SOLUBILITY ENHANCEMENT OF ATORVASTATIN SOLID DISPERSION WITH THE INCLUSION OF BIOENHANCER

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ABSTRACT

The study focused on the development of a solid dispersion system (SDs) consisting of atorvastatin (ATV); berberine (BER); polymers: eudragit®L-100 (EDL) and polyvinyl pyrrolidone K 30 (PVP-K 30) to enhance the solubility and dissolution of poorly water-soluble drug and inclusion of bioenhancer in combination. The SDs were formulated using the conventional melting technique. The ATV, BER, PMs, and SDs were studied for the initial level of interaction by Fourier transforms infrared spectroscopy (FTIR). Further, SDs with satisfactory *in-vitro* dissolution were subjected to solid-state characterization by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray crystallography (XRD). SDs-5 formula containing ATV: BER with EDL®L-100 (1:1:5), ATV: BER: PVP-K30 (1:1:5) showed the satisfactory formation of the tertiary mixture and better dissolution as compared to other ratios, physical mixing and pure form of drugs. The phase solubility studies revealed enhanced solubility with both polymers but more found with PVP K 30 as compared to EDL®L-100, although both are hydrophilic polymers, the ease of hydrogen bond formation of PVP K 30 builds more profound solubility. FTIR study showed the absence of interaction. DSC and XRD studies indicated decreased crystallinity in SDs. SEM of SDs further confirmed there were no observable drug particles on the surface. Based on the results, the *in-vitro* dissolution of the ATV was improved with ease in the incorporation of berberine through the SDs method. Hence, solid dispersion techniques can be effectively used for inclusion as well as for solubility enhancement.

Keywords: Atorvastatin, Berberine, Solid dispersion, Melting, Solubility, Dissolution.

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INTRODUCTION:

Atorvastatin Calcium (ATV) is well known HMG-Co-A reductase inhibitor; help to lower plasma cholesterol level by interrupting endogenous cholesterol synthesis hence, makes it the ideal agent to treat all types of hyperlipidemia, and as a first-line agent for treatment[1]. Also for primary prevention of risk associated with myocardial infarction and other cardiovascular diseases[2]. Subsequently, poor aqueous solubility and low bioavailability of 12 % contribute to severe first-pass metabolism hence, Biopharmaceutical Classification System (BCS) places ATV in class II drug[3,4]. Lipid-lowering efficacy of ATV depends on doses, so higher doses have to be given to achieve the therapeutic concentration, which may direct dose-related side effects[5]. Various strategies were used, that could improve ATV solubility like co-crystallization[6], nanoparticle formulation[7], self-emulsifying drug delivery system (SEDDS)[8], and solid dispersion [9,10].

Berberine is a dietary isoquinoline alkaloid that occurs in the root and stem bark of *Berberis, Berberis aristata,* and also in *Argemone Mexicana* with *Eschscholzia californica* in traces[11]. It has gained more research interest for its broad spectrum of activity as an anti-inflammatory, free radical scavenging, anti-diabetic, anticancer, nephroprotective, neuroprotective, antiplatelet, antibacterial, and antiobesity activity[12-15]. The low water solubility of berberine in food and the gastrointestinal tract limits the exploitation of its health-promoting properties [15, 16].

Poor oral bioavailability usually results from drug metabolism, a substrate for p-gp, and poor solubility, and thus, a major challenge for its effectiveness as an oral dosage form[17]. This problem can be overcome by incorporating the drug in a hydrophilic carrier[18]. Solid dispersion is most of the most promising approach for increasing the drug dissolution rate and it can be carried out by many methods[19]. Also can be used for taste masking purposes[20]. It is a molecular mixture of poorly water-soluble drugs in hydrophilic carriers where the polymer drives the release profile[21].

Eudragit®L100 (EDL) is an anionic copolymerization product of methacrylic acid and methyl methyacrylate. The ratio of the free carboxyl group to the ester is 1:1 approximately in a polymer. The increase in solubility of a polymer depends on its concentration and the pH of the system. Eudragit polymers have been extensively evaluated for the release of various drugs and found to be effective [22, 23].

Polyvinyl pyrrolidone (PVP K-30) are non-ionic polymer soluble in water and organic solvents and is pH stable. It binds with hydrogen bonding with the drug and also increases in viscosity further inhibiting the formation of crystalline nuclei of the drug thus making the drug in a more amorphous state this property increases the solubility of a drug in the presence of a polymer[24].

The melting method used for the formulation of solid dispersion was quite easy and solvent-free method, however, this method commonly operates at high temperatures (more than 100 ^{0}C) which could suffer from the stability of the drug, this issue can be resolved by using a control temperature system like a hot plate where the temperature could be assured and cost of the solvent can be minimized[25, 26].

The concomitant use of herbs affects the pharmacokinetic properties of drugs. It may lead to beneficial effects or therapeutic failure with toxicities[27]. The bioavailability enhancement of poorly soluble drugs by co-administration with bio-enhancers has drawn increased attention in the research area[28, 29, 30]. Rather, the pre-treatment of bio-enhancers can be incorporated into a single system by improving the solubility of both components, this makes it patient-friendly. So, This study mainly focused on combining bioenhancers from a natural source with a synthetic source in a single composite compartment with better functionality than the individual drug, So that the dose-depending side effect of statin therapy can be minimized, frequency of dosing to avoid the possible resistance, also to overcome the limitation of berberine for desirable therapeutic effect with improved solubility.

Therefore, the main goal of the current study was to explore the feasibility and ease of formation of solid dispersion of atorvastatin with the inclusion of berberine, also study aimed to enhance the solubility and dissolution rate of drugs by using solid dispersion formulation via the conventional melting method. However, there are limited

studies done in a combination of both. Only studies with the pretreatment of berberine were explored.

MATERIAL AND METHODS:

Materials:

Atorvastatin calcium was gifted by Hetero Laboratories Private Limited, India. Berberine was procured from Tokyo Chemical; Japan while eudragit®L100 and PVP K-30 were provided as a gift sample from Anshul Life Sciences Mumbai, India. All the required chemicals were purchased from Loba Chemie Pvt. Ltd Mumbai, India. Throughout the study, double distilled water was used and all other compounds were of analytical grade quality only.

Methods

Solubility and Polymer concentration optimization

Phase solubility and saturation solubility by Higuchi and Connor's method were tried for polymer concentration determinations to understand the effect of polymer concentration and the amount of polymer required for enhancing the solubility. Initially, an excess of ATV and BER was separately placed in a screw-capped glass vial with dissolution medium (10ml, pH 1.2 HCL) containing eudragit®L 100 and PVP K 30 with different concentrations in respective ratios 1:3, 1:4, 1:5 [31]. After the concentration of polymer which shows enhanced solubility was further tested in PM and SDs. The same process was applied to the physical mixture and prepared SDs. Then the samples were shaken at 37±0.5 ^{0}C for 24 h in a rotary shaker (REMI 12 L). Samples were filtered through a 0.45 µm Whatman filter paper after 24 h. The filtrate was diluted and examined spectrophotometrically (UV-visible spectrophotometer, XE-3200 Lab India) at 247 nm for ATV and 348 nm for BER. The data were correlated with the previously reported studies [32].

Preparation of Solid Dispersion

The SDs of atorvastatin with the inclusion of berberine comprising three distinct stoichiometric weight ratios (1:1:3, 1:1:4, 1:1:5; w/w) (atorvastatin: berberine: eudragit®L100 and PVP K 30) were formulated by melting method as reported with little modification[33]. Atorvastatin, berberine, eudragit®L100, and PVP K-30 were heated; the order was decided according to the melting point of all the drugs and polymers with vigorous stirring. The molten mass was then solidified by keeping it at room temperature. The congealed mass was pulverized and passed through sieve number 30 meshes, packed in an airtight container, and stored in a desiccator till further testing. The prepared SDs with two polymers were named accordingly, SDs L3, SDs L4, SDs L5, and SDs K3, SDs K4, and SDs K5 respectively.

