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Improved solubility and stability of aripiprazole in binary and ternary inclusion complexes using methyl-β-cyclodextrin and L-arginine

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Abstract: The aim of this study was to improve the solubility of aripiprazole (ARP) by fabricating binary and ternary inclusion complexes with methyl-β-cyclodextrin (MβCD) and L-Arginine (LA). Physical mixing and lyophilization were used in the following molar ratios: 1:1, 1:2.5, 1:4, 1:9, 1:1:1, 1:1:0.27, 1:4:1, 1:9:1, 1:3.6:3.6. The developed formulations were analyzed by solubility and dissolution. They were characterized by FTIR, XRD, DSC, SEM and TGA. Ternary formulations prepared by the lyophilization method showed improved dissolution rates in simulated gastric fluid (SGF). The results showcased that the addition of MβCD and LA in inclusion complexes enhanced the solubility and decreased crystallinity. The amorphous nature of Aripiprazole in lyophilization was confirmed by XRD diffractograms. Drug release was dominated by the first-order kinetics (R2 = 0.9932) with the Fickian type of diffusion mechanism (n<0.450). LY18, LY19, LY20, and LY21 have the highest solubility (30, 35, 43 and 48 times higher than the pure drug respectively). Furthermore, it was observed that the method of preparation, as well as a specific drug to polymer and amino acid ratio, are critical for achieving high drug solubility and stability. These complexes appeared to be a promising product for the development of new drug delivery systems.

Keywords: Aripiprazole, MβCD, L-arginine, physical mixing, lyophilization.

INTRODUCTION

Aripiprazole (ARP) is an antipsychotic medicine that is used to treat schizophrenia and bipolar disorder (Sinha 2018). It is a white crystalline powder. It is either a BCS class IV or BCS II drug with poor aqueous solubility (Chennuri and Prasanthi 2018, Jamróz *et al.*, 2018, Łyszczarz *et al.*, 2020). It is available in the market in different dosage forms, including oral tablets, oral disintegrating tablets, oral solutions and intramuscular injections. It is a weakly alkaline drug with pH-dependent solubility (McFall *et al.*, 2019, Piazzini *et al.*, 2020).

Cyclodextrins (CDs) and their derivatives are used for enhancing the solubility of drugs by forming inclusion complexes by placing different drugs in the vids of their molecule (Bashir *et al.*, 2020). Normally a CD structure contains six or eight glucose units and is arranged in the form of 6, 7, or 8 membered macro- rings (Wüpper *et al.*, 2021). These rings are called α, β and ϒ CD. CD is an oligosaccharide with multiple glucose subunits (Fernández *et al.*, 2019). It has α-1,4 glycosidic linkage. Chemically modified CDs are also available to overcome low aqueous solubility and nephrotoxicity that is related to β- CD. The CDs can affect the dissolution rate, safety profile of drug, bioavailability, and drug stability. This makes them an efficient excipient of drug formulations. Hydroxyl propyl-β-CD (HPβCD) and MβCD are good candidates to increase drug solubility (Mahdavi *et al.*, 2022). They reduce the side effects and lead to the stabilization of the pharmaceutical formulation. The dissolution rate of the ARP-CD complex can be increased without changing the parent structure of the API.

LA is an important amino acid (Li *et al.*, 2018). It has recommended daily intake of 20 grams per day. It has many other benefits like boosting circulation (cardiovascular disorder) and blood flow (erectile dysfunction) and promoting muscle strength (oxidative stress). It can be used as a complex to decrease the amount of MβCD and produce an even better drug effect. It is also reported to increase the stability and solubility of the drug (Jagtap and Chandrakant 2018).

For the first time, we present the exact ternary molar ratio which shows the increased solubility. The solubility enhancement was observed with different combinations of MβCD and LA. The binary and ternary systems were characterized using SEM, FTIR, DSC, TGA and XRD for their formulations.

MATERIALS AND METHODS

Materials

The ARP was gifted from Global pharmaceuticals, Islamabad. The MβCD was gifted by Vision

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Pharmaceuticals Islamabad. Pepsin was purchased from Sigma-Aldrich (St. Louis, MO, USA). Ethanol and LA were supplied by Sigma-Aldrich (St. Louis, MO, USA). Hydrochloric acid (HCl) was purchased from Merck (Germany). All other solvents used were of analytical grade.

