulation. It can be concluded that solid dispersions of aripiprazole incorporated in oral disintegrating tablets are a very useful approach for better release of aripiprazole in an efficient manner.

INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water [1]. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people [2]. An oral disintegrating tablet (ODT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT [3, 4]. US FDA defined ODT tablets as "a solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the

tongue". The US Food and Drug Administration Guidance for orally disintegrating tablets are: i) ODTs should have an *in vitro* disintegration time of approximately 30 sec or less, ii) Generally, the ODT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both patients and regulators [5-7]. Aripiprazole is an atypical anti-psychotic drug, that has serotonin 5-HT1A receptor partial agonist and 5-HT2A receptor antagonist properties as well as being a partial agonist at dopamine-D_2 receptors. The fundamental principle used in the development of the orally disintegrating tablets is to maximize its pore structure [8,9]. The aim of the present research was to enhancement of dissolution rate of aripiprazole fast dissolving tablets using super disintegrants.

MATERIALS AND METHODS

Chemicals: Aripiprazole API was procured from Sura Labs, Hyderabad, Telangana. Croscarmellose sodium, HPMC 6cps, magnesium stearate, micro crystalline cellulose, talc are purchased from Merck Specialities Pvt. Ltd., Mumbai, India.

Analytical determination:

Determination of absorption maxima by UV:

10 mg of aripiprazole was dissolved in 10 ml of methanol (primary stock). From this primary stock solution 1 ml was taken in a 10 ml volumetric flask and volume made up to 10 ml with pH 6.8 phosphate buffer (100µg/ml – secondary stock). From secondary stock solution 1 ml was taken and volume made up to 10 ml with pH 6.8 phosphate buffer (10µg/ml). Final concentration was taken for determining the wavelength of drug by UV [10].

Preparation of standard calibration curve of aripiprazole:

10 mg of aripiprazole was dissolved in 10 ml of methanol (primary stock). From this primary stock solution 1 ml was taken in a 10 ml volumetric flask and volume made up to 10 ml with pH 6.8 phosphate buffer (100µg/ml – secondary stock). From this secondary stock solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml was taken and diluted up to 10 ml with pH 6.8 phosphate buffer to get the concentrations as 5, 10, 15, 20 and 25µg/ml respectively. After preparing these concentrations were taken for UV-Spectrophotometric study at respective wavelength by keeping pH 6.8 phosphate buffer as blank [11,12].

Preparation of aripiprazole tablets by direct compression method [13-16]:

Drug, super disintegrant HPMC 6cps the amount (2, 4, 6, 8 mg) were weighed and permitted for blending for 5 min (F1, F2, F3, F4 respectively). Drug, super disintegrant croscarmellose sodium the amount (2, 4, 6, 8 mg) were weighed and permitted for blending for 5 min (F5, F6, F7, F8). The obtained blend was lubricated with magnesium stearate and glidant (talc) was added and blending was continued for further 5 min. The resultant mixture was directly compressed into tablets by using 6 mm round punch of rotary tableting machine. Compression force was kept constant for all formulations.

Drug content:

3 Tablets were randomly selected, weighed, finely powdered and quantity of powder equivalent to one tablet was added to 100 ml of pH 6.8 phosphate buffer in a conical flask. A conical flask was then placed on a rotary shaker. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using UV-Visible double beam spectrophotometer at a wavelength of 250 nm against pH 6.8 phosphate buffer as blank. Concentrations and amount of drug present in one tablet were calculated with the help of calibration curves.

Table 1: Formulation of aripiprazole oral dispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aripiprazole	10	10	10	10	10	10	10	10	10
HPMC 6cps	2	4	6	8	-	-	-	-	4
Croscarmellose sodium	-	-	-	-	2	4	6	8	4
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
MCC	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total	100	100	100	100	100	100	100	100	100

(All ingredients are expressed in mg only)

