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Original Article

SOLID DISPERSION TECHNIQUE TO ENHANCE THE SOLUBILITY AND DISSOLUTION RATE OF ARIPIPRAZOLE BY FUSION METHOD

SHASHIKUMAR YADAV*, M. VEENA, M. SRINIVAS

Department of Pharmaceutics, Sri Indu Institute of Pharmacy, Sheriguda, IBP, R. R. Dist, Telangana 501510
Email: shashikumarpharmacy@gmail.com

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ABSTRACT

Objective: The objective of the present study was to enhance the solubility and dissolution rate of Aripiprazole (APZ), a water insoluble drug, by a solid dispersion technique.

Methods: Solid dispersions (SD) of APZ were prepared by fusion method using water-soluble carriers like, polyethylene glycol 4000 (PEG 4000), Croscarmellose sodium (CCS) and Crospovidone (CP) and were characterized by in-vitro dissolution, Fourier transform infrared (FTIR) spectroscopy and Differential scanning calorimetry (DSC) studies.

Results: PEG 4000 physical mixtures containing APZ, showed enhanced dissolution rate as compared with pure drug. Binary solid dispersions showed an improvement in the dissolution rate when compared to the physical mixtures (PM) and pure drug. From ternary solid dispersions with CCS, formulation code SD9 showed 88.2% and with CP, formulation code SD15 showed 70.9%, whereas pure drug showed 18.8 % drug release at the end of 60 min. Based on the in-vitro dissolution studies of solid dispersions, the SD9 was selected to prepare tablets. From the dissolution studies of tablets, the formulation 4F3 showed rapid dissolution than other formulations and pure drug. FTIR, DSC studies suggesting that there was no physical and chemical interaction in between APZ and carriers.

Conclusion: Hence, it can be concluded that ternary solid dispersions in association with super disintegrants were more effective to increase the dissolution rate of low soluble drug than solid binary dispersions, physical mixtures, and pure drug.

Keywords: Solid dispersion, Aripiprazole, Drug carriers, Solubility, Dissolution rate, FTIR, and DSC.

INTRODUCTION

Poorly water soluble drugs whose absorption and bioavailability is limited by dissolution, for such drugs, particle size reduction increases the dissolution thereby increases the absorption and bioavailability. The particle-size reduction is obtained by grinding or triturating, milling, micronization, spray drying [1]. Another important method to reduce the particle size is solid dispersion technique [2]. Solid dispersion is the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent, or melting-solvent method. Water-soluble polymers are used as carriers or matrix materials in the preparation of solid dispersions. Aripiprazole is a poorly soluble and is primarily used for the treatment of schizophrenia or bipolar disorder [3]. Aripiprazole is insoluble in water**.** The half-life of aripiprazole is 75 h and peak plasma concentration attains within 3-5 h**.** Aripiprazole solubility and dissolution rate were improved by different approaches like mouth dissolving film [4], orally disintegrating tablets [5], complexation with β-cyclodextrin [6].

The present study was aimed to know the effect of individual and combination of PEG 4000 and CCS/CP solid dispersions on solubility and dissolution rate of aripiprazole. Solid dispersions were prepared by fusion method and characterized by using differential scanning calorimetry, infrared spectroscopy. The optimized solid dispersion was formulated as tablets using super disintegrants and evaluated for pre and post compression parameters.

MATERIALS AND METHODS

Materials

In the present research work, Aripiprazole was obtained as gift sample from Suven Life Sciences, Hyderabad. Polyethylene glycol 4000 (PEG 4000), Croscarmellose sodium (CCS), and Crospovidone (CP) were purchased from S. D. Fine Chemicals Ltd (Mumbai, India). All other chemicals used in the work were of analytical grade.

Method of preparation of solid dispersion (SD) by fusion method

Accurately weighed carrier (PEG 4000) was taken into a china dish and melted at 50 °C. At that temperature, calculated amount of drug was added (Binary solid dispersions), or drug and co-carrier (CCS/CP) was added (Ternary solid dispersions) (table 1) and then thoroughly mixed for 1-4 min followed by cooling on ice bath. Then scrapped the powder from china dish and passed through sieve no. 60 and stored in a desiccator.

Method of preparation of physical mixture (PM)

The required amounts of drug and carrier (Binary) or drug, carrier and co-carrier (Ternary) were mixed in a mortar and pestle to form a physical mixture. The mixture was passed through sieve number 60 and stored in desiccator [7].