Methods

The solid dispersion formulations were prepared by using different molar ratios, obtained from quality by design as shown in table 1.

Table 1: Composition of different formulations

Method	Formation Code	ARP: MβCD/ARP: MβCD: LA
Physical Mixture	PM1	1:1
	PM2	1:2.5
	PM4	1:4
	PM5	1:9
	PM6	1:1:1
	PM7	1:.3.6:3.6
	PM8	1:2.5:0.27
	PM10	1:4:1
	PM11	1:9:1
Lyophilization Method	LY12	1:1
	LY13	1:2.5
	LY15	1:4
	LY16	1:9
	LY17	1:1:1
	LY18	1:3.6:3.6
	LY19	1:2.5:0.27
	LY20	1:3.6:3.6
	LY21	1:4:1
	LY22	1:9:1

Preparation of the physical mixture

The accurately weighed constituents were softly mixed in a glass mortar and pestle for 5-7 minutes (min) until homogenized. This mixture is passed through the sieve of 80 µm. This mixture was transferred to properly dried amber-colored glass bottles till further use (Carneiro *et al.*, 2019).

Preparation of inclusion complexes by lyophilization method

For the preparation of samples accurately weighed amounts of ARP, MβCD and LA were used in specific ratios. The clear solutions of the complexes were obtained by dissolving them in ethanol in a round bottom flask separately. An orbital shaker was used to mix these components at 150 rpm for 24 hours at room temperature and recovered by a rotary evaporator by evaporating ethanol. Samples were further recovered through 100 ml of distilled water and were placed overnight in a scientific freezer at -60^{o}C. Lyophilizer was used to freeze dry the samples and the dried powder was sieved through a diameter 80 µm. The final product was then transferred to amber-colored glass bottles (Li *et al.*, 2018).

Preparation of capsules of formulations

For the dissolution studies, 10 mg of the pure drug and all the prepared formulations were filled in soft gelatin capsules in triplicate.

In vitro evaluation and characterization

Saturation solubility study

A solubility study was performed according to Higuchi and Conners, 1965. Accurately weighed samples (0.4g) were transferred to a glass test tube having 10ml of deionized water. Samples were shaken for 2min on vortex mixture at about 1400 rpm. The samples were fixed on a shaking incubator (Benchtop shaking incubator S1990R) at 37°C for 3 days and operated at 150 rpm and centrifuged for 15 min at 6000 rpm. The supernatant liquid was decanted in a separate glass test tube. With the help of 0.45 µm syringe filter (Acrodisc GF syringe filter, Pall life sciences the USA), 1ml of the upper clear layer was diluted to 5 ml by deionized water. These samples were analyzed for ARP content at 219 nm by using UV-Vis 1600 spectrophotometer (Shimadzu Spectro-photometer, Tokyo, Japan). Control testing was also performed to authenticate the results. The standard curve was used to calculate the concentrations of aripiprazole (Tănase *et al.*, 2020).

In-vitro dissolution studies

All the samples were enclosed in the capsule shells and the dissolution test was performed using the pedal method (USP dissolution apparatus II, 2009). The Simulated gastric fluid (SGF) was used as a dissolution medium and its temperature was maintained at 37.0±5^{o}C. For the preparation of SGF, 2g of sodium chloride and 3.2g of purified pepsin is added to 7.0 ml of HCl, and sufficient water was added to make 1000ml. With the help of a pipette, 10 ml of sample was taken out after 5, 15, 30, 60, and 120 min by a syringe filter (0.45µm). Fresh 10 ml SGF was added after each sample was taken. Samples were ultimately analyzed at 219nm using UV1700, Shimadzu Kyoto Japan (Tănase *et al.*, 2020).

Attenuated total reflection fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR Spectroscopic imaging is a comprehensive way of collecting information about chemical composition. The molecular structure of the material provides specific vibrational spectra. ATR-FTIR tests were performed using ATR-FTIR 7600 spectrometer (Lambda). The ATR-FTIR spectra of drug, polymer, amino acid and samples were obtained in the range of 500-4000 cm^{-1} (Saeed *et al.*, 2019).

X-ray diffractometry (XRD)
X-Ray Diffractometer (JDX-3532 JEOL Japan) was used to obtain diffractometric patterns of aripiprazole, polymer, and prepared samples between scanning ranges of 5° - 50° at the scanning rate of 1°/ min (Latif *et al.*, 2021).

