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Employment of liquisolid approach in the development optimization and evaluation of an oral disintegrating tablet of aripiprazole

Vishranth N [1], Preethi Sudheer[1]*, Darshan P R [1], Venkatesh Prasad S[1], Imran Pasha[1]

[1] Department of Pharmaceutics, Krupanidhi College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bengaluru 560035, India.

* Corresponding Author. E-mail: preetisudheer@gmail.com(P.S.); Tel. +91-890-488 0379.

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ABSTRACT: The major problems associated with the oral route of administration are low solubility, low permeability, and hepatic degradation of drugs, leading to low bioavailability issues. Therefore, in this study, a biopharmaceutics classification systems (BCS) class II drug aripiprazole was chosen to develop an oral disintegrating tablet using liquisolid technology to enhance the solubility and dissolution rate of the drug. Liquisolid compact of aripiprazole was prepared using polyethylene glycol (PEG 400) as a nonvolatile solvent, microcrystalline cellulose (MCC) as a carrier, and Aerosil 200 as a coating material. The formulations were optimized via the 23-factorial design. The optimum formulation was further converted to oral disintegrating tablets with the help of the super disintegrant, cross povidone, and the produced tablets were evaluated. The water solubility of aripiprazole was observed to have increased from 4.5µg/ml to 0.13mg/ml in the liquisolid form and angle of repose was found to be reasonably passable. As was observed from the experimental design, the solvent, solvent: carrier, and carrier were seen to have a significant influence on the selected responses. The X-ray diffraction pattern of the optimized formula indicated a reduction in the peak number and the peak intensities compared to the pure drug. The tablets prepared of liquisolid compacts displayed good tableting properties. The disintegration time was found to be 40 seconds. The stability studies indicated no apparent changes in the properties after a storage period of 3 months. The liquisolid compacts are an inexpensive method of preparing oral disintegrating tablets of Aripiprazole with an assurance of suitable dissolution property of the drug.

KEYWORDS: Aripiprazole; liquisolid compacts; oral disintegrating tablets; solubility; bioavailability

1. INTRODUCTION

The factors contributing to oral bioavailability includes solubility in water, drug permeability, first-pass metabolism, dissolution rate, pre-systemic metabolism, and susceptibility to efflux mechanisms. Low solubility and permeability are the two most common causes of low oral bioavailability. According to biopharmaceutics classification system (BCS), BCS II and BCS IV drugs possess poor aqueous solubility. Developing a formulation using a class IV drug is nearly impossible unless the dose needed is very small. [1,2]

The tremendous pharmaceutical research in low oral bioavailability has led to the development of fast dissolving formulations. Oral disintegrating technology, which makes the formulations that rapidly dissolves or disintegrates in the oral cavity without any additional water intake and provides the drug in suspension or solution form in bio-fluids. [3,4,5]

One of the useful methods for improving oral bioavailability of BCS class II drugs is liquisolid (LS) compacts technology under the powder solution technology. By this technique introduced by Spireas et al., water insoluble drugs can be converted into rapid release solid dosage forms. LS technique refers to mixing liquid drugs with appropriate carriers and coating products, liquid medications may be converted into seemingly dry, non-adherent, free-flowing, and compressible powder mixtures. [6,7,8]

Increased surface area, aqueous solubility and improved wetting properties due to the presence of nonvolatile solvent are some of the factors that contribute to superior release profiles from these systems. [9] When there are many factors to be investigated in an experimental approach, to screen the most influential factors and interactions between factors on the responses, we use a 2k factorial design approach. [10]

Among the mental illness, schizophrenia stands out in 1% of the population worldwide as one of the most severe and disabling conditions. It is characterized by an impaired relationship with reality. Antipsychotic medications act by blocking the dopamine D2 receptors in dopaminergic pathways of brain

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cells. These non-selective agents block the dopamine receptors mesocortical, tuberoinfundibular, and nigrostriatal pathways as well. [11]

While most atypical antipsychotic drugs block D2 receptors, and its antagonistic effect on serotonin receptors, 5-HT2A and 5-HT2C receptors especially on 5-HT2A nigrostriatal pathway, reduces the risk of extrapyramidal side effects Ex: clozapine, quetiapine, aripiprazole, risperidone, olanzapine. [12] Aripiprazole is a partial agonist antipsychotic that functions as an atypical antipsychotic at the dopamine (D2) receptors and an antagonist to the serotonin (5-HT2A) receptors. It is a BCS Class II compound, which has a poor solubility and poor bioavailability. It is well absorbed orally, undergoes extensive extravascular distribution, metabolized primarily through three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation, involving two P450 enzymes: CYP3A4, CYP2D6. The drug owing to its poor solubility provides an oral bioavailability of only 75%. Depending on conditions, its plasma half-life is 75 h. As it belongs to BCS Class II, it requires improvement in its solubility profile. [13]

Therefore, in the proposed research work, LS technology is selected as method to improve the solubility and dissolution rate of aripiprazole and which is further extended to oral disintegrating tablet. This tablet dosage form expected to overcome the common problem of nonacceptance of the conventional tablet dosage forms by the psychosis patients.

2. RESULTS AND DISCUSSION

2.1. Pre-formulation studies

2.1.1. FTIR

The FTIR was performed for the drug, aphysical mixture of drug and excipients and is shown in Figure 1. Aripiprazole showed a characteristic peak at 3437 cm^{-1} due to N-H stretching vibration, which falls in the range of 3500-3300 cm^{-1}, 3068 cm^{-1} which is observed at aromatic C-H stretching (3100-3000 cm^{-1}) C-H stretch occurs at 2945 cm^{-1}, 3000-2850 cm^{-1} and 1676 cm^{-1} due to carbonyl stretching vibration 1690-1640 cm^{-1}, C-N stretch shows at 1197 cm^{-1} 1360-1080 cm^{-1}, and a peak at 775 cm^{-1} 800-600 cm^{-1} due to the C -Cl stretch. The principal peaks of aripiprazole, even in the physical mixture indicate no apparent interaction with (MCC, PEG 400, crospovidone, and Aerosil) used.

