Section A-Research paper
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A STUDY ON EFFECT OF HYDROPHILIC CARRIER AND SUPERDISINTEGRANTS IN ENHANCEMENT OF ARIPIPRAZOLE DISSOLUTION PROFILE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Objective: The present research aimed to increase the solubility and dissolution rate of a poorly water soluble Aripiprazole (APZ) drug by a solid dispersion technique.

Methods: Solid dispersions (SD) of APZ were prepared by fusion method using hydrophilic carrier Polyethylene glycol 6000 (PEG 6000) and co-carriers like, Croscarmellose sodium (CCS) and Crospovidone (CP) in different proportions and also prepared physical mixtures. These dispersions were characterized by in-vitro drug dissolution, Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) studies.

The optimized solid dispersion (6SD9) was formulated into fast-dissolving tablets (F1-F6) by direct compression method and evaluated for its pre and post compression parameters.

Results: PEG 6000 physical mixtures containing Aripiprazole (6PM3), showed enhanced dissolution rate when compared with pure drug (APZ). Binary solid dispersions (6SD3) 59.32 % showed an improvement in the dissolution rate when compared to the Physical Mixtures (6PM3) 50.56% and pure drug (APZ) 17.38% drug release was resulted at the end of 60 min. From ternary solid dispersions with CCS, formulation code 6SD9 showed 92.62% and with CP, formulation code 6SD15 showed 73.34%, whereas pure drug showed 20.27 % drug release was resulted at the end of 60 min. So, based on the in-vitro dissolution studies of solid dispersions, the 6SD9 was selected to prepare tablets (F1-F6) by direct compression method using tableting excipients MCC and Mannitol as diluents and CCS, CP, SSG as super disintegrants. The prepared tablets were evaluated for its quality. From the results of dissolution studies of tablets, the formulation F3 95.25% showed rapid dissolution rate than other formulations and pure drug

20.27%. FTIR, DSC studies suggest that there was no physical and chemical interaction in between pure drug (APZ), carriers and co-carriers.

Conclusion: Hence, the present study can conclude that ternary solid dispersions in association with super disintegrants were more effective in increasing the dissolution rate of poorly soluble drug than binary solid dispersions, physical mixtures and pure drug.

Key words: Solid Dispersion, Aripiprazole, Drug Carriers, Solubility, Dissolution Rate, Binary, Ternary, FTIR, and DSC.

INTRODUCTION:

Poorly water-soluble drugs whose absorption and bioavailability is limited mainly by dissolution. For such drugs, one of the best approaches to increase solubility is particle size reduction which improves the dissolution and thereby enhances the absorption and bioavailability of drugs. Particle-size reduction is obtained by milling or triturating, grinding, micronization, and spray drying [1]. Another important approach to reducing particle size is the solid dispersion technique [2]. Solid dispersion is nothing but the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the solvent method, melting, or melting-solvent method. Water soluble polymers are used as carriers or matrix materials in the preparation of solid dispersions. Aripiprazole is poorly soluble and is primarily used for the treatment of schizophrenia or bipolar disorder [3]. Aripiprazole is practically insoluble in water. The Aripiprazole half-life is 75 h and maximum or peak plasma concentration attains within 3 hours to 5 hours. Aripiprazole drug solubility and dissolution rate was improved by different approaches like mouth dissolving film [4], orally disintegrating tablets [5], and complexation with β-cyclodextrin [6].

So, the poor aqueous solubility of an active pharmaceutical ingredient (Aripiprazole) is one of the most critical challenges in pharmaceutical research and development. This antipsychotic drug has an poor therapeutic impact because of its minimal and idiosyncratic oral bioavailability to treat schizophrenia.

The present study aimed to know the effect of individual and combination of PEG 6000 and CCS/CP solid dispersions on the solubility and dissolution rate of Aripiprazole. Physical mixtures, binary, and ternary solid dispersions were prepared by the fusion method and characterized by using differential scanning calorimetry (DSC), and infrared spectroscopy (FTIR). The optimized solid dispersion (6SD9) was formulated into tablets by direct compression method using tableting excipients MCC and Mannitol as Diluents and CCS, CP, SSG as super disintegrants and evaluated for tablet quality parameters then finally reported optimized formulation (F3) with increased solubility than pure drug.

MATERIALS AND METHODS

Materials

In the present research work, Aripiprazole (APZ) was obtained as a gift sample from Suven Life Sciences, Hyderabad. Polyethylene glycol 6000 (PEG 6000), Croscarmellose sodium (CCS), Crospovidone (CP), Sodium Starch Glycolate (SSG), Mannitol, Microcrystalline Cellulose (MCC), Magnesium stearate, Talc were purchased from supplier S.D. Fine Chemicals Ltd, Mumbai, India and other chemicals used in the research work were of analytical grade.

Preparation Method of Solid Dispersions (SD) by Fusion Method:

Binary Solid Dispersions (6SD1 -6SD3):

Accurately weighed water-soluble carrier (PEG 6000) was taken into a china dish and melted at 50^{o}C and added Aripiprazole drug (Table 1) and then mixed well with glass rod for 3 minutes followed by cooling on an ice bath.