Preparation of Physical Mixture

Physical mixtures [PMs] with the same weight ratio as SDs were prepared by mixing them in a mortar and pestle to get a homogeneous mixture and designated for eudragit®L100 and PVP K 30 as PM-L3, PM-L4, PM-L5, and PM-K3, PM-K4, PM-K5. The physical mixtures were kept in a screw-cap vial in a silica desiccator until they were used

Drug: bioenhancer: carrier	Ratio	Physical mixture	Melting method
Atorvastatin: Berberine: Eudragit®L 100	1:1:3	PM- L3	SDs L 3
	1:1:4	PM- L4	SDs L 4
	1:1:5	PM -L5	SDs L 5
Atorvastatin: Berberine: PVP K -30	1:1:3	PM- K3	SDs K 3
	1:1:4	PM- K4	SDs K 4
	1:1:5	PM -K5	SDs K 5

Table 1: Composition of the physical mixture and solid dispersion prepared by the melting method

*Name of the formulations

PM: Physical mixture prepared with atorvastatin, berberine, eudragit®L100, and PVP K 30 in a different ratio of polymer.

SDs L and SDs K: Solid Dispersion of both drugs with eudragit®L100 and PVP K 30.

Estimation of drug content

The ATV and BER content present in a prepared SD formulation was calculated using the previously described method [34]. Shortly, ~20 mg equivalent amount of SDs was put into a 100 ml volumetric flask in 10 ml of methanol and diluted with freshly prepared 90 ml of 1.2 pH HCl buffer with proper mixing and then filtered by using 0.45 µm membrane filtration. A specific amount was taken from the above stock solution and further diluted. Then by using a UV-visible spectrophotometer (Lab India, Model- XE 3200), the absorbance was measured at 247 nm and 348 nm (wavelength was selected based on UV scanning and by plotting of calibration curve) respectively against blank. All the values are taken in triplicate and then calculated by using the following equation.

$$\text{Drug Content} = \frac{\text{Measured Content}}{\text{Theoretical content}} \times 100$$

***In-vitro* dissolution studies**

In vitro dissolution studies of pure ATV, BER, PM, and prepared SDs were performed in 1.2 pH HCl using USP type II paddle dissolution apparatus as per the reference available in the literature. The temperature was maintained at 37 ±0.5oC at 50 rpm. Formulated SDs-L 5 and SDs-K 5 were selected for the dissolution studies as per the result obtained in polymer concentration optimization where the ratio followed the highest solubility as per Higuchi and Connor's method. ~20 mg of ATV, BER, PM, and formulated SDs of ratio (1:1:5) were taken for the dissolution study and mixed into 900 ml of dissolution medium in the dissolution flask. At fixed time points the 5 ml sample was withdrawn from the medium and replaced with fresh medium to maintain the sink condition. The sample was filtered if necessary and analyzed spectrophotometrically at a predetermined wavelength at 247 and 348 nm against the blank. All the experiments were carried out in triplicate and the mean value result was presented [35,36].

Fourier Transform Infrared Spectroscopy (FTIR)

Bruker spectrometer (ALPHA, IIE, FT-IR SPECTROMETER) was used for the measurement of FTIR spectra of pure ATV, BER, physical mixture [1:1:5], and selected solid dispersion. The FT-IR connected software O/IR 8.0+, OPUS/IR, package version 8.0 was used to investigate the compatibility of both drugs and used polymers. The scan range for sample investigation was between 4000-400 cm^{-1} using a spectra resolution of 4 cm^{-1}. The earlier developed process was followed for FTIR interpretation[37,38].

Differential Scanning Calorimetry (DSC)

A Differential scanning calorimeter Mettler Toledo with STARe Software (DB V 16.40) was used for the DSC study with a previously established method for the determination of thermal properties of plain ATV, BER, and polymers with prepared SDs. Briefly, 2 mg weighed samples were placed in covered aluminum pans and heated in a scanning oven under nitrogen flow at a rate of 10 0C min-1 from 25 0C to 400 0C. 50 ml/ min [39,40].

Powder X-ray (PXRD)

In this, samples of pure ATV, BER, PM, and selected SDs formulations of both polymers were analyzed using the PXRD instrument Rigaku Miniflex benchtop X-ray diffractometer, 600 CU K ALPHA. The ~50 mg of sample were placed into the section and CuKα radiation was used to irradiate the samples. The produced diffraction pattern for each sample and prepared SDs were studied at angle 2θ, with a range scale of 10 to 70. The changes in the peak which represent the crystallinity phase were noted and compared with the reported study [41,42].

SEM Studies

Pure ATV, BER, their physical mixture, and prepared SDs morphology were explored by scanning electron microscopy (Carl Zeiss, Supra 55, Germany) The sample was fixed using mutual conductive adhesive tape on aluminum stubs and sputter-coated with a gold layer at 20 mA for the 30s in an ion sputter coater pressure of 8-10 pa before the observation at an accelerating voltage of 20 kV[43].

STATISTICAL ANALYSIS

To compare the obtained variation between the test samples, the two-way ANOVA was used for the statistical analysis using the Graph Pad Prism

software tool. The data is displayed as mean ± standard deviation. A p-value of 0.005 or less was regarded as statistically significant.

RESULTS AND DISCUSSION:

Solubility and Polymer concentration optimization

The preliminary solubility studies for optimization of concentration and effect of polymer on the solubility of pure ATV and BER were depicted in Table 2, indicating that, the solubility of ATV and BER was significantly affected by the concentration of eudragit®L100 and PVP K-30. It was observed that the concentration and nature of the polymer was also an important criterion for enhancing the solubility of drugs. When eudragit®L 100 and PVP K-30 were used in different ratios, the increase in the concentration of polymer increases the solubility at a certain level which is further confirmed with dissolution studies. The highest increase in solubility was found with the 1:5 ratio of the polymer. The physical mixture containing ATV, BER, and polymers showed enhanced solubility as compared to a plain drug, but less when compared with the SDs as described in Table 2. Amongst the two polymers, more solubility was observed with PVP-K 30 which contributed to the hydrophilic nature of the PVP K 30 molecule as it easily forms the hydrogen bond with the molecule. The reported concentration of eudragit®L100 and PVP K-30 also suggested the significant involvement of drug and polymer compatibility. Also, the concentration of polymer may improve the complication of its water-soluble nature.

Drug: Carrier ratio	Solubility (µg/ml)	Drug to Carrier ratio	Solubility (µg/ml)
Pure ATV	29.45 ±0.26	Pure BER	21.59 ± 0.45
ATV: eudragit®L100 (1:3)	31.79 ± 0.31	BER: eudragit®L100 (1:3)	22.76 ± 0.31
ATV: eudragit®L100 (1:4)	46.23 ± 0.05	BER: eudragit®L100 (1:4)	40.71 ±0.08
ATV:eudragit®L100 (1:5)	54.22 ± 019	BER: eudragit®L100 (1:5)	51.50 ±0.31
ATV : PVP K-30 (1:3)	35.96 ± 0.16	BER: PVP K-30 (1:3)	23.33 ± 0.49
ATV : PVP K-30 (1:4)	48.20 ± 0.11	BER: PVP K-30 (1:4)	42.88 ± 0.08
ATV : PVP K-30 (1:5)	57.44 ± 0.19	BER: PVP K-30 (1:5)	55.97 ± 0.22

Table 2: solubility data for initial concentration of polymer

Content	Solubility (µg/ml)	Content	Solubility (µg/ml)
PM-L (1:1:5)	57.44 ± 0.19	PM-K (1:1:5)	62.28 ± 1.68
SDs-L 5	87.25 ± 1.25	SDs-K-5	92.12 ± 1.45

Table 3: solubility data for physical mixture and solid dispersion.