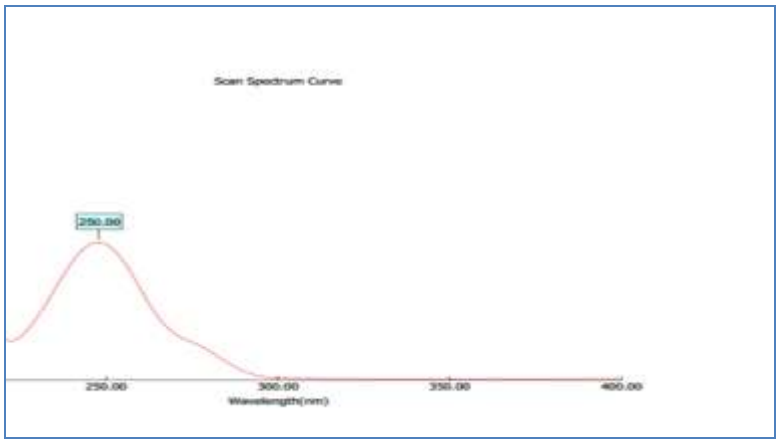

Figure 1: Spectroscopic determination of aripiprazole (absorbance maxima)

Table 2: Linearity of aripiprazole in pH 6.8 phosphate buffer at 250 nm

Conc. (µg/ml)	Absorbance
0	0.0
5	0.210
10	0.379
15	0.556
20	0.767
25	0.946

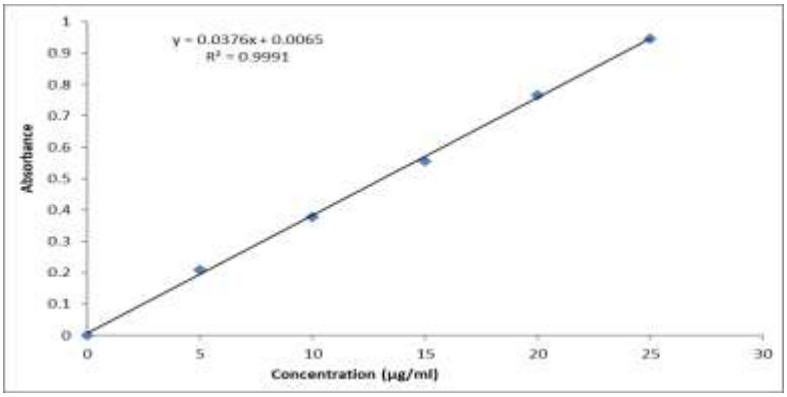

Figure 2: Standard graph of aripiprazole in pH 6.8 phosphate buffer

Drug-excipient compatibility studies:

