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Solubility and Dissolution Enhancement of Poorly Soluble Drug Aripiprazole through Solid Dispersion

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A B S T R A C T

Aripiprazole (ARP) having lowest water solubility indicates class II drugs of BCS. These classes of drugs could potentially exhibit dissolution rate limited absorption. The objective of the present study is to improve the solubility and dissolution of Aripiprazole through solid dispersion (SD) technique. ARP-SDs were prepared by Kneading (KNE), Solvent evaporation (SE), Melt solvent (MS) and Microwave irradiation (MW) methods using PEG 4000, PEG 6000 at 1:1, 1:4 ratios. ARP-SDs were studied in solution state by solubility, *in vitro* dissolution rate and solid state by FTIR, XRD, and relative dissolution parameters through PCP Disso V3 software. The FTIR studies indicate no interaction in all the ARP-SDs, the powder XRD studies indicate lot of decrement in the principle peak heights of ARP in ARP-SDs suggest the transformation of crystalline ARP into nearer amorphous state predicting micronization mechanism. The solubility was improved linearly with increase in concentrations PEG 4000 and PEG 6000. The amount of ARP release from ARP-SDs prepared by KNE were found to be greater than other ARP-SDs and was in the order KNE>SE>MS >MW >PM>ARP. The dissolution of ARP-SDS, obeyed first order kinetics and model fitted with Hixon crowel. One-way ANOVA results suggest the DP_{60}, and DE_{60} values were significantly higher ($P<0.01$) in ARP-SDS than pure drug. The result concludes that solid dispersion technique was can be used increase the solubility and dissolution of poorly soluble drug Aripiprazole.

Key words: Aripiprazole, ANOVA, FTIR, XRD, PEG 4000, PEG 6000

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INTRODUCTION

Among the 40% of FDA approved drugs, nearly 90% are poorly water soluble drugs[1]. Solubility of drugs is the rate limiting step for dissolution, so low solubility affects the drug dissolution rate, failing to achieve adequate blood concentrations. In addition, *in vitro* studies cannot fully simulate the human body environment and have *in vitro - in vivo* correlation, and studies are often terminated in the clinical trial stage. Conventional solubilization techniques include adding solubilizers[2-4], hydrotropes[5], cosolvents[6], prodrugs[7], pH modulation and salt modification[8], micronization and novel solubilization techniques includes cyclodextrin (CD) inclusion[9-12],solid dispersions (SDs), super critical[14], and nanocrystal have been used to increase the solubility and dissolution rates of poorly water soluble drugs. Aripiprazole is a Biopharmaceutics Classification System (BCS) Class II third-generation atypical antipsychotic, which is a dopamine D receptor and 5HT 1A 2 receptor partial agonist, therefore, using it for the treatment of schizophrenia and bipolar disorder[17]. Aripiprazole (ARP) is a lipophilic weak base (pK =7.46) with low aqueous solubility and pH-dependent permeability. Since aripiprazole belongs to BCS class II drug, the clinical use of aripiprazole is limited due to its poorly water soluble characteristics. Therefore, the appropriate formulation design to overcome the dissolution concern is crucial for practical use. The present work was aim to formulate and evaluate ARP solid dispersions (SDs) to increase the solubility, dissolution rate and bioavailability.

Materials and Methods:

Materials

Aripiprazole (ARP) is obtained from Caplin point Ltd. Chennai, India. PEG 4000 and PEG6000were procured from SD fine chemicals Ltd, Mumbai. All chemicals and solvents used were of analytical grade.

Methods

The solid dispersions (SDs) of ARP were prepared with PEG4000, PEG6000 at 1:1and 1:4 ratios usingKneading (KNE), Solvent evaporation (SE), Melt solvent(MS) and Microwave irradiation (MW) methods. The formulae were given in table1.

Physical mixtures (PM): Physical mixtures of ARP with PEG 4000 and PEG 6000 were obtained by mixing the components together with a spatula.

Kneaded systems (KNE): Kneaded systems of ARP with PEG 4000 and PEG 6000 were obtained bytriturating the components in mortar with dichloromethane for 1hr. Taking care that wet condition should be maintained throughout the trituration period. Further mass was dried in vacuum oven, pulverized and sieved through #120 and stored in desiccator until further evaluation.

