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Research Article

FORMULATION AND EVALUATION OF ARIPIPRAZOLE ORO-DISPERSIBLE TABLETS: OPTIMISATION THROUGH FACTORIAL DESIGN OF EXPERIMENTS

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ABSTRACT

The main objective of this study was to prepare and evaluate fast dissolving tablets of aripiprazole using three different types of superdisintegrants. Various formulations were prepared by direct compression using different concentrations of superdisintegrant i.e. namely Kyron T-104, Kyron T-154 and Kyron T-314. The compatibility studies between drug and excipients were carried out using Fourier Transform Infrared spectroscopy. The blend was evaluated for additive properties. The tablets formulated using factorial design was evaluated for physical properties and *in-vitro* drug release. From this study formulation containing Kyron T-154 was found to possess better disintegration time of 15 sec, water absorption ratio (77.5 %), and wetting time (22.7 sec) with taste masking property at low concentration and hence formulation containing was Kyron T-154 optimized.

KEY WORDS: Fast dissolving tablet, Superdisintegrant, Kyron T-154, disintegration, taste masking property, Factorial design.

INTRODUCTION

Oral medication conveyance is as of now the best quality level in the pharmaceutical business where it is viewed as the most secure, the most advantageous and most temperate technique for medication conveyance with the most noteworthy patient consistence [1, 2].

Oro-dispersible tablets (ODTs) are being named as oro-dispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets. ODT when placed in the mouth they disperse fast before being swallowed and these are uncoated tablets. When the disintegration tests have been conducted up to test for disintegration of tablets it disintegrates within 180 seconds [3, 4].

ODTs have thrived tremendously as an advantageous, safe, and satisfactory option in contrast to traditional tablets and capsules. The business achievement and reasonability of such items requires the improvement of the formulation with incredible attractiveness such as disintegration time, physicochemical dependability, and pharmacokinetic profiles which ought to be relevant and bioequivalent to oral dosage form [5].

Superdisintegrants are another variant of super-retaining materials with customized swelling properties. These materials are not wanted to assimilate noteworthy measures of water or watery liquids, however, intended to swell quickly. Superdisintegrants are utilized for the disintegrable solid dosage form as an auxiliary weakener [6].

Tolerant resistance to treatment and particularly the schizophrenic patients abstaining from swallowing their medicine by hiding conventional tablets under their tongues is experienced circumstance in psychiatry. It is apparent that the patient's personal satisfaction will be expanded by methods for the fast ODT innovation used in psychiatry [7].

In the present study the mouth dissolving aripiprazole an oral atypical anti-psychotic agent tablets were developed using various concentrations of superdisintegrants. Direct compression technique was used to compress the trial formulations. Factorial design was chosen to optimize the tablet formulation and to evaluate all the parameters such as weight variation, hardness friability, drug content, wetting time, water absorption ratio, in-vitro disintegration time, in-vitro drug release.

MATERIAL AND METHODS

Aripiprazole was received from Suven life sciences, Kyron T-314, Kyron T-154, Kyron T-104 was received from Corel Pharm chem., Ahmadabad, PVP K30 was procured from Yarrow chem. Mumbai, magnesium stearate and Talc was received from SD fine Chem. Pvt. Ltd. Mumbai.

Preparation of Aripiprazole ODTs

All ingredients were triturated individually in a mortar and passed through sieve number 60. Then required quantity of all ingredients were weighed for a batch size of 50 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally, magnesium stearate and talc were added as lubricant. This uniformly mixed blend was compressed in to tablets containing 20 mg drug using 6 mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method. Total weight of tablet was kept 100 mg.

Drug- excipients compatibility study

The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of tablets was studied by Fourier Transform Infrared (FTIR) spectroscopy. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan) facility (model - 8400S). KBr disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic

press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

***In-vitro* evaluation of powder blends**

Angle of repose

Angle of repose is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the co-efficient friction (μ) between the particles. Hence the rougher and more irregular surface particles will have greater angle of repose. 100 gms of the blend was accurately weighed and carefully poured through the funnel whose tip was secured at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend was poured until the apex of the conical pile just touches the tip of the funnel. Angle of repose is calculated by the following formula.

