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Improvement of solubility and dissolution rate of Biopharmaceutical Class II drug atorvastatin calcium by using an essential amino acid L-leucine

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Abstract

Background and objective: Atorvastatin calcium is an antihyperlipidemic agent that is characterized by low aqueous solubility and high membrane permeability. This study was designed to enhance the solubility and the dissolution rate of atorvastatin calcium in the water and physiological pH (pH 6.8) by using L-Leucine as solubilizing agent utilizing different solid dispersion methods.

Methods: Solid dispersion masses were prepared by kneading method and solvent evaporation methods at different weight ratios (1:1, 1:2: and 1:4) of the drug to the carrier. Saturated solubility studies were carried out in aqueous media, and the *in*-vitro studies were performed in physiological pH Fourier transform infrared spectroscopy were used to detect any interaction between the drug and the carrier.

Results: The kneading method increase the solubility of atorvastatin calcium by 1.27, 1.43, and 1.81 folds from kneading method 1, kneading method 2, and kneading method 3, respectively. The solubility of atorvastatin calcium in solvent evaporation 1, solvent evaporation 2, and solvent evaporation 4 was increased by 2.53, 2.66, and 3.1 folds (P = 0.002). Solvent evaporation 2 (1:2 ratio) was selected as the best formula in terms of dissolution profile because it has faster and complete drug release after 5 minutes when compared with solvent evaporation 1, kneading method 1, kneading method 2, and kneading method 3 and contain less amount of L-Leucine when compared with solvent evaporation 3. Fourier transform infrared studies indicated no chemical reaction between the drug and carrier.

Conclusion: L-leucine significantly improved the solubility and dissolution profile of poorly water-soluble atorvastatin calcium.

Keywords: Atorvastatin calcium (ATC); Leucine (LUC); Solid dispersion (SD).

Introduction

The oral administration of a drug is the main and important method of using drugs for systemic effects. When a new drug is discovered, one of the first challenges a pharmaceutical company faces is whether or not the drug can be successfully administered by the oral route for its proposed pharmacological effect.[1] More than 40% of hydrophobic drug candidates fail to reach the market due to insufficient bioavailability, even though these drugs might exhibit potential pharmacodynamic activities.[2] Pharmacological actions of a drug depend upon the bioavailability and ultimately upon the solubility of drug molecules in the biological fluids and its permeability through the gastrointestinal mucosa. Solubility is an important parameter for achieving the desired concentration of drug in systemic circulation for therapeutic response.

Drugs that are poorly soluble in water are associated with slower drug absorption, eventually leading to variable bioavailability and inadequate response. The Biopharmaceutical Classification System (BCS) categorizes drugs into four classes: Class I, Class II, Class III, and Class IV depending on their solubility

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and permeability characteristics.[3] Drugs belonging to BCS Class II have poor water solubility and high membrane permeability, and thus they are ideal candidates for improving bioavailability by one of the solubilities enhancing techniques.[3,4]

Many methodologies can be used to enhance the solubility of poorly water-soluble drugs in biological fluids and further improve their bioavailability and therapeutic effectiveness. Some of these methods are micronization, sonocrystallization, supercritical fluid process, chemical modification, pH adjustment, complexation, hydrotropy, co-solvency, and solid dispersion.[5]

Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates, and consequently the bioavailability of class II drugs.[6]