Differential scanning calorimetry (DSC)
DSC measurements of powder samples were performed using a PerkinElmer STA 6000 simultaneous TGA/DSC analyzer. The thermal behavior of the samples was compared with the pure drug by heating at a rate of 10°C per min from 30°C to 500°C under dry nitrogen gas with a flow rate of 20 ml / min (Bashir *et al.*, 2020).

Thermogravimetric analysis (TGA)
TGA measurements of powder samples were performed using a PerkinElmer STA 6000 simultaneous TGA/DSC analyzer. The sample 2 to 5 mg was taken in an aluminum pan and the weight loss was monitored during heating at a rate of 10°C per min from 30°C to 500°C under dry nitrogen gas with the flow rate of 20 ml /min.

Scanning Electron microscopy (SEM)
Surface morphology analysis (topology) of pure drug and formulated complexes of ARP with different methods and ratios were performed using a scanning electron microscope (SEM, Perkin Elmer, USA) (Al-Qubaisi *et al.*, 2019).

STATISTICAL ANALYSIS

Graph pad Prism 6 software was used to apply One Way Analysis of Variance (ANOVA) on the drug release data keeping the significance level to $P < 0.05$.

RESULTS

Saturation solubility study
ARP is practically insoluble in water (solubility less than 1 µg). But the complexes prepared show different behavior. It was observed that the binary formulations prepared by physical mixing gave improved solubility results than the pure drug and were dependent upon the amount of polymer. When L-arginine is added the solubility was not enhanced. This showed that L-arginine has some effect on the interaction of the drug and the polymer. The binary samples prepared by the lyophilization method showed increased solubility than physical mixing. The ternary samples prepared by lyophilization showed the highest result. LY17, LY18, LY19, LY20, LY21 and LY22 showed 2000, 2150, 3080, 2725, 4400 and 4900 times increase in solubility respectively which is the highest among all the inclusion complexes of aripiprazole reported up till now (McFall, Haley *et al.*, 2019). So, the ternary formulations prepared by lyophilization were the best method of preparation.

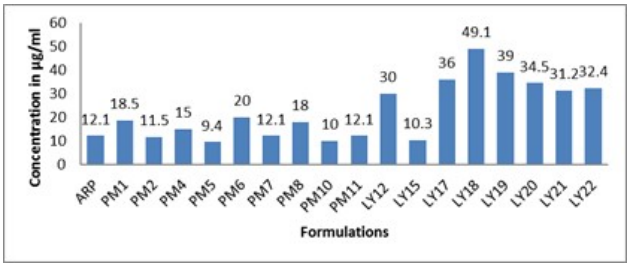

Fig. 1: Dissolution study of different inclusion complexes formulations.

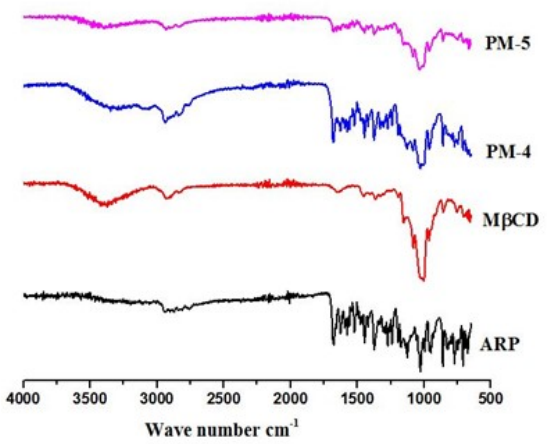

Fig. 2: Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR) of ARP, MβCD, PM4, and PM5.

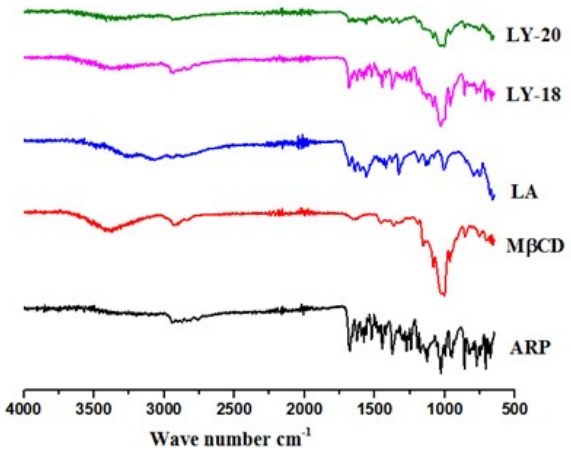

Fig. 3: Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR) of aripiprazole, MβCD, L-Arginine, LY18, LY-20.