Drug Content analysis

The drug content of different physical mixtures and solid dispersion were studied. The drug contents of all the physical mixtures and solid dispersions were found within the range of 86.07 ± 0.11.

In vitro dissolution study result

The rate-limiting step for the absorption of the poorly soluble drug is the dissolution rate. Thus, they showed dissolution-dependent bioavailability. The dissolution study of all drug samples, physical mixture, and solid dispersion was performed in 1.2 pH HCL. Fig. 1 revealed the comparative release performance of ATV and BER from pure form, their physical mixture, and both formulations. The pure ATV showed about ~29.45% berberine was about ~21.59 %, the physical mixture with polymer eudragit®L100 was about ~58.44 % and the physical mixture with PVP K-30 polymer was ~64.23 % whereas the formulated SDs with both polymers showed ~88.52 % with eudragit®L100 and ~93.45 % with PVP K- 30 polymer in first 60 minutes, indicating that, improvement of dissolution may be contributed to hydrophilic polymer PVP K30, which can reduce the interfacial tension between the drug and the releasing medium. Also, the reduction in the particle size during the process of solid dispersion formulation could be another

assisted mechanism for the improvement in dissolution. The dissolution was found to be more in SDs as compared to physical mixtures and pure drugs.

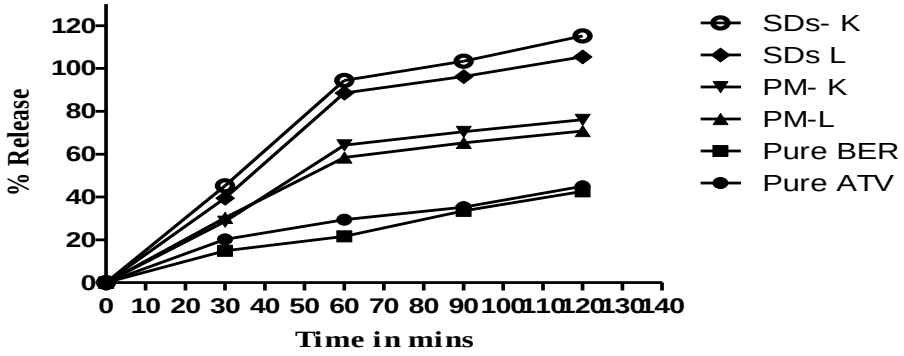
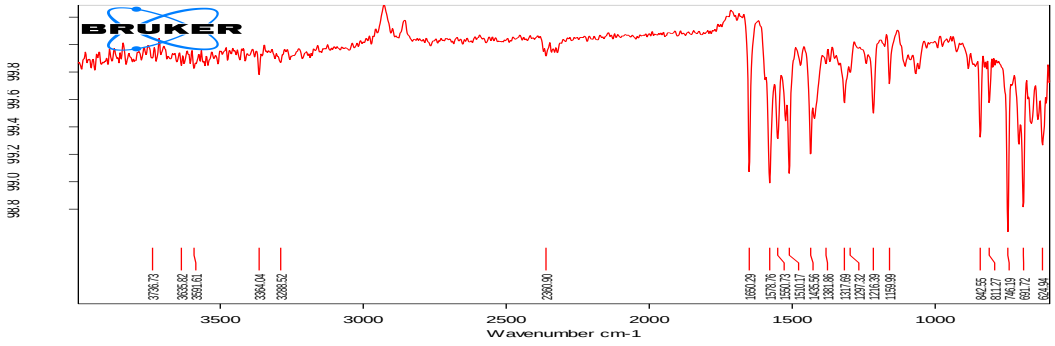


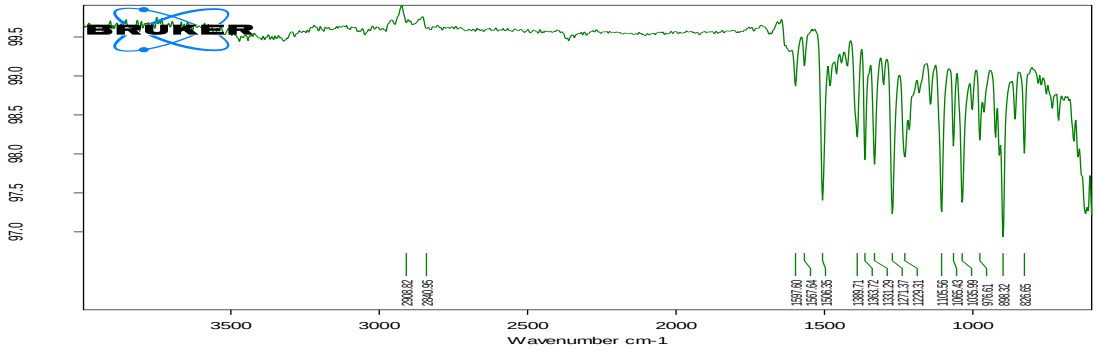
Figure 1: A comparative *In -vitro* dissolution study of solid dispersion, their physical mixture, and pure ATV and BER

FTIR analysis

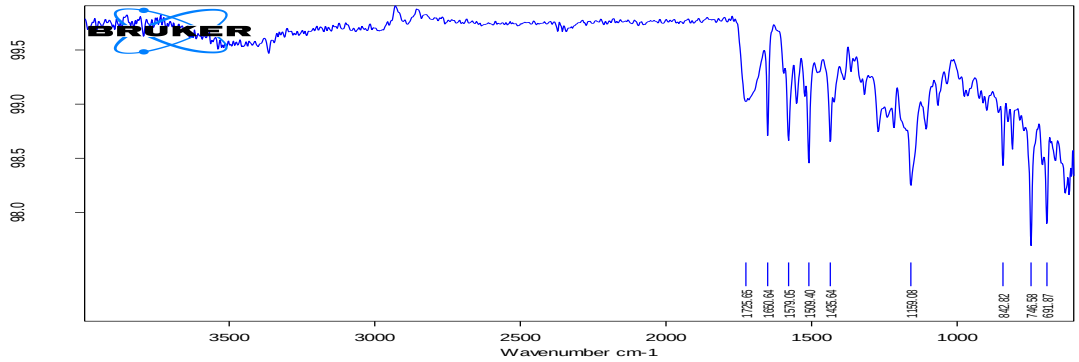
Figure. 2 (A to D) shows the FT-IR spectrum of pure ATV, BER, physical mixture, and prepared SDs. It was used to ascertain the interaction of drugs and polymer if any. The spectrum of pure ATV (fig. 2A) exhibited characteristic peaks at 1660cm-1(C-O carboxylic acid stretching), 2930-1 (C-H stretching), 3200-3500 cm-1 represent (O-H stretching, due to intermolecular hydrogen bond), 1400-1600-1 with three peaks (C-C aromatic stretching),1215 cm-1 (C-F stretching), 834 cm-1para substitution of benzene cause ring vibration. The spectrum of pure BER (Fig. 2B) showed identified peaks at 1506 cm-1 (aromatic C=C stretching), 3049 cm-1 (C-H stretching due to aromatic nature), 1597 cm-1 (C=N stretching to imine group), 1362 cm-1(C-H deformation to aromatic). Comparing PM-L (fig.2 C) shows retention of original peaks and the same is a condition for PM-K (fig. 2D). While SD-L (Fig. 2 E) and SD-K (fig.2 F) showed O-H between 3200 and 3500 cm-1 and C=O stretching at 1660 cm-1in ATV spectrum was replaced by a broader band in SDs, indicating possible hydrogen bonding of drug and polymer and this could prevent the drugs recrystallization and increase the stability of SDs. Additionally, the spectrum exhibits the retention of ATV, and BER peaks in the lower frequency range, proving that ATV, BER, and polymer do not interact with each other.