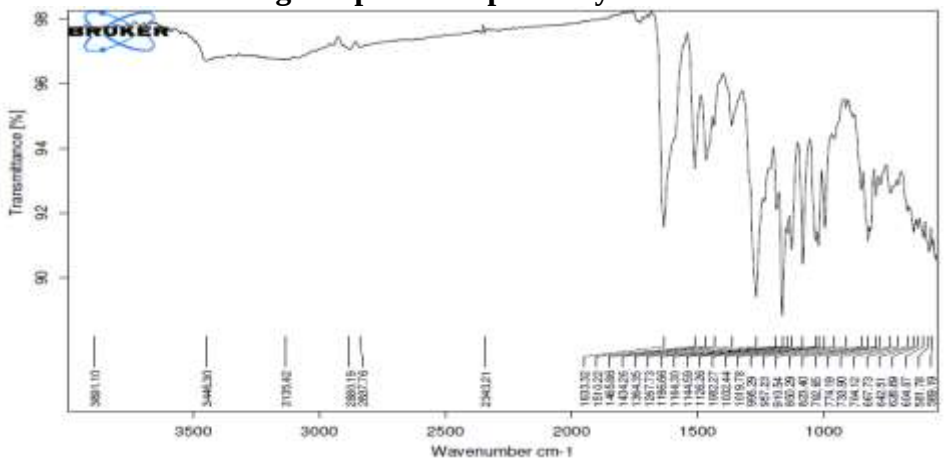

Figure 3: FT-IR Spectrum of aripiprazole API

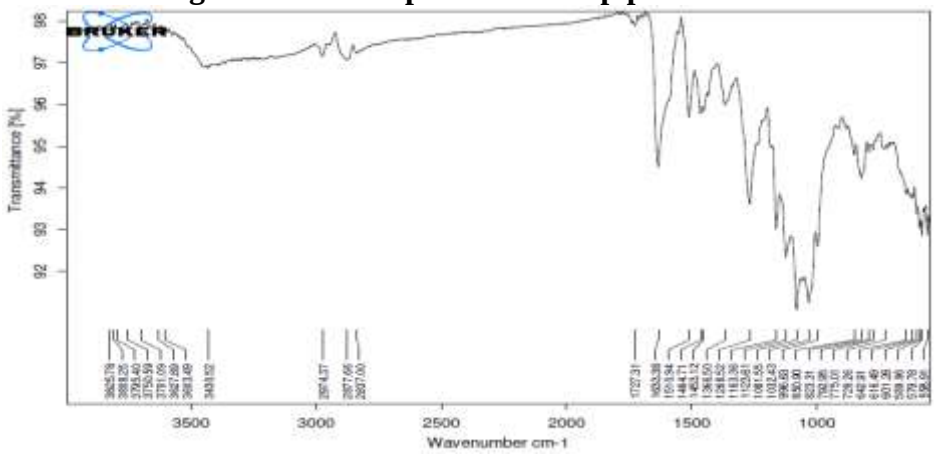

Figure 4: FT-IR spectrum of optimized formulation

Table 3: Interpretation

Functional group	Frequency of pure drug	Frequency of optimized drug
C-Cl	1019.78	999.63
C-O-C	1032.44	1032.43
C=C	1126.26	1123.61
C=O	1144.59	1163.36
C-H	1082.27	1081.55
N-H	1273.73	1268.52
C-N	1364.35	1366.50

From the above graph, it was showed no interactions between drug and excipients. Both API and excipients compatibility with each other.

DSC:

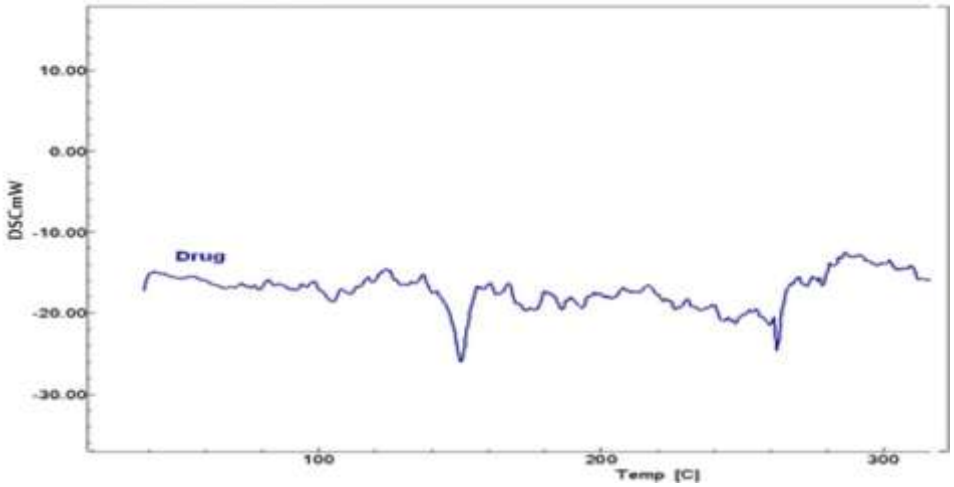

Figure 5: DSC of aripiprazole API

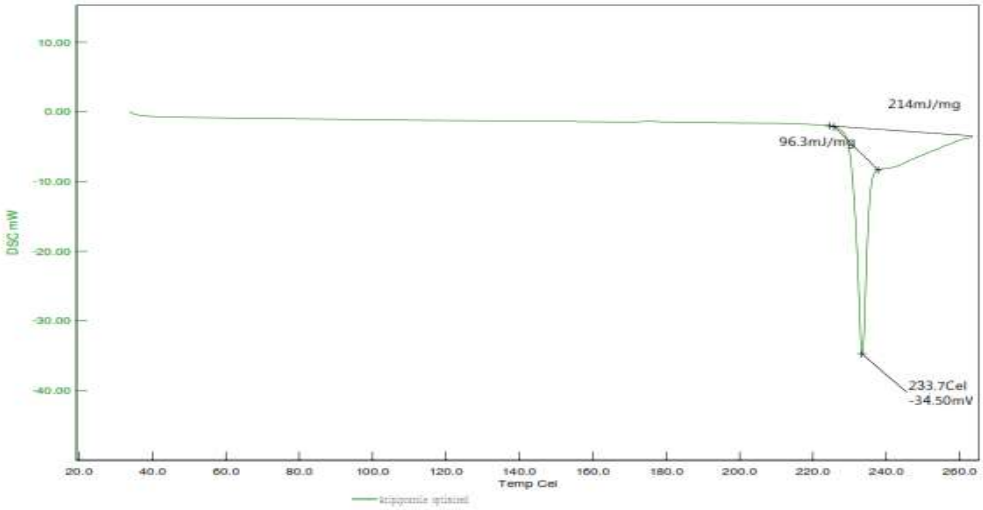

Figure 6: Evaluation of pre-compression parameters of powder blend

Table 4: Evaluation of pre-compression parameters of powder blend

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Angle of repose (θ)	Hausner's ratio
F1	0.46±0.06	0.53 ±0.02	13.20±0.05	26 ±0.08	1.15±0.07
F2	0.52±0.07	0.60±0.07	15.38 ±0.04	26±0.07	1.15±0.08
F3	0.49 ±0.06	0.56 ±0.07	12.50±0.06	28 ±0.06	1.14±0.06
F4	0.53±0.06	0.63±0.02	15.87±0.03	28±0.06	1.18±0.06
F5	0.46±0.08	0.55±0.03	16.36± 0.05	25 ±0.06	1.19±0.07
F6	0.58±0.04	0.65±0.02	10.76±0.07	26±0.12	1.12±0.04
F7	0.51±0.04	0.59 ±0.05	13.55±0.04	27 ±0.05	1.15±0.08
F8	0.48 ±0.05	0.56 ±0.06	14.28±0.06	25 ±0.02	1.16±0.08
F9	0.55 ±0.05	0.63 ±0.06	12.69±0.04	29±0.02	1.14±0.09

*(*Results are the mean of 3 observations ± SD)*

Evaluations of post-compression parameters of aripiprazole ODTS:

Table 5: Evaluation of post compression parameters of aripiprazole oral dispersible tablets

Formulation	Weight variation	Thickness (mm)	Hardness Kg/cm^2	% Friability	Drug content
F1	102.61 ±1.02	2.73 ±0.17	1.8±0.5	0.58 ±0.04	99.74±0.68
F2	100.96±1.46	2.69±0.16	1.73±0.8	0.66±0.05	99.76±0.53
F3	98.38±1.18	2.80±0.25	1.72±0.4	0.60±0.03	97.58±0.67
F4	99.19 ±1.35	2.60± 0.25	1.75±0.1	0.62±0.08	98.85 ±0.54
F5	101.35 ±1.12	2.61 ±0.14	1.8±0.3	0.58±0.06	99.86 ±0.38
F6	103.64 ±1.05	2.79 ±0.16	1.82±0.5	0.65 ±0.06	99.54 ±0.67
F7	98.66 ±1.24	2.62 ±0.11	1.75±0.2	0.62 ±0.05	99.12±0.56
F8	99.63 ±1.31	2.71 ±0.12	1.79±0.4	0.66 ±0.04	99.63±0.36
F9	100.21±1.15	2.63±0.17	1.71±0.9	0.59±0.07	98.59±0.77

Table 6: Evaluation of post compression parameters of aripiprazole ODTS

Formulation	Disintegration time (sec)	Wetting time (sec)	*In vitro* dispersion time (sec)	%Water absorption ratio
F1	34±0.5	32±0.3	36±0.4	95
F2	31±0.8	29±0.7	33±0.8	95
F3	30±0.6	28±0.4	33±0.6	94
F4	31±0.7	29±0.6	34±0.8	97
F5	34±0.4	31±0.7	37±0.3	95
F6	29±0.7	27±0.5	30±0.7	97
F7	26±0.6	24±0.5	29±0.8	98
F8	20±0.8	18±0.8	22±0.7	99
F9	26±0.9	24±0.6	28±0.3	98

***In vitro* dissolution studies:**

Table 7: *In vitro* dissolution study of aripiprazole tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	25.4	20.48	29.72	41.16	30.75	30.83	32.47	46.35	24.56
10	39.6	32.68	41.16	53.56	46.24	36.72	58.14	75.48	48.48
15	48.6	46.37	53.56	65.26	60.45	56.16	81.21	98.26	72.36
20	64.3	59.34	65.26	81.35	74.45	87.4	98.31		99.37
30	76.4	72.12	81.35	95.64	82.38	99.51			
45	86.4	84.36	99.43		96.41				
60	99.56	99.32							

