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The development of ternary and quaternary solid dispersion based hydrotropic blends of atorvastatin calcium

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Abstract

Background and objective: Atorvastatin calcium (ATV) has a solubility in aqueous solutions of greater than 0.1 mg/ml to less than 1 mg/ml, which is very slightly soluble. When developing dosage forms for these medications, formulation scientists still face challenges. This study's goal was to use various hydrotropic agents in the formation of solid dispersion-based hydrotropic blends to improve the solubility properties of atorvastatin calcium.

Methods: In this study, twenty-two distinct binary, ternary, and quaternary formulations of ATV were prepared by employing five different hydrotropic agents and combining at least two hydrotropic agents in concentrations of 10% and 20% (w/v). Moreover, solid dispersion by the solvent evaporation method and physical mixture-based hydrotropic blends in the ratio of (1:2) have been formulated. The produced formulations were characterized using an FTIR analysis.

Results: According to the findings, binary formulations containing 20% (w/v) concentrations of sodium benzoate (SB), sodium salicylate (SS), and resorcinol (R) enhanced the solubility ratio of ATV by 439.31, 689.57, and 106.21 folds, respectively. Furthermore, ternary formulations (FT14) and quaternary formulations (FQ18) resulted in the enhancement of ATV solubility by 938.45 and 995.12 folds, respectively. Ternary solid dispersion demonstrated the highest enhancement in solubility ratio by 87.68 folds and resulted in a higher dissolution rate of ATV than pure samples of the drug. Finally, FTIR analyses excluded any interactions between medications and excipients by showing no noticeable shift in the peaks.

Conclusion: Solid dispersion based hydrotropic blends can provide the production of the dosage forms of practically insoluble drugs with a favorable enhancement ratio in solubility.

Keywords: Atorvastatin calcium; Solid dispersion; Hydrotropic blends; Dissolution rate; Physical mixture.

Introduction

Poor aqueous solubility of active pharmaceutical ingredients plagues both consumers and the pharmaceutical industry because, in the drug industry, poor water-soluble and dissolving drug profiles pose a challenge.[1] Due to their reduced bioavailability, poorly water-soluble medications have many problems in designing pharmaceutical dosage formulations for oral delivery systems.[2] Low solubility results in poor absorption and bioavailability and is associated with increased side effects because it requires administering a large dose of medications. Despite multiple attempts to alleviate these challenges, solubility remains the biggest obstacle in drug production.[3]

Nearly more than 90% of medications are taken orally.[3] Adequate and provable pharmacokinetic profile of orally administered drug compounds and the bioavailability of drug absorption are strongly dependent on the solubility of

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the aqueous medium compound.[4] In the pharmaceutical sector, almost 40% of novel chemical entities (NCEs) are nearly water-insoluble. These weakly water-soluble medications with sluggish absorption cause inadequate and variable bioavailability as well as gastrointestinal mucosal irritation. Improving drug solubility and, therefore, oral bioavailability is one of the most demanding aspects of the process of medication production, particularly for the delivery of oral medicines. There are some ways in different kinds of literature to enhance the solubility of drugs that aren't water-soluble.[5,6]

Nowadays, a variety of procedures or processes are utilized to improve the solubility of various pharmacological formulations. Different solubilization methods have different benefits and drawbacks for formulations. Hydrotropic solubilization is one of the procedures used in the pharmaceutical industry to improve the water solubility of various dosage forms. [7] The term "hydrotropy" was coined by Neuberg to describe how high concentrations of alkali metal salts in certain organic acids can increase a solute's solubility. [8]

Hydrotrope assemblies differ from other solubilizers in their association patterns and other geometrical properties. The molecular self-association of a hydrotrope with solute molecules is what allows it to increase the solubility of an aqueous solution.[9] The mixed hydrotropic technique is the process of making drugs that don't dissolve well in water dissolve better by mixing them together, which may have a miraculous synergistic effect. Utilization of it in the formulation of water-insoluble drug dosage forms is an important step in the advancement of pharmaceutical products.[10]

One of the most efficient ways of improving the solubility of insoluble pharmaceuticals is the preparation of solid dispersions by dispersing one or more hydrophobic medications in inert hydrophilic carriers comprising hydrotropic agents in the solid state.[11] Another method to improve the poor drug's solubility involves using hydrotropic agents in the formulation of solid dispersion.[12]

ATV is an anti-hyperlipidemic drug that can decrease blood cholesterol levels. It works by reversibly inhibiting HMG-CoA reductase, a rate-limiting step in cholesterol production.[13] Atorvastatin is a BCS class II medication.[14] It is a crystalline powder that ranges from white to off-white. If the pH is lower than 4, it is insoluble in water. To attain its peak plasma concentration (Tmax), it takes 1-2 hours.[15] However, it is not very soluble in water (0.1 mg/mL), has a crystalline structure, and is broken down quickly in the liver, so it is only 12% bioavailable when taken by mouth.[16] (Figure 1)

The objectives of this study were to use various types of hydrotropic agents to boost the solubility and dissolution rate of ATV through the formation of solid dispersion-based hydrotropic blends.