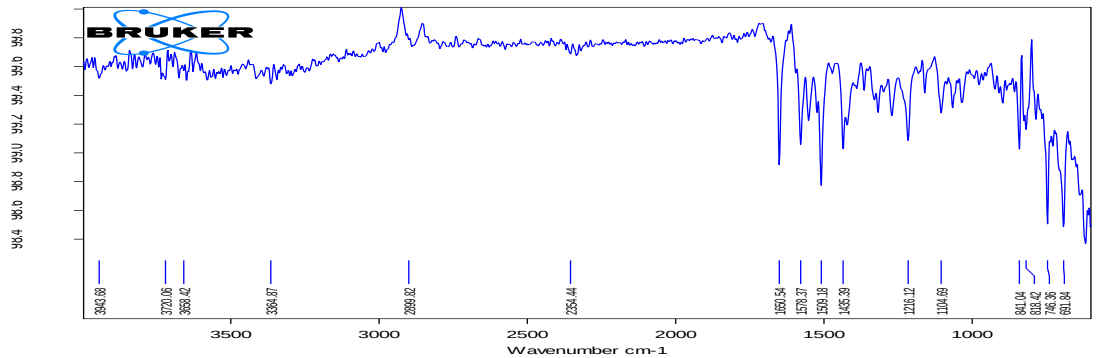
A) ATV



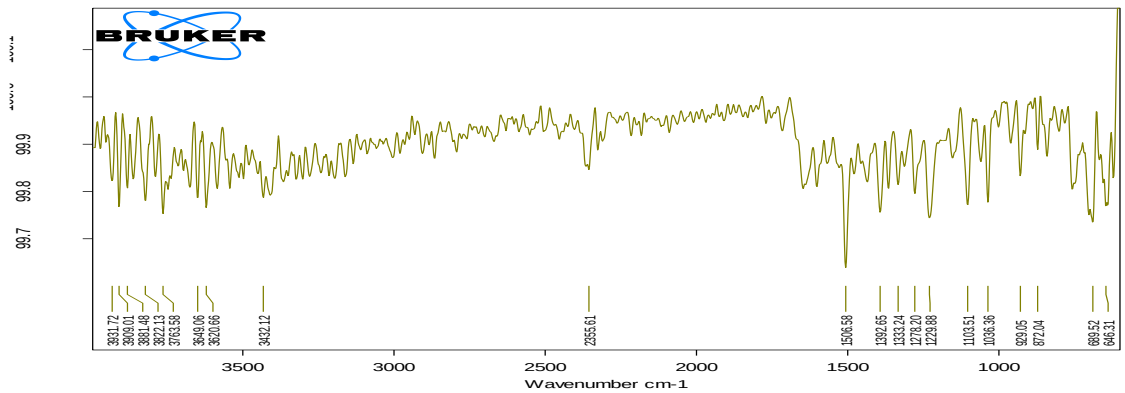
B) BER



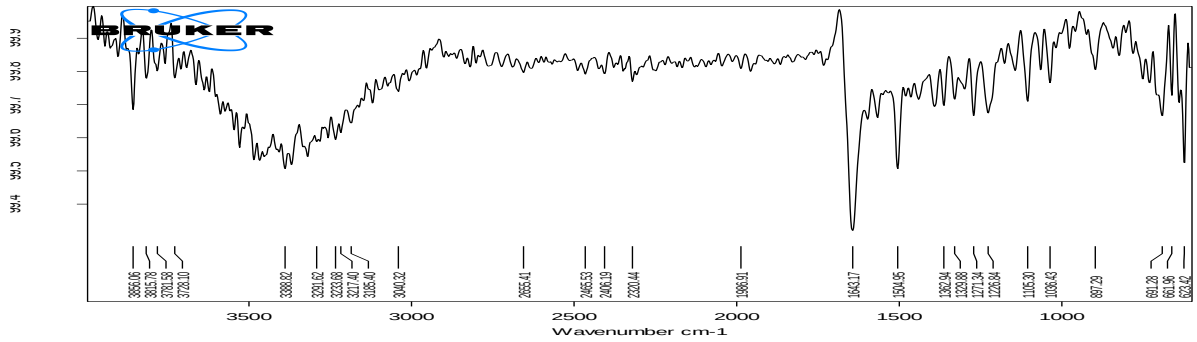
C) PM-L 5



D) PM-K-5



E) SDs-L-5



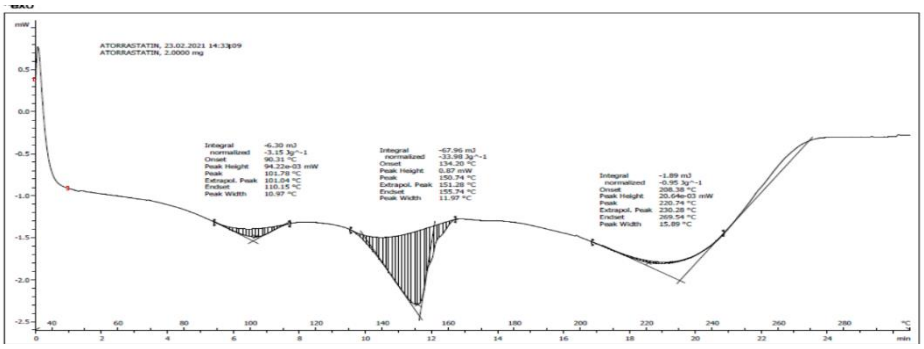
F) SDs- K-5

Figure 2: FT-IR Spectra of (A) Pure ATV (B) BER (C) PM by eudragit®L 100 (D) PM by PVP K -30 (E) SDs- with eudragit ®L 100 (F)SDs with PVP K -30

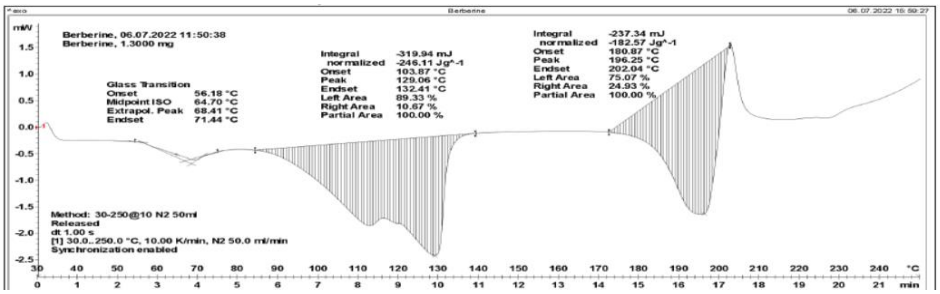
DSC

The DSC of ATV, BER, PM-L, PM-K, and SDs are displayed in Fig. 3 (A-F). The thermograms of ATV(fig.3 A) showed two endothermic peaks, a broad peak at 800C-1200C is related to water loss, followed by another endotherm recorded at 1550C -1700C corresponding to the melting of atorvastatin, the third peak 210-2500C may be attributed to a degradation product of ATV.