Characterization of solid dispersions

Estimation of drug content

A quantity of solid dispersion equivalent to 30 mg of aripiprazole was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 0.1N HCL. The volume was then made up to the mark with 0.1N HCL. The solution was filtered and diluted suitably and aripiprazole content in the samples was estimated using UV-Visible spectrophotometer at λ max of 219 nm.

Aqueous solubility study

This study was carried out to determine the aqueous solubility of drug by the shake-flask method [8]. In this method, an excess quantity of drug and solid dispersions in separate glass flasks containing10 ml of distilled water. The samples flasks were shaken in an orbital shaker for 24 h. The samples were filtered through Whatman filter paper. The filtrates were diluted suitably and absorbance was measured at 219 nm.

Fourier transforms 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 the range of 400-4000 cm^{-1} and resolution was 2 cm^{-1}.

Table 1: Formulation of solid dispersions with PEG 4000

Code No (Physical mixtures)	Code No (Solid dispersions)	Drug: carrier: Co carrier ratio	Drug (mg)	PEG4000 (mg)	CCS (mg)	CP (mg)
PM1	SD1	1:1	50	50	0	0
PM2	SD2	1:2	50	100	0	0
PM3	SD3	1:3	50	150	0	0
PM4	SD4	1:1:0.5	50	50	25	0
PM5	SD5	1:2:0.5	50	100	25	0
PM6	SD6	1:3:0.5	50	150	25	0
PM7	SD7	1:1:1	50	50	50	0
PM8	SD8	1:2:1	50	100	50	0
PM9	SD9	1:3:1	50	150	50	0
PM10	SD10	1:1:0.5	50	50	0	25
PM11	SD11	1:2:0.5	50	100	0	25
PM12	SD12	1:3:0.5	50	150	0	25
PM13	SD13	1:1:1	50	50	0	50
PM14	SD14	1:2:1	50	100	0	50
PM15	SD15	1:3:1	50	150	0	50

Differential scanning calorimetry

Thermograms were obtained by using differential scanning calorimeter (Schimadzu DSC 60). Samples were sealed in aluminum pans 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**

In this study, 900 ml of 0.1 HCL (pH1.2) as dissolution medium was placed in a vessel of USP apparatus–II (Lab India DS 8000 (paddle type)). The dissolution medium was allowed to equilibrate to the temperature of 37 °C±0.5 °C. Solid dispersion and pure drug powder were poured into the vessel and the study was conducted with 75 revolutions per minute (rpm) for 1 h. At definite time intervals withdrawn 5 ml of sample, filtered and fresh 5 ml media was replaced to maintain sink condition. The obtained samples were analyzed using UV-Double beam spectrophotometer at 219 nm.

Precompression parameters

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients [9]. It gives the information needed to define the nature of the drug substance and provide a dosage form. Hence, the Angle of repose, Carr's index, and Hausner's ratio pre-formulation studies was performed for the obtained samples.

Formulation and evaluation of tablets

Based on the in-vitro dissolution studies, the optimized solid dispersion was selected for tablet preparation (table 2). Aripiprazole solid dispersion and all other ingredients were mixed thoroughly and compressed into tablets by direct compression method on 16 stations rotary tableting press (Cadmach Machinery Pvt. Ltd., Ahmadabad) using 9 mm standard flat punch. The obtained tablets were evaluated for in-vitro dissolution, hardness, friability, weight variation and drug content.

Table 2: Formulation of PEG 4000 SD tablets

Ingredients	4F1	4F2	4F3	4F4	4F5	4F6
SD9 (mg)	175	175	175	175	175	175
CCS (mg)	---	20	20	---	---	50
CP (mg)	---	---	----	20	---	--
Sodium Starch Glycolate(SSG) (mg)					20	--
Mannitol (mg)	----	----	70	70	70	--
MicroCrystalline Cellulose(MCC) (mg)	150	100	30	100	100	22
Magnesium Stearate (mg)	3	3	3	3	3	2
Talc (mg)	2	2	2	2	2	1

RESULTS AND DISCUSSION

Drug content

The drug content in the prepared solid dispersions was found in between 98.1 % and 99.2%. Solid dispersions showed high drug content and low standard deviations of the results. It indicates that the drug is uniformly dispersed in the solid dispersions.