2.1.2. Saturation solubility studies

The solubility results of the drug in propylene glycol (PG), PEG 400, Tween 80 (0.5%), Tween 60, and glycerin are represented in Figure 2. Aripiprazole's solubility was found to be highest in PEG 400, (87.6 µg/ml). As the solubility of the drug in nonvolatile solvent is important to make uniform molecular dispersion for improving the dissolution rate, PEG 400, was designated as solvent for developing formulations.

Figure 1. (A) Infrared spectra of aripiprazole; (B) IR spectra of physical mixture of Aripiprazole, MCC, PEG, crospovidone and Aerosil

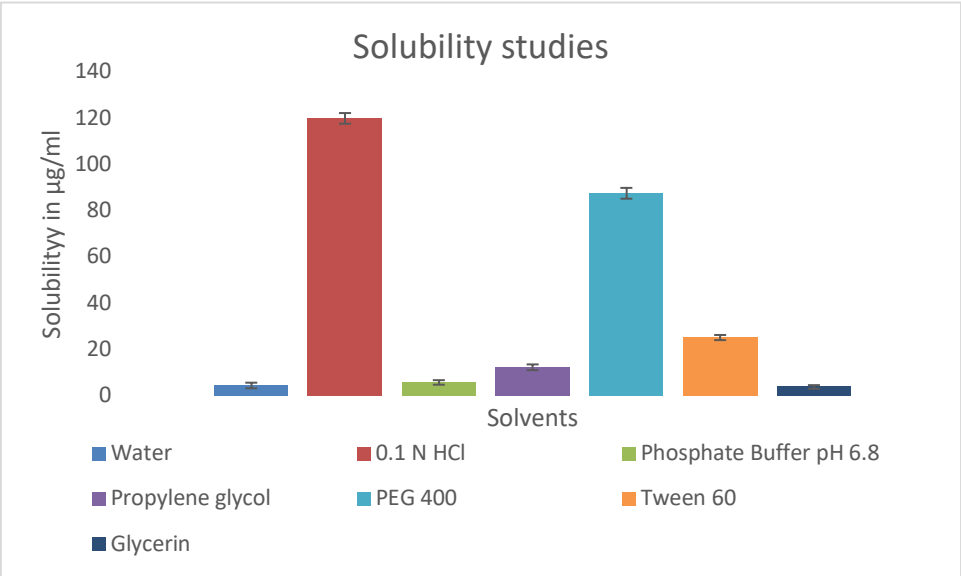
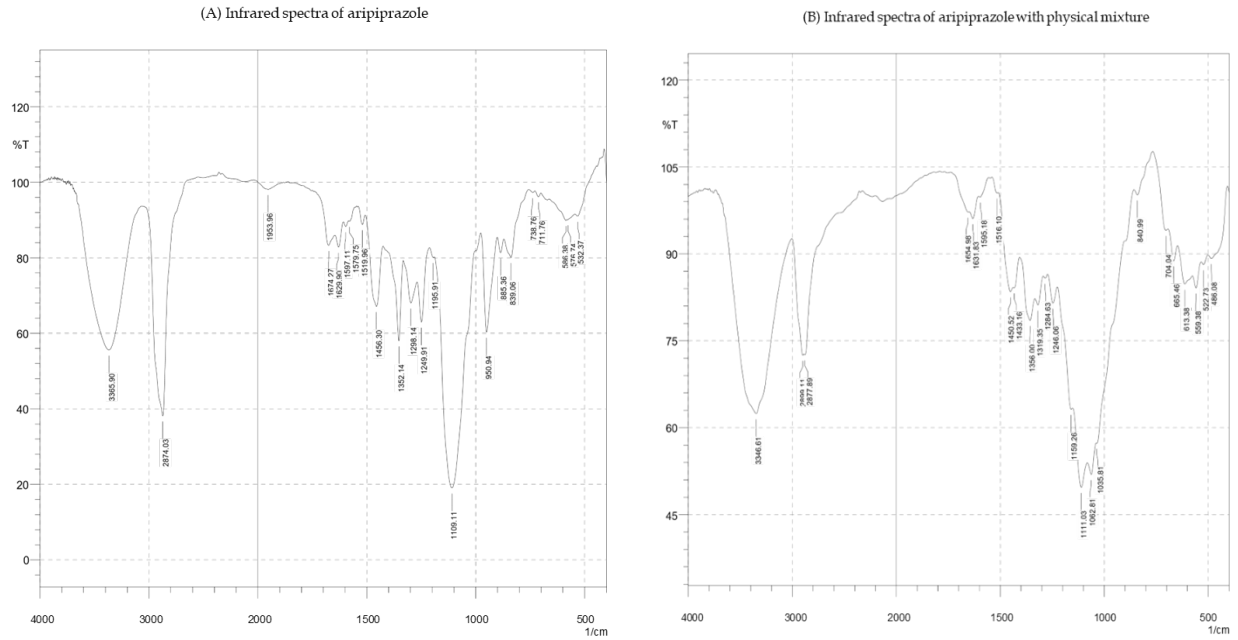


Figure 2. Solubility of Aripiprazole in various solvents (Mean ±STD, n=3)



2.2. Preparation of Liquisolid compacts

As per Spireas, materials with larger adsorption properties can be used as carrier materials. So in this study micro crystalline cellulose was used as carrier. In addition to the inherent liquid nature of nonvolatile solvents, hygroscopic nature of these agents increases the liquid content, that may decrease the flowability. So, the coating material, Aerosil 200 was used to improve the flowability. Aripiprazole loaded LS compacts were prepared using different excipient ratios on the basis of the experimental runs using PEG 400 as solvent, MCC as carrier and aerosol as coating agent.

2.3. Evaluation of the formulations

All nine formulations were evaluated for solubility, angle of repose and drug content. The results of experimental runs (Table 4) showed an angle of repose between 34 to 38^0, F3 formulation showed highest solubility of 0.169 mg/ml compared to other formulations. The results are shown in (Table 4).

It is demonstrated that LS systems with a greater angle of repose values have a higher proportion of liquid and a lower proportion of powder excipient. The LS systems with a low angle of repose, on the other hand, have a lot of carrier material (MCC) and very little liquid. As per the LS hypothesis, when a drug dissolved in a liquid vehicle is incorporated into a carrier material such as cellulose, which has both porous surfaces closely knitted interior matrix, it results in both absorption and adsorption. Before saturation of this process, the absorbed liquid was taken by the internal structure and reverted to its original state. Coating material provides high adsorptive properties and availability of vast surface area per unit weight, resulting in LS with the desired flowability. The above facts demonstrate that the micronized form of cellulose has a more significant effect on enhancing the system's flowability.