Ternary Solid Dispersions (6SD4-6SD15):

Drug and co-carrier (CCS/ CP) were added to molten PEG 6000 carrier (Table 1) and then thoroughly mixed for 3 min followed by cooling on an ice bath. Then scrapped the powder from the china dish then the powder was passed through sieve no. 60 and stored in a desiccator.

Preparation Method of Physical Mixture (6PM1-6PM15):

The required amounts of drug and carrier (Binary) or drug, carrier, and co-carrier (Ternary) (Table 1) were taken in a poly bag and shaken well to form a physical mixture for 15 minutes. The mixture was passed through sieve number 60 and stored in a desiccator [7].

Table 1: Formulation of Solid Dispersions and Physical Mixtures

Code No (Physical mixtures)	Code No (Solid dispersions)	Drug: Carrier: Co Carrier Ratio	DRUG(mg)	PEG6000(mg)	CCS(mg)	CP(mg)
6PM1	6SD1	1:1	50	50	0	0
6PM2	6SD2	1:2	50	100	0	0
6PM3	6SD3	1:3	50	150	0	0
6PM4	6SD4	1:1:0.5	50	50	25	0
6PM5	6SD5	1:2:0.5	50	100	25	0

6PM6	6SD6	1:3:0.5	50	150	25	0
6PM7	6SD7	1:1:1	50	50	50	0
6PM8	6SD8	1:2:1	50	100	50	0
6PM9	6SD9	1:3:1	50	150	50	0
6PM10	6SD10	1:1:0.5	50	50	0	25
6PM11	6SD11	1:2:0.5	50	100	0	25
6PM12	6SD12	1:3:0.5	50	150	0	25
6PM13	6SD13	1:1:1	50	50	0	50
6PM14	6SD14	1:2:1	50	100	0	50
6PM15	6SD15	1:3:1	50	150	0	50

Characterization of Solid Dispersions:

Estimation of drug content:

A solid dispersion powder equivalent to 30 mg of aripiprazole was weighed accurately and transferred into a 100 ml volumetric flask then dissolved by adding methanol. The volume was then made up to the mark with methanol. Then the solution was filtered, diluted and the sample was estimated for aripiprazole content in the solid dispersions using UV-Visible spectrophotometer at λ max of 219 nm.

Calibration curve of Aripiprazole:

100 mg of Aripiprazole pure drug was dissolved in 100 ml of methanol (1mg/ml stock solution). 1 ml of above solution was taken and make up with 100ml by using methanol (10µg/ml). The solution was filtered through Whatmann filter paper No. 41and scanned between wavelenth 200 nm to 400 nm and λ max was observed at 219 nm.

The above stock solution (10µg/ml) solution was subsequently diluted with methanol to obtain series of dilutions containing 2, 4, 6, 8 and 10 µg/ml of Aripiprazole solution. The absorbance of the above dilutions was measured at 219 nm by using UV-Spectrophotometer taking methanol as blank. Standard graph was plotted by taking Concentration on X-Axis and absorbance on Y-Axis. Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis (Fig.1).

Aqueous solubility study:

This study was carried out to determine aqueous solubility of drug by the shake-flask method [8]. In this method, an excess quantity of pure drug and solid dispersions was taken in separate glass flasks containing 10 ml of distilled water. The flasks were shaken well in an orbital shaker for 24 hours. The drug and solid dispersion samples were filtered and the filtrates were diluted suitably and absorbance was measured at 219 nm.

Drug-Excipient Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR spectra of aripiprazole & solid dispersions were obtained by KBr pellet method. Drug samples and KBr powder were mixed and sample discs were prepared by compressing the powder at a pressure of 5 tons in a hydraulic press. The samples were scanned in range of 400-4000 cm^{-1} and resolution was 2 cm^{-1}.

Differential Scanning Calorimetry:
Thermograms were obtained by using a differential scanning calorimeter (Shimadzu DSC 60). Samples were sealed in an aluminum pan and heated from 0 °C to 350 °C at a heating rate of 10 °C / min under nitrogen gas and the empty aluminum pan was used as a reference.

In vitro dissolution study for Solid Dispersion:
For this study, 900 ml of 0.1N HCl (pH 1.2) dissolution medium was placed in vessel of USP apparatus–II (paddle type) (Lab India DS 8000). The dissolution medium was allowed to equilibrate to the temperature of 37 °C ± 0.5 °C. Solid dispersions and pure drug powder was poured into the vessels and the study was conducted with 75 revolutions per minute (rpm) for 1 hour. At predetermined time intervals withdrawn 5 ml of dissolution media from each vessel and filtered and then added fresh 5 ml dissolution media to vessels to maintain sink condition. The withdrawn dissolution samples were analyzed using UV spectrophotometer at 219 nm.

Formulation and Evaluation of Fast dissolving Tablets:

As per in-vitro dissolution studies of Aripiprazole solid dispersions, the 6SD9 solid dispersion was selected to formulate into tablets. The formulations are made with different excipient ratios (Table 2: F1-F6). Aripiprazole solid dispersion (6SD9) and Mannitol, Microcrystalline Cellulose (MCC) as diluents, Croscarmellose sodium (CCS), Crospovidone (CP) and Sodium Starch Glycolate (SSG) as super disintegrants, Magnesium Stearate is used as a lubricant and Talc as a glidant were mixed thoroughly in a poly bag and shaken well to form a blend. The Precompression parameters like Bulk Density, Tapped Density, and Angle of repose, Carr's index, and Hausner's ratio were evaluated for the obtained blend. The powder blend was compressed into tablets by direct compression method on Cadmach 16 station rotary tableting

press at constant compression force and compressed tablets were evaluated for its quality parameters like hardness, friability, weight variation and drug content, disintegration time and percent drug release in 0.1N HCl (pH 1.2) dissolution medium.