While the thermograms of BER showed, at 100.10°C, 192.62°C, and 288.86°C, the melting endothermic peak at 288.86°C. The DSC curve of the PM L 5 and PM-K 5 showed a shifted peak on lower transition energy which could easily accommodate the drug entrapment with the help of polymer. While no endothermic peak related to pure ATV and pure BER was observed in SDs L-5 and SDs K -5, which revealed that, the dispersion of drug molecules in the polymer solution occurred. The thermal changes that occur in DSC graphs confirm the formation of SDs, this was again confirmed by XRD and SEM studies.



A)



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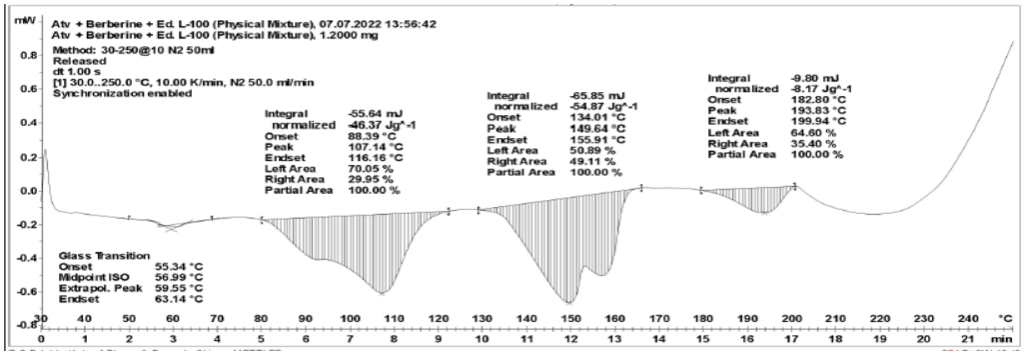

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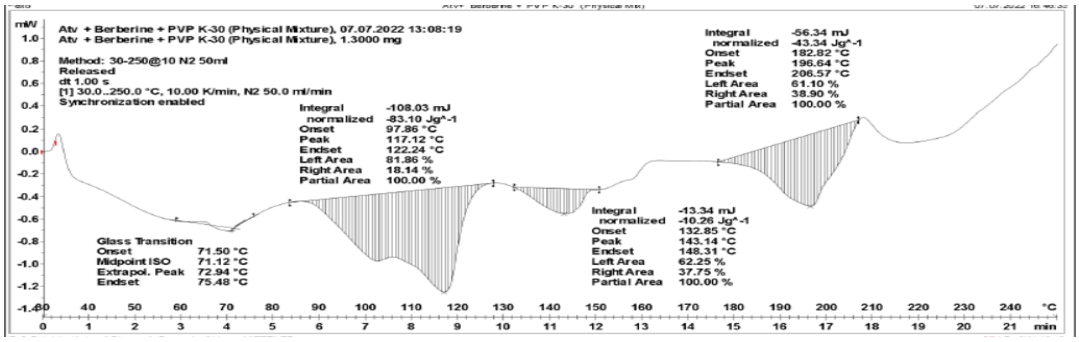

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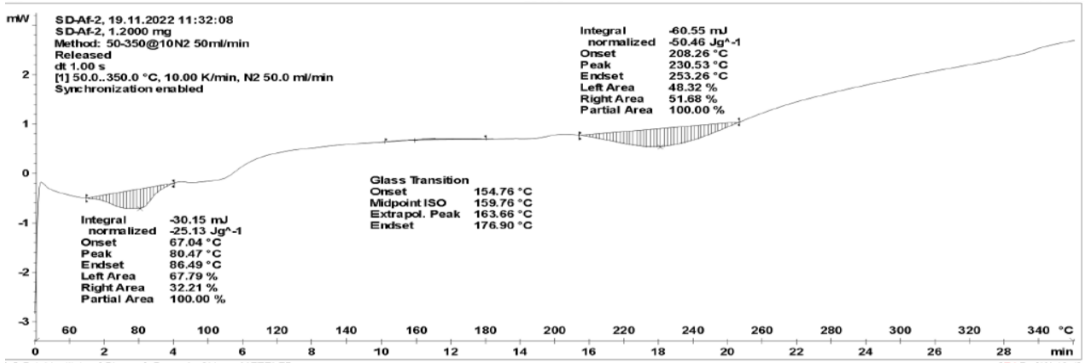

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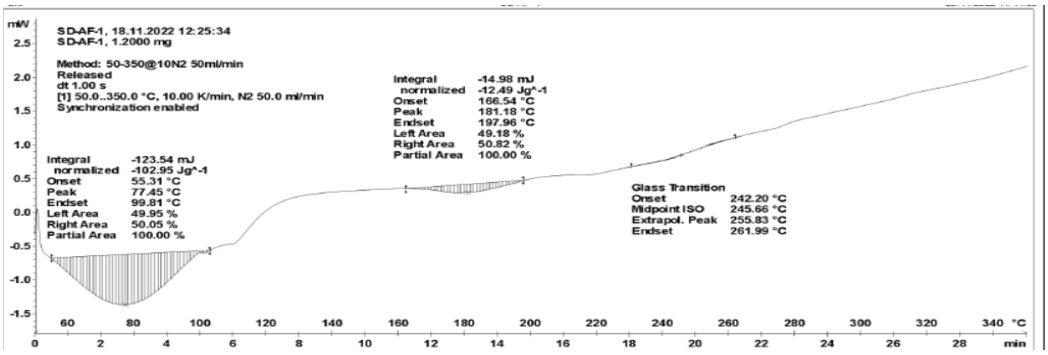


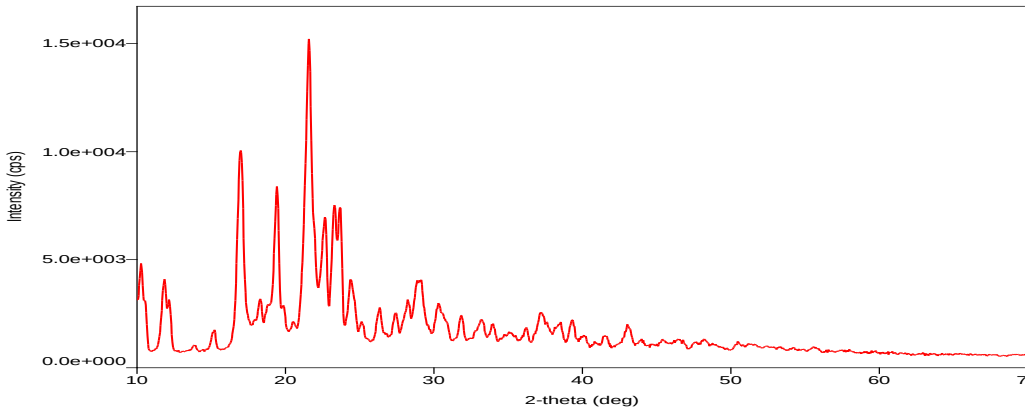
F)

Figure. 3 DSC thermograms of (A) ATV, (B) BER, (C) PM-L (D) PM-K (E) SD-L 5 (F)SD-K 5

PXRD study

Powder X-ray diffraction could further verification of drug crystal conversion. The PXRD pattern was depicted in Fig. 4. The pure ATV exhibited sharp and intense diffraction peaks at 2θ values of 10.29, 10.55, 11.84, 12.19, 19.44 21.57, 22.59, 23.29, 23.68, 24.44, 28.98. The sharp characteristic peak at diffraction angles (2θ) of

13.34, 16.65, 25.77, and 32.47 was observed with pure berberine indicating the presence of crystallinity. All the peaks' intensity reduced in a physical mixture while only one major peak was observed in SDs which might correspond to the diffraction of polymer eudragit®L100 and PVP K-30