$$\theta = \text{Tan}^{-1}(h/r)$$

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

Bulk density

Bulk density may be defined as a mass of a powder divided by the bulk volume. Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and 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 quantity of blend was tapped for fixed time duration (around 250). The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was evaluated. The tapped density (*t) was calculated using the formula

$$*t = M/V_t$$

Compressibility index

The simplest way for measure free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (C.I) which was calculated using the formula,

$$\text{C.I (\%)} = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density}}$$

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the using the formula,

$$\text{Hausner ratio} = *t/*d$$

Where *t=tapped density. *d=bulk density

***In-vitro* evaluation of the prepared tablets**

Weight variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness

Control of physical dimensions of the tablets such as size and thickness are essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by using screw gauge. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging.

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using screw gauge. The average thickness and standard deviation were reported.

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average reading was noted.

Friability

Friability of the tablets was determined using Roche Friabilator. This device was set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula was calculated.

$$F\ \% = (1 - W_0/W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a petri plate with a 10 cm diameter. 10 ml of water at $37^0C \pm 0.5^0C$ containing eosin, a water-soluble dye, was added to the petri plate. A tablet was carefully placed on the surface of tissue paper. The time required for water to attain the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

Swelling index

Swelling index is the volume in milliliters that is occupied by 1 gm of drug after it has swollen in an aqueous liquid for 4 h. The methods of studying swelling index for Kyron T-314, and Kyron T-154 were carried out. Swelling index was calculated from mean readings of three determinations [8].

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri plate containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio R, was determined using following equation:

$$R = W_a - W_b / W_b \times 100$$

Where W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

Drug content

Weighed tablets (5) were powdered using mortar and pestle. An accurately weighed amount of powder equivalent to 20 mg of aripiprazole was taken into 100 ml volumetric flask, the solution was filtered through Whatman filter paper after dissolving in pH 4.0 acetate buffer and the filtrate was collected and suitably diluted with pH 4.0 acetate buffer if required and assayed [9].

***In-vitro* disintegration time**

Disintegration time (DT) was measured using a modified disintegration method. For performing this test, a petri plate was filled with 10 ml of water at 37^0 C±0.5^0C. The tablet was carefully put in the centre of the plate and the time for the tablet to entirely disintegrate into fine particles was noted.

***In-vitro* release**

In-vitro drug release of aripiprazole oro-dispersible tablets was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 900 ml pH 4.0 acetate buffer at 37^0C ± 0.5^0C. The speed of rotation of paddle was set at 50 rpm. 5 ml samples were withdrawn at time points of 1, 3, 5, 7, 10, 15, 20 min and same volume was replaced with pH 4.0 acetate buffer. Absorbance of solution was checked by UV spectrophotometer at a wavelength of 223 nm and drug release was determined from standard curve.

Experimental design

A 3^2 full factorial design was employed to evaluate the individual and combined effects of the formulation variables. In this design, two factors were evaluated; two of them at three levels, the experimental trials were performed at all nine possible combinations. The independent variables studied were type of superdisintegrant, concentration of superdisintegrant, the chosen dependent variables or responses chosen was disintegration time. All analyses were performed using the Minitab 18 Software [10]. The detailed composition of the prepared ODTs is presented in Table 1.

Table 1: Experimental runs, independent variables and measured responses of the 2^3 full factorial experimental design

Run	Type of superdisintegrant	Conc. of superdisintegrant	DT (sec)
1	Kyron-T-104	1.5	27
2	Kyron-T-314	2.5	4
3	Kyron-T-154	2.5	7
4	Kyron-T-314	1.5	6
5	Kyron-T-154	2.0	15
6	Kyron-T-104	2.0	21
7	Kyron-T-104	2.5	14
8	Kyron-T-314	2.0	10
9	Kyron-T-154	1.5	26