Table 2: Tablet Formulations with Solid Dispersion and Excipients

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Solid Dispersion (6SD9)	150	150	150	150	150	150
CCS	---	20	20	---	---	40
CP	---	---	---	20	---	--
SSG	---	----	---	---	20	--
Mannitol	----	----	70	70	70	--
MCC	145	125	55	55	55	105
Mg. Stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2

RESULTS AND DISCUSION:

Standard Calibration curve of Aripiprazole:

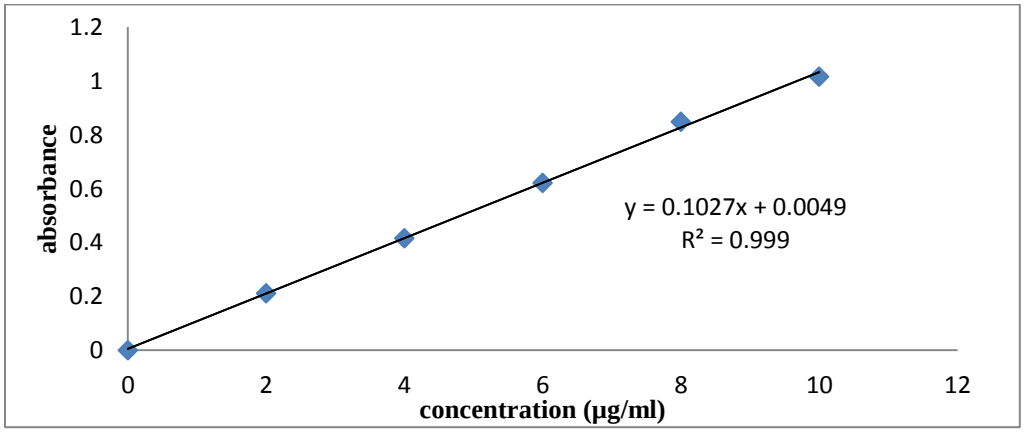

Fig. 1: Standard calibration curve of Aripiprazole(APZ).

Drug content:

The drug content in all prepared solid dispersions was found in between 98 % and 102%. Solid dispersions showed high drug content and low standard deviations of the results. Thus, It indicates that the uniform dispersion of the drug in the solid dispersions.

Aqueous solubility studies:

The aqueous solubility studies were conducted in distilled water for pure drug and solid dispersions. Pure Aripiprazole drug exhibited solubility of 2.01 µg/mL in distilled water whereas solid dispersions exhibited a solubility of 4.01 µg/mL in distilled water. Aqueous solubility studies indicated that the solubility of solid dispersions was increased when compared to the solubility of the pure drug in distilled water which might be due to the presence of hydrophilic carriers in solid dispersions has shown better wettability and large surface area to the drug crystals. The fast and rapid dispersability might have also contributed to the increase in solubility [10]. Due to the co-carrier disintegration nature, solid dispersion particle may disintegrate and promotes increased solubility than pure drug [11, 12].

Fourier Transform Infrared Spectroscopy (FTIR):

Fourier Transform Infrared Spectroscopy method was used to characterize and compare the various functional groups present on the Aripiprazole molecule of pure drug and solid dispersions formulations. The infrared (IR) spectrums obtained are shown in Fig. 2. Pure Aripiprazole drug and Fig. 3 optimized solid dispersion (6SD9). Both spectrums shows broad peaks respectively in the region between 3203 and 3437 cm-1 indicates the presence of N-H stretching vibration, C-H stretch occurs at 2948, 2889 cm-1, carbonyl stretching vibration is seen at 1676 cm−1 and 1629 cm−1, Aromatic C-O stretch shows at 1241, 1242 cm-1, while the saturated C -O stretch appeared at 1041 cm-1 and 1060 cm-1. The results from FT-IR spectroscopy showed that all the characteristic bands of Aripiprazole molecule remain unaffected in solid dispersions and no change in the characteristic pattern of absorption bands. Thus FTIR study suggested absence of interactions between Aripiprazole and carriers.

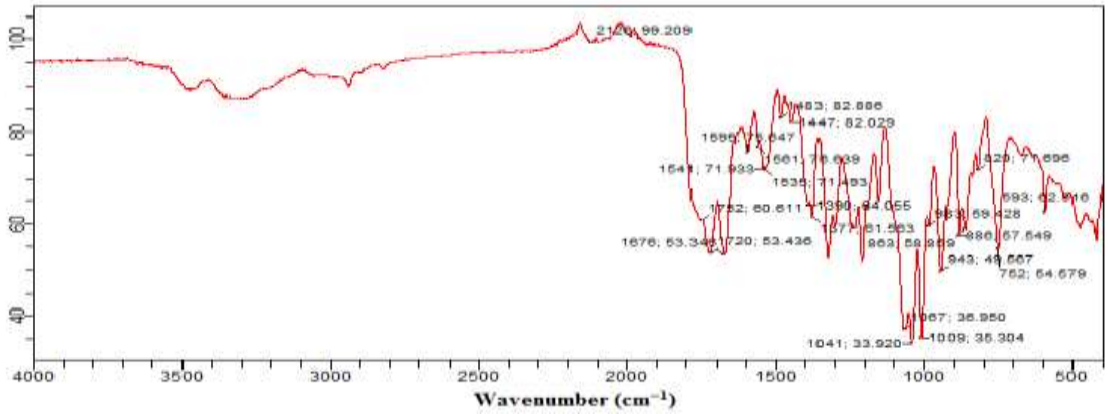

Fig. 2: FTIR spectrum of Pure Aripiprazole (APZ)