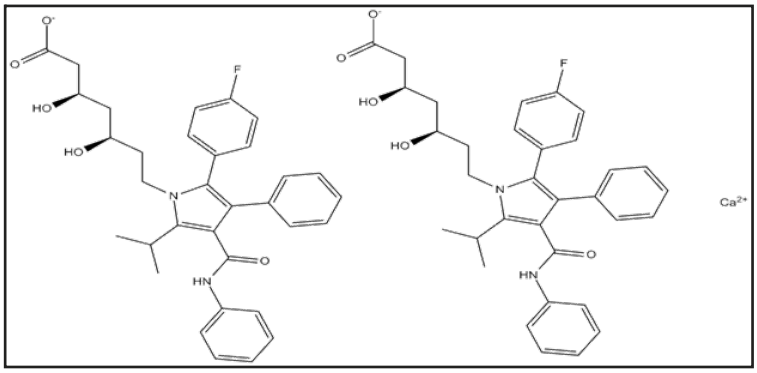

Figure 1 Chemical structure of atorvastatin calcium.[17]

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Methods

Design, setting, and time of study

This experimental study was carried out at the college of pharmacy/ Hawler Medical University, from the 1st of January 2022 to the 1st of July 2022.

Materials

ATV pure sample was purchased from (MEDIVER.LTD.Co, UK). Hydrotropic agents were obtained from (Scharlau, Spain) and all other chemical substances and solvents used were of all analytical grades.

Calibration curve of ATV in distilled water and 0.05 M phosphate buffer (pH 6.8)

The stock solutions of 100 µg/ml have been prepared by dissolving 10 mg of (ATV) 10% methanolic water and 0.05 M phosphate buffer (pH 6.8), respectively. From the aforesaid stock solutions, 20 ml were drawn into a 100 ml volumetric flask to generate a working standard solution of 20 µg/ml. Appropriate dilutions from the working solution were made with 0.05 M phosphate buffer (pH 6.8) solutions in the concentration range of 2-18 µg/ml and 2-20 µg/ml, respectively. The absorbance of the resulting drug solutions was recorded.

Phase solubility study of atorvastatin calcium (ATV)

Determination of equilibrium solubility of ATV in different hydrotropic agents (FB1-FB10)

The phase solubility study was started with the determination of (ATV) solubility in distilled water. According to Higuchi and Connors, solubility tests were carried out.[18]The solubility of ATV in different hydrotropic solutions was determined by the flask shake method.[19] Different solutions of 10% and 20% concentrations from hydrotropic agents (R, SB, SS, M, and PEG) in distilled water have been prepared as shown in table 1, separately. An excess amount (E.A.) of the drug was added to 100 ml volumetric flasks filled with hydrotropic solutions until a saturated solution was obtained.*

Determination of equilibrium solubility of ATV in binary (FT11-FT16) and ternary (FQ17-FQ22) hydrotropic blends

The solubility of ATV was investigated in different hydrotropic agents, individually. According to the results, three of them were selected to be used for further investigations, including SS, SB, and R. From the aforesaid selections, binary and ternary hydrotropic blends were prepared in different ratios as shown in Table 1. The maximum concentration was 20% for all of them, and distilled water was used as a solvent. An excess amount of the drug was added until a saturated solution was obtained.*

Formulation of ternary (FTHS1) and quaternary (FQHS1) hydrotropic solid dispersion (HSD) of ATV

Solvent evaporation method (SEM)

For the preparation of ternary and quaternary hydrotropic solid dispersions of ATV, (1.5g SS, 0.5g SB) and (0.5g R, 1g SS and 0.5g SB) were accurately weighed, accordingly. Both formulations were taken into a 100 ml beaker and mixed properly for a few minutes. After that minimum possible amount of distilled water about (3 ml) sufficient to dissolve the above hydrotropic blends was added at 80 °C. To enhance the dissolution rate of hydrotropic blends magnetic stirrer at 80 ± 1°C and 500 rpm was used. After complete dissolution of the aforesaid hydrotropic blends, 1g of the drug (ATV) according to the (drug to carrier ratio 1:2) was added to both beakers and dissolved, the temperature was maintained in the range of 55-60 °C to enhance the evaporation of water. The stirrings were automatically stopped when almost all water evaporated, and hydrotropic solid dispersions (semi-solid mass) were achieved. Both wet hydrotropic solid dispersions were spread on several watch glasses as a thin film, and then watch glasses were kept in the oven (hot dry air) (Schwabach FRG, Germany) and the temperature was maintained at 40 ± 2 °C for the next 24 hours until the constant weight was

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obtained. In conclusion after complete drying, the obtained masses were crushed, pulverized with the help of glass mortar and pestle, and then passed through sieve number 60# to get uniform particle size. The formulated ternary and quaternary hydrotropic solid dispersion powders were labeled and stored in an airtight glass bottle. As a result, two different formulations have been designed (FTHS1 and FQHS1).[21,22]

Ternary (FTP3) and (FQP3) quaternary physical mixture (PM) of hydrotropic blends

For the preparation of the ternary and quaternary physical mixture of hydrotropic blends in the ratio of (1:2) accurately (1g ATV, 1.5g SS, and 0.5g SB), and (accurately 1g ATV, 0.5g R, 1g SS, and 0.5g SB) were weighed. Then with the help of a glass mortar and pestle, all ingredients were mixed intensely for about 10 minutes with intensive trituration. After that mixed powder was passed through sieve number 60# to get uniform particle size. The formulated binary physical mixture powder was labeled and stored in an airtight glass bottle.[21]

Determination of equilibrium solubility of ATV in FTHS1, FQHS1, FTP3, and FQP3

The solubility of the drug in ternary and quaternary hydrotropic solid dispersion and physical mixture powders was determined by the flask shake method.[19] An excessive amount of the ternary and quaternary hydrotropic solid dispersion, and physical mixture powders (FTHS1, FQHS1, FTP3, and FQP3), were added to the different volumetric flasks of 25 ml that were filled with distilled water until saturated solutions were achieved.*