Aqueous solubility studies

The solubility studies were conducted in aqueous media for pure drug and solid dispersions. Pure aripiprazole showed a solubility of 2.01 µg/ml in distilled water, whereas in PEG 4000 solid dispersions, the solubility of 3.6 µg/ml in distilled water. Aqueous solubility studies indicated that solubility of solid dispersions was increased when compared to the solubility of pure drug in distilled water which might be due to the presence of water-soluble carriers in solid dispersions gave better wettability and large surface area to the drug crystals. The fast and rapid dispersibility might have also contributed to the increase in solubility.

Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectrums of pure aripiprazole and PEG 4000 solid dispersions are shown in fig. 1 and 2. In both figures, aripiprazole shows broad peak 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 remain unaffected in solid dispersions. Thus, FTIR study suggested that the absence of interactions between aripiprazole and carriers.

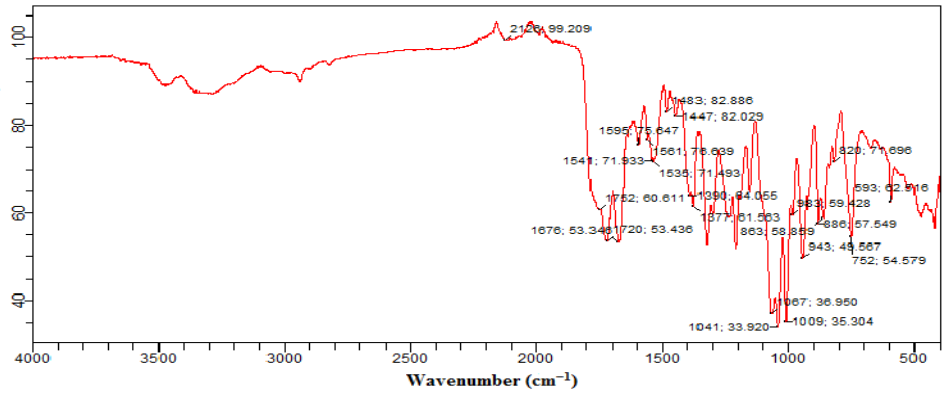

Fig. 1: FTIR spectrum of pure aripiprazole (APZ)

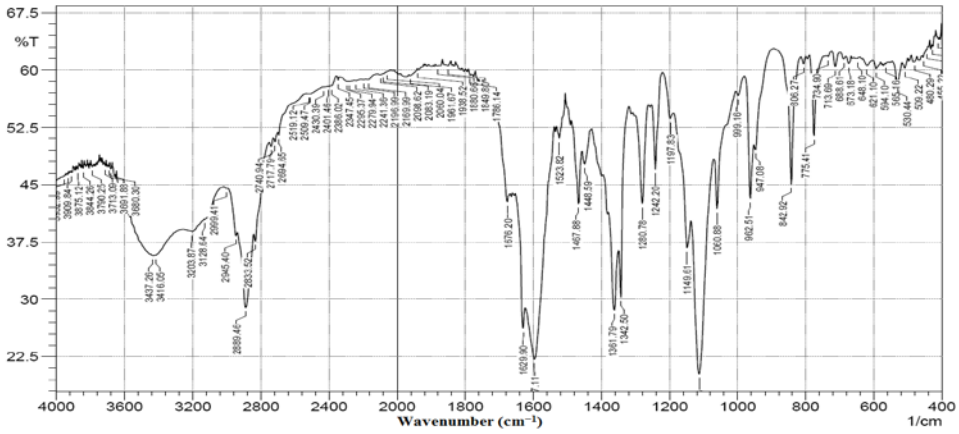

Fig. 2: FTIR spectrum of solid dispersion (SD9) Differential scanning calorimetry (DSC)

A new polymorph of aripiprazole characterized by DSC thermogram shows an endothermic peak in the range of 122-124 °C [10]. From the differential scanning calorimetry thermograms (fig. 3 & 4), the pure aripiprazole shows a sharp melting endotherm at 122.5 °C (fig. 3). DSC thermogram of PEG 4000 SD showed, the presence of broad melting peak of aripiprazole at 121.9 °C (fig. 4) suggesting that conversion from crystalline to amorphous form in the SD may be responsible for increased dissolution rate of the drug and there was no physical or chemical interaction in between APZ and carriers.

In vitro dissolution of aripiprazole solid dispersions

Binary solid dispersions

Solid dispersions were formulated to improve the dissolution of the poorly soluble drug, aripiprazole by using fusion method with water soluble carriers, showed enhancement in dissolution rate in comparison to physical mixtures and pure drug alone.