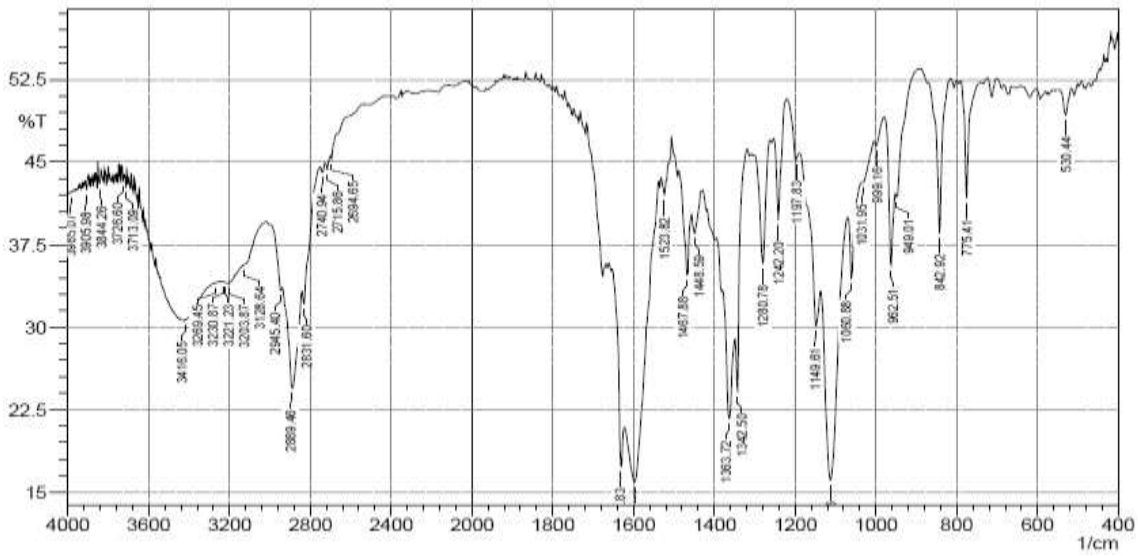

Fig. 3: FTIR Spectrum of Solid Dispersion (6SD9)

Differential Scanning Calorimetry (DSC):

Thermal stability of optimized solid dispersions (6SD9) was analyzed using DSC technique. From the differential scanning calorimetry study, thermogram of Aripiprazole in solid dispersion exhibits a melting endotherm at 134.5 °C (Fig.4**)** is evident that there was no physical or chemical interaction in between Aripiprazole, carriers and co-carriers.

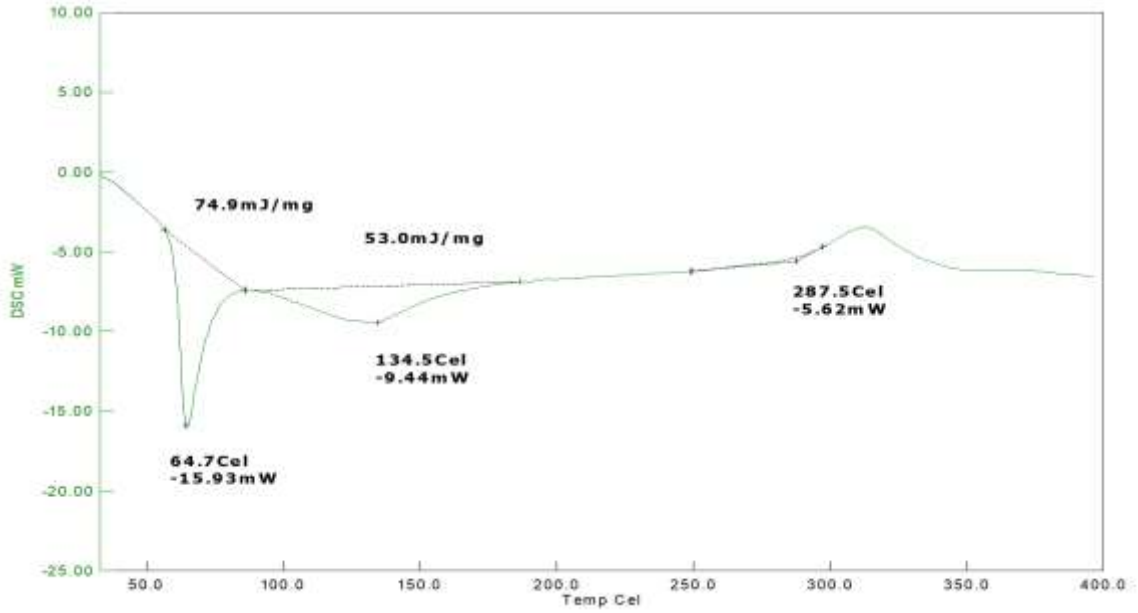

Fig. 4: Differential Scanning Calorimetry Thermogram of Solid Dispersion (6SD9)