Dissolution studies
The dissolution profile showed that in the case of physical mixing, the solubility of binary complexes PM1, PM4, PM6 PM8 and PM9 were 18.5, 15, 30.5, 18 and 21.9 times increased respectively while PM2, PM5, PM 7, PM10 and PM11 showed no significant change ($P< 0.05$). But in the case of lyophilized samples, LY15 showed no significant increase in solubility and LY 12 showed 30

times increase (P<0.05). While the ternary samples exhibit a remarkable increase in solubility (LY17, LY18, LY19, LY20, LY21 and LY22 gave 36, 49.1, 39, 34.5, 31.2 and 32.4 times increase respectively (P<0.05).

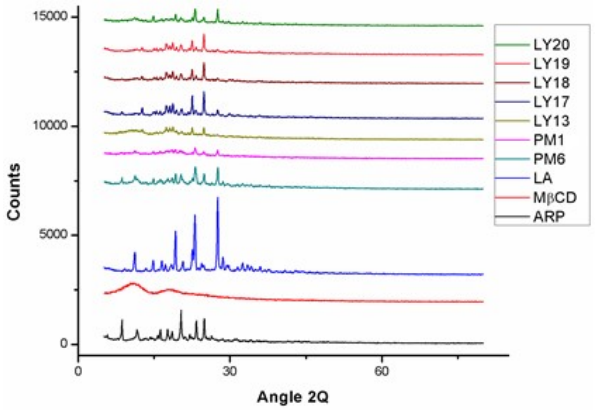

Fig. 4: XRD diffractograms of ARP, MβCD, LA, PM1, PM6, LY13, LY 17, LY 18.

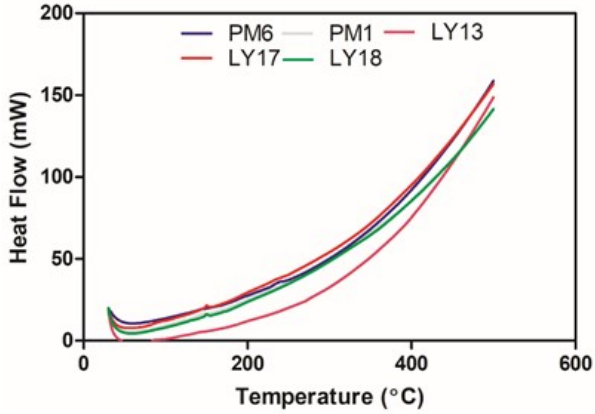

Fig. 5: Differential Scanning Calorimetry (DSC) of PM1, PM6, LY13, LY 17, LY 18.

Attenuated total reflection fourier transform infrared spectroscopy (ATR-FTIR)

The ATR-FTIR spectra of the ARP gave characteristic peaks at 1672cm^{-1} (carbonyl peak), 1027 cm^{-1} (C-O-C stretch), and 763 cm^{-1} (C-Cl stretching). MβCD spectra gave peaks at 1019.12 (C-O-C stretch), 3385.81cm^{-1}(O-H stretching), 2919 cm^{-1} (CH, stretch) 1362.68 cm^{-1} (OH bending vibrations) and 1452.98 cm^{-1} (C-H bending vibrations). LA showed a peak at 3251 cm^{-1} (broad OH carboxylic), 3067 cm^{-1} (NH guanidine), 2860 cm^{-1} (CH stretch), 1318cm^{-1} (CN stretch) and 1563 cm^{-1} (presence of amide). This is already reported by

Binary complexes by physical mixing

Sample PM1 and PM2 gave blueshift (1674cm^{-1} and 1675cm^{-1}) while PM4 and PM5 gave redshift (1671.29 cm^{-1} and 1671.31cm^{-1}) for carbonyl peak. Sample PM1, PM2, PM4 and PM5 showed redshift for C-O-C stretch (1024cm^{-1}, 1023cm^{-1}, 1021.72cm^{-1} and 1021.12cm^{-1} respectively). All the samples give red shift for C-Cl peak (761cm^{-1}, 757cm^{-1}, 757cm^{-1}, 754cm^{-1}).