*The volumetric flasks were shaken for 24 hours using a magnetic stirrer (ISOLAB, Germany) at 25 ± 1°C and 500 rpm. Then laid for equilibration for the next 48 hours, the solutions were passed through a syringe filter (BIOFIL, China) of 0.45 µm. Finally, after appropriate dilutions, the filtrates were analyzed for drug content spectrophotometrically using a UV-VIS spectrophotometer at 240 nm against the blank. The results were shown in table 3. The aforesaid experiments were done in triplicate. Finally, to determine the solubility enhancement ratios of the prepared formulation the following formula was used:[20]

$$\text{Solubility Enhancement Ratio (SER)} = \frac{\text{Solubility of ATV in hydrotropic solutions}}{\text{Solubility of ATV in distilled water}} \quad \text{... (Eq 1)}$$

Post formulation studies

Estimation of percent of drug content

Quantities of (FTHS1, FQHS1, and FTP3), 60mg equivalent to (20 mg of ATV) were accurately weighed and separately, dissolved in 10 ml methanol. Then transferred to 100 ml volumetric flasks that were filled with 0.05 M phosphate buffer (pH 6.8). Then volumetric flasks were stirred for 30 minutes using a magnetic stirrer at 25 ± 1° C and 500 rpm. The solutions were filtered using a syringe filter of 0.45 µm membrane filter. Finally, after appropriate dilutions, further diluted to make the absorbance fall within the standard curve. The filtrates were analyzed for drug content spectrophotometrically using a UV-VIS spectrophotometer at 242 nm against the blank 0.05 M phosphate buffer (pH 6.8).[14] The results were shown in Table 2 ,and the following equation was used.[23]

$$\text{\% of Drug Content} = \frac{\text{Actual Drug Content}}{\text{Total Drug Content}} \times 100 \quad \text{... (Eq 2)}$$

In-vitro drug release study

The in-vitro dissolution study for different solid dispersions and physical mixtures of hydrotropic blends (FTHS1, FQHS1, and FTP3), and a pure sample of atorvastatin calcium (ATV), equivalent to (20mg of atorvastatin calcium) were performed in a USP Type II paddle-type apparatus (Pharma Test PT-DT7, Germany) using 900 ml of 0.05 M phosphate buffer (pH 6.8) at 37±0.5 °C, as dissolution medium and 75 rpm as the paddle rotation speed.[26] The powders were tightly fixed to a muslin cloth and then fixed with the paddles in a dissolution flask. At predetermined time

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intervals, 5, 10, 15, and 30 minutes, 5ml of the samples of the dissolution medium were withdrawn and then replaced by fresh media of dissolution. The samples were filtered using a syringe filter with a millipore membrane of 0.45 µm pore diameter. The filtrates were analyzed for drug content spectrophotometrically using a UV-VIS spectrophotometer at 242 nm against the blank 0.05 M phosphate buffer (pH 6.8).[16, 24] The results were shown in Table 3 ,and the following equation was used.[23]

$$\% \text{ of Drug Release} = \frac{\text{Practical Drug Content}}{\text{Theoritical Drug Content}} \times 100 \quad \text{... (Eq 3)}$$

Compatibility study by Fourier transform infrared spectroscopy (FT/IR)

The Fourier-transform infrared (JASCO, Japan) study was used to exclude any drug and carrier interactions between pure ATV and hydrotropic agents, individually. This study was done for the prepared formulations and physical mixtures of pure ATV and hydrotropic agents (FB23-FB27) in the ratio of (1:1). The Fourier transform infrared spectra were obtained and the measurements were attempted over the range of 4000 cm^{-1} to 400 cm^{-1}.[25]

Statistical data analysis

All the values were represented as the mean of three values ± standard deviation, and all the experiments were done in triplicate. The Excel program for Windows 2016 version and the statistical package for the social sciences (SPSS) version 22.00 were used for the construction of the calibration curve and statistical analysis of the data. Two samples of an independent t-test with the support of a statistical package for the social sciences (SPSS, 22.00) and a one-way ANOVA and post hoc test were also used, and a calculated *P*-value of less than 0.05 was used to consider the statistically significant differences between formulations.

Results

Determination of maximum absorbance (λ max) of atorvastatin calcium (ATV)

The wavelengths corresponding to maximum absorbance (λ max) were found at 240 nm and 242 nm using 10% methanolic water and 0.05 M phosphate buffer (pH 6.8) solutions, and the correlation coefficient for the linear regression equation was determined to be 0.9985 and 0.9991, respectively.

Phase solubility study of atorvastatin calcium (ATV)

Determination of equilibrium solubility of ATV in different hydrotropic agents

According to the formulations, ten different binary formulations of atorvastatin calcium (FB1-FB10) have been prepared and the solubility of atorvastatin in different hydrotropic solutions was shown in Table 1.

Determination of equilibrium solubility of ATV in binary and ternary hydrotropic blends

The solubility of ATV in binary and ternary hydrotropic blends were shown in Table 1. According to the aforesaid methods, three hydrotropic agents which were responsible for maximum solubility of ATV were selected and six different ternary and quaternary formulations of atorvastatin calcium (FT11-FT16) and (FQ17-FQ22), respectively, have been prepared by combining hydrotropic agents and the total concentration of formulations was 20% (w/v).

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Table 1 Saturation solubility of ATV in different formulations.