In vitro Dissolution of Aripiprazole Solid Dispersions:

Binary solid dispersions:

Solid dispersions were developed to improve the dissolution of a poorly soluble Aripiprazole drug by fusion method with water-soluble carrier PEG 6000. The percentage drug release from binary solid dispersions and pure drug are shown in Fig.5 Solid dispersions (6SD1-6SD3) showed enhancement in dissolution rate in comparison to Physical Mixtures (6PM1-6PM3) and pure drug alone. Among the PEG 6000 binary solid dispersions, 6SD3 showed 47.64 % drug release in 5 minutes and 59.32 % release in 60 minutes which is more percentage drug release than other binary solid dispersions. Among the PEG 6000 binary physical mixtures, 6PM3 showed more percentage drug release than other binary physical mixtures (35.66 % and 50.56 % release in 5 minutes and 60 minutes respectively) Fig.5. Binary solid dispersions showed marked improvement in the dissolution rate when compared to the physical mixtures and pure drug (17.38 %), which can be due to the effect of the drug: PEG 6000 ratio in binary solid dispersion, which leads to the absence of crystallinity nature of the drug and increases in the solubility [13], whereas in case of PMs drug exist in crystalline form. Hence, the dissolution studies indicated that as the proportion of the carrier increases, the dissolution of the drug was increased [14, 15].

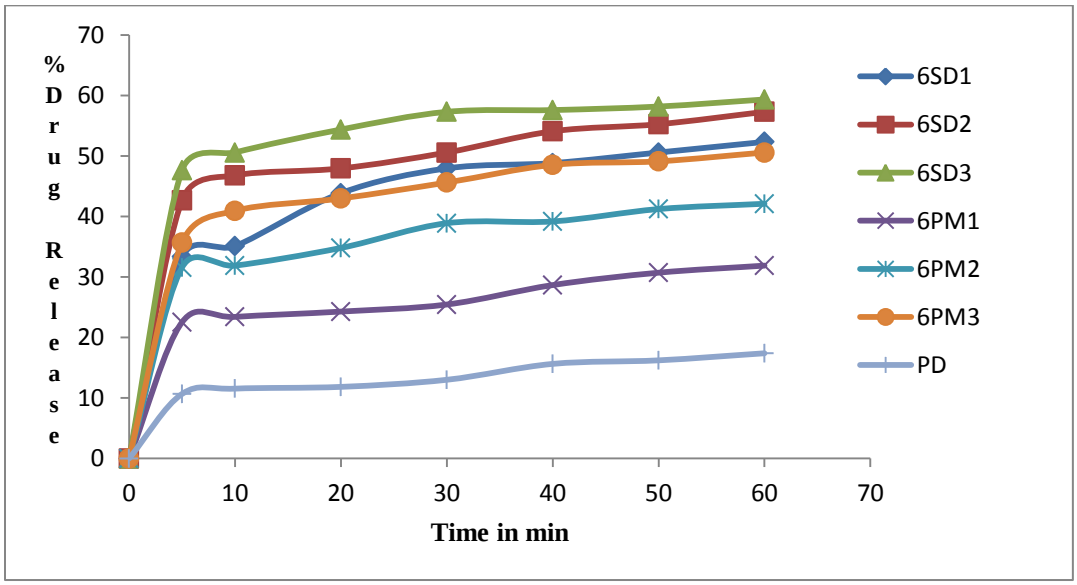

Fig. 5: Comparison of dissolution profiles of APZ, PEG 6000 Physical mixtures (6PM1-6PM3) and PEG 6000 Binary Solid dispersions (6SD1-6SD3).

Ternary solid dispersions (6SD4-6SD15):

Ternary Solid Dispersions were prepared with mixture of PEG 6000 and CCS or CP in different weight ratios (Table-1). Dissolution profiles of ternary solid dispersions and pure drug are presented in Fig.6 for 6SD4-6SD9 and Fig. 7 for 6SD10-6SD15. From Fig. 6 formulation code 6SD9 (D: PEG 6000: CCS = 1:3:1) showed 86.49 % drug release in 5 minutes and 92.62% release in 60 minutes. From Fig. 7 formulation code 6SD15 (D: PEG 6000: CP = 1:3:1) showed 51.14 % drug release in 5 minutes and 73.34% release in 60 minutes, but pure drug released only 20.27 % at the end of 60 minutes.

From Fig. 6 & 7, formulation code 6SD9 solid dispersion exhibited rapid and higher dissolution than all other ternary solid dispersions. The possible reasons for improved dissolution of 6SD9 formulation might be solubilizing effect of Poly ethylene glycol which increases drug wettability and improve the dissolution [16] and Croscarmellose sodium absorbs water and shows swelling and wicking [17] which results in increased drug wettability and dispersibility in dissolution medium. So the combined carriers in solid dispersions showed higher improvement in the dissolution rate of APZ compared with use of individual water soluble carriers [14].