The presentation of the drug in solution form in PEG 400 increased the wettability and surface availability, significantly contributing to the drug's increased dissolution profile. An increase in wetting resulted in an increased rate of dissolution from LS compacts. PEG 400 reduces the interfacial stress between the medium and the tablet's surface, allowing drug particles to wet more easily. The results are given in Figure 3.

2.4. Evaluation of the experimental design and optimization of formulation trials

The formulation variables for the preparation of LS compacts were optimized using 2^3 factorial designs, using JMP software version 13. The same design was chosen to screen the effect of variables on the selected responses. Concentration of solvent, carrier and coating material were used as factors on the responses angle of repose and solubility. The design generated 9 experimental trials. The experimental design was evaluated for suitability of fit. The summary of the model fit is given in Table 5. Among all the

factors chosen, the quantity of solvent and solvent: carrier ratio and amount of carrier were found to be highly significant factors (p<.0.5) in the preparation of LS compacts. (Table 5). As the ratio of solvent increased, the solubility was found to be increased. However, there was a considerable impact on both responses solubility and sliding angle in various proportions of solvent and carrier materials. Ratio of carrier: coating agent and quantity of coating agent did not contribute that effectively in solubility and angle of repose.

Actual vs predicted graph of both solubility and angle of repose is given in Figure 4. The p value of 0.019 and 0.046 respectively for solubility, angle of repose and narrow bands with accumulation of points around the predicted mean value (as given in Fig. 6) indicates the experimental results were similar to the predicted results.

Table 4. Evaluation of the formulation

Sl. No	Formulation	Loading factor(L)	R	Solubility (mg/ml)	Angle of repose θ	% Drug content
1	F1	0.258	108	0.137	36	92.6±0.28
2	F2	1.78	71	0.122	36	98.3±0.28
3	F3	0.223	114	0.169	38	100.85±0.49
4	F4	1.78	100	0.107	36	85.45±0.21
5	F5	1.11	114	0.117	38	93.55±0.21
6	F6	1.11	160	0.134	38	90.2±0.28
7	F7	0.357	71	0.165	35	96.85±0.49
8	F8	0.223	160	0.118	36	92.45±0.49
9	F9	0.357	100	0.118	34	91.35±0.38

R = Carrier/coating ratio
L = Weight of liquid drug/ weight of carrier

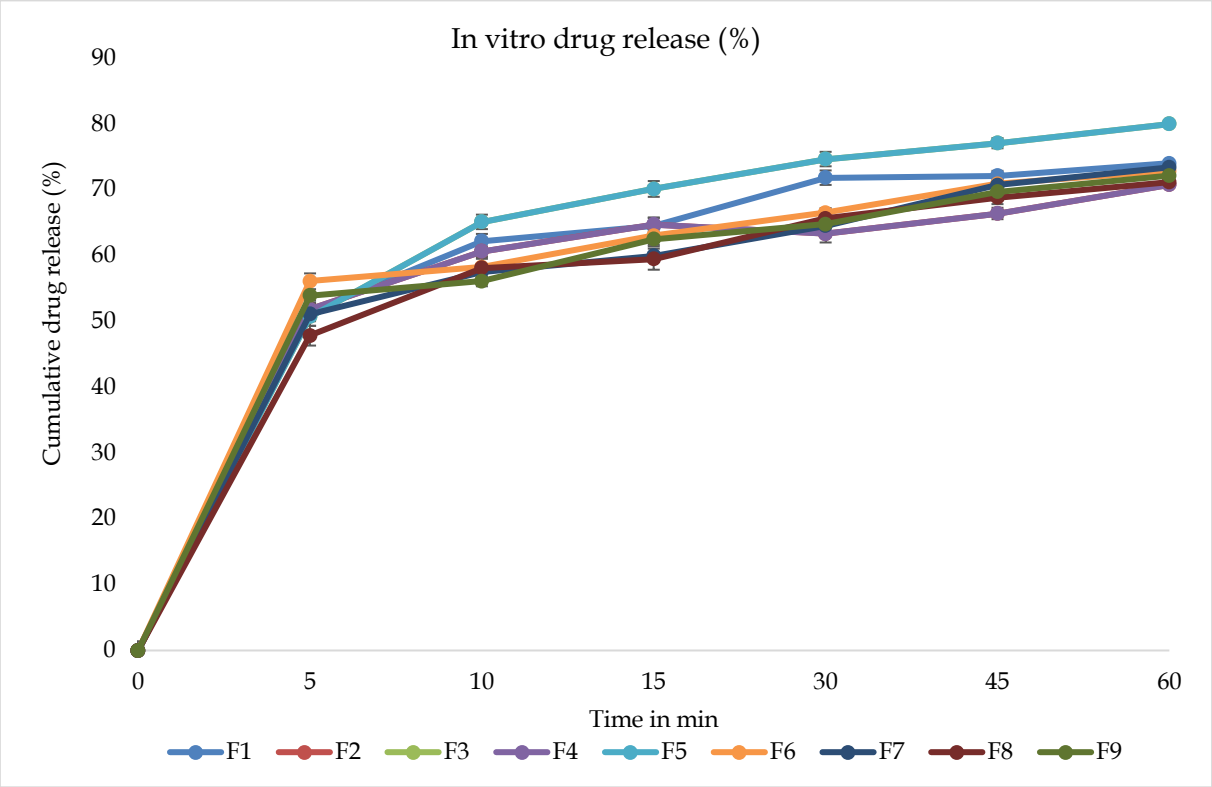


Figure 3. *In vitro* drug release profile of liquisolid compacts in PBS pH 6.8(Mean ± STD, n=3)

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Table 5. Statistical evaluation of factors and their level of significance

Sl no	Source	Log Worth	P Value
1	Solvent (ml)*Carrier (mg)	2.168	0.00679
2	Solvent (ml) (0.5,2.5)	2.059	0.00873
3	Carrier (mg) (500,800)	1.916	0.01212
4	Carrier (mg)*Coating material(mg)	1.206	0.06225
5	Coating material(mg) (5,7)	1.020	0.09547

Desirability function is indication of one-time measurement of all the responses which predicts optimum levels of all the factors. And it's the additive effect of all individual functions. In our experimental trials, we could achieve a maximum desirability of only 0.24. The desirability function indicates the effect of individual factors and its combinations and its overall effect on the responses selected. A desirability of 0.24 indicates only 24% possibility that the selected factors and its ranges had impact on the responses such as solubility and angle of repose. The surface response curves may involve main effects, interactions, quadratic and cubic terms to account for curvature effects. Surface plots of the entire experimental design are given in Figure 5. The surface profiler, shows no many curvature effects and thus indicates a minimum interaction and absence of higher order interactions. The factor, optimum responses and the predicted polynomial equation corresponding to the optimum formula are given in Table 6. The formula as per surface response diagram gives the information that the negative sign indicates the antagonistic effect of the variable on the response and positive sign indicates agonistic effect. So solvent is having antagonistic effect on angle of repose and positive effect on solubility.