Solvent evaporation (SE): SE systems of ARP with PEG 4000 and PEG 6000 were obtained by dispersing the drug and PEG 4000, PEG 6000 in 15 ml of dichloromethane. Further the solvent was removed under vacuum until dry. The dried mass was pulverized and sieved through #120 and stored in desiccator until further evaluation.

Melt solvent method (MS): These systems were prepared by heating the PEG 4000 and PEG 6000 at controlled temperature until it melts, in molten polymer mass the ARP is dispersed and immediately solidified in an ice bathunder vigorous stirring. The final solid mass is crushed, pulverized and sieved through #120 and stored in desiccator until further evaluation.

Microwave irradiated systems (MW): These systems were prepared by adding aqueous solution of PEG4000 and PEG6000 slowly into a solution of ARP dissolved in dichloromethane with continuous stirring. The mixture was subjected for irradiation in microwave oven for 90 sec at 60^0C, after reaction completes add adequate amount of dichloromethane to remove the residual. The resulting mixture was stirred for 1h and evaporated under vacuum until dry. The resulting powder was grinded and passed through #120 and stored in a desiccator for further evaluation.

Table 1: Formulae of ARP-SDs with PEG 4000 and PEG 6000

Batches	Drug	Polymer	Ratio	Method
FA-1	ARP	PEG-4000	1:1	PM
FA-2	ARP	PEG-4000	1:4	PM
FA-3	ARP	PEG-4000	1:1	MS
FA-4	ARP	PEG-4000	1:4	MS
FA-5	ARP	PEG-4000	1:1	SE
FA-6	ARP	PEG-4000	1:4	SE
FA-7	ARP	PEG-4000	1:1	KN
FA-8	ARP	PEG-4000	1:4	KN
FA-9	ARP	PEG-4000	1:1	MW
FA-10	ARP	PEG-4000	1:4	MW
FB-1	ARP	PEG-6000	1:1	PM
FB-2	ARP	PEG-6000	1:4	PM
FB-3	ARP	PEG-6000	1:1	MS
FB-4	ARP	PEG-6000	1:4	MS
FB-5	ARP	PEG-6000	1:1	SE
FB-6	ARP	PEG-6000	1:4	SE
FB-7	ARP	PEG-6000	1:1	KN
FB-8	ARP	PEG-6000	1:4	KN
FB-9	ARP	PEG-6000	1:1	MW
FB-10	ARP	PEG-6000	1:4	MW

Evaluation

FTIR studies: A Shimadzu FTIR-281-spectrophotometer was used to study the interaction between ARP and added polymers by comparing FTIR spectra. The spectra were recorded for ARP, PEG 4000, PEG 6000 and optimized SDs. Samples were prepared for 3min at a force of 5.2Tcm^{-2} in KBr disks equipped with a hydrostatic press. The range of scanning was 450-4000cm^{-1}.

Saturation solubility studies: During the study a little excess amount of ARP-SDs were added in a series of 25 ml stopper flask containing distilled water. The solutions were shaken for 24hr intermittently in rotary flask shaker to attain the equilibrium with the un dissolved drug particles. Then measured amount of the filtered drug solution was withdrawn after 24 hr and appropriately diluted with 0.5 % w/v SLS in pH4 buffer and were measured using UV spectrophotometer at 255 nm for ARP content.

Drug content uniformity: In each case ARP-SDs equivalent to 20 mg of ARP was precisely weighed and transferred to 50 ml volumetric flask. 50 ml of dried methanol was added and shaken for 30 min to extract the ARP. The volume was appropriately dilute with 0.5 % w/v SLSin pH4 buffer and measures the absorbance at 255 nm for ARP content.

RESULTS AND DISCUSSION

The production yield of ARP-SDs were in the range of 90.01 to 96.18 for FA-1 to FB-20, minimal loss during the preparation suggest proposed methods were reproducible. The % drug content of ARP in ARP-SDs were in the range of 98.22±0.3444 to 99.68±0.3089for FA-1 to FB-20 with low SD (< 2%) drug remained uniform in each batch prepared.

Saturation solubility study: The solubility of ARP and its SDs were shown in figure 1. The solubility of ARP in distilled water was 0.062 ± 0.000121 M×10^{-4} and solubility of ARP from the ARP-SDs was increase linearly with respect to the method, type of carrier and ratios.