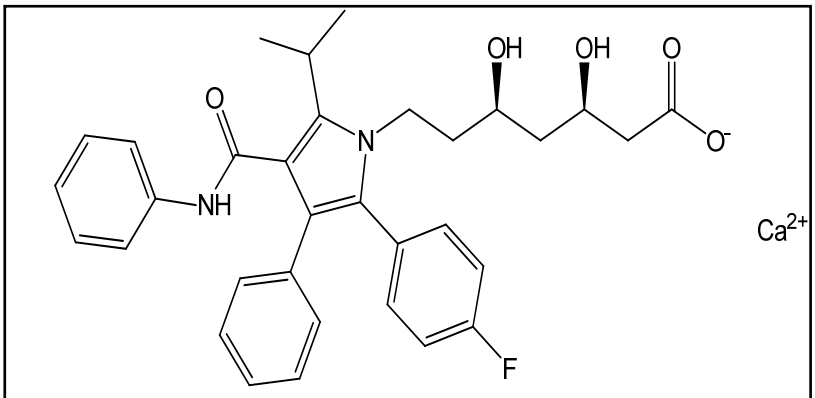
Solid dispersion (SD) is defined as "a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by melting (fusion), solvent or melting solvent method."[7] The common methods used for the preparation of SD include fusion, solvent evaporation, melting solvent, melt extrusion, kneading, and physical mixture methods.[8]

SD technique is an effective way to enhance the bioavailability of poorly water-soluble drugs because of its ability to reduce the particle size of the drug, improve wettability, conversion of drug from crystalline to amorphous form, which improves dissolution and bioavailability, and enhance the porosity of the formulation as well as provide a uniform distribution of low dose drugs at solid state.[9]

Atorvastatin calcium (ATC) "is a member of lipid-lowering agent. It is a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate, an early rate-determining step effective treatment for patients with elevated LDL cholesterol".[10]

Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity. ATC chemically it is (3R, 5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1-H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid (Figure 1).[11]

ATC belongs to BCS class-II drugs and thus has low aqueous solubility and bad bioavailability after oral use.[3,12] A successful formulation of ATC into oral solid dosage form depends upon the method used to increase its water solubility and oral bioavailability.



(3*R*,5*R*)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate

Atorvastatin Calcium

Figure 1 The chemical structure of atorvastatin calcium

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According to Mangal et al., amino acids have been investigated for improving the dissolution of poorly soluble drugs by forming co-amorphous dispersions.[13] We hypothesized that solid dispersion of ATC with the amino acid L-leucine or Leucine (LUC) (Figure 2) might form an amorphous dispersion and improvement of solubility and dissolution rate of the drug.

The objective of this study is to enhance the solubility and the dissolution rate of Atorvastatin calcium (ATC) in water and physiological pH (pH 6.8)through the use of L-Leucine (LUC) as solubilizing agent utilizing different solid dispersion (SD) methods.

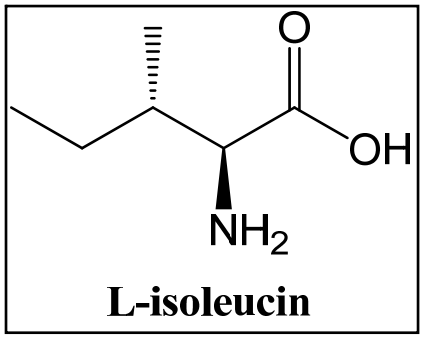

Figure 2 The chemical structure of L-Isoleucine

Methods

Design, setting, and time of the study

This experimental research study was carried out in the College of Pharmacy, Hawler Medical University, from 1st of May 2020 to 1st of July 2020.

Materials

ATC was kindly gifted from Awamedica Pharmaceutical Company, Erbil. Iraq and LUC were procured from Simson Pharma. Mumbai. India. Other chemicals are of analytical grade. Distilled water was prepared in the laboratory.

Determination of ATC maximum absorbance (ƛ max) and calibration curve

A standard solution of ATC at a concentration of 100 mcg/ml was prepared by dissolving 10 mg of ATC in 100 ml methanol.[14] A diluted solution of ATC was obtained by appropriate dilution of the first standard stock solution with Distilled water and phosphate buffer pH 6.8 were the solubility and dissolution studies performed, the obtained solution was scanned using Biotech UV/Vis spectrophotometer in the range of 200-400 nm to determine the wavelength of maximum absorption (ƛ max) of the drug in phosphate buffer and distill water.

Series of diluted solutions at a concentration of 5,10, 15, and 20 mcg/ml were prepared by suitable dilution of the second standard solution of ATR with distilled water and phosphate buffer.[16] The solutions were scanned spectrophotometrically at the ƛ max of the drug to obtain the calibration curve.