2.5. Evaluation of optimized formulation

On the basis of prediction formula, the optimized formulation was prepared and evaluated for solubility, angle of repose, drug content and XRD diffraction studies. The XRD pattern of optimized LS formula was compared to the pure drug. The pattern exits sharp intensified peaks in case of pure drug. Whereas the number and intensity of the peaks were found be reduced in the optimized formulation (Figure 6). This suggests the reduced crystallinity of the aripiprazole when converted as a liquid system of cosolvent PEG400 with carrier as microcrystalline cellulose with coating agent as Avicel P 400.

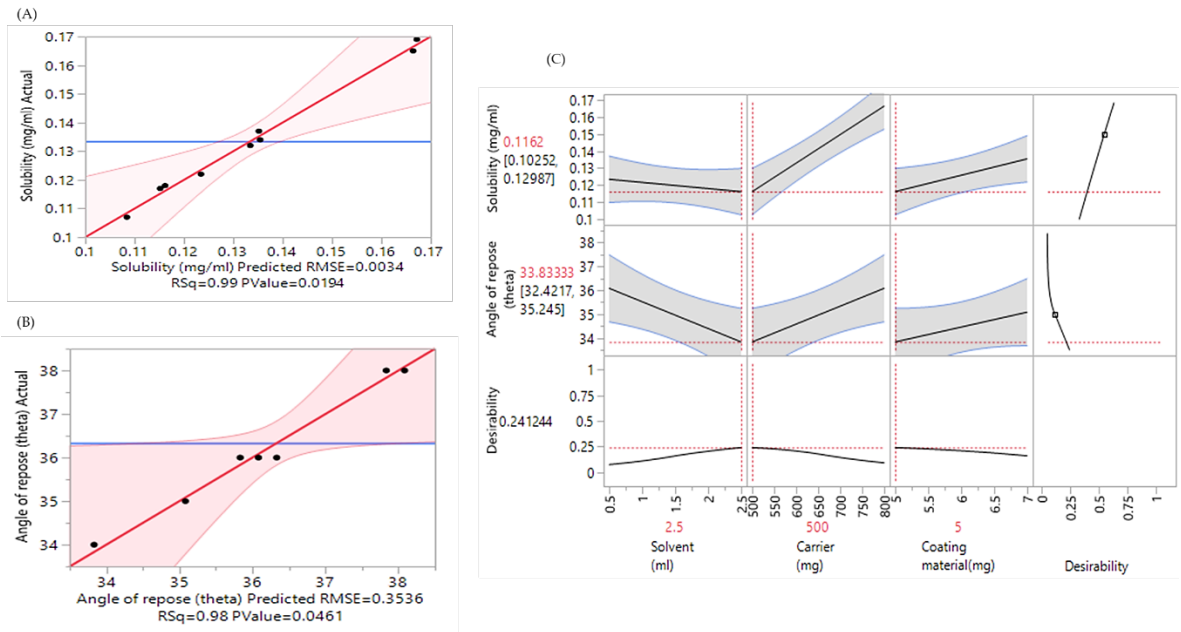

Figure 4. A) Actual vs predicted plot for the response solubility; B) Angle of repose; C) maximum desirability function

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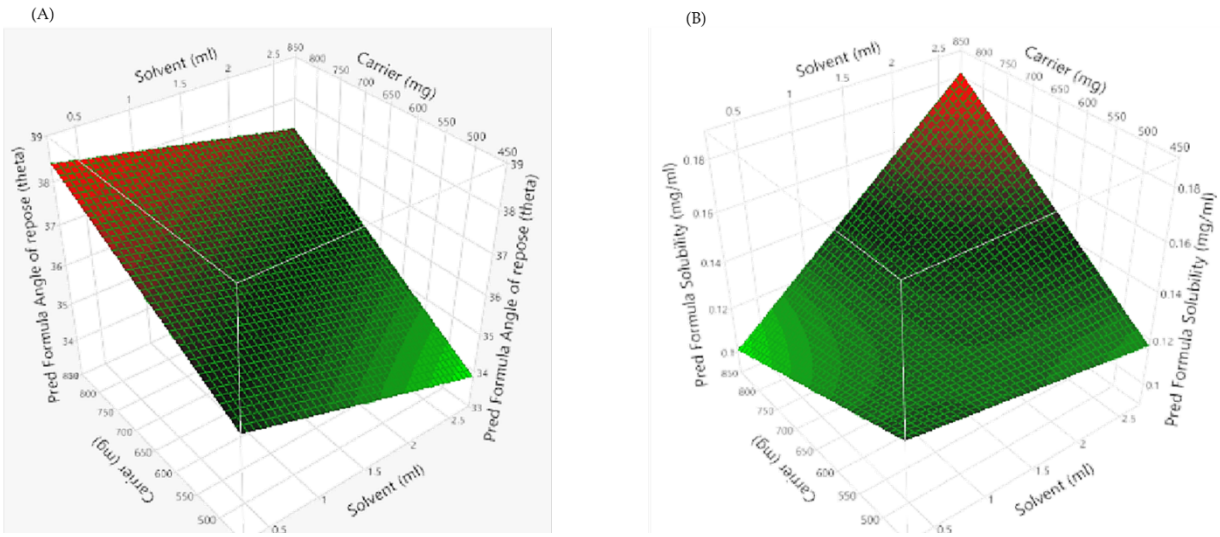