FTIR studies: FTIR spectrum of ARP and its optimized ARP-SDs were given in figure 2 and data in table 2.The FTIR spectrum of ARP displayed an absorption band at 3457 cm^{-1} corresponds to the N-H stretching of the secondary amide group of the lactam ring, 2944 cm^{-1} corresponds to aromatic CH=CH- stretching vibration, 1670 cm^{-1} corresponds to carbonyl group stretching vibration and 1365 cm^{-1} corresponded to the C-N stretching vibration of the aromatic amine. The optimized ARP-SDs showed all the characteristic bands of ARP and remain unaffected and shifted slightly towards lower to higher wavelength indicates negligible or no interaction.

Table 2: FTIR data of ARP and its SDS

Batches	N-H Stretchingcm^{-1}	CH=CH Stretchingcm^{-1}	C=O Stretchingcm^{-1}	C-N Stretchingcm^{-1}
ARP	3457	2944	1670	1375
FA-2	3453	2879	1674	1342
FA-4	3450	2880	1674	1342
FA-6	3453	2879	1673	1341
FA-8	3453	2880	1674	1343
FA-10	3422	2879	1672	1341
FB-2	3428	2878	1670	1375
FB-4	3436	2879	1672	1341
FB-6	3459	2879	1677	1342
FB-8	3462	2878	1679	1343
FB-10	3467	2878	1672	1341

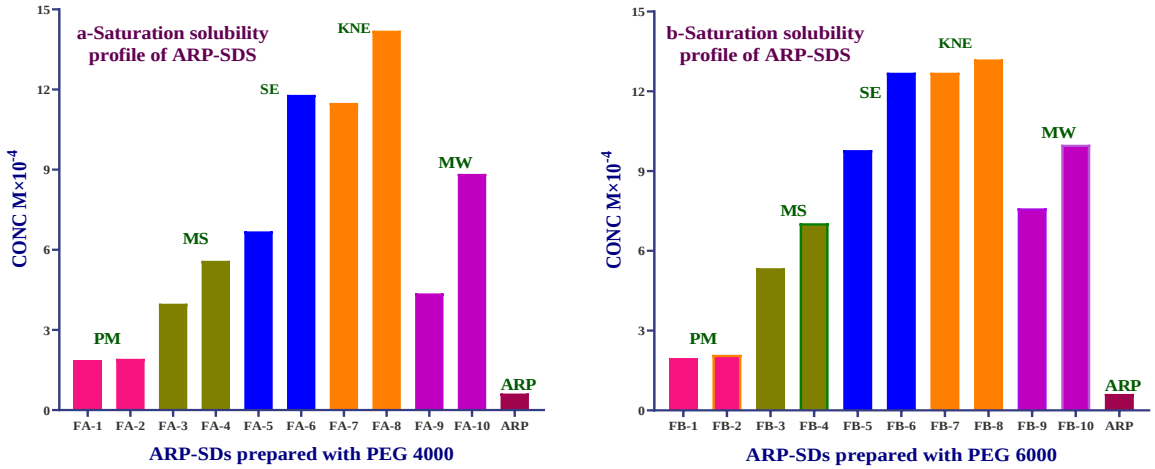

Figure 1: Saturation solubility profiles of ARP-SDS a) with PEG400 b) with PEG 6000