Determination of ATC solubility

The saturation solubility study of ATC was carried out in distilled water. The excess quantity of ATC was taken in 100 ml conical flask containing 50 ml of distilled water. The solution was shaken and left for 24 hours with continuous stirring.[17] After 24 hours, the prepared drug suspension was filtrated through What man filter paper no.1 and a sample from the filtrate was taken, suitably diluted with the respective solvent.[18]

The absorbance of the diluted solution was obtained at ƛ max of the drug using UV-Visible spectrophotometer.

Preparation of SD

SD masses were prepared by kneading method (KM) and solvent evaporation (SE) methods at different weight ratios (1:1, 1:2: and 1:4) of the drug to the carrier, respectively. Table 1 illustrates the quantity of ATC and LUE used to prepare solid dispersion masses at different ratios.

Kneading method

A measured quantity of a mixture of ATC and LUC for each weight ratio were placed in a mortar, and the mixture were kneaded thoroughly for 20 minutes with ethanol until the powder mixtures were transformed to paste. The obtained pastes were dried in an oven at 60°C until it reached a constant weight, pulverized, and passed through 250µm sieve.[3,19]

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Solvent evaporation method

For the preparation of SD mass by solvent evaporation method, the desired quantity of ATC for the respective ratios were placed in a glass mortar and dissolved by adding methanol. Then, the measured amounts of LUC were added to get a homogeneous mixture.[20] The solvent evaporated from the mixtures in an oven at 60°C. The obtained solid mixtures were pulverized and passed through 250µm sieve. Finally, the samples were kept in desiccators until the next experiments.

Determination of percentage drug content in the prepared solid dispersion

The percentage drug content was determined by dissolving the amount of solid dispersion masses, which is equivalent to 20 mg of ATC in 50 ml of methanol, the mixtures were suitably diluted with distilled water and UV absorbance was measured at the ƛ max of the drug.[24] Drug concentration was determined from the calibration curve, and percentage drug content was determined from the below equation.[25]

$$\% \text{ Drug content} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Fourier transforms infrared (FTIR) studies

To evaluate the compatibility of ATC with LUC, Fourier transforms infrared studies were performed using JASCOFT/IR-4600 spectrometer. FT-IR analysis studies were carried out using samples of ATC, LEU, and SD mixtures of the drug and the carrier at 1:2 ratio for both used methods.[21]

In-vitro drug release

The dissolution rate of ATC formulations was determined using (PHARMA TEST PT -DT7) dissolution Apparatus type II with paddle stirrer at 37 ± 0.5 °C and stirring at 50 rpm. The dissolution medium was 900 mL of phosphate buffer (pH 6.8).[22] 5 ml samples were withdrawn from the dissolution vessels at specific time intervals (5, 10, 20, 30, and 45 min) which were immediately replaced with the same volume of fresh dissolution medium.[23]

ATC quantity was estimated at 245 nm with a UV spectrophotometer, and the percentage of drug release for each formulation was determined through the calibration curve.

Statistical analysis

The effect of formulation variables on the solubility and dissolution rate of the prepared ATC formulations were tested for significance by using paired samples t-test with the aid of the statistical package for the social sciences (SPSS 21) program. The difference was considered statistically significant when (P = 0.002). The calibration curves of ATC in different aqueous media and the dissolution profiles were constructed using Microsoft Excel 2019 program. Linearity of the calibration curves is expressed through the correlation coefficient, r. A correlation coefficient close to 1 is considered that the calibration curve is linear. The correlation coefficient was determined using Microsoft Excel 2019 program.