No. of formu-lations	Compositions (% w/v) (g/100ml)						Total ratios of carriers or (ATV+ carriers) ratio	Concentration in (mg/ml)	Solubility Enhancement Ratio (SER)
	ATV	SB	SS	R	M	PEG			
FB1	E.A.	10g	-	-	-	-	10%	57.49 ± 2.4	246.46
FB2	E.A.	-	10g	-	-	-	10%	31.77 ± 1.4	445.99
FB3	E.A.	-	-	10g	-	-	10%	6.9 ± 0.58	53.54
FB4	E.A.	-			10g		10%	0.15 ± 0.026	1.16
FB5	E.A.	-	-	-	-	10g	10%	0.19 ± 0.0033	1.45
FB6	E.A.	20g	-	-	-	-	20%	**88.89 ± 1.14**	**439.31**
FB7	E.A.	-	20g	-	-	-	20%	**56.63 ± 1.01**	**689.57**
FB8	E.A.	-	-	20	-	-	20%	**13.69 ± 0.42**	**106.21**
FB9	E.A.	-	-	-	20g	-	20%	0.12 ± 0.002	0.94
FB10	E.A.	-	-	-	-	20g	20%	0.26 ± 0.0042	2.012
FT11	E.A.	-	10g	10g	-	-	20%	86.11 ± 4.31	668.03
FT12	E.A.	-	15g	5g	-	-	20%	60.08 ± 10.25	466.11
FT13	E.A.	10g	10g	-	-	-	20%	82.07 ± 35.75	636.66
FT14	E.A.	5g	15g	-	-	-	20%	**120.97 ± 7.36**	**938.45**
FT15	E.A.	10g	-	10g	-	-	20%	51.43 ± 5.44	399.01
FT16	E.A.	15g	-	5g	-	-	20%	55.41 ± 3.02	429.85
FQ17	E.A.	6.66g	6.66g	6.66 g	-	-	20%	52.77 ± 9.07	409.42
FQ18	E.A.	5g	10g	5g	-	-	20%	**128.27 ± 5.42**	**995.12**
FQ19	E.A.	7.5g	5g	7.5g	-	-	20%	110.60 ± 5.28	858.05
FQ20	E.A.	5g	7.5g	7.5g	-	-	20%	118.53 ± 14.72	919.58
FQ21	E.A.	7.5g	7.5g	5g	-	-	20%	70.31 ± 1.23	545.44
FQ22	E.A.	6.25g	8.75g	5g	-	-	20%	106.016 ± 1.13	822.47
FB23*	1g	1g	-	-	-	-	(1:2)	-	-
FB24*	1g	-	1g	-	-	-	(1:2)	-	-
FB25*	1g	-	-	1g	-	-	(1:2)	-	-
FB26*	1g	-	-	-	1g	-	(1:2)	-	-
FB27*	1g	-	-	-	-	1g	(1:2)	-	-
FTHS1	1g	0.5g	1.5g	-	-	-	(1:2)	**11.30 ± 2.26**	**87.68**
FQHS1	1g	0.5g	1g	0.5g	-	-	(1:2)	**6.88 ± 0.92**	**53.34**
FTP3	1g	0.5g	1.5g	-	-	-	(1:2)	**8.76 ± 0.92**	**67.96**
FQP3	1g	0.5g	1g	0.5g	-	-	(1:2)	3.94± 0.74	30.60

The Mean of three values ± Standard Deviation. * Only FTIR studies were done.

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Determination of equilibrium solubility of ATV in FTHS1, FQHS1, FTP3, and FQP3

After formulations of different solid dispersions based hydrotropic blends and physical mixtures of ATV, including (FTHS1, FQHS1, FTP3, and FQP3), and solubility of atorvastatin calcium in each formulation was determined. The results of ATV solubility in each kind of formulation were shown in Table 1 and Figure 2, respectively. Based on the statistically significant differences between prepared formulations, some of them have been selected for further investigations.

Post formulation studies

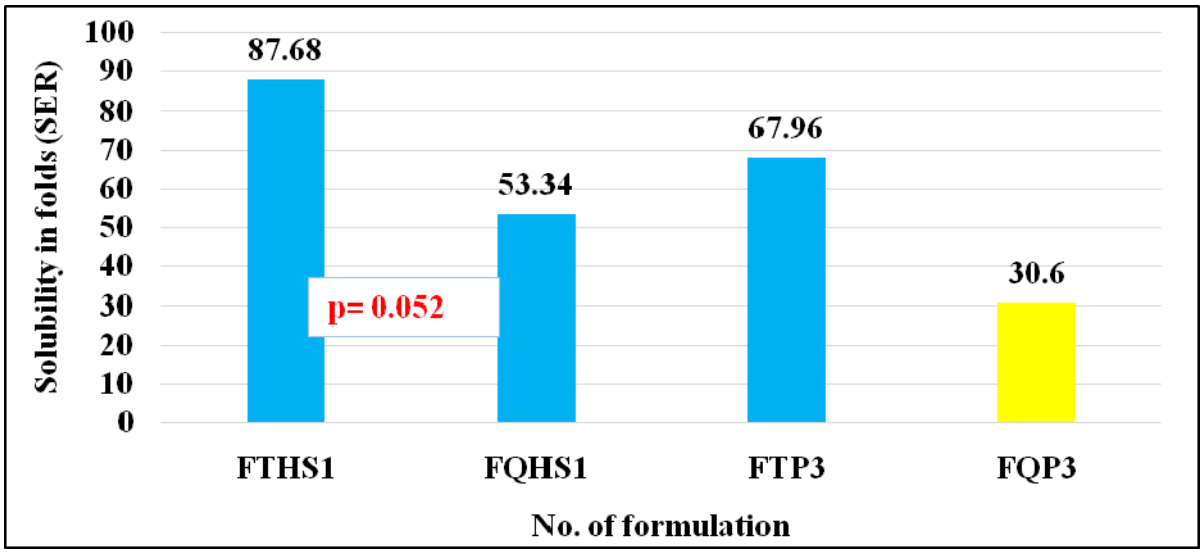
Estimation of percent of drug content

The percentages of the ATV content in the nominated formulations were shown in Table 2.