Ternary complexes by physical mixing

Sample 6, 7, 10 and 11 gave slight shifting of peak (1673 cm^{-1}, 1672 cm^{-1}, 1672.99 cm^{-1}) and 1674.31cm^{-1}) while sample 9 gave red shift (1628.29 cm$^{-1)}$ for carbonyl peak. Sample 6, 7, 9, 10 and 11 showed slight shifting of peak for C-O-C stretch (1020cm^{-1}, 1022cm^{-1}, 1018cm^{-1}, 1020 cm^{-1} and 1022cm^{-1} respectively). All the samples gave red shift for C-Cl peak (760cm^{-}1, 762cm^{-1}, 756cm^{-1}, 762cm^{-1}, 755cm^{-1}).

Binary Complexes by Lyophilization Method

Sample 12, 15 and 16 gave blueshift (1672cm^{-1}, 1674 cm^{-1} and 1674 cm^{-1}) for carbonyl peak. Samples 12 and 16 showed a blue shift (1024cm^{-1}, 1029cm^{-1} respectively) and sample 15 gave a redshift (1010 cm^{-1}) for C-O-C stretch. Sample 12 gave a broad peak for C-Cl, while samples 15 and 16 gave a redshift (799cm^{-1}, 753cm^{-1}).

Ternary Complexes by Lyophilization Method

Sample 17, 18, 19 and 21 gave redshift (1670cm^{-1}, 1670 cm^{-1}, 1669cm^{-}1, 1669cm^{-1}) in case of sample 20 the peak disappears while 21 gave blue shift 1673cm^{-1} for carbonyl group. Samples 17, 18 and 22 showed red shift (1036 cm^{-1}, 1029cm^{-1}, and 1034cm^{-1} respectively), 19 and 20 gave blue shift (1013cm^{-1}, 1014cm^{-1}) while in the case of 21 there is a slight change of peak intensity for C-O-C stretch. Samples 17, 18, 19 and 22 gave redshift for C-Cl peak (799cm^{-1}, 785cm^{-1}, 835cm^{-1}, 795 cm^{-1} respectively), sample 21 gave blue shift 754cm^{-1} while sample 20 showed a slight shifting of peak (760cm^{-1}).

X-ray diffractometry (XRD)

XRD patterns of aripiprazole, MβCD, LA, and different formulations are given in fig. 4 for comparative study. ARP is crystalline in nature with higher intensity peaks at 8.65, 11.55, 16.25, 17.65 20.25, 20.3, 20.35, 23.35, and 24.90. LA demonstrated the nature of crystal structure with 2θ distinct peaks at 11.2°, 14.7°, 16.45°, 17.25°, 18.45°, 19.25° and with higher peak intensity at 23.05° and 27.55°. However, MβCD is amorphous in nature. In the case of all the formulations, the drug peak is noticeably decreased and completely disappeared in the case of LY13, LY18, and LY19. It means that the guest molecules ARP and L-arginine) are in the case of LY18 and LY19 the peak disappeared. Suggesting that, the ternary complexes were the best formulations.

Differential Scanning Calorimetry (DSC)

The melting endotherm of aripiprazole was at 141°C (Mihajlovic, Tijana *et al*. 2012) which means that the raw material is from form III. L arginine gave a peak at 100°C. (Khan, Sajjad and Joshua Boateng, 2018). The MβCD is amorphous in nature. All the formulations gave a very small peak at 142^{o}C while in the case of LY13 the peak completely disappeared.

Table 2: Saturation solubility of selected samples

Sample	% Increase in Solubility (µg/ml)	Sample	% Increase in Solubility (µg/ml)
ARP	0.04	LY12	16
PM1	1.7	LY13	19
PM2	24.9	LY15	15
PM4	22.32	LY16	6.6
PM5	19.8	LY17	18
PM6	15.4	LY18	86
PM7	9.2	LY19	123
PM8	17.2	LY20	109
PM10	18.5	LY21	176
PM11	13.2	LY22	196