Figure 5. Surface response diagram; a) Angle of repose b) Solubility

Table 6. The optimum formula with predicted responses and actual responses and formulas

Prediction formula	Optimum responses		Actual responses	
Factors	**Angle of repose (theta)**	**Solubility (mg/ml)**	**Angle of repose (theta)**	**Solubility (mg/ml)**
	36.08	0.1334	0.130	36
Solvent (ml) (X_1)	1.5	1.5		
Carrier (mg) (X_2)	650	650		
Coating material(mg)	6	6		
(Angle of repose)	**36. 08** = 36.33 + -0.625 * "Solvent (ml) - 1.5) + 1.125 * "Carrier (mg)"- 650) / 150) + 0.375 * "Coating material (mg)" - 6) + "Solvent (ml)" - 1.5) * "Carrier (mg)") - 650) / 150 * 0.125 + "Solvent (ml)" - 1.5) * "Coating material (mg)") - 6) * 0.375 + "Carrier (mg)" - 650) / 150 * "Coating material(mg)") - 6) * 0.125			
(Solubility)	**0.1334**= 0.1334 + 0.013 * "Solvent (ml)" - 1.5) + 0.0059 * "Carrier (mg)" - 650) / 150) + 0.003 * "Coating material (mg)" -6) + "Solvent (ml)") - 1.5) * "Carrier (mg)") - 650) / 150 *0.015 + "Solvent (ml)") - 1.5) * "Coating material(mg)") - 6) *0.0019 + "Carrier (mg)") - 650) / 150 * "Coating material(mg)" -6) * -0.0046			

2.6. Formulation of oral disintegrating tablets

2.6.1. Precompression properties of blends of oral disintegrating tablets

The optimum LS blend after incorporation of cross povidone and was evaluated under various precompression parameters (Table 7). The angle of repose of 34.55° flow behavior suggests a passable flow behavior. The bulk density of 0.335 g/ml and tapped density 0.384g/ml, compressibility index 13.8 %, void volume 7 ml, Hausner ratio 0.11 and a porosity of 12.76 % suggests suitability of converting the blend into tablet form.

2.7. Evaluation of oral disintegrating tablets

Drug content of the tablets was found to be 92.22± 0.304 and friability of 1.01±0.003 and disintegration time of 44 sec. Other parameters were within the limits Hardness of 4.5±0.006 kg/cm indicates the suitability of an easy disintegration within the mouth cavity, as given in Table 8. This was due to the liquid in the Ls formulations interfering with the formation of interparticle bonds (H-bonds in case of MCC). It was demonstrated that the Lf value and the hardness of the tablets have an inverse relationship, which meant that as the Lf value increased, the tablet hardness decreased. This is because increasing the Lf value increases the amount of solvent used while decreasing the amount of highly porous material and coating material, resulting in decreased tablet hardness. (Table 8).

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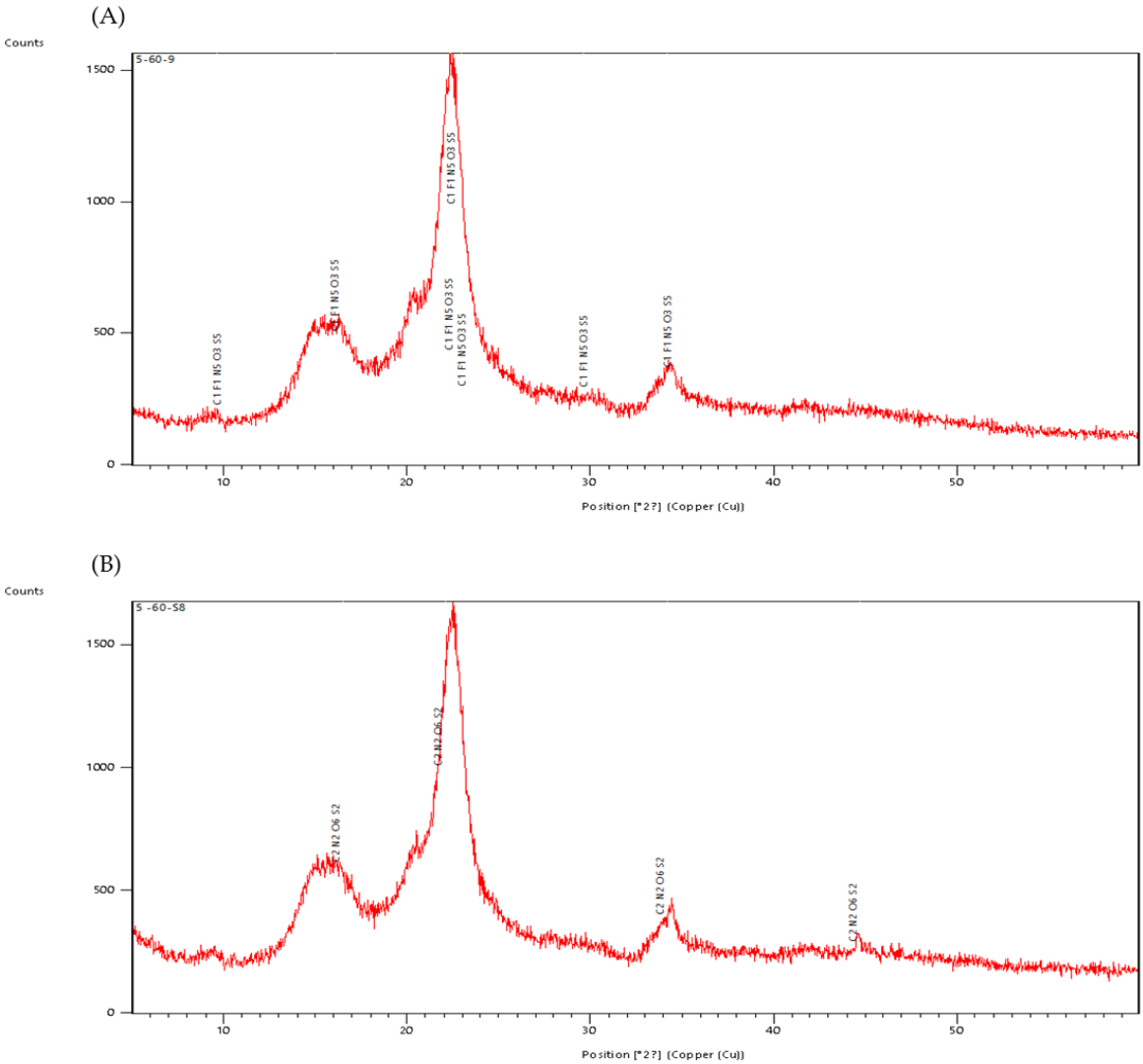