Table 2 Percentage of ATV content in the ternary and quaternary solid dispersion-based hydrotropic blends and physical mixture.

No. of formulations	Method of preparation	% of Drug Content
FTHS1	SEM	104.93 ± 0.56
FQHS1	SEM	103.57 ± 3.23
FTP3	TM	108.02 ± 1.91

The Mean of three values ± Standard Deviation.



P: *P*-value (Probability value).

Figure 2 ATV solubility enhancement ratio atorvastatin in ternary and quaternary solid dispersion and physical mixtures based hydrotropic blends.

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Post formulation studies

Estimation of percent of drug content

The percentages of the ATV content in the nominated formulations were shown in Table 2.

In-vitro Drug Release (Dissolution) Study

The cumulative percentage of drug release in the prepared formulations and pure ATV was shown in Table 3 and Figure 3, respectively. The comparison between prepared (nominated) formulations with a pure sample of drug and the statistically significant differences between each of them, individually, are shown in Figure 3.

Table 2 Percentage of ATV content in the ternary and quaternary solid dispersion-based hydrotropic blends and physical mixture**.**

No. of formulations	Method of preparation	% of Drug Content
FTHS1	SEM	104.93 ± 0.56
FQHS1	SEM	103.57 ± 3.23
FTP3	TM	108.02 ± 1.91

The Mean of three values ± Standard Deviation.

Table 3 Cumulative percentage of drug release of a formulated and pure sample of atorvastatin calcium (ATV).

No. of formulations	Cumulative % of drug release (Dissolution rate)			
	5 Minutes	10 Minutes	15 Minutes	30 Minutes
FTHS1	65.93 ± 0.05	72.99 ± 0.81	89.95 ± 0.45	95.34 ± 0.07
FQHS1	39.92 ± 0.29	54.19 ± 0.02	62.40 ± 0.26	82.31 ± 1.08
FTP3	52.52 ± 0.82	65.29 ± 1.35	80.63 ± 3.06	90.56 ± 0.72
Pure ATV	27.02 ± 0.26	40.55 ± 0.17	45.31 ± 0.28	62.74 ± 0.45

The Mean of three values ± Standard deviation.

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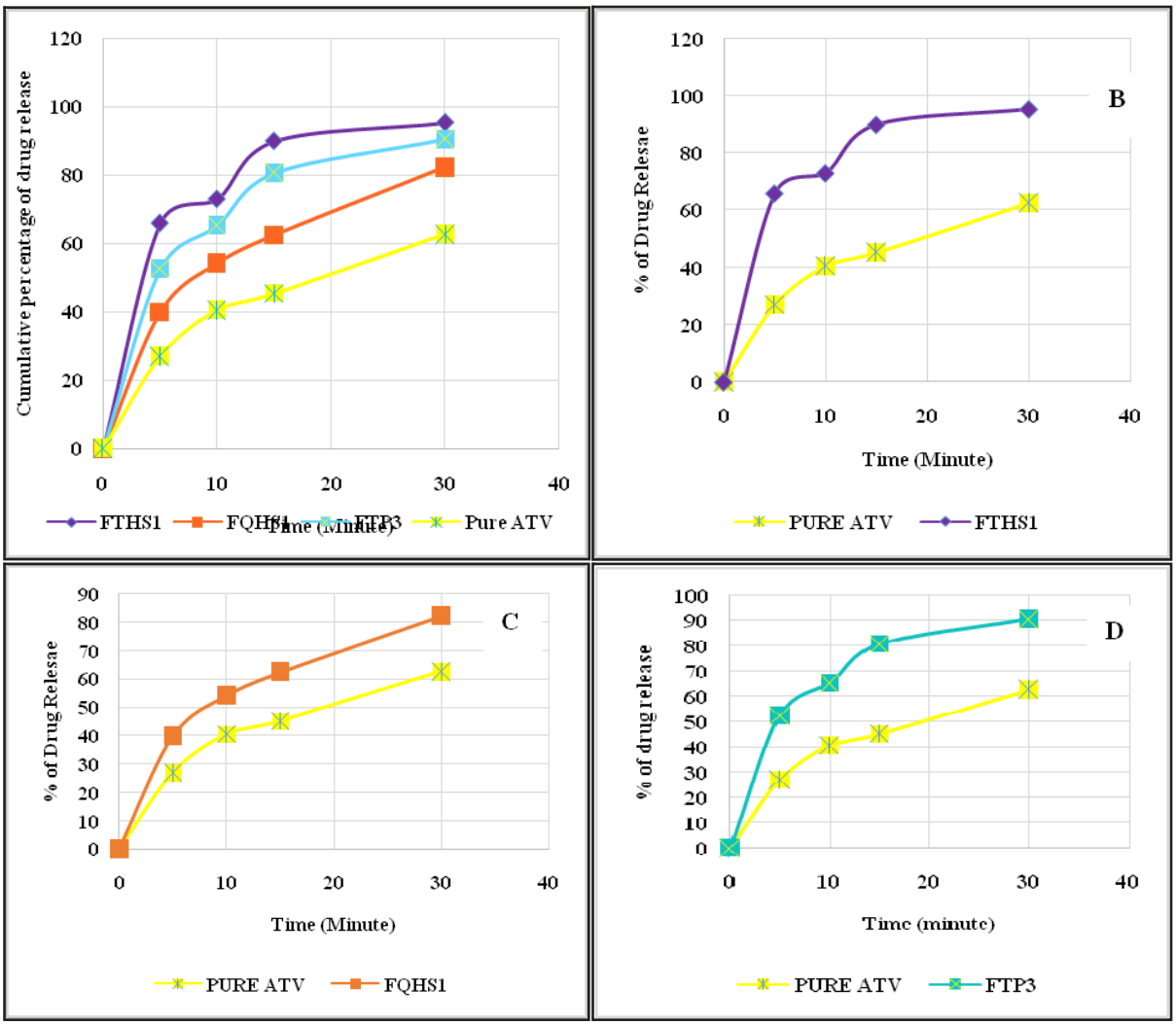

Figure 3 A/ Cumulative percentage of drug release, comparison in the percentage of drug release of pure ATV with, B/ FTHS1, C/ FQHS1, and D/ FTP3.