RESULTS AND DISCUSSION

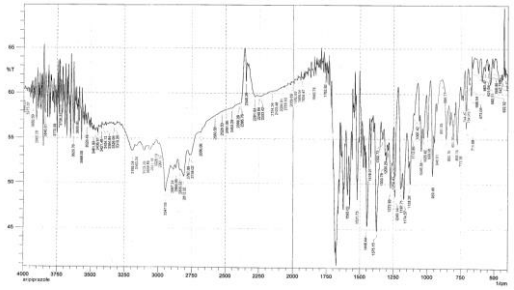

Figure la: IR spectra of Aripiprazole

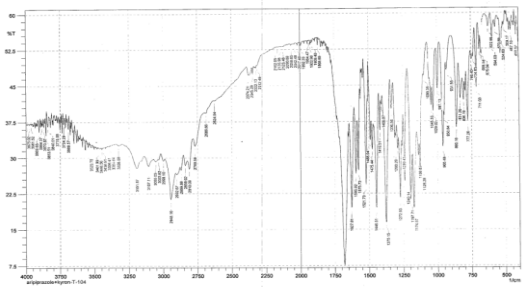

Figure 1b: IR of Aripiprazole + Kyron-T-104

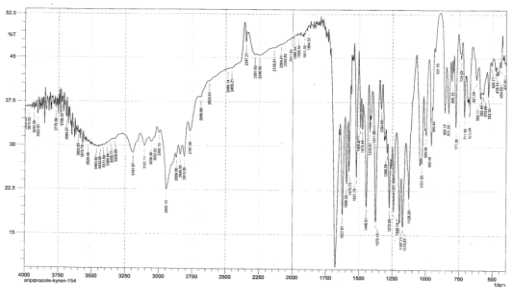

Figure 1c: IR of Aripiprazole + Kyron-T-154

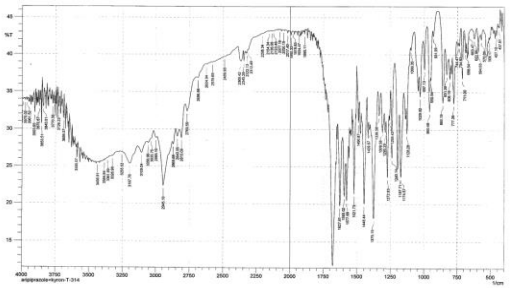

Figure 1d: FTIR of Aripiprazole + Kyron-T-314

In the present studies Aripiprazole fast dissolving tablets were prepared using three types of superdisintegrants (Kyron T-104, Kyron T-154, Kyron T-314). IR spectroscopic studies revealed that drug was compatible with all the excipients (Fig 1a, 1b, 1c, 1d)

Determination of flow properties

The blends of all the batches were evaluated for different parameters. Angle of repose was found to be in the range of 25.67 and 30.64. Tapped density between 0.63 and 0.76 (gm/cc) and

bulk density was found to be between 0.55 and 0.64 (gm/cc). Hausners ratio ranged between 1.01-1.09. Carr's Index was found to be in between 6-14. All the formulations showed good blend properties for direct compression technology.

Results for hardness, friability, content uniformity and disintegration time are indicated in table 3 and were found to be well within the limits. The hardness of the tablets was observed to be in the range of 2.2 to 3.5 kg/cm^2 and friability was observed to be in the range of 0.2 to 0.8% which showed good mechanical resistance. The drug content was observed to be in the range 98.95±1.23 to 99.95±1.43. In the development of oro-dispersible tablets the most important factor that should be evaluated is DT. In the present studies all the formulated have shown DT in the range of 27 to 4 sec. The formulation containing Kyron T-104 and Kyron T-154 at 2 % concentration showed DT within the limit i.e., 21 and 15 secs respectively and the formulation containing Kyron T-314 as a disintegrant showed DT of 10 secs at same concentration. Kyron T-314 used in oral pharmaceutical formulation (Suspension, Dry syrup, Mouth dissolving tablet / Dispersible tablet / Chewable tablet) is an anion exchange resin and when the tablet comes in contact with aqueous medium it swells because of the penetration of the aqueous medium which replace the air adsorbed on the particles, weakens the intermolecular bonds and breaks the tablet into fine particles [11].

The Wetting time and disintegration time decrease with increase in the concentration of superdisintegrants. The wetting time was in the range of 9 to 27secs. Water absorption ratio was performed for ensuring the moisture sorption and water uptake properties of superdisintegrants [11,12]. The water absorption ratio of the formulated tablets were found in the range of 63.9 to 99.9%. The in-vitro drug release studies were performed for the formulations prepared using three different superdisintegrants (Kyron T-104, Kyron T-154, Kyron T-314), drug concentration was calculated from the standard calibration curve. The percent drug release of all the batches were found within the limit as depicted in Table 2. As Kyron T-104 and Kyron T-154 acts as taste masking agent for the bitter drug like aripiprazole and also has superdisintegrant property so among this two type one can be taken as optimized formulation and as per the studies performed Kyron T-154 at 2% showed all the parameters well within the limit thus this was selected as optimized formulation without further increase in the concentration of Kyron T-154 (2.5%).