Figure 6. X Ray diffraction pattern of A) pure drug, B) optimized liquisolid formulation

Table 7. Precompression parameters

Sl no.	Properties	Results
1	Angle of Repose(θ)	34.55
2	Untapped density(g/ml)	0.335
3	Tapped density (g/ml)	0.384
4	Compressibility index (%)	13.8
5	Void volume(ml)	7
6	Hausner ratio	0.11
7	% Porosity	12.76

Table 8. Evaluation of ODTs (Mean ±STD, n=3)

Drug content (%)	Hardness(kg/cm²)	Friability%	Disintegration test (seconds)	Weight Variation (%)
92.22± 0.304	4.5±0.006	1.01±0.003	44±0.5	<5%

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2.7.1. Comparative in vitro release studies

The comparative *in vitro* drug release profile of pure drug and ODT prepared from optimized LS compact against a marketed tablet (Arip) indicated that the optimum formulation's drug release was 93.31±0.351 %. Whereas the pure drug released a maximum of 32.5 4% and the marketed formulation (Arip 5mg) exhibited a maximum drug release of 79.82%. (Figure 7)

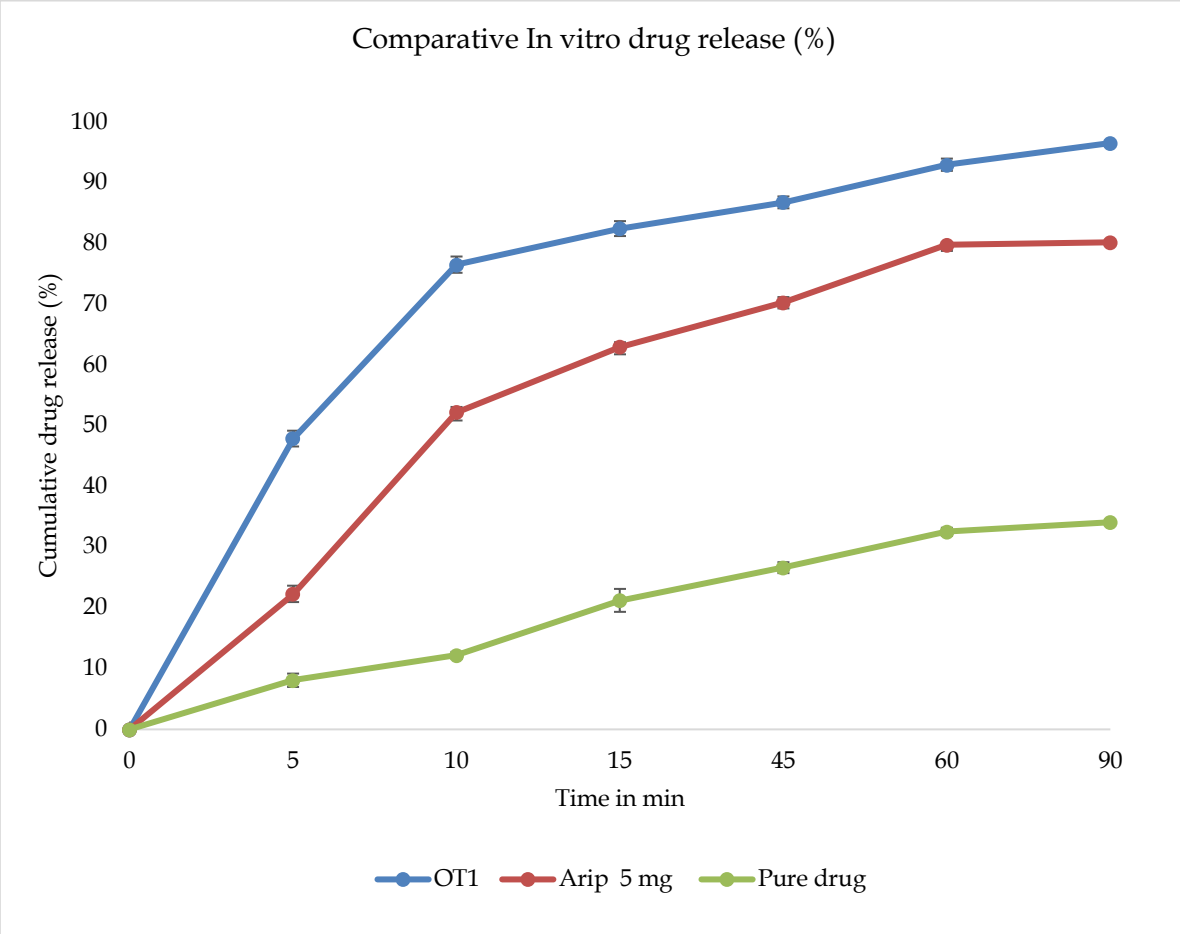
2.7.2. Differential Scanning Calorimetry (DSC)

The DSC thermograms of pure drug and the final formulation indicated that there was a decrease in the intensity and area of the melting endotherm of the formulation in comparison to the pure drug, which assures subsequent increase in the solubility of the drug as given in Figure 8.

2.8. Stability studies

The results of short-term stability studies indicated that there was no evident change in the physical appearance, drug content and disintegration time of the selected formulation at the end of 3 months storage period. The stability data is represented in Table 9.

Figure 7. Comparative *in vitro* release profile of pure drug (F1), marketed formulation (arip 5mg), optimized formulation (OT1) in phosphate buffer 6.8 (F3)(Mean ± STD, n=3)



3. CONCLUSION

Aripiprazole is an antipsychotic BCS class II drug that suffers from solubility problems and also low bioavailability issues due to hepatic metabolism. In order to achieve a suitable means of drug administration in the condition of psychosis, oral disintegrating tablets would be ideal. LS compacts were found to be an excellent method to improve the solubility of Aripiprazole, which could result in a free-flowing powder. The solubility and *in vitro* drug release properties of Aripiprazole LS compacts were significantly higher than those of the pure drug. The LS compacts were converted to oral disintegrating tablets using super-disintegrants. In contrast to aripiprazole, the dissolution profile of the oral disintegrating tablets was 20

times higher. To conclude, LS compacts and their presentation as an oral disintegrating tablet may be a promising strategy for improving therapeutic efficacy and patient compliance.