Results

The calibration curve of ATC was constructed by plotting the known dissolved quantity of ATC in distilled water and phosphate buffer pH6.8 against corresponding absorbance obtained at the ƛ max of the drug (Figures 3 and 4). This simple, reproducible estimation method was constructed by scanning different solutions at different concentrations

Table 1 The quantity and ratios of ATC and LUC in the prepared formulations

Material quantity (mg) /Ratio	Pure	KM1	KM2	KM3	SE1	SE2	SD3
ATC	20	20	20	20	20	20	20
LUC	-	20	40	60	20	40	60
ATC: LUC	-	1:1	1:2	1:3	1:1	1:2	1:3

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ranging from 5-20mg/ml at 240 nm for distilled water and 245nm for phosphate buffer solution against the blank. The standard graph obtained was linear, with a correlation coefficient of 0.999 and .998 for distilled water and phosphate buffer, respectively.

Solubility studies of ATC and ATCSD

Saturated solubility studies were carried out for pure drug and prepared solid dispersions in distilled water at room temperature. Figure 5 illustrates the solubility of ATC and the enhancement of ATC solubility in the presence of LUC. The solubility data expressed as mean±SDE (n=3) and the data of columns (KM1, KM2, KM3, SE1, SE2, and SE3) were significantly different when compared to pure ATC solubility (P = 0.002).

Determination of percentage drug content in the prepared solid dispersion

The drug content in the prepared solid dispersion formulations was estimated through the standard calibration curve. The amount of ATC in all the formulations was within the accepted range (Table 2).