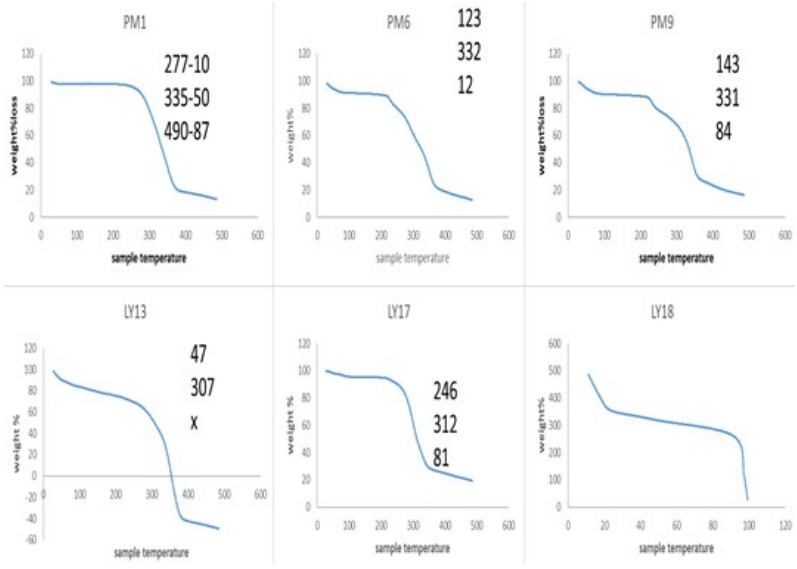

Fig. 6: TGA graphs of PM1, PM6, PM9, LY13, LY17, LY18 inclusion complexes.

Thermogravimetric Analysis (TGA)

The endothermic peak of aripiprazole was visible at 142 ^{o}C. Mass change of aripiprazole is 0.39% (Liu, Wenwen *et al.*, 2021). The residual weight is compared which showed that all the physical mixtures and lyophilized products are stable except LY13, while LY17 is the highest.

Scanning Electron microscopy (SEM)

ARP appeared as flake crystals, MβCD appeared as spherical particles and had an amorphous character and LA appeared as non-linear crystals which were following the previously reported results. The SEM images of selected inclusion complexes are shown in fig. 8.

DISCUSSION

Solubility studies were carried out to understand the effect of LA and MβCD on the binary and ternary compounds. There was a remarkable increase in solubility in the case of ternary complexes prepared by the lyophilization method. This showed that the method of preparation, amount of polymer and amino acid are critical in solubility.

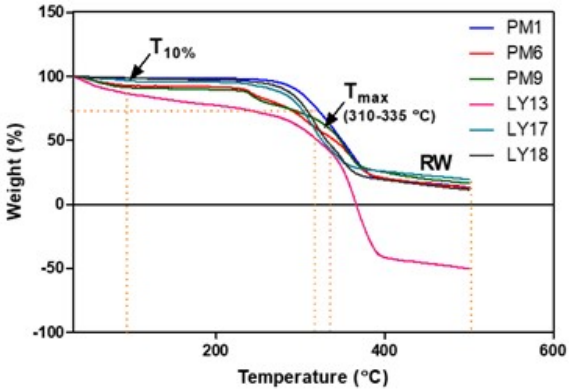

Fig. 7: TGA results of aripiprazole inclusion complexes PM1, PM6, PM9, LY13, LY17, LY18**.**

Dissolution studies revealed that the MβCD and L-arginine were excellent solubility enhancers for all the preparations. This has also been reported earlier (Aiassa