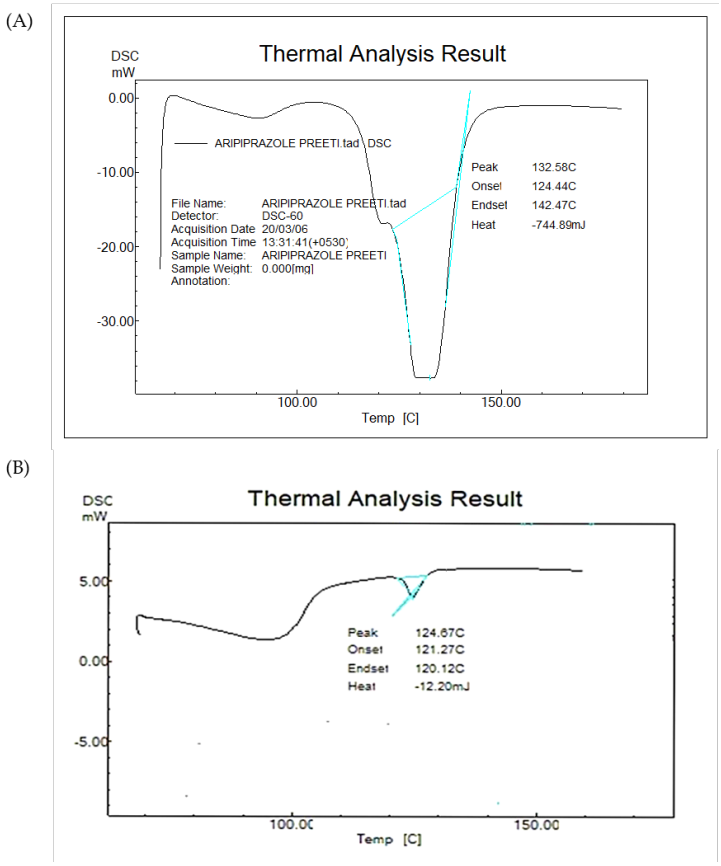


Figure 8. DSC thermogram of (A) Aripiprazole (B) Optimized formulation

Table 9. Stability studies(Mean ±STD, n=3)

Sl no	Observation	25±0.5°C/60% RH±5%	40±0.5°C/75% RH±5%	Optimized formula
1	Disintegration time (Sec)	45	48	44
2	Drug content (%)	91.83±0.01	90.99±0.08	92.06±0.01
3	Physical appearance	White bi convex tablet	White bi convex tablet	White bi convex tablet

4. MATERIALS AND METHODS

Aripiprazole was gifted by Whatson Pharmaceuticals (India Pvt ltd).The liquid vehicle; poly ethylene glycol 400 (PEG), carrier; microcrystalline cellulose and coating material; Aerosil 200 along with other polymers and chemicals solvents used were purchased from SD fine chemicals (Mumbai, India).

4.1. Pre-formulation studies

4.1.1. Compatibility studies by Fourier transformed infrared spectroscopy (FTIR)

The drug excipient compatibility was assessed by FTIR. Aripiprazole and physical mixture of drug with excipients were analyzed by potassium bromide pellet method in an FTIR spectrophotometer (Shimadzu 8400 series) in the region between 4000-400 cm^{-1}. [14]

4.1.2. Saturation solubility studies

Saturation solubility studies of aripiprazole were carried out in water, 0.1 N HCl, phosphate buffer pH 6.8, propylene glycol, PEG 400 and Tween 80. Saturated solutions of drug were prepared by adding an

additional quantity of drug in to the above vehicles, and were kept on a bath shaker for 72 h at 25^{0}C. Concentration of the drug present in the. samples were determined spectroscopically at 255 nm. [15]

4.2. Preparation of Liquisolid compacts

This method involved 3 steps

Step 1. Required quantity (5mg) of Aripiprazole was dissolved in the liquid vehicle; poly ethylene glycol 400 (PEG) and was mixed until a drug solution was obtained.

Step 2. The carrier material microcrystalline cellulose was added drug solution in a mortar and was mixed thoroughly till a homogenous product is obtained.

Step 3. The homogeneous powder was then combined with the adequate quantity of coating material (Aerosil 200) to obtain an admixture. [16]

4.3. Optimization of formulations

The formulation variables for the preparing LS compacts were optimized using factorial design, using JMP software version 11, where concentration of solvent, carrier and coating material were used as factors on the responses angle of repose and solubility (Table 1, 2). [16] The design generated 9 experimental trials as given in Table 3. The formulation was prepared as per the experimental trials and evaluated for the responses as given in Table 3.

4.4. Evaluation of liquisolid compacts

4.4.1. Sliding angle

Sliding angle is a useful parameter for understanding the flow behavior of LS powder. A weighed quantity of powder is placed on to one end of a glass slide, and raised till the powder starts sliding. The angle the slide made with the horizontal plane is sliding angle. [17]

4.4.2. Saturation solubility studies

The saturation solubility is carryout by dissolving 10 mg drug equivalent LS compact formulation in 10 ml of water and followed by 72 h of shaking on a bath shaker. After 72 h, the solution was filtered, filtrate was further diluted suitably with ethanol. The solution is measured for the concentration of drug by Shimadzu UV spectrometer at 256 nm. [10,18]

Table 1. The factors and their levels chosen in the experimental design

Factors	**Ranges**	
Levels	**Low (-)**	**High (+)**
Solvent (ml)	0.5	2.5
Carrier material (mg)	500	800
Coating agent (mg)	5	7

Table 2. Responses

Responses	**Lower limit**	**Upper limit**
Solubility(mg/ml)	0.05	0.25
Angle of repose (ø)	30	35

Table 3. Formulation trials generated by experimental design and their unit weights