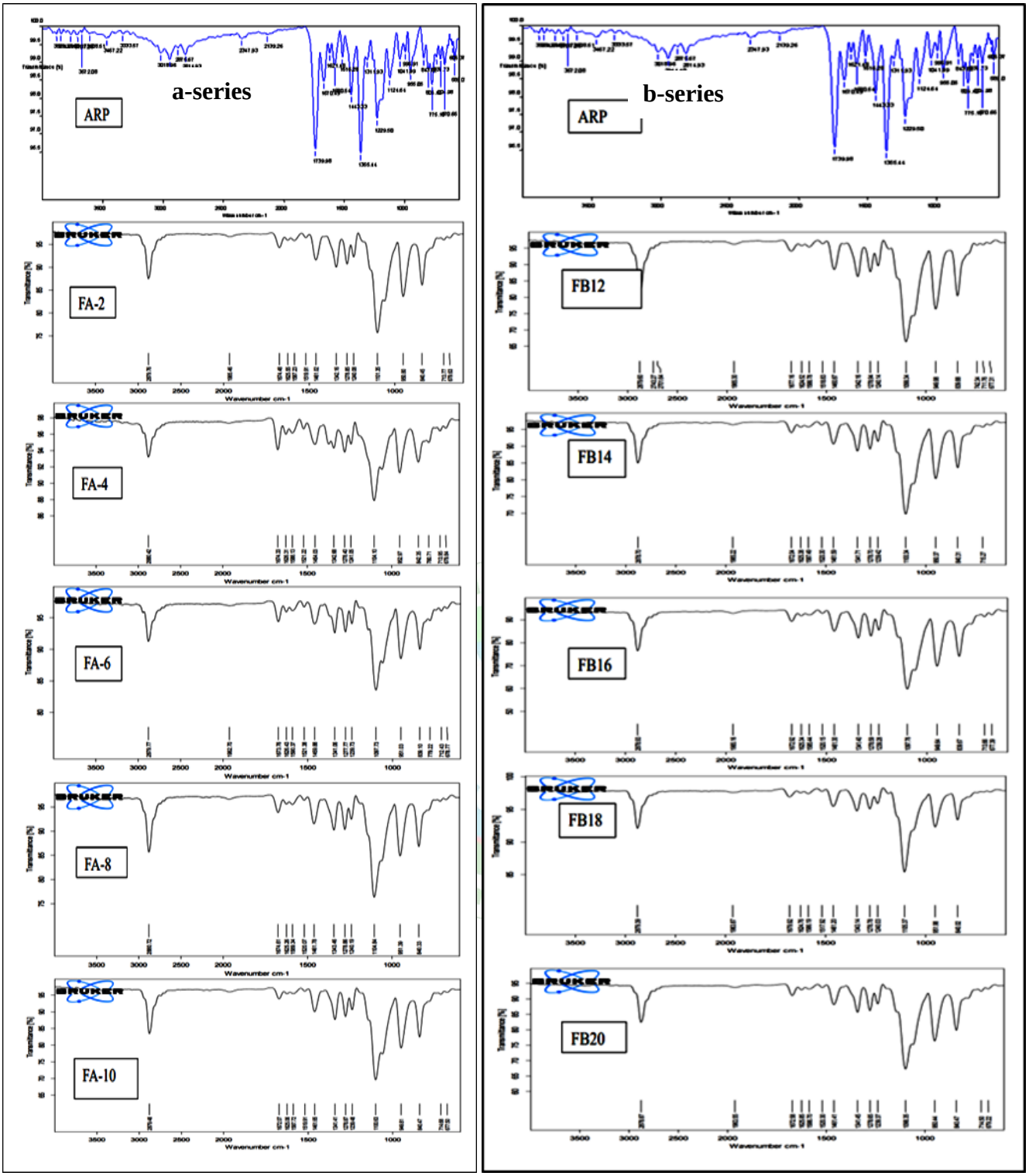

Figure 2: Comparative FTIR of pure drug and its SDS a) with PEG-4000 b) PEG 6000

XRD studies: XRD spectrum of ARP and its optimized ARP-SDs were given in figure 3. All the principle diffraction peaks of ARP were appeared in optimized ARP-SDs with considerable reductionin the peak intensities. The reduction in peak heights and intensities is indicative of modification of crystallinity, since the peak position (angle of diffraction) is an indication of crystal structure and the peak heights are a measure of the sample crystallinity. The overall results confirms conversion of crystal ARP into nearer amorphous, the optimized ARP-SDs prepared by KNE with PEG 4000 at 1:4 shows more reduction in the peak heights, intensities and near amorphousness when compare to other ARP-SDs. These observations were in accordance with the results of the FTIR studies.