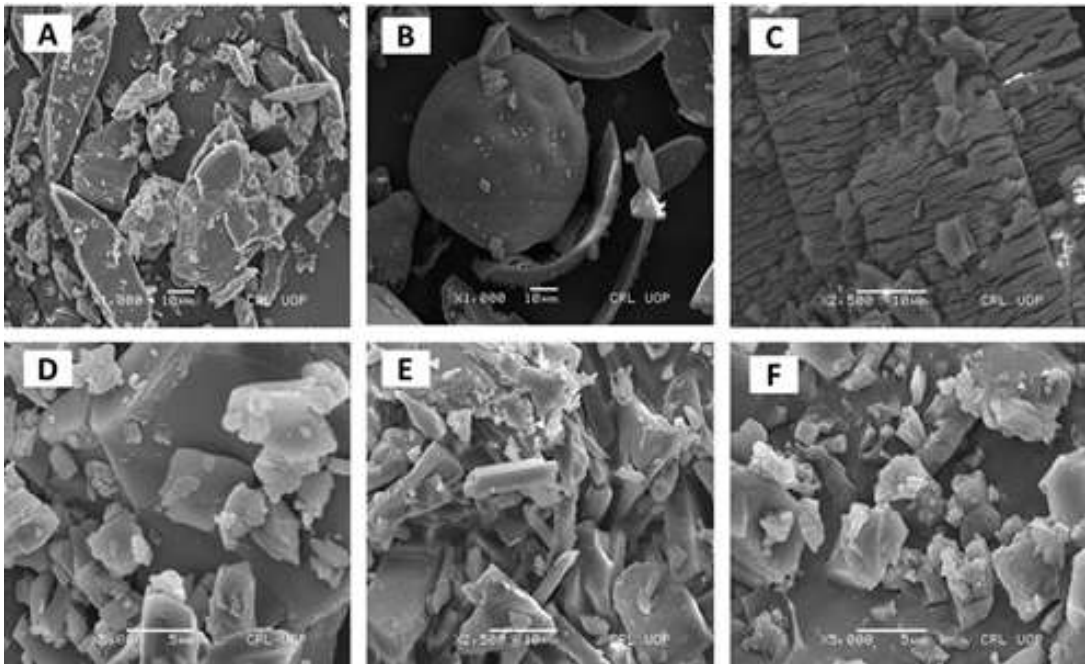

Fig. 8: SEM images of (A) ARP; (B) MβCD; (C) LA; (D) PM4, (E) LY 18, (F) LY20.

et al., 2021). The possible mechanism for this could be the inclusion of ARP into the carrier, dispersibility, wettability and increase in surface area by the MβCD and amino acid (Suvarna *et al.*, 2017, Ueda *et al.*, 2018). The highest dissolution was observed by LY22.

FTIR graphs indicated the bonding between the molecules of complexes. The behavior was found to be different for physical mixing and lyophilization. In the case of physical mixing, the binary complexes gave (1674 cm^{-1} and 1675 cm^{-1}) but with the increase of polymer the drug peak was decreased (1671.29 cm^{-1} and 1671.31 cm^{-1}) which is also shown in the previously reported study (Nakamoto 2008). While in case of binary samples of lyophilization the results are different. The peak intensity of the drug is increased. So, inclusion complexes prepared by different methods showed different behavior. The ternary samples prepared by physical mixing (1673cm^{-1}, 1672cm^{-1}, 1672.99cm^{-1}) gave a blueshift for carbonyl peak. While in the case of lyophilized ternary samples, the drug can be identified in CH, CO, and the fingerprint region but surprisingly with low-intensity peaks (red shift) which means that there is a good interaction of the ARP with the MβCD and LA as compared to physical mixing. Sample no 17 gave a very promising result for carbonyl peak, C-O-C stretch and C-Cl (1670cm^{-1}, 1029cm^{-1}, 785cm^{-1} respectively). This means that the maximum amount of drug is entrapped in the polymer and LA is also incorporated. But the sample no. 18 showed a very different response as the drug peak completely disappeared in the ATR-FTIR spectra, this could be due to the increase in the concentration of LA. The LA probably engaged all the available -OH groups and which ultimately resulted in fewer drug interactions. So, it could be concluded that the ratio of LA is very important for inclusion. It was observed that sample 17, where the specific LA concentration (1:1:0.27) produced maximum results in the dissolution profile of the complexes. The same study is also observed for the binding capacity of amino acids and cyclodextrin derivatives (Khan S and Boateng 2018, Sherje *et al.*, 2018).

XRD pattern of formulations of almost all formulations showed low-intensity peaks which clearly illustrated that the crystalline nature of the drug is decreased. The lyophilized samples gave even better results for amorphous character than physical mixing. The powder XRD patterns were conducted to rule out the amorphous and/or crystalline structure of the ARP, MβCD and LA while the ratio of amorphous-crystalline was studied for their binary and ternary complexes prepared by different methods. The physical mixture of the binary complexes demonstrated reduced peaks for the ARP at 8.65, 23.35, and 24.90.