The drug release from solid binary dispersions of PEG 4000 is shown in fig. 5. From the PEG 4000 binary solid dispersions, SD3 showed more percentage drug release than other binary solid dispersions (44.6 % and 53.8 % release in 10 min and 60 min respectively). Among the PEG 4000 binary physical mixtures, PM3 showed more percentage drug release than other binary physical mixtures (29.8 % and 35.9 % release in 10 min and 60 min respectively).

Binary solid dispersions showed an improvement in the dissolution rate when compared to the physical mixtures and pure drug, which can be due to effect of drug: PEG ratio in binary solid dispersion, it leads to the absence of crystallinity nature of the drug and increases in the solubility [11], whereas in case of PMs drug exist in crystalline form. Hence, the dissolution studies indicated that as the concentration of carrier increases, dissolution of the drug was increased.

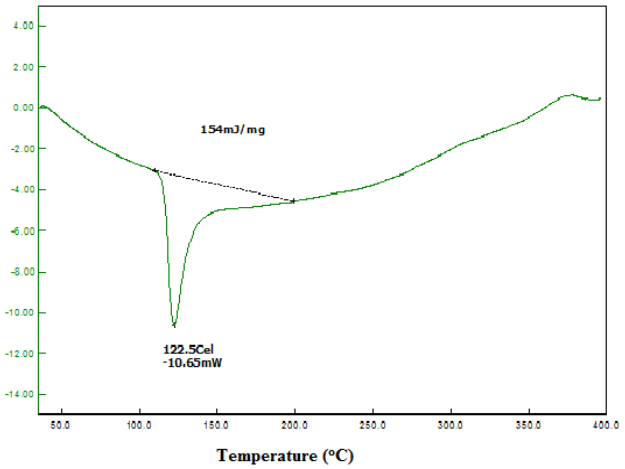

Fig. 3: Differential scanning calorimetry thermogram of pure aripiprazole (APZ)

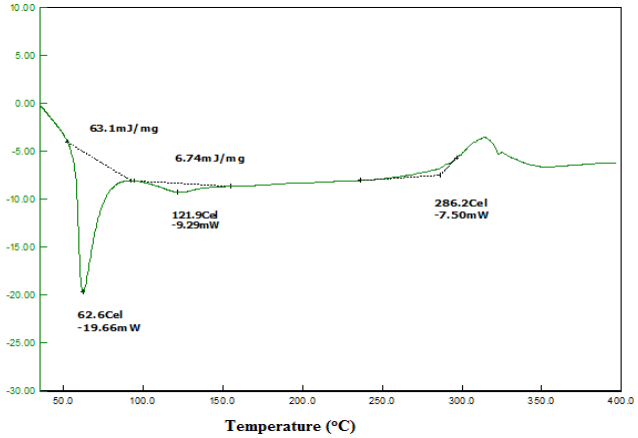

Fig. 4: Differential scanning calorimetry thermogram of solid dispersion (SD9)

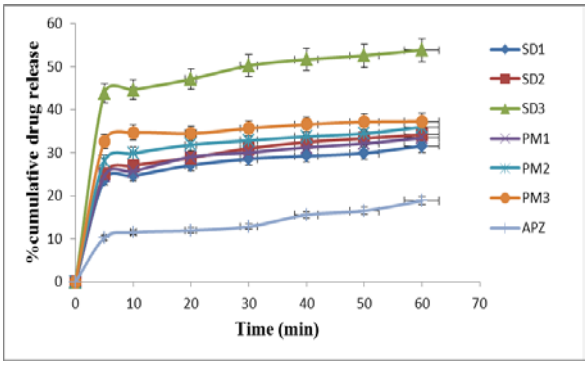

Fig. 5: Dissolution of pure APZ, binary solid dispersions from SD1-SD3 and physical mixtures from PM1-PM3

Ternary solid dispersions

From solid dispersions with CCS (fig. 6), formulation code SD 9 (D: PEG 4000: CCS = 1:3:1) showed 78.1 % and 88.2 % release in 10 min and 60 min respectively and from solid dispersions with CP (fig. 7), formulation code SD15 (D: PEG 4000: CP = 1:3:1) showed 63.9 % and 70.9 % release in 10 min and 60 min respectively, whereas pure drug has released only 18.8 % at the end of 60 min. The SD9 solid dispersion gave fast and improved dissolution compared to the all other ternary solid dispersion, which might be due to the use of hydrophilic carriers PEG 4000 and croscarmellose sodium. Croscarmellose absorbs water and swells 4 to 8 folds in less than 10 s and shows swelling and wicking [12].