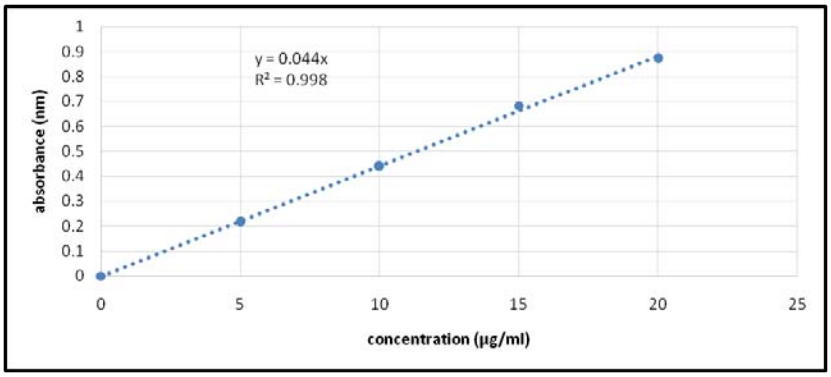

Figure 3 Calibration curve of ATC in distilled water

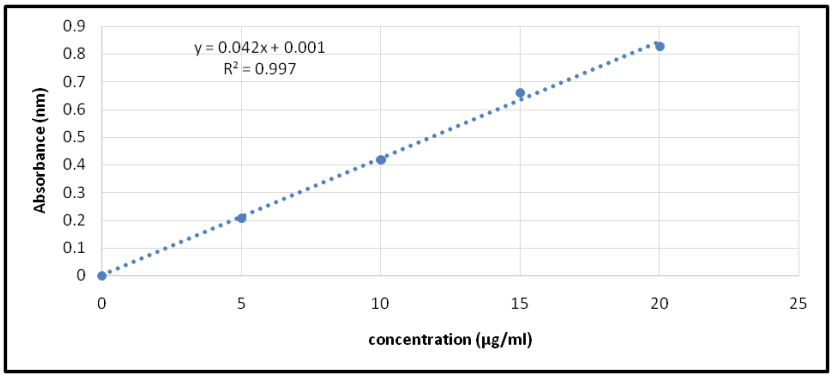

Figure 4 Calibration curve of ATC in phosphate buffer

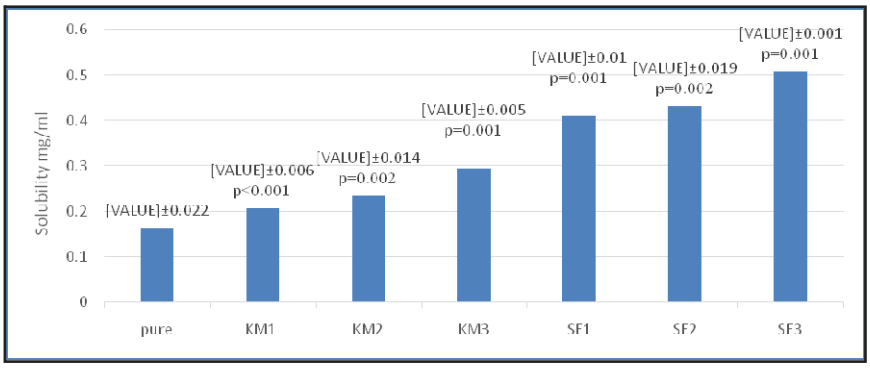

Figure 5 Results of solubility studies of pure ATC and ATC solid dispersion

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Fourier transforms infrared (FT-IR) studies

FT-IR studies were performed to identify possible interaction between the drug and the carrier after solid dispersion by the two proposed methods in the form of band shifting in the spectrum.

The spectrum of ATC and LUC and spectrums of ATC-LUC solid dispersion in 1:2 ratio from solvent evaporation and Kneading methods are shown in (Figures 6 and 7).

Table 2 Percentage drug content in the prepared formulations

Formulation	% Drug content*
KM1	103.4±0.021
KM2	98.32±0.009
KM3	101.25±0.0044
SE1	99.6±0.013
SE2	100.12±0.033
SE3	98.9±0.061