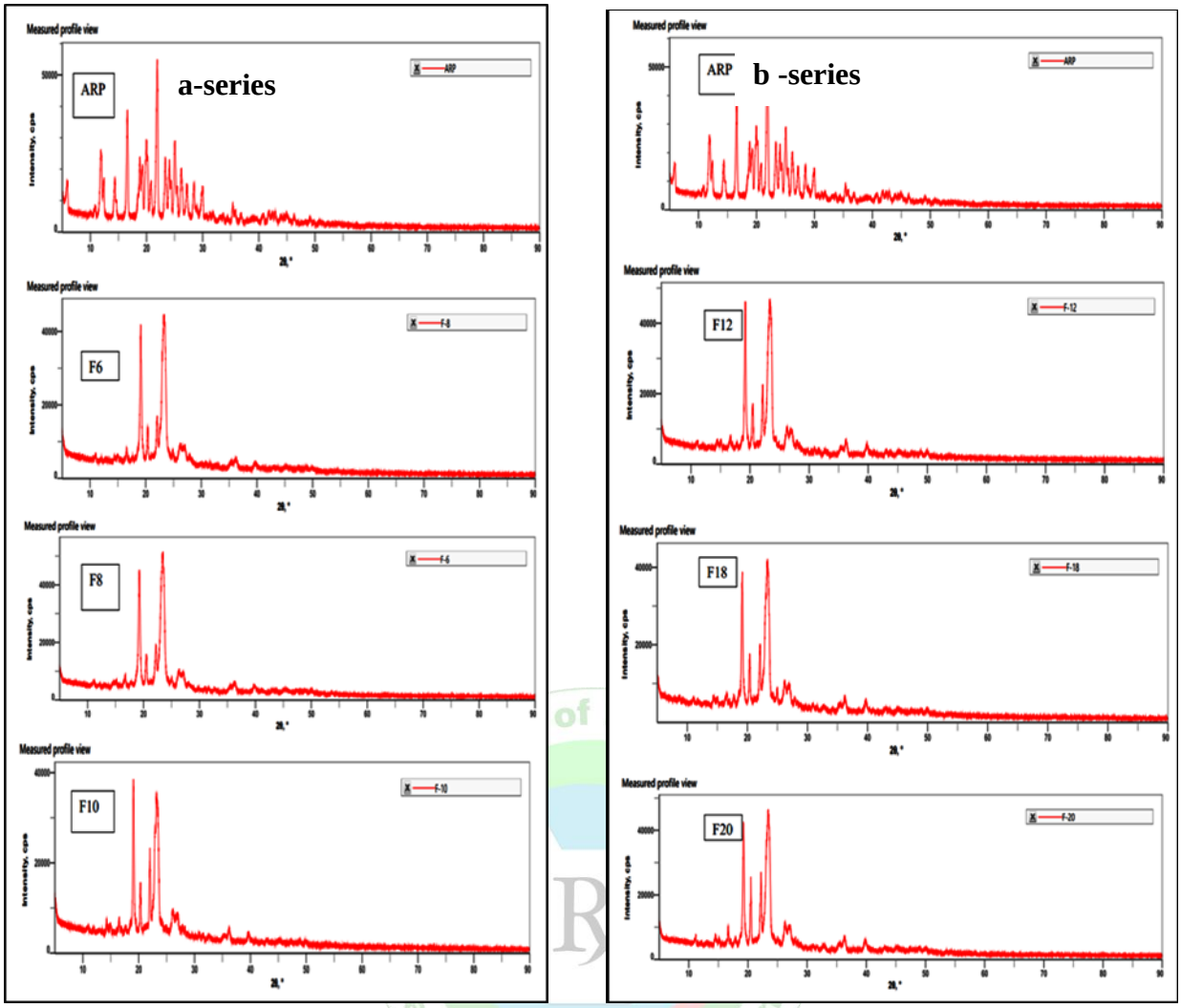

Figure 3: Comparative XRD of pure drug and its SDS a) with PEG-4000 b) PEG 6000

Dissolution studies: When an assumed SDswas dispersed in a dissolution medium, a very rapid dissolution is often observed this criteria has been used to characterize ARP-SDs with PEG 4000 and PEG 6000 during dissolution rate tests. During dissolution study the dispersed amount method was used to generate comparativedissolution profiles and relative dissolution parameters viz., t_{50}, DP_{30}, DP_{60} (% released in 30 and 60 min respectively), RDR_{60} (relative dissolution rate at 60 min of SDS by comparing with pure drug at 60 min) and DE_{30} and DE_{60} usingPCP DISS0 V.3.0 to interpret the results.Another parameter DE (dissolution efficiency) was also used characterize the dissolution data. Further mechanism of drug release from ARP-SDS were assessed by fitting into various models. The relevant data and profiles were given in tables 3 and figure 4.