Pareto chart of the effects used to determine the magnitude and the importance of an effects visually is shown in Figure. There is a reference line on the chart which corresponds to the critical t value (t = 2.306). Pareto chart of the effects used to determine the magnitude and the importance of an effects visually is shown in Figure. There is a reference line on the chart which corresponds to the critical t value (t = 2.306. Pareto chart of the effects used to determine the magnitude and the importance of an effects visually is shown in Figure. There is a reference line on the chart which corresponds to the critical t value (t = 2.306). Pareto chart of the effects used to determine the magnitude and the importance of an effects visually is shown in Figure. There is a reference line on the chart which corresponds to the critical t value (t = 2.306). Pareto chart of the effects used to determine the magnitude and the importance of an effects visually is shown in Figure. There is a reference line on the chart which corresponds to the critical t value (t = 2.306) and any effects that exceeds this reference line is significant.

Table 2: Dissolution studies of aripiprazole using three different superdisintegrants

Run	Time in min		
	1min	3 min	5 min
1	67.5±0.99	88.2±1.64	93.4±0.52
2	100	-	-
3	90.0±1.56	98.6±0.45	-
4	81.3±0.75	88.2±1.64	96.92±0.21
5	88.0±1.64	96.9±0.21	-
6	77.8±0.41	84.0±0.24	95.1±1.21
7	88.2±1.64	90.0±1.56	98.6±0.45
8	88.2±1.64	96.6±0.21	-
9	76.1±0.12	84.0±0.24	93.4±0.52

Note: Values are expressed as Mean ±SD, n=3

Table 3: Results of evaluation parameters for factorial experimental batches

Run	Weight variation (%)	Hardness (kg/cm^2)	Friability (% w/w)	Drug content (%)	Water absorption ratio (%)	Wetting time (sec)
1	99±1.63	3.5±0.19	0.5	98.97±1.47	63.9±0.45	27.7±0.5
2	100±1.53	2.6±0.36	0.4	99.95±1.43	99.9±0.16	9±0.21
3	100±1.29	2.4±0.81	0.3	99.87±1.05	87.0±0.37	15±0.8
4	100±1.42	2.3±0.01	0.7	98.95±1.23	81.41±0.97	17.7±0.58
5	100±1.52	2.6±0.16	0.4	99.58±1.32	77.5±0.89	22.7±0.5
6	95.5±0.21	2.2±0.14	0.8	99.45±1.89	55.7±0.56	23±0.17
7	100±1.21	2.5±0.17	0.2	99.95±1.43	90.8±0.45	19.7±0.58
8	100±1.45	2.4±0.02	0.5	99.47±1.56	83.0±1.32	13±0.62
9	98.6±1.63	2.3±0.94	0.8	99.31±1.29	99.0±4.03	25±0.17