From Fig.8 Ternary solid dispersions showed higher dissolution rate of aripiprazole than binary solid dispersions, physical mixtures and pure drug.

As per present study, PEG 6000 solid dispersions exhibited higher dissolution with increasing the carrier and co-carrier proportions, when compared to the PEG 6000 physical mixtures and pure aripiprazole which can be due to the possible explanations proposed by Craig and Ford [18, 19] which include: crystalline size reduction of drug, a solubilizing effect of the PEG 6000 carrier, lack of aggregation of drug crystallites, excellent wettability, dispersibility of the drug, dissolution of the drug in the hydrophilic PEG 6000 carrier, conversion of the drug from crystalline state to the amorphous state and due to co-carrier disintegration nature, solid dispersion particle may disintegrate and promotes the increased solubility than pure drug [20].

Study observations clarified that the Ternary solid dispersions were more effective to improve the dissolution rate of poorly soluble drug than binary solid dispersions and physical mixtures.

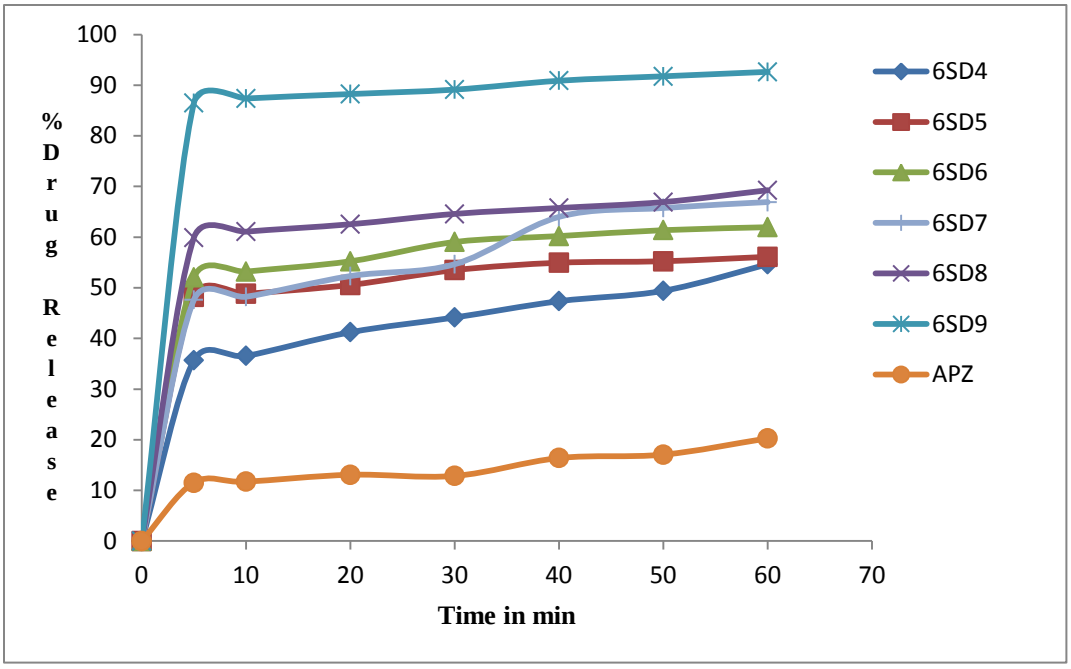

Fig. 6: Dissolution of Pure APZ and Ternary Solid dispersions with CCS from 6SD4-6SD9.

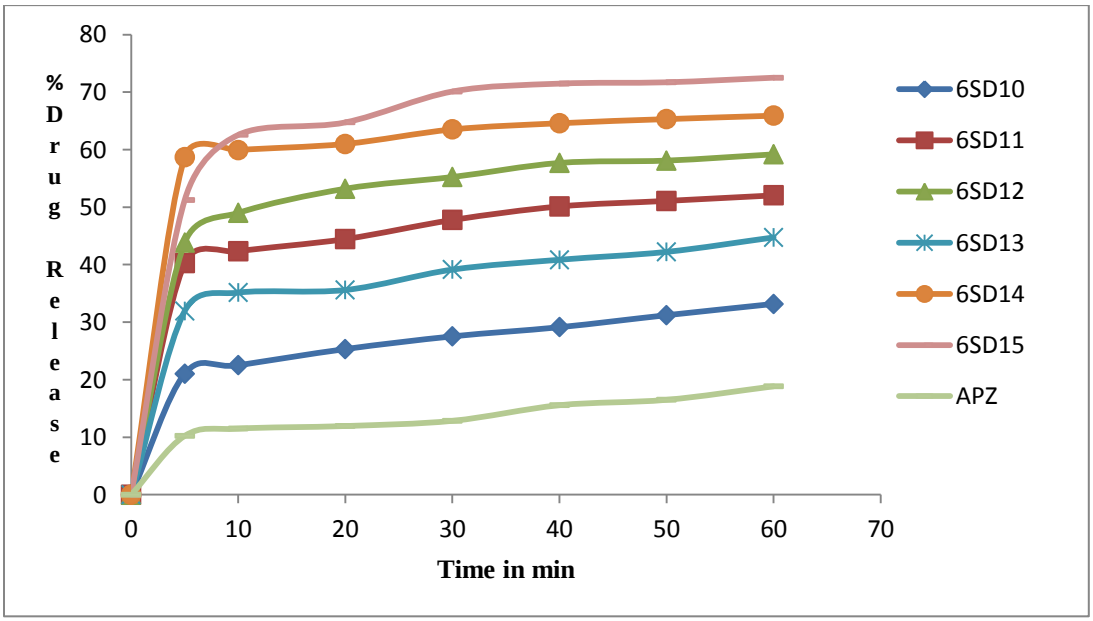

Fig.7: Dissolution of Pure APZ and Ternary Solid dispersions with CP from 6SD10-6SD15.