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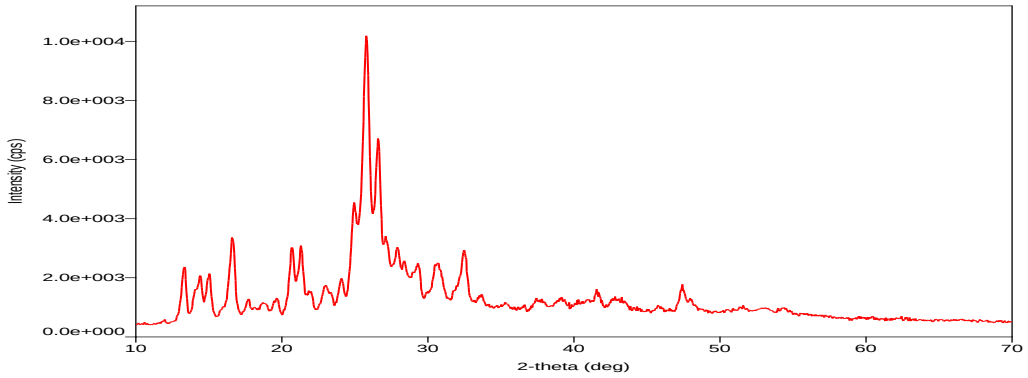

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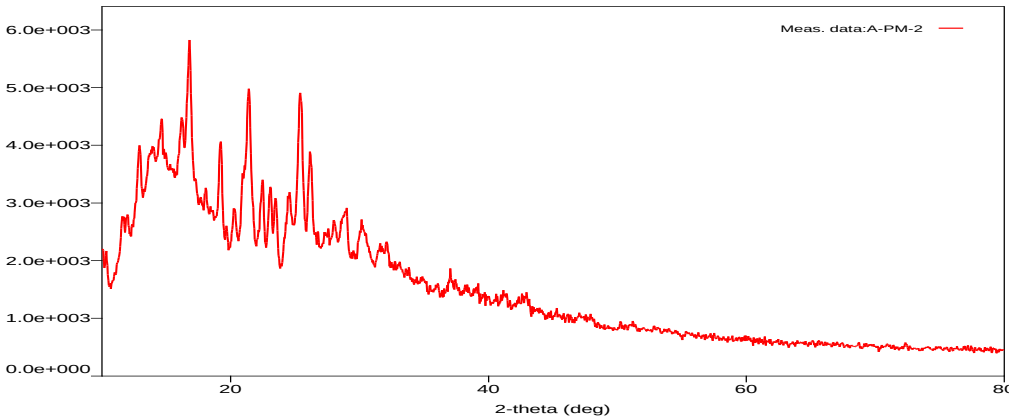

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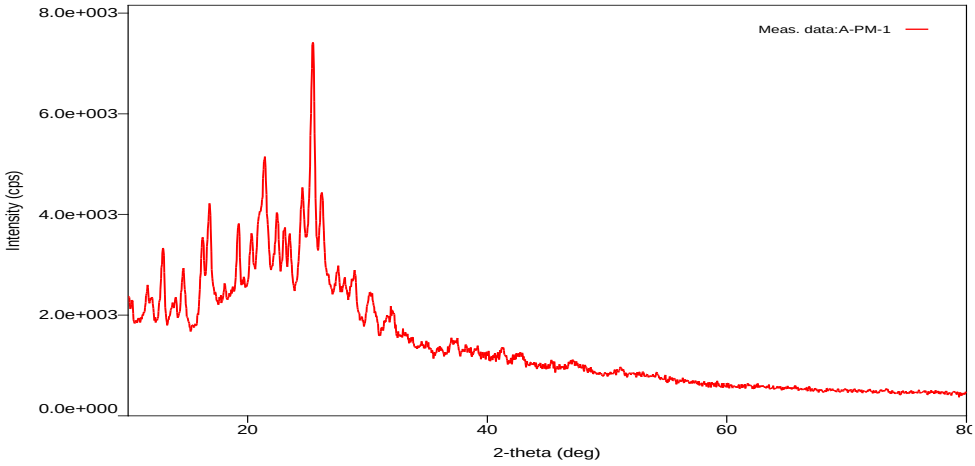
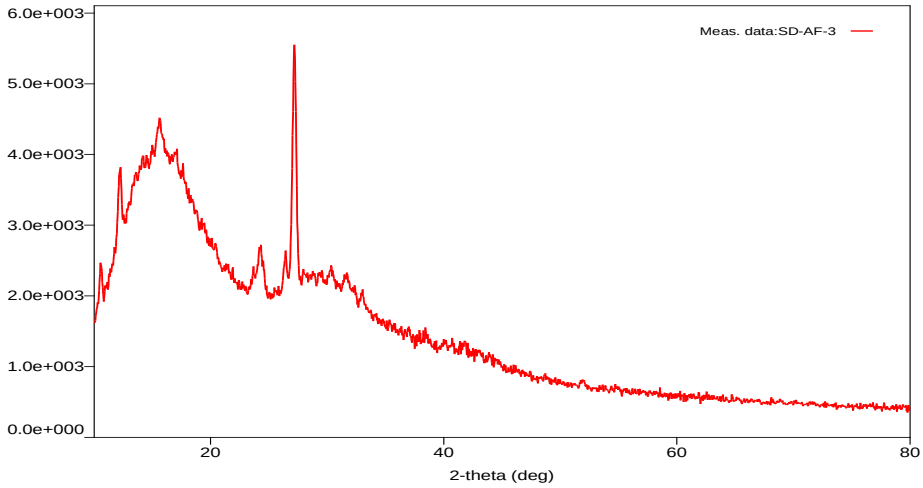
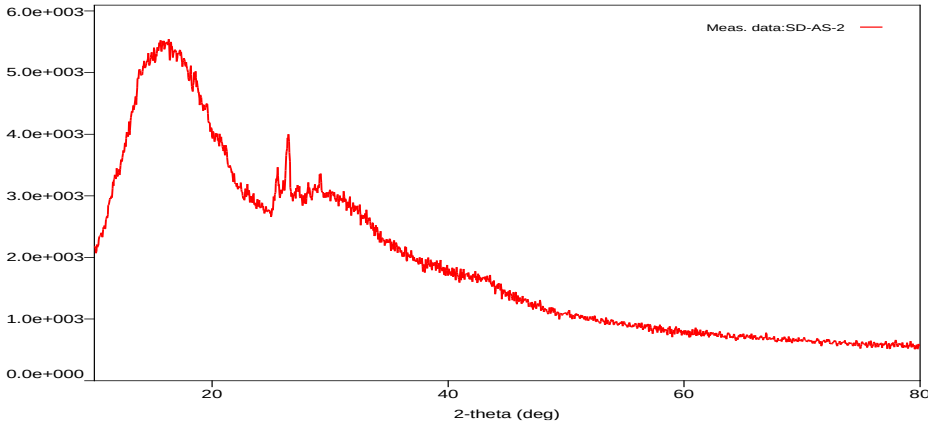


D)



E)

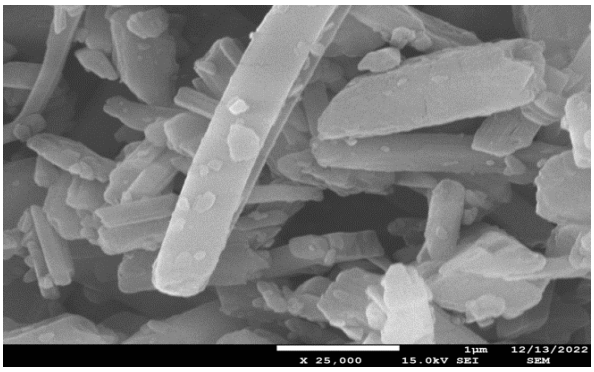


F)