All the values are expressed as Mean ±SD

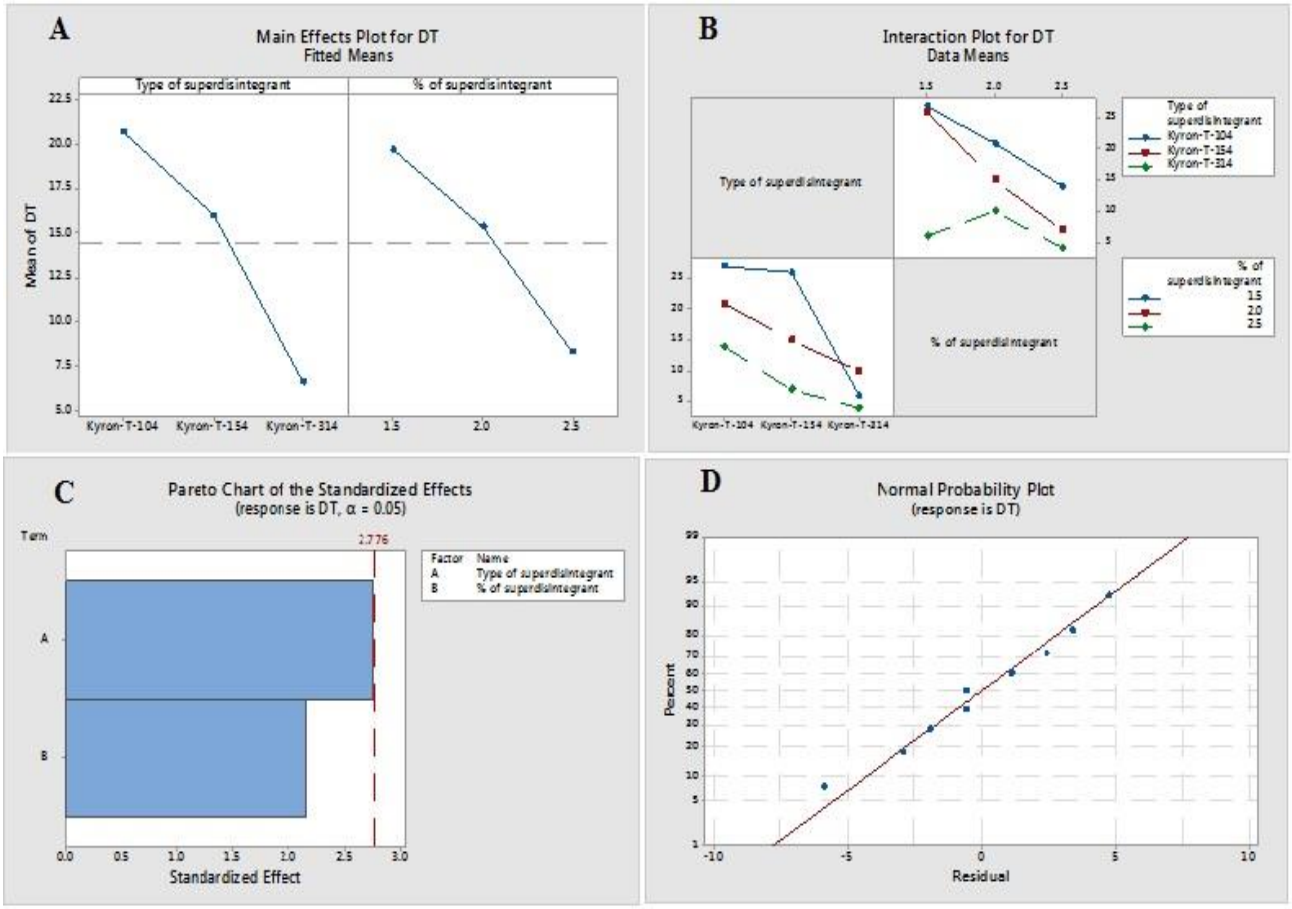

Figure 2: (A) Main effect plot for disintegration time (B) Interaction plot for disintegration time (C) Pareto chart of the standardized effect (D) Normal probability plot

The order of independent variable on which DT depends was found to be in order of type of superdisintegrant > concentration of superdisintegrant as shown in Figure (A). The type of superdisintegrant Kyron T-314 has greatest influence on DT as shown in Figure (B). A pareto chart of the effect used to determine the importance and magnitude of an effect visually as shown in Figure (C) there is a reference line on the chart which corresponds to critical 't' value (t= 2.776) and any effect that is lower to this reference line is insignificant but cannot be neglected. The normal probability plot for DT in Figure (D) shows that the distribution of residual over zero line follows a bell-shaped curve, but the points present on left and right makes it to some extent skewed as these are not on extreme ends thus can be neglected [13].

CONCLUSION

In the present study, orodispersible tablets of aripiprazole was prepared by direct compression technique. The prepared tablets were found to be within the official limits with respect to all the parameters. The disintegration time and dissolution studies were performed for the 1-9 runs. All the formulations showed the optimum disintegration time and cumulative percentage drug release within minutes. But formulation batch 5 was found to be less friable and also require less concentration of Kyron T-154 and which acts as both superdisintegrant and taste masking agent. Therefore batch 5 was most robust formulation and considered to be optimized batch. Further studies are required to test the taste masking effect of the formulation on humans.

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