*mean of 3 values ± SDE

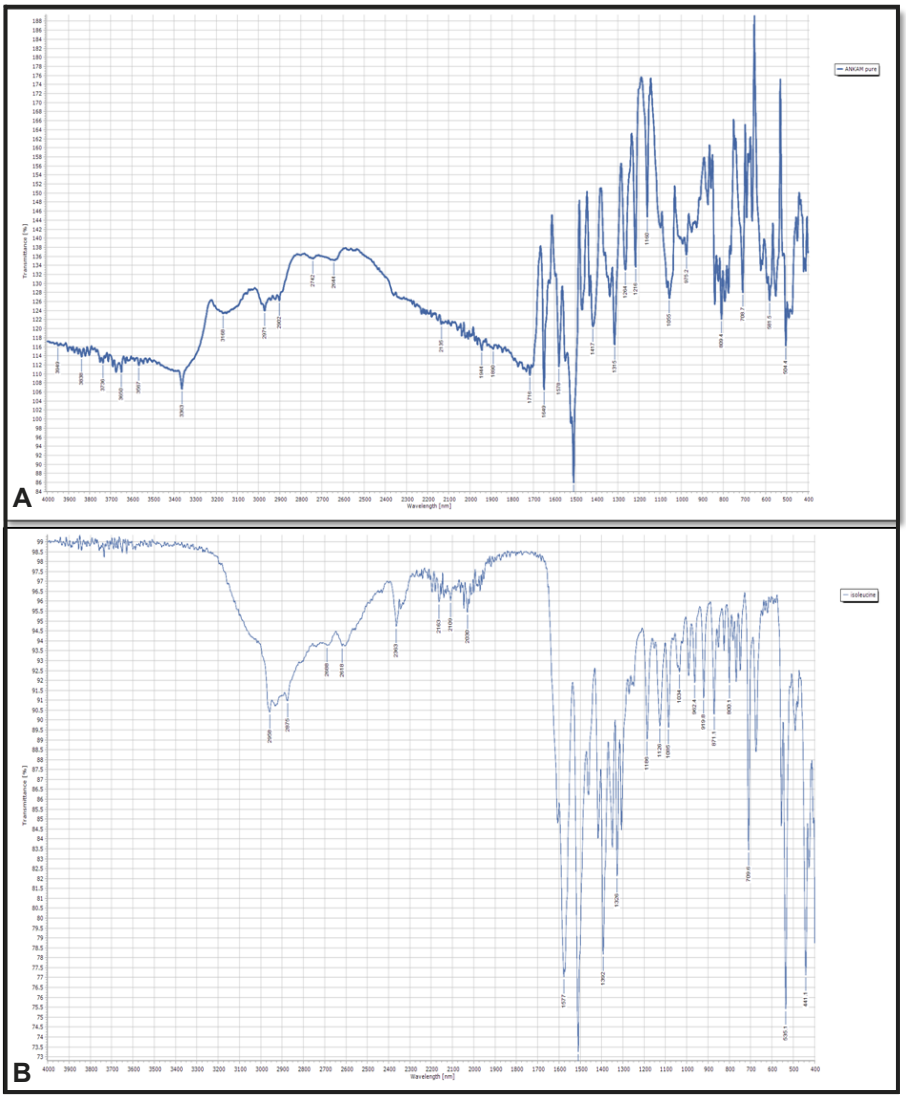

Figure 6 (A) FT-IR spectrums of ATC, (B) LUC

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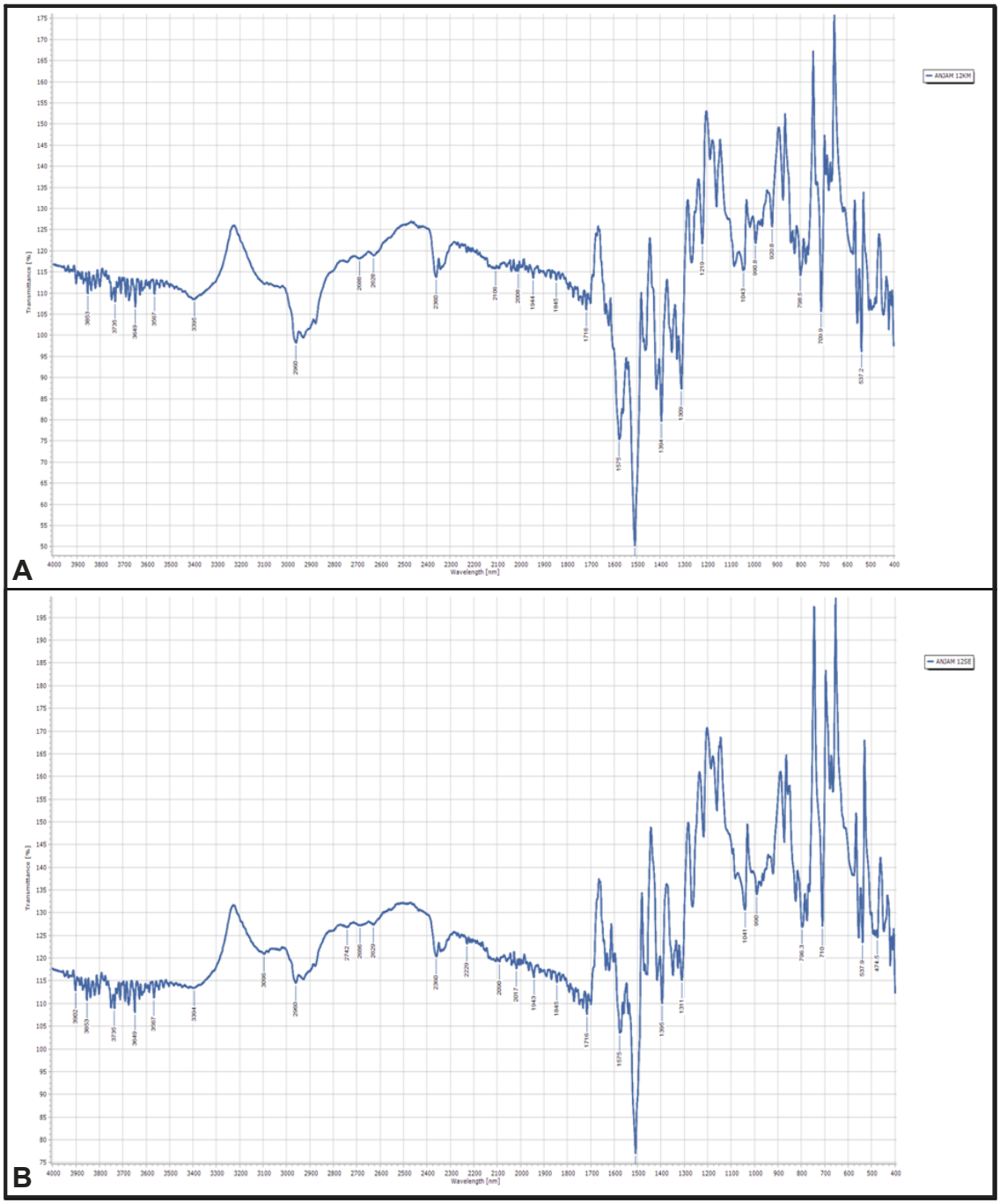