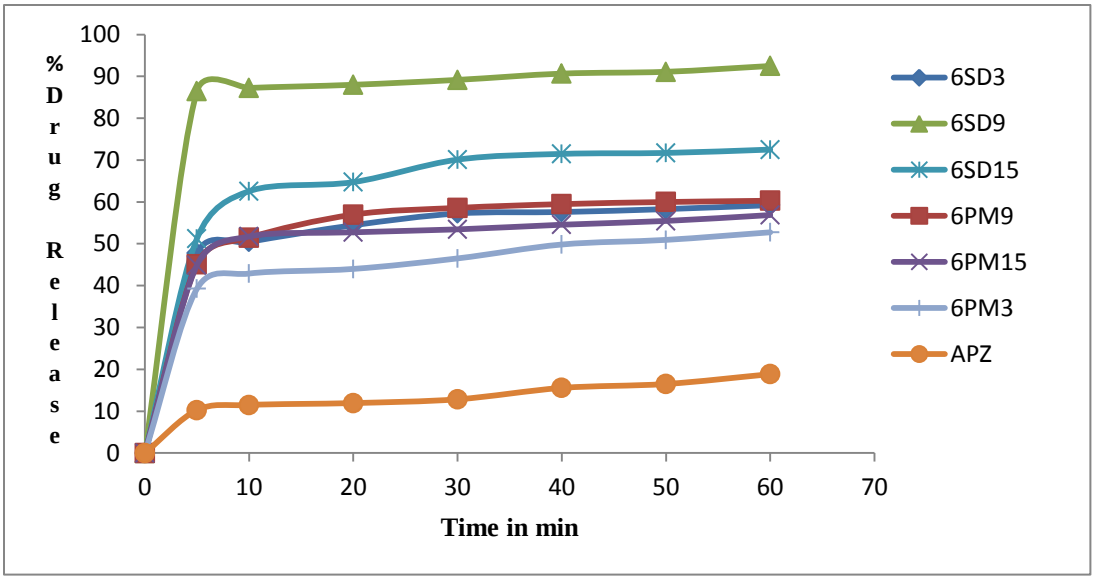

Fig. 8: Comparison of dissolution of pure APZ, Physical Mixtures (6PM3, 6PM9, 6PM15) and Solid dispersions (6SD3, 6SD9, 6SD15).

Formulation and Evaluation of Fast dissolving Tablets:

Blend Evaluation: Thoroughly mixed 6SD9 blend was evaluated for Bulk Density, Tapped Density, and Angle of repose, Carr's index, and Hausner's ratio and obtained results (Table 3) revealed that the excellent flow characteristic of solid dispersions which indicates its suitability for direct compression method.

Table 3: Pre-compression parameters of PEG 6000 SD (6SD9)

Formulation code	Bulk density (g/cc)	Tapped density(g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
F1	0.2886±0.009	0.318±0.06	23.16±1.46	9.59±1.23	1.104±0.07
F2	0.2787±0.003	0.310±0.01	24.7±0.78	10.4±0.97	1.11±0.05
F3	0.2786±0.002	0.305±0.02	22.46±0.63	8.11±0.89	1.06±0.08
F4	0.2928±0.005	0.317±0.03	23.44±0.49	7.88±1.23	1.08±0.04

F5	0.2778±0.006	0.311±0.01	21.89±1.20	10.93±0.87	1.12±0.05
F6	0.285±0.002	0.312±0.05	25.03±0.12	8.63±0.64	1.09±0.02

* Table values are expressed as mean Standard Deviation ±n=3

Tablet Evaluation: The prepared tablets were evaluated for its compression parameters like hardness, friability, weight variation test, disintegration time and obtained results showed in Table 4. F3 formulation tablet showed low hardness compared to other formulations. Friability of all formulation tablets were found between 0.26 to 0.43% which is well below the standard NMT 1 %. From the disintegration test, the prepared tablets were disintegrated rapidly and it was found between 25 seconds - 43 seconds. F3 formulation tablets showed least disintegration time than others.

Table 4: Post-compression parameters of PEG 6000 SD Tablets

Formulation code	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Disintegration time in Seconds	Drug content %
F1	2.7±0.10	0.43±0.04	300±1.15	30	99.99
F2	2.9±0.07	0.37±0.07	299.6±1.43	32	100.1
F3	2.5±0.04	0.31±0.02	300.4±1.07	25	100.5
F4	3.3±0.15	0.42±0.08	300.4±1.26	43	100.3
F5	3.2±0.12	0.26±0.03	300.6±1.43	40	101
F6	3.1±0.09	0.32±0.05	300.2±1.93	38	101

*Table values are expressed as mean Standard Deviation ±n=3

Tablet drug content: Ten tablets were individually weighed and crushed using mortar and pestle to make powder. Weighed the powder equivalent to 30mg of aripiprazole drug and transferred to 100 ml volumetric flask and dissolved in 100 ml of Methanol. The solution was filtered and drug content was determined by UV visible-spectroscopy at a wavelength of 219 nm. The obtained results showed in Table 4.