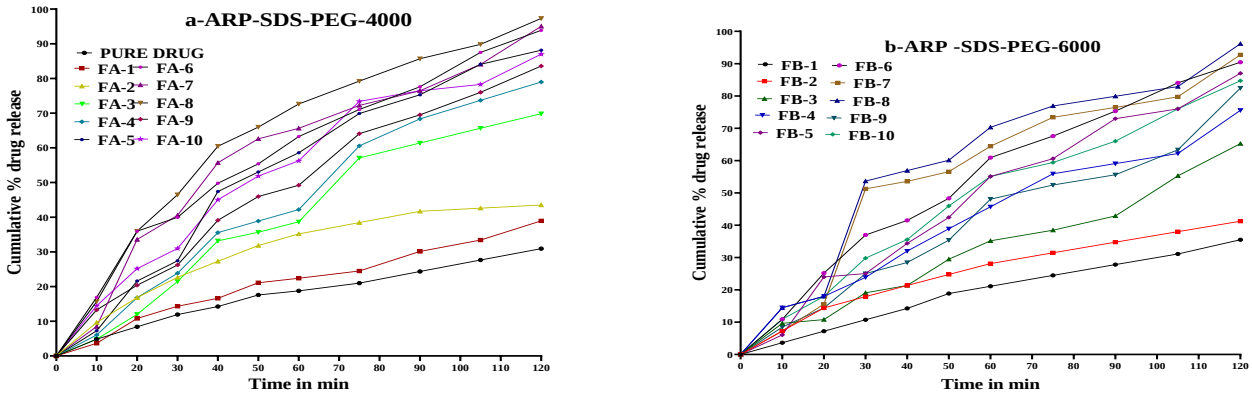

Figure 4: Comparative *In vitro* dissolution profile of pure drug and its SDS a) PEG4000 b) PEG6000

Table 3: Comparative *in vitro* dissolution parameter data of ARP- SDS

Dissolution parameters	**Pure drug**	**FA1**	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**	**FA10**
DP_{30}	9.2	16.1	24.9	24.9	30.7	39.1	44.7	44.8	53.0	33.6	37.9
DP_{60}	17.5	29.6	43.5	43.5	51.9	62.9	69.4	69.5	77.9	55.8	61.4
DE_{30}	6.41	12.60	9.20	9.20	11.79	14.19	24.18	20.77	24.97	15.60	18.39
DE_{60}	10.99	18.47	20.25	20.25	23.91	31.00	38.17	38.92	43.49	28.27	32.62
RDR_{60}	1	1.87	1.87	2.06	2.24	3.12	3.37	3.49	3.87	2.62	2.99
Dissolution parameters	**Pure drug**	**FB1**	**FB2**	**FB3**	**FB4**	**FB5**	**FB6**	**FB7**	**FB8**	**FB9**	**FB10**
DP_{30}	9.2	10.4	13.6	20.12	26.9	34.9	39.91	44.82	46.78	28.21	33.45
DP_{60}	17.5	19.8	25.31	36.23	46.63	57.63	63.98	69.56	71.98	48.35	55.67
DE_{30}	6.41	5.41	10.20	5.41	10.20	10.01	14.80	14.19	18.18	16.16	19.77
DE_{60}	10.99	10.78	16.62	10.78	16.62	18.00	25.02	26.57	32.22	36.04	39.71
RDR_{60}	1	1.12	1.49	1.12	1.49	1.87	2.43	2.93	3.25	3.43	3.75

The results of the *in vitro* drug release studies indicated higher dissolution rate from ARP-SDs when compared to ARP pure form. Overall, the rank order of improvement in dissolution rate of ARP with different hydrophilic polymer is PEG 4000 > PEG 6000; with methods KNE > SE > MS > MW > PM > pure drug; with ratios 1:4 > 1:1 this may be due to molecular dispersion of ARP in inert hydrophilic matrix. The increased dissolution rate ARP fromARP-SDsis mainly due to micro dispersion of ARP in hydrophilic carriers and also enhanced wettability because of decrease in crystallinity of ARP justified by XRD. The regression coefficient values of ARP-SDS-PEG 4000 were found to be 0.9149 to 0.9901 for first order; 0.9789 to 0.9968 for Hixan crowel model and for ARP-SDS-PEG 6000 0.9132 to 0.9946 for first order; 0.9536 to 0.9954 for Hixan crowel. These values suggest the best fit model was Hixan crowel for all ARP-SDsand drug release follows first order mechanism.