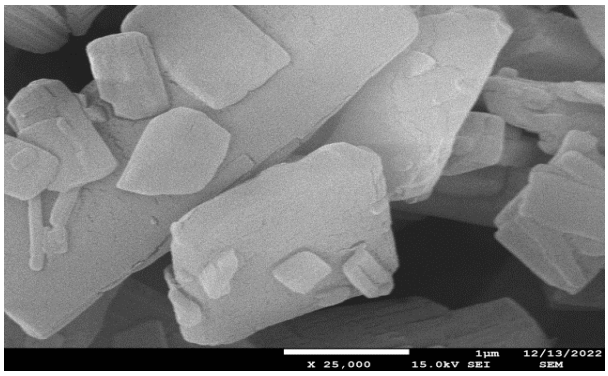
Figure 4. X-RD (A) ATV, (B) BER, (C) PM-L (D) PM-K (E) SD-L 5 (F)SD-K 5

SEM

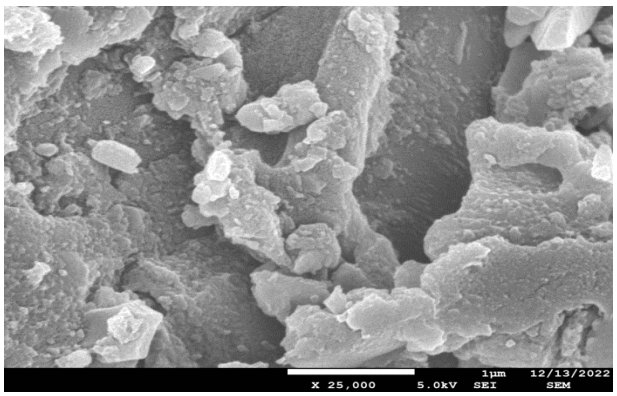
SEM images of pure ATV, pure BER, and corresponding SDs of both polymers are shown in Figure 5 (A-D). ATV demonstrated a rod-shaped crystal lattice (Fig. 5(A)). The morphological features for BER (Fig. 5(B)) were observed as cuboidal shapes. The emergence of the new morphological shape was observed in SDs (Fig. 5 (C) and (D)). The distortion of both shapes was seen compared to the pure drug indicating the efficient formation of the SDs System.



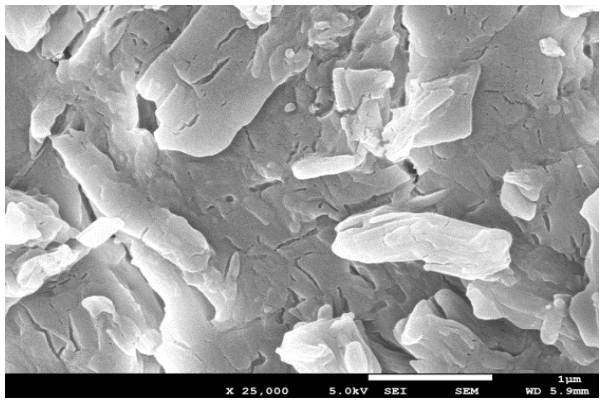
A) ATV



B) BER



C) SDs K 5 (K 30)



D) SDs L 5 (EDL 100)

Figure 5. SEM of (A) ATV (B) BER (C) SDs K 5 (D) SDs L 5

CONCLUSION:

The present work can be used for the formulation of tertiary solid dispersion which improves the solubility of atorvastatin and berberine compared to the physical mixture and the pure drugs. To identify the physical state of the drug in SDs, PXRD was adopted and it revealed the reduction in crystallinity of the pure drugs. Furthermore, the absence of shifts in the FTIR peaks of the solid dispersion compared to the physical mixture indicates a lack of significant interaction between the drug and herb, components in the solid dispersion. In conclusion, this study proves that it is possible to increase the solubility of poorly water-soluble by preparing it as a solid dispersion. Further, it can be concluded that, based on solubility and dissolution data, the expected increase in bioavailability may be observed which will be checked for pharmacokinetic and pharmacodynamic studies of the formulation.

CONFLICT OF INTEREST

The authors have no conflict of interest associated with this study.

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REFERENCES:

1. YiCong Ye. XiLiang Zhao. ShuYang Zhang. Use of Atorvastatin In Lipid Disorders And Cardiovascular Disease In Chinese Patients. Chinese Medicinal Journal. 2015; 128(2): 259–266. Doi.org/ 10.4103/03666999.149226.
2. Lea P. McTavish D. Atorvastatin: a review of its pharmacology and therapeutic potential in the management of hyperlipidaemias. Drugs. 1997; 53: 828-847. https://doi.org/10.2165/00003495-199753050-00011
3. Jadhav Y. Parashar B. Ostwal P. Jain M. Solid Dispersion Solubility Enhancement for poorly Water Soluble Drug. Research Journal Pharmaceutics and Technology. 2012; 5(2): 190-197.
4. Dong W. Su X. Xu M. Hu M Sun Y. Zhang P. Preparation, Characterization, And In Vitro/ Vivo Evaluation of Polymer-Assisting Formulation of Atorvastatin Calcium Based On

Solid Dispersion Technique. Asian Journal of Pharmaceutical Sciences. 2018; 13(6):546-54.