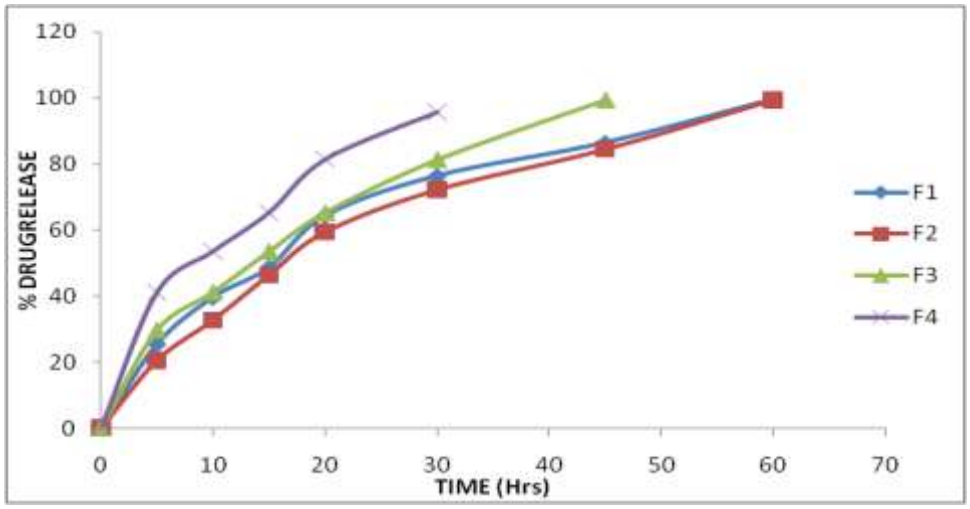

Figure 7: *In vitro* drug release study of aripiprazole (F1-F4)

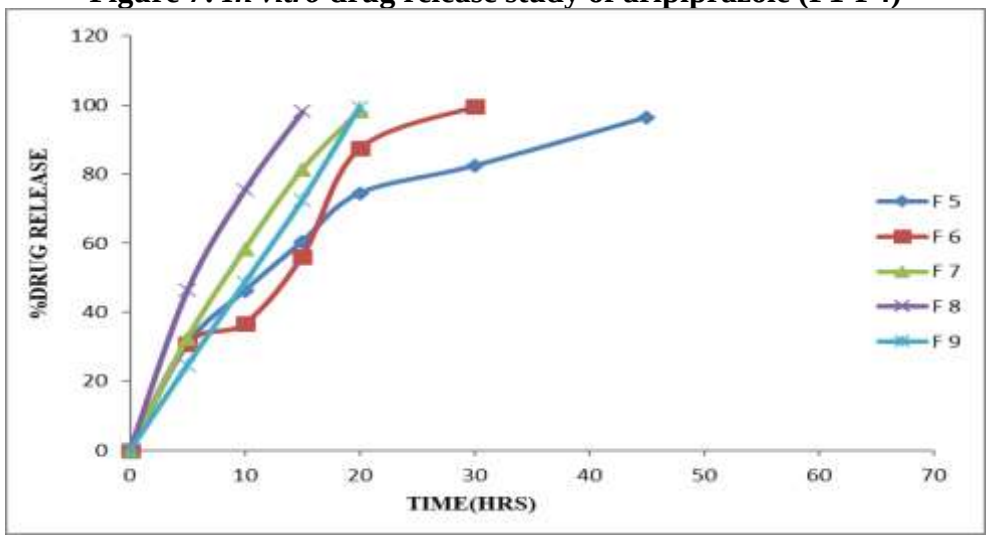

Figure 8: *In vitro* drug release study of aripiprazole (F5-F9)