ANOVA: One way ANOVA ($p < 0.05$) was used to test the statistical significant difference between pure and ARP-SDs. Dunnett multiple comparison test was used to analyse through Graph Pad Prism V9 and the data were given in tables 5,6.Significant differences in the means of DP_{60}, DE_{60} were tested at 95% confidence.TheDP_{60} and DE_{60} values of ARP-SDs were significantly higher ($P<0.05$) when compared toDP_{60}, DE_{60}values of pure ARP.

Table 5: ANOVA data using Dunnett multiple comparison tests for pure ARP and its SDS with PEG-4000.

DP_{60}					
Group	**Comparison**	**Mean**	**Mean difference**	**P value**	**Significant**
ARP	----------	17.47	----------	--------	------
FA-1	ARP VS FA-1	28.60	-11.13	****P<0.0001	Yes
FA-2	ARP VS FA-2	44.38	-26.91	****P<0.0001	Yes
FA-3	ARP VS FA-3	43.43	-25.97	****P<0.0001	Yes
FA-4	ARP VS FA-4	51.63	-34.17	****P<0.0001	Yes
FA-5	ARP VS FA-5	61.77	-44.30	****P<0.0001	Yes
FA-6	ARP VS FA-6	69.60	-52.13	****P<0.0001	Yes
FA-7	ARP VS FA-7	71.30	-53.83	****P<0.0001	Yes
FA-8	ARP VS FA-8	78.77	-61.30	****P<0.0001	Yes
FA-9	ARP VS FA-9	56.50	-39.03	****P<0.0001	Yes
FA-10	ARP VS FA-10	62.20	-44.73	****P<0.0001	Yes
DE_{60}					
FA-1	ARP VS FA-1	18.58	-7.317	****P<0.0001	Yes

FA-2	ARP VS FA-2	20.73	-9.470	****P<0.0001	Yes
FA-3	ARP VS FA-3	20.40	-9.133	****P<0.0001	Yes
FA-4	ARP VS FA-4	20.40	-12.62	****P<0.0001	Yes
FA-5	ARP VS FA-5	23.88	-19.74	****P<0.0001	Yes
FA-6	ARP VS FA-6	32.93	-27.97	****<0.0001	Yes
FA-7	ARP VS FA-7	38.67	-27.47	****<0.0001	Yes
FA-8	ARP VS FA-8	43.51	-32.25	****<0.0001	Yes
FA-9	ARP VS FA-9	29.59	-18.33	****<0.0001	Yes
FA-10	ARP VS FA-10	32.34	-21.07	****<0.0001	Yes

Table 6: ANOVA data obtained by using Dunnett multiple comparison tests for pure ARP and its SDS with PEG-6000.

DP_{60}					
Group	**Comparison**	**Mean**	**Mean difference**	**P value**	**Significant**
ARP	----------	17.47	----------	--------	------
FB-1	ARP VS FB-1	19.90	-2.000	0.4010	ns
FB-2	ARP VS FB-2	26.00	-8.100	****<0.0001	Yes
FB-3	ARP VS FB-3	36.27	-18.37	****<0.0001	Yes
FB-4	ARP VS FB-4	46.60	-28.70	****<0.0001	Yes
FB-5	ARP VS FB-5	57.43	-39.53	****<0.0001	Yes
FB-6	ARP VS FB-6	63.53	-45.63	****<0.0001	Yes
FB-7	ARP VS FB-7	69.53	-51.63	****<0.0001	Yes
FB-8	ARP VS FB-8	71.23	-53.33	****<0.0001	Yes
FB-9	ARP VS FB-9	48.37	-30.47	****<0.0001	Yes
FB-10	ARP VS FB-10	55.40	-30.47	64.03	****<0.0001
DE_{60}					
FB-1	ARP VS FB-1	10.88	0.640	0.9969	ns
FB-2	ARP VS FB-2	16.68	-5.167	****<0.0001	Yes
FB-3	ARP VS FB-3	18.00	-6.483	****<0.0001	Yes
FB-4	ARP VS FB-4	25.18	-13.67	****<0.0001	Yes
FB-5	ARP VS FB-5	26.46	-14.94	****<0.0001	Yes
FB-6	ARP VS FB-6	31.48	-19.96	****<0.0001	Yes
FB-7	ARP VS FB-7	36.32	-24.80	****<0.0001	Yes
FB-8	ARP VS FB-8	40.60	-29.08	****<0.0001	Yes
FB-9	ARP VS FB-9	14.65	-3.130	**0.00074	Yes
FB-10	ARP VS FB-10	16.54	-5.023	****<0.0001	Yes

CONCLUSION:

The present research demonstrates that the solid dispersion technique can be successfully utilized using PEG 4000 and PEG 6000 to increase the solubility and dissolution of model poorly soluble drug Aripiprazole. Further the study concludes that the solid dispersion technique modifies the crystallinity of Aripiprazole and disperse homogeneously with the hydrophilic polymers.