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Compatibility study by Fourier transform infrared spectroscopy (FT/IR)

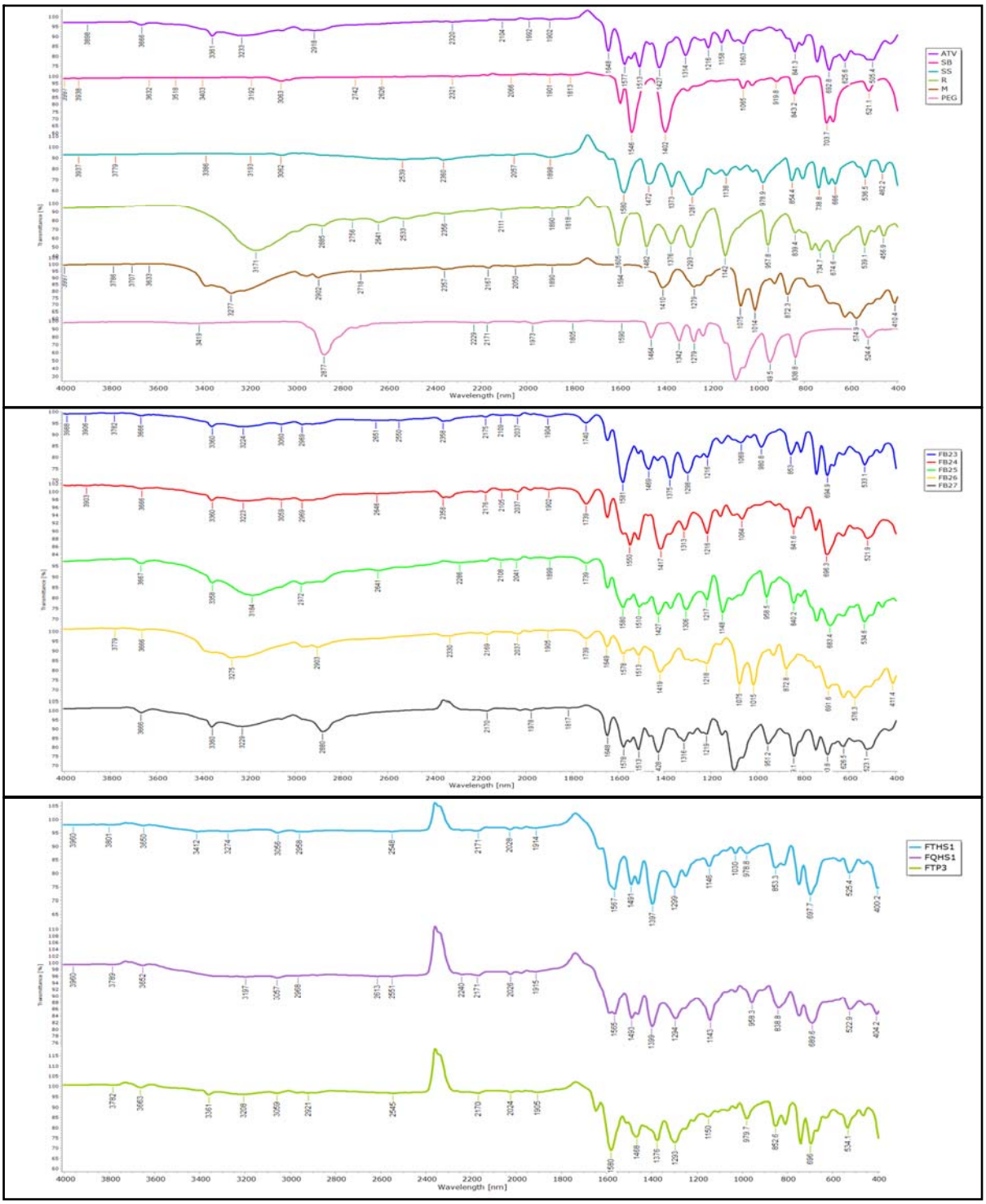

Figure 4 IR spectrum of ATV, SB, SS, R, M, PEG, FB23, FB24, FB25, FB26, FB27, FTHS1, FQHS1, and FTP3.

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Discussion

A major physicochemical parameter controlling several junctures of drug discovery and development is the solubility of the active pharmaceutical component. Poor therapeutic response is caused by a drug's low water solubility.[27,28] The solubility and dissolving properties of ATV were established by measuring its solubility in distilled water. As a consequence, using the equilibrium technique, the drug's solubility in distilled water was calculated to be 0.1289 mg/ml, ATV is characterized as a very slightly soluble medication. According to the USP solubility descriptive terms, ATV is a very slight soluble medication in water, with a solubility range of 0.1 mg/mL to less than 1 mg/ml.[29] Ali and Known with their partners reported the same ATV solubility in D.W using the equilibration method, and the result was 0.120 mg/ml. It follows that the results of this study are consistent with previous research.[30,31]