Figure 7 (A) FT-IR spectrums of ATC-LUC 1:2 solid dispersion by kneading method, (B) ATC-LUC 1:2 solid dispersion by solvent evaporation method

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In-vitro drug release

Pure ATC drug and its prepared formulations (KM1, KM2, KM3, SE1, SE2, and SE3) were evaluated for their percentage of drug release after 45 min as shown in (Figures 8 and 9). Comparison and statistical differences between the mean percentage drug release of ATC and the prepared formulations are shown in Table 3.

Table 3 Comparison of cumulative percentage drug release of ATC and the treated formulations with LUC

Comparison	Comparison of mean percentage drug release after 45 min using paired sample t test		
	Time (min)	% drug release	*P* value
Pure-Km1	45	63.04±0.98-83.43±0.22	0.001
Pure-Km2	45	63.04±0.98-93.6±0.5	0.010
Pure-Km3	45	63.04±0.98-101.52±0.05	0.010
Pure-SE1	45	63.04±0.98-95.58±0.36	<0.001
Pure-SE2	45	63.04±0.98-99.52±0.45	<0.001
Pure-SE3	45	63.04±0.98-100.08±0.12	<0.001

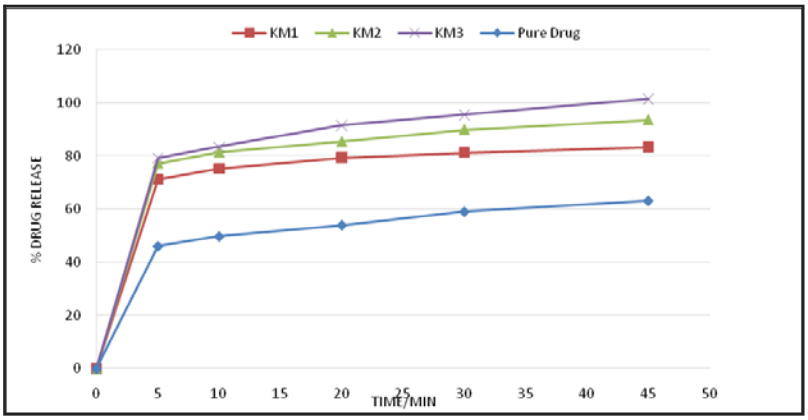

Figure 8 Dissolution profile of ATR calcium and the prepared solid dispersion formulations with LUC by KM method

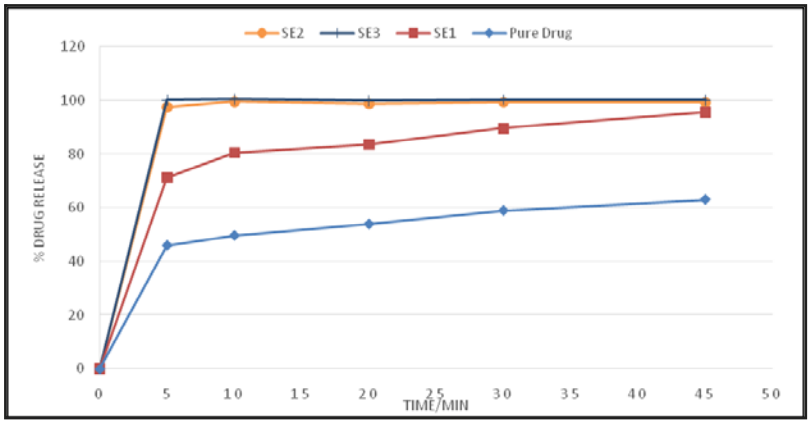

Figure 9 Dissolution profile of ATC and the prepared solid dispersion formulations with LUC by SE method