The higher degree of amorphous nature of MβCD caused the crystalline peak of the drug to be reduced. But by the lyophilization method, the binary complexes of MβCD with the ARP had demonstrated merged peaks for the ARP at 8.65, 10.95 and 11.2. The peak at 14.8 and 27.55 are not vanished as compared to the physical mixtures. But the overall distinct peak intensities of the drug are reduced demonstrating the binary system amorphousness. The ternary complexes demonstrate a greater amount of amorphousness than the binary system. The ternary complexes had demonstrated reduced peaks for the drug

in their physical mixtures of sample 6. There was a further decrease in the crystallinity of the drug by increasing the amount of LA in the ratio 19. The ternary complex 16 through the lyophilization method demonstrated further reduction of peaks i.e., at 16.25, 17.65 and 20.25 as compared to the physical mixtures. But there was a marked increase in the peak at 24.90. This pattern was also seen in the mixture ratio of 17.

There was a gradual reduction of peaks from 8.65 to 23.45 as compared to the physical mixtures of 6. But within the same class of lyophilized method of preparation, the two classes 16 and 17 did demonstrate different results. At 11.55 the peak intensity was the same for both the formulations. While at 20.25 and 20.30, 20.35 there was a rise in peak intensity in the latter ternary complex. Yet again, the peak at 24.90 was higher in intensity than the physical mixtures. Increasing the ratio of LA from 0.27 to 3.6 causes the peak intensity to reduce gradually throughout but there was a jump at 11.55. The ratio of 1:3.6:3.6 demonstrated the highest degree of amorphous character as compared to the physical mixtures of the same ratio. Both the XRD and FTIR support the findings that ternary complexes in the ratio of 1:1:0.27 are the best candidate for enhancing the solubility of ARP.

All DSC scans showed a very small endothermic peak at 150°C. While peak at 141°C is not visible in all the ternary samples prepared by lyophilization. The peak of L-arginine completely disappeared in all the samples. While in the case of binary complexes prepared by lyophilization (LY13), both the peaks are not visible which means that the drug and L arginine is completely included in the CD cavity. A broad endothermic peak can be seen in the entire products prepared by the lyophilization method with LY13 being the maximum. This peak is spanning from room temperature to 100°C, being a maximum of around 80°C. This peak could be due to the loss of water that has been strongly bounded to the cyclodextrin cavity or hydration shell.

The thermal stability of PM1, PM6, PM9, LY13, LY17, and LY18 was evaluated by thermogravimetric analysis (TGA) as described in fig. 7. TGA scans illustrate the weight loss in a three-step process, where the weight loss occurs with temperature in an inert atmosphere containing N_2. Initially, 10% was observed at $T_{10\%}$, which was reached at 277±4°C, 123±5°C, 143±3°C, 47±1.5°C and 246±7°C for PM1, PM6, PM9, LY13 and LY17, respectively. After moisture loss, second weight loss (endothermic peak) was monitored at T_{max} (335±4.5°C), which was found to be 50±2.5%, 55±3.3%, 51±1.4%, 71±4.2%, and 66±2.2%, for PM1, PM6, PM9, LY13 and LY17, respectively. Residual weight was measured at 490°C, which was significantly indifferent to all the samples.

The SEM results of binary physical mixtures show that the drug-MβCD-complex results in a decrease in crystallinity of the drug (Wu *et al.*, 2018). The number of flake crystals is reduced but present in the mixture. The ternary complexes formed showed drug encapsulated in the hydrophilic polymer while LA is dispersed on the surface. Binary and ternary complexes prepared by the lyophilization method show the change in drug morphology. Flake crystals were not visible while some nonlinear LA particles were dispersed in the complex (Ferrari *et al.*, 2021). In the case of sample LY, the structure of the drug is completely changed. The drug is incorporated inside the cyclodextrin cavity while the LA seemed to be in the inside of the polymer cavity, the same is reported for Indomethacin in a previous study.

CONCLUSION

The complexation of ARP with MβCD and LA was a successful strategy for making inclusion complexes. The LA gave a synergistic effect with MβCD. The method of preparation of inclusion complexes played a very important role. In the case of physical mixing, the solubility was greatly enhanced but the formulations were not much stable. While in the case of lyophilized formulations, the stability was enhanced promptly. The dissolution rate is 80% increased which justifies the addition of LA as an auxiliary substance to reduce the amount of ARP and MβCD in formulation leading to fewer side effects and cost-effectiveness. Furthermore, it was also concluded that the specific amount of LA with MβCD was critical in the stability and dissolution of ARP. These ternary lyophilized products are quite helpful for increasing the therapeutic efficacy and stability of the ARP.

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