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Conflict of interest

No conflict of interest.

REFERENCES

1. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: Basic science and product development. J Pharm Pharmacol 2010; 62:1607-1621.
2. Wang C, Yang Y, Cui XH, Ding SW, Chen Z. Three different types of solubilization of Thymol in tween 80: micelles, solutions, and

emulsions- A mechanism study of micellar solubilization. J Mol Liq 2020; 306:112901.
3. Jin G, Ngo HV, Wang J, Cui JH, Cao QR, Park C, et al. Electrostatic molecular effect of differently charged surfactants on the solubilization capacity and physicochemical properties of salt-caged nano suspensions containing pH-dependent and poorly water-soluble Rebamipide. Int J Pharm 2022; 619:121686.
4. Saraf A, Sharma S, Sachar S. Evaluation of surfactants as solubilizing medium for Levofloxacin. J Mol Liq 2020; 319:114060.
5. Cui Y. Parallel stacking of caffeine with riboflavin in aqueous solutions: the potential mechanism for hydrotropic solubilization of Riboflavin. Int J Pharm 2010; 397:36-43.
6. Miyako Y, Khalef N, Matsuzaki K, Pinal R. Solubility enhancement of hydrophobic compounds by cosolvents: role of solute hydrophobicity on the solubilization effect. Int J Pharm 2010; 393:48-54.
7. Sanches BMA, Ferreira EI. Is prodrug design an approach to increase water solubility? Int J Pharm 2019; 568:118498.
8. Cerreia VP, Chierotti MR, Gobetto R. Pharmaceutical aspects of salt and cocrystal forms of APIs and characterization challenges. Adv Drug Deli Rev 2017; 117:86-110.
9. Sarabia VA, Caja MDM, Olives AI, Martin MA, Menendez JC. Cyclodextrin inclusion complexes for improved drug bioavailability and activity: synthetic and analytical aspects. Pharmaceutics 2023; 15:2345.
10. Cid Samamed A, Rakmai J, Mejuto JC, Simal Gandara J, Astray G. Cyclodextrins inclusion complex: preparation methods, analytical techniques and food industry applications. Food Chem 2022; 384: 132467.
11. Constantin M, Cosman B, Ascenzi P, Simionescu BC, Fundueanu G. New chromatographic insights on drug: cyclodextrin inclusion complexes and their potential use in drug delivery. Expert Opin Drug Deli 2022; 19:1696-1709.
12. Vasconcelos T, Prezotti F, Arau ´jo F, Lopes C, Loureiro A, Marques S, et al. Third-generation solid dispersion combining Soluplus and poloxamer 407 enhances the oral bioavailability of Resveratrol. Int J Pharm 2021; 595:120245.
13. Lee J, Lee JJ, Lee S, Dinh L, Oh H, Abuzar SM, et al. Preparation of Apixaban solid dispersion for the enhancement of Apixaban solubility and permeability. Pharmaceutics 2023; 15:907.
14. De Oliveira PV, Sanaiotto O, Kuhn KZ, Oltramari A, Bortoluzzi AJ, Lanza M, et al. Micronization of Naringenin in supercritical fluid medium: in vitro and in vivo assays. J Drug Deli Sci Tech 2023; 82:104382.
15. McGuckin MB, Wang JW, Ghanma R, Qin NY, Palma SD, Donnelly RF, et al. Nanocrystals as a master key to deliver hydro phobic drugs via multiple administration routes. J Control Release 2022; 345:334-353.
16. Cheshmehnoor P, Rabbani S, Haeri A. Quercetin nanocrystals pre pared by a novel technique improve the dissolution rate and antifibrotic activity of Quercetin. Nanomedicine 2023; 18:89-107.
17. Jordan, S., Koprivica, V., Chen, R., Tottori, K., Kikuchi, T., Altar, C.A., 2002. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. EurJPharmacol 2002; 441:137-140