Liqui-solid formulation	Pattern	Drug Aripiprazole(mg)	Solvent(ml)	Carrier material(mg)	Coating material(mg)	Unit dose weight (mg)
F1	000	5	1.5	650	6	662.6
F2	−−+	5	0.5	500	7	512.5
F3	+++	5	2.5	800	7	814.8
F4	−−−	5	0.5	500	5	510.0
F5	−++	5	0.5	800	7	812.5
F6	−+−	5	0.5	800	5	810.5
F7	+−+	5	2.5	500	7	514.8
F8	++−	5	2.5	800	5	812.8
F9	+−−	5	2.5	500	5	512.8

4.4.3. Drug content determination

LS formulation containing (10 mg) equivalent amount of aripiprazole was weighed, transferred into 10 ml volumetric flask and was diluted suitably using ethanol. The solution was measured for the concentration of drug by Shimadzu UV spectrometer at 256 nm. [19]

4.4.4. In vitro drug release study

In vitro drug release study for F_1-F_9 formulations was carried out using USP type II dissolution test apparatus. The LS compacts formulation was introduced into the dissolution media i.e., PBS pH 6.8 was maintained at 37±2^{0}C and was stirred at 50 rpm. At the time intervals of 10, 15, 30, 45, 60, 90, and 120min samples were withdrawn, and compensating with an equal volume of fresh media was done maintain sink condition. The absorbance was measured UV spectrophotometrically at a λ max of 256 nm. [16]

4.4.5. XRD studies

XRD patterns of Aripiprazole and the LS compacts were studied using an X ray diffractometer D8 Discover, Bruker Axs, Germany). The pattern is collected between 10 to 90^0 angles at a gap of 0.01^0. [17]

4.5. Evaluation of experimental design

The responses, angle of repose and solubility of all nine formulations were incorporated into the experimental design and the model was evaluated for its suitability of fit. Based on the design space identified, the optimum formulation was prepared and evaluated further.

4.6. Precompression parameters of optimized formulation blends

4.6.1. Angle of repose

After adjusting the height of the funnel with apex of powder cone, formulation was made to pass through the funnel. The powder cone's radius (r) and height(h) were noted, and the angle of repose was estimated bythe following equation. [20]

$$\tan \theta = h/r$$

4.6.2. Bulk and tapped density and compressibility index

After pouring a known mass of blend into a graduated cylinder, and measuring the volume, apparent bulk density was calculated. Tapped density was calculated by the same blend in the cylinder to fall onto a hard surface at 2 second intervals from a height of 10 cm. The tapping was continued until there was no more difference in volume. The densities were calculated by the following formulas. [21]

$$\text{Bulk or tapped density} = \frac{(\text{weight of powder})}{\text{Bulk or tapped volume}}$$

The following formula was used to measure the compressibility index:

$$\text{Compressibility index} = \frac{Tapped\ density - bulk\ density}{Tapped\ density} * 100$$

4.6.3. Hausner ratio and porosity

Hausner ratio is a related index that can be used to denote flow properties. The following formula was used to measure Hausner ratio.

$$\text{Hausner ratio} = \frac{Tapped\ density}{Bulk\ density} * 100$$

Porosity: Porosity given by the formula

$$Porosity = \frac{Bulk\ volume - True\ volume}{Bulk\ voume} * 100$$

4.7. Preparation of oral disintegrating tablet of aripiprazole

The optimized LS compact formula was added to the mortar and pestle mixed with crospovidone (2 % w/w of unit weight tablet) and blended to get a directly compressible powder. The powder blend was compressed into desired tablet weight. [22]

4.8. Evaluation of aripiprazole ODTs

4.8.1. Assay

From a composite sample of tablet triturate (5 Nos), 10 mg drug equivalent of power and dissolved in 10 ml of ethanol. After suitable dilution with ethanol, the concentration of the drug was measured spectroscopically at 255 nm. [22]

4.8.2. Weight variation

Weight variance was calculated by weighing 20 tablets calculating the average, as well as the individual weight.

$$\text{Weight variation} = \left(\frac{Induvidual\ weight - Average\ weight}{Averageweight}\right) * 100$$

4.8.3. Hardness and friability

The force needed to break the tablet diametrically in kg wasmeasured. Monsanto's hardness tester was used to take an average of five trials. [6]

Friability: Tablets (10 Nos) were weighed and mounted in a Roche friabilator at 25 rpm rotation for 4 minutes. All of the tablets were dedusted and weighed. The formula was used to measure the percentage of friability.

$$\%\ \text{Friability} = \frac{W1-W2}{W1} * 100,$$

where W_1 and W_2 are the weights before and after the test

4.8.4. Disintegration test

Disintegration test was carried out using USP apparatus. One tablet was inserted in each of six tubes, and the basket rack was poisoned in a 1-liter beaker of distilled water at 37 ±2 °C, so that during the up and down movement it maintained a distance of 2.5 from the surface and bottom of the beaker. The time for tablet disintegration was noted. [22]

4.8.5. Water absorption ratio

After placing 5 ml water on a small Petri plate, a piece of tissue was spread on its top. The tablet was placed on the paper, allowed to wet it thoroughly. After that, the wetted tablet was reweighed. The following formula was used for calculating water absorption ratio

$$R = \left(\frac{Wa - Wb}{Wb}\right) * 100$$

Where, Wb and Wa are the respective weights before and after the study. [23]

4.8.6. In-vitro dissolution test

In-vitro dissolution study wasperformed by using USP Type II Apparatus (Paddle) using 900 ml PBS pH 6.8 maintained at 37±20C and a stirring speed of 50 rpm. Sample volume of (10 ml) was collected at specific time intervals of 5,10,15,30,50, and 60 minutes. The sink condition was maintained by replacing an equal volume of fresh medium. The absorbance was measured by UV spectrometer at λ max of 256 nm. [24]

4.8.7. Differential Scanning Calorimetry (DSC)

The thermal behavior of aripiprazole and the optimized formulations were studied using DSC thermo grams. The samples were exposed to 0 to 200°C at a heating rate of 5°C/min under a nitrogen flow rate of -40°C/min through the DSC cell. The thermograms were recorded. [25]

4.9. Stability studies:

Stability analyses were conducted as per ICH guidelines at 25±2° C/60 % RH ±5% and 40±2° C/75 % RH ±5% for 3 months. Physical appearance, disintegration time and drug content of the optimized formulation were studied. [25]

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