5. Arca M. Giovanni P. Treating statin-intolerant patients. Diabetes, metabolic syndrome and obesity: targets and therapy.2011; 4:155-166. Doi: 10.2147/DMSO.S11244
6. Yudi W. Wisudyaningsih B. Siswoyo T. Enhancement of Solubility And Dissolution Rate of Atorvastatin Calcium By Co-Crystallization. Tropical Journal of Pharmaceutical Research. 2017; 16 (7): 1497-1502 ISSN: 1596-5996 (print); 1596-9827 (electronic) http://dx.doi.org/10.4314/tjpr.v16i7.6.
7. Ahmed A. Sengupta R. Atorvastatin Calcium Loaded Chitosan Nanoparticles: In Vitro Evaluation and In Vivo Pharmacokinetic Studies in Rabbits. Brazilian Journal of Pharmaceutical Sciences. 2015; 51(2):467-77. https://doi.org/10.1590/S1984-82502015000200024
8. Snela A. Jadach B. Froelich A. Skotnicki M. Milczewska K. etal. Self-Emulsifying Drug Delivery Systems With Atorvastatin Adsorbed On Solid Carriers: Formulation And In Vitro Drug Release Studies. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2019; 577:281-90. doi.org/10.1016/j.colsurfa.2019.05.062
9. Bobe R. Subrahmanya R. Suresh S. Gaikwad T. Patil D et al. Formulation and Evaluation of Solid Dispersion of Atorvastatin with Various Carriers. International Journal of comprehensive pharmacy. 2011; 2(1):1-6.
10. Ranim S. Wehad I. Mohammad H. Preparation and Evaluation of nifedipine Solid Dispersions. Research Journal Pharmacy and Technology 2020; 13(9):4148-4152. doi:10.5958/0974-360X.2020.00732.5
11. Song D. Hao J. Fan D. Biological Properties and Clinical Applications of Berberine. Frontiers of Medicine. 2020; 14(5):564-82.
12. Feng X. Sureda A. Jafari S. Memariani Z. Tewari D. et al. Berberine in Cardiovascular and Metabolic Diseases: From Mechanisms to Therapeutics. Theranostics. 2019; 9(7):1923.
13. Imenshahidi M. Hosseinzadeh H. Berberine and Barberry (Berberis Vulgaris): A Clinical Review. Phytotherapy Research. 2019; 33(3):504-23.
14. Guo S. Wang G. Wu T. Bai F. Xu J. et al. Solid Dispersion of Berberine Hydrochloride and Eudragit® S100: Formulation, Physicochemical Characterization, and Cytotoxicity Evaluation. Journal of Drug Delivery Science and Technology. 2017; 40:21-27. https://doi.org/10.1016/j.jddst.2017.02.003
15. Pirillo A. Catapano L. Berberine, A Plant Alkaloid with Lipid-And Glucose-Lowering Properties: From In Vitro Evidence to Clinical Studies. Atherosclerosis. 2015; 243(2):449-61.
16. Battu S. Repka A. Maddineni S. Chittiboyina G. Avery M. et al. Physicochemical Characterization of Berberine Chloride: A Perspective In The Development of A Solution Dosage Form For Oral Delivery. Aaps Pharmscitech. 2010; 11:1466-1475.
17. Shi C. Tong Q. Fang J. Wang C. Wu J. et al. Preparation, Characterization, and In Vivo Studies of Amorphous Solid Dispersion of Berberine With Hydrogenated Phosphatidylcholine. European Journal of Pharmaceutical Sciences. 2015; 74:11-17. Doi.Org/10.1016/J.Ejps.2015.04.001
18. Benet Z. Wu Y. Hebert F. Wacher J. Intestinal Drug Metabolism and Anti Transport Processes: A Potential Paradigm Shift in Oral Drug Delivery. Journal of Controlled Release. 1996; 39(2-3):139-43.
19. Kim S. Shi Y. Kim J. Park K. Cheng X. Overcoming the Barriers in Micellar Drug Delivery: Loading Efficiency, In Vivo Stability, And Micelle–Cell Interaction. Expert Opinion on Drug Delivery. 2010; 7(1):49-62.
20. Singh J. Walia M. Harikumar S. Solubility Enhancement by Solid Dispersion Method: A Review. Journal of Drug Delivery and Therapeutics. 2013;3(5):148-55.
21. Thoke S. Gayke A. Dengale R. Patil P. Sharma Y. Review On Taste Masking Approaches And Evaluation of Taste Masking. International Journal of Pharmaceutical Sciences. 2012; 4(2) :1895-1907.
22. Vyas J. Parmar H. Patel H. Comparative Study of Etoricoxib Loaded Solid Dispersion And Beta-cyclodextrin Complexes For Improvement of Dissolution Profile. Research Journal of Pharmaceutical Dosage Forms and Technology. 2020;12(2):63-7.

23. Cetin M. Atila A. Kadioglu Y. Formulation And In Vitro Characterization of Eudragit® L100 And Eudragit® L100-PLGA Nanoparticles Containing Diclofenac Sodium. Aaps Pharmscitech. 2010; 11:1250-1256.
24. Sunnam S. Sodhi I. Joshi P. Samal SK. Sangamwar T. Correlating Precipitation Inhibition Efficacy of EUD EPO And PVP K30 On The Supersaturated Solution of Atorvastatin Calcium With Caco-2 Permeability Enhancement. Journal of Drug Delivery Science and Technology. 2020;57:101692.
25. Jagtap S. Tagad R. Shendge R. A Brief Review on Kollidon. Journal of Drug Delivery and Therapeutics. 2019; 9(2):493-500.
26. Issa A. Marchidan D. Cojocaru V. Anuța V. Preparation and Evaluation of Meloxicam Solid Dispersion by Melting Method. Farmacia. 2013; 61(6):1216-32.
27. Fasinu S. Rapp K. Herbal Interaction with Chemotherapeutic Drugs—A Focus on Clinically Significant Findings. Frontiers in Oncology. 2019;9:1356.
28. Stojančević M. Pavlović N. Goločorbin-Kon S. Mikov M. Application of Bile Acids in Drug Formulation And Delivery. Frontiers in Life Science. 2013; 7(3-4):112-22.
29. Xie Y. Zhang D. Zhang J. Yuan J. Metabolism, Transport and Drug–Drug Interactions of Silymarin. Molecules. 2019; 24(20):3693. Doi.Org/10.3390/Molecules24203693
30. Mohanalakshmi S. Bhatt S. Kumar A. The Enhanced Antihyperlipidemic Potential of Gemfibrozil Under Co-Administration With Piperine. Current Research in Pharmacology and Drug Discovery. 2021; 2:100021.
31. Nirmala D. Chakradhar A. Sudhakar M. Preparation and Characterization of Pitavastatin Solid Dispersions. Research Journal of Pharmacy and Technology. 2016; 9(5):555-8.
32. Baskaran M. Talluri B. Kuppusamy G. Karri V. Kollipara R. Formulation Development of Atorvastatin Calcium Tablets By Gel Liquisolid Compact Technique For Improving Solid-State Stability And Dissolution Profile. Journal of Drug Research and Development. 2016; 2(4):1-7.
33. Mohan A. Madhavi M. Jyosthna P. Preparation, In Vitro and In Vivo Characterization of Solid Dispersions of Oxcarbazepine Using The Melting Technique. The Pharma Innovation. 2015; 3(12, Part B):99.
34. Choudhary H. Yadav B. Patel P. Das P. Pillai S. Formulation and Evaluation of Ramipril Fast Dissolving Tablet Using Solid Dispersion. Research Journal Pharmmacy and Technology 2019; 12(8): 3764-3772. doi: 10.5958/0974-360X.2019.00645.0
35. Saker R. Ibrahim W. Haroun M. Preparation and Evaluation of Nifedipine Solid Dispersions. Research Journal of Pharmacy and Technology. 2020; 13(9):4148-52.
36. Jahangiri A. Barzegar-Jalali M. Garjani A. Javadzadeh Y. Hamishehkar H.etal . Pharmacological And Histological Examination Of Atorvastatin-PVP K30 Solid Dispersions. Powder Technology. 2015; 286:538-545.
37. Sunnam S. Sodhi I. Joshi P. Samal K. Sangamwar T. Correlating Precipitation Inhibition Efficacy of EUD EPO And PVP K30 On A Supersaturated Solution of Atorvastatin Calcium With Caco-2 Permeability Enhancement. Journal of Drug Delivery Science and Technology. 2020; 57:101692.
38. Shamsuddin F. Ansari H. Ali J. Atorvastatin Solid Dispersion for Bioavailability Enhancement. Journal of Advanced Pharmaceutical Technology & Research. 2016; 7(1):22.
39. Narasaiah V. Reddy B. Kishore K. Kumar M. Rao P. et al. Enhanced Dissolution Rate of Atorvastatin Calcium Using Solid Dispersion With PEG 6000 By Dropping Method. Journal of Pharmaceutical Sciences and Research. 2010; 2(8):484.
40. Bhaduka G. Rajawat S. Formulation Development and Solubility Enhancement of Voriconazole By Solid Dispersion Technique. Research Journal Pharmacy and Technology. 2020; 13(10):4557-64.
41. Thirupathaiah A. Shyam R. Enhancement of Solubility and Dissolution of Atorvastatin By Solid Dispersion Technique With Novel

Carriers. Der Pharmacia Lettre. 2016; 8:180-91.

42. Choudhary A. Rana C. Aggarwal G. Kumar V. Zakir F. Development and Characterization of An Atorvastatin Solid Dispersion Formulation Using Skimmed Milk For Improved Oral Bioavailability. Acta Pharmaceutica Sinica B. 2012;2(4):421-8.
43. Nasrin F. Development And In Vitro Characterization of Atorvastatin Calcium Poloxamer 407 Solid Dispersions Systems. International Journal of Pharmacy and Technology. 2014;5 (4):6090-6103.