A promising strategy with significant potential for poorly soluble medicines is hydrotropic solubilization. The use of organic solvents is not necessary for this approach.[32] As previously stated, ATV is very slightly soluble in distilled water (0.1289 mg/ml); therefore, various potential (hydrotropic) agents were examined to determine their ability to boost ATV solubility. Since no universal hydrotropic agent has been proven to be successful with all hydrophobic medications to date. As a consequence, it is important to test a large number of hydrotropic agents to select the optimal hydrotropic agent for a poorly soluble drug.[29,33]

The solubility of ATV significantly increased in the presence of the maximum concentration (20% w/v), as indicated by the findings. The greatest enhancement in the solubility of ATV was obtained by SS (689.57 folds), and also there was an amazing improvement in the solubility of ATV in the presence of SB and R, because they increased the pure drug's solubility by (439.31 folds), and (106.21 folds), separately. These discrepancies in solubility improvement might be attributed to the chemical structure of each hydrotropic agent since each has a unique structure and hydrotropic capabilities for solubilizing low water-soluble medicines.[34]

The structure of hydrotropic agents contains several functional and chemical groups, affects the structure of the used solvent (water), increases the hydration properties of the hydrotropic agents, and has an amazing impact on the solubility and hydrotropic characteristics.[35,36] The best agents (sodium salicylate, sodium benzoate, and resorcinol) were chosen for further investigation because they had the greatest solubility enhancement ratio.

The best candidates have been chosen, and as shown in table 1, six different ternary (FT11 to FT16) and quaternary (FQ17 to FQ22) formulations of ATV have been formed from mixed hydrotropic blends. The rationale for employing mixed hydrotropic blends is that they increase the solubility,ithas a miraculous synergistic improvement effect on the solubility of low water-soluble drugs, and also has the benefit of allowing for the use of low concentrations of various hydrotropic agents in combination rather than as single agents, which may help to reduce the individual, unfavorable side effects and toxicities of the agents.[10,37]

Ternary and quaternary formulations of SS and SB (FT14) and (R, SS, and SB) (FQ18) resulted in remarkable solubility enhancement of ATV, and it was able to account for enhancement of the solubility by (938.45 folds) and (995.12 folds), respectively. These synergistic miraculous improvements may be due to the mixed blend of candidate agents and their chemical structures.[8] The best formulations were (FT14) and (FQ18) for solid dispersion preparation.

In this present experimental study, two different ternary and quaternary hydrotropic solid dispersions (FTHS1, and FQHS1) have been designed, as shown in Table 1.

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The preparation of solid dispersion from blends of hydrotropic agents, also known as solid dispersion-based hydrotropic blends (HSD), is done using a variety of techniques, including solvent evaporation and kneading methods.[38] All hydrotropic solid dispersions are formulated in the ratio of (1:2), 1 g of ATV, and 2 g of hydrotropic agents because the maximum concentration of hydrotropic blends based on the aforementioned selections was (20% w/v).

As can be shown in table 1, all the formulated solid dispersion (SD) resulted in the remarkable enhancement of solubility, these may be attributable to the benefits of SD, since the augmentation of SD's dissolving rate by hydrophilic carriers may be brought on by improved solubility, wettability, porosity, and particle size reduction.[39] Outperforming all other formulations, the ternary hydrotropic solid dispersion by solvent evaporation approach (FTHS1) greatly enhanced the solubility of ATV (87.68 folds). To select the best formulations for post-development studies, as can be seen in figure 2, the solvent evaporation method did not reveal any statistically significant differences between ternary and quaternary HSD since the probability value was (>0.05).

The physical mixtures (FTP3 and FQP3), both showed considerable improvements in ATV solubility. The significant increase may be attributed to the advantages of the physical mixture by the trituration method since this approach resulted in decreasing powder particle size, increasing exposed surface area, and producing a uniform distribution of particles.[25] Ternary-formed physical mixture had a higher solubility improvement by (67.96 times) than the quaternary formulated form, and statistically significant differences were identified between the groups, as evidenced by the *P*-value of (0.0021).

One of the most often used quality control tests is the uniformity of the drug products' content. A drug potency that stays within the acceptable deviation from the target value (generally, 85-115% of the label claim for most products) is necessary for ensuring a therapeutic concentration in systemic circulation and lowering the risk of adverse events.[40] As can be seen in Table 2, the percentage of drug content uniformity in all selected formulations is within the acceptable range between the range of (104.93% to 108.02%). These findings strongly imply that the drug content of each formulation is within the predicted range, demonstrating the suitability and repeatability of the formulation preparation process.[14]

Dissolution testing was done to make sure that after an oral administration, a given amount of the drug product will be released at a specified time.[40] Dissolution behavior is an important tool for developing novel formulations and might be used as a criterion for choosing formulations.[41] Moreover, the use of muslin cloth instead of USP type I basket type apparatus was another innovation performed in this study. In many pharmaceutical trials, the prepared powders have been enclosed in a muslin cloth and securely tied using paddle -type apparatus. For instance, Pund et al, employed muslin cloth to calculate the percentage of drug release from pastillated diclofenac sodium solid dispersion.[42]

In (Table 3) and (Figure 3. A), respectively, the cumulative percentage of drugs released from all ATV formulations, and a pure sample of ATV were displayed. The results clearly illustrated the increase in the rate of ATV dissolution with either hydrotropic solid dispersions or physical mixing with hydrotropic carriers. All formulations and pure ATV required 30 minutes for the maximum percentage of medication to be released (T_{30min}). Additionally, for each of the formulations (FTHS1, FQHS1, and FTP3), the concentration of drug release at 30 minutes (C_{30min}) was 95.34%, 82.31%, and 90.56%, respectively. Nevertheless, the (C_{30min}) for ATV in its pure state as the powder was 62.74%.