Tablet Dissolution Test: Dissolution test was performed for all prepared tablets and obtained results are shown in Table 5. Out of six formulations, F3 showed higher % drug release than other formulation tablets and pure drug (Fig.9) and showed more than 95 % drug release at 60 minutes end of the dissolution test which might be due to the use of super-disintegrant (CCS) which absorb the water and swells when exposed to an aqueous environment and promote the rapid disintegration of tablets. Mannitol and Micro Crystalline Cellulose (MCC) coats the solid dispersion particles there by prevent the aggregation and increase the absorption of water and promote the faster disintegration [21].

Based on the tablet evaluation study, F3 formulation is the best formulation for preparation Aripiprazole fast dissolving tablets for commercial development.

Table 5: % Drug Release of Tablet formulations at end of the dissolution test

Formulation code	% Drug Release in 60min
F1	69.55
F2	65.17
F3	95.25
F4	72.76
F5	69.55
F6	69.25
Pure Drug	20.25

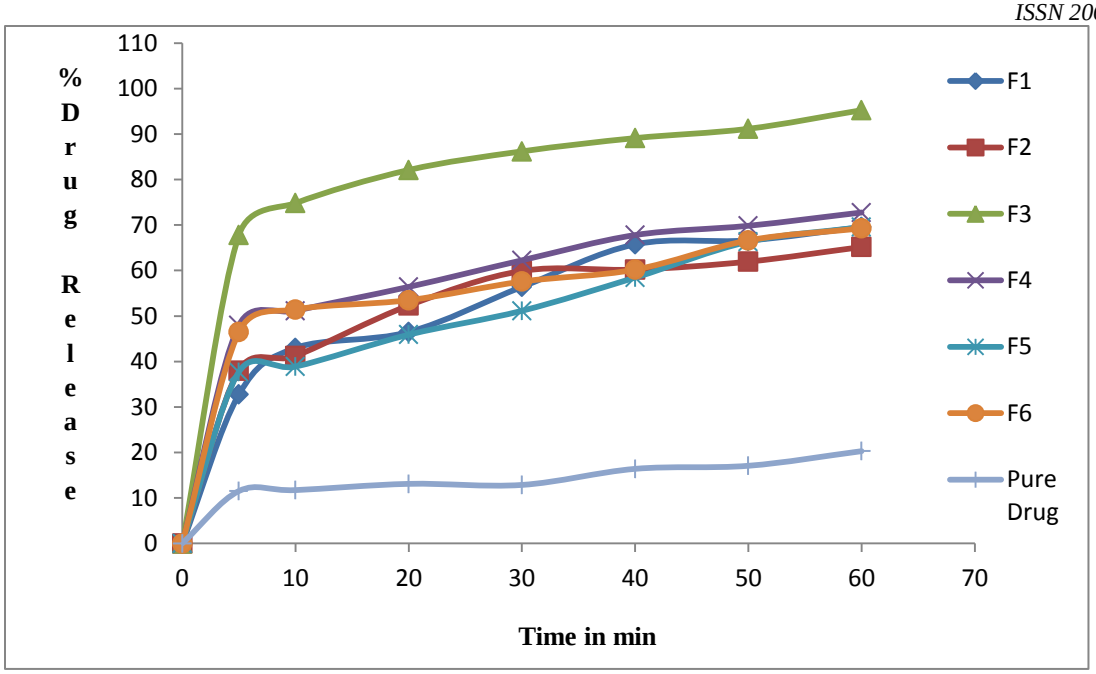

Fig.9: Dissolution profiles of pure APZ and Solid Dispersion Tablets (F1-F6).

CONCLUSION:

Aripiprazole Solid dispersions were prepared by fusion method using hydrophilic carrier PEG 6000, and super disintegrants Croscarmellose sodium (CCS) and Crospovidone (CP) to enhance the solubility and dissolution rate of poorly soluble aripiprazole drug and characterized. The FTIR and DSC studies indicating that the absence of interaction between drug and carrier and co-carrier. From the dissolution study of solid dispersions, 6SD9 exhibited higher dissolution rate than other binary and ternary solid dispersions which may be due to presence of hydrophilic carrier and increased co-carrier proportion. The 6SD9 was selected for the formulation of tablets (F1-F6) and F3 formulation showed higher dissolution rate than other tablets formulations which can be due to the use of super-disintegrant (CCS) which absorb the water and swells when exposed to an aqueous environment there by promote the rapid disintegration of tablets. Mannitol and Micro Crystalline Cellulose (MCC) coats the solid dispersion particles there by prevent the aggregation and increase the absorption of water and promote the faster disintegration [21]. Hence, the present study concluded that ternary solid dispersions were more effective in increasing the dissolution profile of poorly soluble Aripiprazole drug than binary solid dispersions, physical mixtures and pure drug.

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