Thus, the dissolution improved as the drug gets wetted. At the same time PEG 4000 dissolved in dissolution medium and release the drug rapidly, So the combined carriers gave a much higher improvement in the dissolution of APZ compared with use of individual water-soluble carriers [13]. It was reported that, solid dispersions prepared with a combination of PEG 4000 and super disintegrants showed marked enhancement in the dissolution rate of aripiprazole than binary solid dispersions, physical mixtures and pure drug (fig. 8).

Hence, PEG 4000 solid dispersions showed higher dissolution with increasing the carrier concentration from 1:1 to 1:3., when compared to the PEG 4000 physical mixtures and pure aripiprazole which can be ascribed due to the possible explanations proposed by Craig and Ford [14, 15] which include: crystalline size reduction of drug, a solubilizing effect of the PEG 4000 carrier, lack of aggregation of drug crystallites, excellent wettability, dispersibility of the drug, dissolution of the drug in the hydrophilic PEG 4000 carrier, conversion of the drug from crystalline state to the amorphous state and the combination of the above mentioned mechanisms. Distribution of drug at the molecular level in SDs promote wetting, thereby improves dissolution, where it is not possible in PMs.

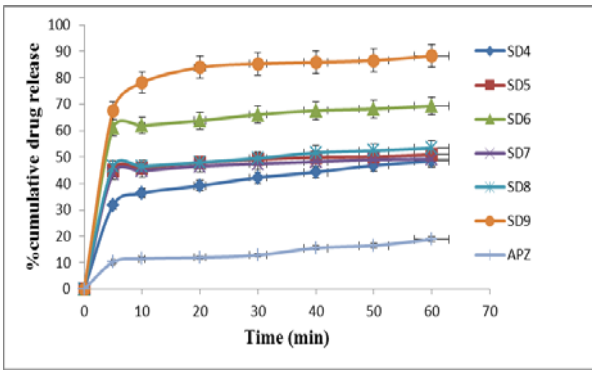

Fig. 6: Dissolution of pure APZ and ternary solid dispersions with CCS from SD4-SD9

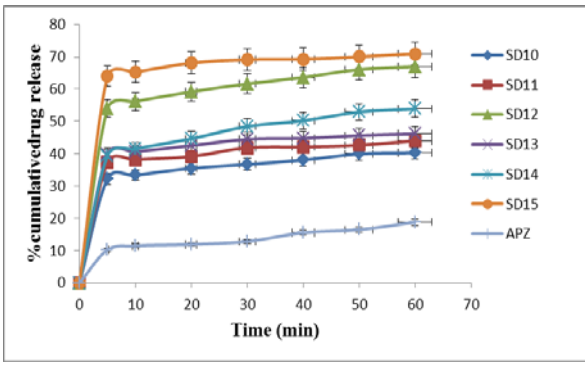

Fig. 7: Dissolution of pure APZ and ternary solid dispersions with CP from SD10-SD15

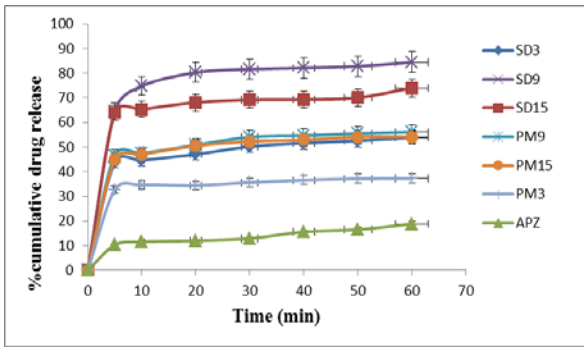

Fig. 8: Comparison of dissolution of pure APZ, physical mixtures PM9,PM15,PM3 and solid dispersionsSD3, SD9,SD15Pre-compression parameters

The PEG 4000 solid dispersions were prepared by fusion method and evaluated. These solid dispersion powders were fine in nature and having an angle of repose in the range of 21 °–24 ° and compressibility index values were within the limits (table 3). These results revealed that the excellent flow characteristic of solid dispersions which indicates its suitability for direct compression method.