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Discussion

The results of solubility studies indicate that ATC is very slightly soluble in water, which results in poor bioavailability after oral administration.[26] In Figure 5, it is clearly observed that the solubility of ATC in solid dispersion was increased compared with the pure drug solubility directly with the concentration of the carrier.

The solubility of ATC was significantly (P = 0.002) increased by 1.27, 1.43, and 1.81 folds from KM1, KM2, and KM3, respectively. In contrast, the solubility of ATC in SE1, SE2, and SE3 was increased by 2.53, 2.66, and 3.1 folds. Also, the solubility of ATC was significantly (P = 0.002) improved in the SE method compared to the KM method. This improvement may be due to better drug particle size reduction, enhanced wetting property of this method, or a crystalline pure drug is converted into amorphous form, increasing the solubility of the drug.[27]

The drug content for all the formulations was within the accepted limit (85%-115%),[28] indicating proper mixing and proper processing procedure.

FT-IR spectroscopy was used to detect any possible changes in the chemical structure and drug–carrier interactions after physical dispersion of the drug in the carrier at 1:2 ratio. The principle absorption bands of ATC appear in the region of 3363, 3168, and 1649 cm^{-1}. These bands are related to OH, NH, and C=O groups, respectively (Figure 6, A). A non- significant shift of these bands is noted after solid dispersion of the drug by solvent and kneading method, which indicates the absence of interaction between the ATC and LUC, and they are compatible in their formulation.

The dissolution profile of untreated pure ATC formulation was obtained from the dissolution data after 5, 10, 20, 30, and 45 minutes. The cumulative percentage of drug release for pure ATC formulation was 63.04% (Figures 7 and 8). This slow and insufficient drug release is due to the low solubility character of ATC in the aqueous medium.[29] After 45 minutes, significant improvement in dissolution rate (Table 3) was observed when the dissolution profile of pure ATC formulation compared with KM1 and SE1 formulations containing a lesser amount of LUC, which indicates the ability and efficiency of LUC as a solubilizing agent in the formulation of poorly water-soluble drugs.

Among the formulation prepared by the kneading method, KM3 showed a complete drug release (101.52%) after 45 minutes, while KM1 and KM2 released 83.43% and 93.6% after the same period of time, respectively (Table 3 and Figure 7), which indicates that percentage drug release for the treated formulation increase with the increase in the concentration of LUC.

Formulation of ATC-LUC solid dispersion by solvent evaporation method had faster and complete drug release (97.65%) and (100.08%) after 5 minutes except for SE1 (71.24%) formulation because it contains less amount of LUC than SE2 and SE3. After 5 minutes, the SE2 formulation produced a significant (P = 0.001) improvement in the dissolution rate and had a faster and complete drug, respectively, compared with the kneading method formulations (Figure 8). This superiority of the SE method over KM is due to more reduction in particle size of ATC and greater enhancement in drug wettability, and finally, improvement in dissolution rate.[27,30] Among the prepared formulations, SE2 was selected as the best formula in terms of dissolution profile because it has a faster and more complete drug release after 5 minutes compared with SE1, KM1, KM2, and KM3. Also, it contains a half quantity of LUC compared to the SE3 formula.

Conclusion

To sum up, adding Leucine as an excipient to atorvastatin calcium showed a significant improvement in the solubility and dissolution rate of Atorvastatin calcium. This is a good indicator of using this substance (LUC) to improve the issue

of solubility and dissolution of poorly water-soluble drugs.

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Competing interests

The authors declare that they have no competing interests.

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