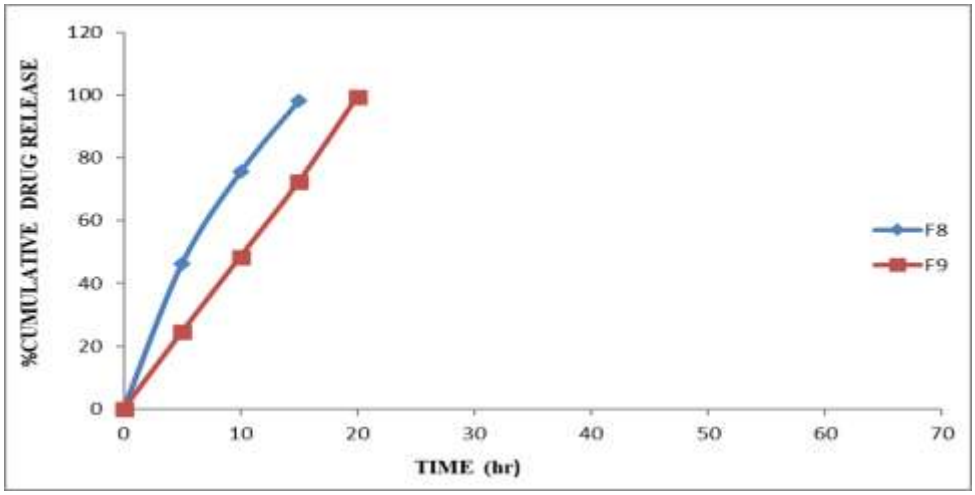

Figure 9: Comparison of F8 and F9 percentage drug release

***In vitro* dispersion time:** *In vitro* dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5 ^{0}C and the time required for complete dispersion was determined. To check for reproducibility, the measurements were carried out in triplicates (n=3). The dispersion time was recorded using a stopwatch.

***In vitro* drug release:** Dissolution test was carried out by using USP type II apparatus. The paddle was rotated at 50 rpm, pH 6.8 phosphate buffer was used as dissolution medium (900 ml) and was maintained at 37 ± 1 ^{0}C. Samples of 5 ml were withdrawn at predetermined intervals (5, 10, 15, 20 and 30), filtered and replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the drug at 250 nm by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

Drug-excipient compatibility studies by FT-IR: The compatibility between the pure drug and excipients was detected by FT-IR spectra obtained on Bruker FTIR Germany (Alpha T). The spectra were recorded over the wave number of 4000 to 550 cm^{-1}.

Differential Scanning Calorimetry (DSC): The possibility of any interaction between the drug and the carriers during preparation of solid dispersion was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture and solid dispersion using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminium pan at a rate of 10 ^{0}C/min conducted over a temperature range of 30 to 350 ^{0}C under a nitrogen flow of 50 ml/min.

RESULTS AND DISCUSSION

Analytical determination: It was found that the estimation of aripiprazole using UV spectrophotometric method at λ_{max} 250 nm in pH 6.8 phosphate buffers had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be 0.999, at the concentration range 5-25 µg/ml. For each formulation blend of drug and excipients were prepared and evaluated for various precompression parameters described earlier in methodology chapter. The bulk density of all formulations was found in the range of (0.46±0.06- 0.58±0.04) and tapped density was in range of (0.55±0.03- 0.65±0.02). The Carr's index and Hausner's ratio was calculated from tapped density and bulk density. The powder blend of all six formulations with Hausner's ration < 1.25 and Carr's index < 18 indicates good flow ability of all powder blends. The flow properties for all the powder blends were good as evidentially proved by the angle of repose values obtained, which ranged between (25-30^0) which is less than 30^0 as greater than 30^0 has poor flow ability which has been observed in case of pure drug.

CONCLUSION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. An attempt was made to formulate and evaluate orally disintegrating tablets of aripiprazole for the effective treatment of psychosis. In this present investigation, aripiprazole tablets were prepared by using super disintegrants. Firstly, spectrum and standard graph was plotted. It was found that the estimation of aripiprazole using UV spectrophotometric method at λ_{max} 250 nm in pH 6.8 phosphate buffers had good reproducibility and this method was used in the study. The prepared formulations were evaluated for pre and post compression studies. All formulations were found to be within limits. Formulations prepared with HPMC 6cps showed good in concentration of 8 mg at 30 min.

Formulations prepared with croscarmellose sodium showed good drug release in the concentration of 8 mg at 15 min. Among 8 formulations F8 was considered as optimized formulation. Among those all formulations F8 was shown maximum drug release at 15 min. In conclusion, formulation of orally disintegrating tablets of Aripiprazole using sublimation method is able to enhance the dissolution rate. This approach is effective, economical and industry feasible.

Funding: This research received no external funding.

Conflicts of Interest: Authors have declared that no competing interests exist.

Consent and ethical approval: It is not applicable.

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