Table 3: Pre-compression parameters of PEG 4000 SD

Formulation code	Bulk density(g/cm³)	Tapped density (g/cm³)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
4F1	0.2873±0.005	0.315±0.03	22.16±1.52	8.88±1.23	1.097±0.07
4F2	0.292±0.003	0.312±0.01	23.7±0.88	6.4±0.97	1.068±0.05
4F3	0.2754±0.002	0.303±0.02	22.29±0.53	7.92±0.89	1.101±0.08
4F4	0.283±0.008	0.311±0.02	24.44±0.89	9.003±1.23	1.098±0.04
4F5	0.2674±0.007	0.308±0.02	22.89±1.20	11.26±0.87	1.153±0.05
4F6	0.271±0.002	0.301±0.03	23.21±1.02	9.96±0.21	1.11±0.03

Tablet preparation and evaluation

Based on the in-vitro dissolution studies of solid dispersions, the SD9 was selected to prepare tablets. Table 4 showed all the post-compression parameters determined for tablets. The prepared tablets hardness was in the range of 2.5–3.1 kg/cm³. Friability weight loss was found in between 0.24±0.01 to 0.35±0.06. From the disintegration test, the prepared tablets were disintegrated rapidly and it was found to be between 80 s-132 s. From the dissolution studies of tablets (fig. 9), the formulation 4F3 showed rapid dissolution than other formulations and pure drug (18.8±1.48 %). The percent drug release from formulation 4F3 in 30 min was 86±0.62% which can be due to the use of super-disintegrant and mannitol. The super-disintegrant absorb the water and swells when exposed to an aqueous environment thereby promote the rapid disintegration of tablets. Mannitol and microcrystalline cellulose (MCC), which coats the PEG particle thereby prevent the aggregation and increases the absorption of water and promote the faster disintegration.

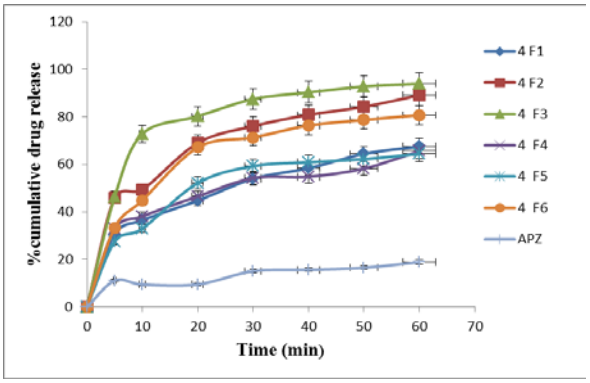

Fig. 9: Dissolution profiles of pure APZ and solid dispersion tablets (4F1-4F6)

Table 4: Post-compression parameters of PEG 4000 SD tablets

Formulation code	Hardness (kg/cm²)	Friability (%)	Weight variation (%)	Disintegration time (s)	% Drug release in 30 min
4F1	2.6±0.09	0.29±0.03	99.1±0.4	90±0.8	53±1.3
4F2	2.5±0.11	0.32±0.02	99.5±0.2	119.6±1.2	76±0.9
4F3	2.7±0.08	0.24±0.01	98.3±0.6	81±0.81	86±0.6
4F4	2.8±0.12	0.35±0.06	97.8±0.5	131.6±1.2	54±1.2
4F5	3.0±0.15	0.27±0.05	99.2±0.8	124.6±2.05	59±0.8
4F6	3.1±0.07	0.35±0.04	98.3±0.2	130±0.8	71±0.4

CONCLUSION

Solid dispersions were prepared by fusion method using hydrophilic carriers and characterized to enhance the dissolution rate of aripiprazole. The dissolution rate of aripiprazole was increased from solid dispersions due to the presence of hydrophilic polymers and increased carrier concentration. From the solid dispersions, SD9 showed higher dissolution rate than others which may be due to the presence of CCS with increased concentration. The SD9 was selected for the preparation of tablets and 4F3 showed higher dissolution rate than other tablets. The FTIR and DSC studies indicating that the absence of interaction between drug and carrier.

ABBREVIATION

CCS-Croscarmellose sodium, CP-Crospovidone, DSC-Differential Scanning Calorimetry, D-Pure Drug, FTIR-Fourier Transform Infrared Spectroscopy, F-Formulation, Fig-Figure, MCC-Microcrystalline cellulose, nm-Nanometer, PEG-Polyethylene glycol, rpm-Revolution per minute, SD-Solid dispersion, USP-United States Pharmacopoeia, UV-Ultraviolet.

CONFLICT OF INTERESTS

Declared none

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