Ternary (FTHS1) and quaternary (FQHS1)

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solid dispersion-based hydrotropic blends of ATV by the solvent evaporation method demonstrated statistically significant differences in comparison with pure samples of the ATV at all-time intervals, as shown in (Figure 3. B and C) respectively. Since the p-value at each time interval was (<0.05).The quick release of the drug, in particular from FTHS1, may be caused by the lack of aggregation and agglomeration with crystalline drugs.[28] The increased wetting of ATV and good dispersibility in the presence of hydrotropic agents and better contact between the drug and the carrier, in addition to the change of one crystalline form to another, might be responsible for the better dissolving rate of ATV from hydrotropic solid dispersion.[43] Both formulations FTHS1 and FQHS1 required 30 minutes to attain their peak levels of drug release, which may have been linked with 95.34% and 82.31% of drug release, respectively. This might be due to the efficacy of the process utilized for the formulation of both solid dispersions since solvent evaporation resulted in homogeneous molecular dispersions of the medication in the hydrophilic carrier matrix.[44,45]

Ternary physical mixing of hydrotropic blends (FTP3) was another method that has been used for enhancement of ATV solubility resulting in a quick dissolution rate of ATV up to 5 min, 52.52% of the drug released, and the maximum concentration of ATV at the required maximum time was 90.56%. However, the significant differences between the dissolution of ATV in FTP3 and a pure sample of ATV were reported, since the *P*-value at all-time intervals was (<0.05), this might be since the significant increase in the dissolution rate of ATV in the ternary physical mixture can be ascribed to the direct solubilization effect of the amphiphilic carriers (hydrotropic agents).[46] Another mechanism for increasing dissolution in physical mixing formulations is the suppression of drug particles of ATV crystal from re-aggregation and by improving drug wettability due to the actions of hydrotropic agents on decreasing surface and interfacial tension.[47,48]

IR spectroscopy is a valuable technique for identifying any alterations that may occur as a result of any interactions between carriers and the drug or other substances during procedures that modify chemical bonds.[27] Figure 4 ,exhibits the FTIR spectra of pure ATV, SB, SS, R, M, PEG, binary physical mixture (FB23-FB27), FTHS1, FQHS1, and FTP3.

As shown the spectrum of a bulk drug (ATV) exhibits characteristic peaks at 3666 cm^{-1} (related to the free O-H stretching vibration), 3361 cm^{-1} (related to the N-H stretching bond), 3233 cm^{-1}, and 3060 cm^{-1} (allocated to an asymmetric and symmetric O-H stretching, respectively), 2969 cm^{-1} (allocated to the C-H stretching), 1648 cm^{-1} and 1577 cm^{-1} (representing asymmetric and symmetric C=O stretching, respectively), 1551 cm^{-1}(allocated to N-H bending), 1513 cm^{-1} and 1427 cm^{-1} (representing C-C aromatic stretching), and 1216 cm^{-1} (related to C-N stretching bonds).[22,49]

Regarding hydrotropic agents, sodium benzoate (SB) showed characteristic peaks at 3063 cm^{-1} (related to acidic O-H stretching vibration), and 1596 cm^{-1} (related to aromatic C=O stretching). Sodium salicylate (SS) exhibits peaks at 3062 cm^{-1} (related to O-H stretching vibration), and 1580 cm^{-1} (related to aromatic C=O stretching). Resorcinol (R) showed a broad and strong peak at 3171 cm^{-1} related to O-H stretching and, 2885 cm^{-1} due to C-H stretching bonds. D-mannitol (M) exhibits peaks at 3358 cm^{-1} and 3277 cm^{-1} due to the asymmetric and symmetric O-H stretching, a peak at 2951 cm^{-1} due to C-H stretching, and peaks at 1075 cm^{-1} and 1014 cm^{-1}due to C-O stretching. Finally, Polyethylene glycol 4000 (PEG) showed prominent characteristic peaks at 3419 cm^{-1} (related to O-H stretching vibration), 2877 cm^{-1} (related to C-H stretching vibration), and 1097 cm^{-1} (related to C-O stretching

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bonds).

Regarding the binary physical mixture formulations (FB23-FB27) (1:1) ratio all characteristic peaks of ATR appeared in all formulations with no significant changes in the wave number compared to their particular spectrum, and also, the prominent peaks of their components without any additional peak which indicated no interaction between ATR and hydrotropic agents.[49,50]

The recognition of ATV peaks conclusively indicates the incorporation of ATV within all formulas without any change in chemical structure or integrity.[51] There were some slight shifts of the peaks in ternary (FTHS1) and quaternary (FQHS1) solid dispersions which indicate the formation of solid dispersions with the respective hydrotropic agents.[52] However, the observed broadening in the stretching peak of the hydroxyl group at 3666 cm^{-1} and the carbonyl group at 1648 cm^{-1} and 1577 cm^{-1} respectively, of ATV in all of the prepared ATV solid dispersion formulations may reflect the possible ATV amorphization and the hydrogen bonding between AT and hydrotropic agents.[53]

Conclusion

The findings of this study demonstrated that using hydrotropic blends for the formulation of solid dispersion by solvent evaporation method and the physical mixture was associated with a remarkable improvement in the solubility and dissolution rate of very slight soluble atorvastatin calcium. Furthermore, ATV incorporated into solid dispersion and physical mixture based on hydrotropic blends, after dissolution study showed a higher percentage of drug release values compared to a pure sample of the drug, this could be attributed to increased wettability and reduced crystallinity of the drug, which leads to improving drug solubility and dissolution. Moreover, an FTIR study was used for characterization of all prepared formulations of ATV and the spectrum revealed that no chemical interaction occurred between the drug and excipients used in the formulation.

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Competing interests

The authors declare that they have no competing interests.

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