ORIGINAL ARTICLE

Atorvastatin Cocrystals: Tablet Formulation and Stability

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Abstract

Introduction: Enhancement of the dissolution rate and solubility of drugs by cocrystals (Cs) may be negatively affected by the manufacturing variables and storage conditions; therefore, the physical and chemical stability of the tablets should be assessed to ensure the maintenance of the Cs' properties. **Objective:** The objective of the study was to formulate atorvastatin calcium-cocrystals (ATC-Cs) into tablets and investigate the effect of storage conditions on drug and quality of the developed tablets. **Materials and Methods:** Five tablet formulations (F1-F5) were developed by direct compression using ATC-Cs prepared by solvent drop grinding and solvent evaporation method using 1:3 drug-coformer molar ratio, using glucosamine and nicotinamide as coformers. The physicochemical properties of the ATC-Cs, their physical mixtures, and the raw ATC, before and after storage were studied by Fourier-transform infrared, differential scanning calorimetry, powder X-ray diffraction, gas chromatography-mass spectrometer, scanning electron microscopy, and dissolution rate. **Results:** ATC proved to be stable in the Cs and the formulated tablets at 25°C and 40°C ± 2°C/75 RH and the results, never the less after 6-months at 40°C, partial dissociation of the prepared Cs occurred due to the weak intermolecular hydrogen bonding between the drug and the coformers. The tablets exhibited an enhanced dissolution rate, similar to the innovator Lipitor® and showed satisfactory results complying with the pharmacopeial specifications. **Conclusion:** The developed ATC-Cs were successfully incorporated into tablets. The prepared tablets showed good quality attributes upon storage. Among all the tablet formulations, F4 was the best in terms of the pre-compression and post-compression parameters.

Key words: Atorvastatin, characterization, cocrystals, dissolution, stability, tablets

INTRODUCTION

High-throughput screening methodologies have been used to identify lead compounds in drug discovery. However, most of the emerging molecules are characterized by poor solubility and/or permeability and the extent of such poorly water-soluble (PWS) drugs in company pipelines amounts to about 60%.[1] Therefore, in modern pharmaceutical development, solubility and dissolution rate enhancement technologies for PWS drugs are becoming very crucial to reduce the number of insoluble drug candidates. Consequently, improvement of drug solubility is considered as one of the most challenging aspects of the drug development process, especially for oral drug delivery systems.

Various approaches have been investigated to enhance the solubility of PWS drugs, which generally depend on the properties of the drugs, nature of chosen excipients, as well as the nature of the target dosage form. Literature review revealed that solubility improvement is based on physical/chemical modifications of the drug substance and several other techniques. Physical modification techniques include particle size reduction, for example, micronization and nanosuspension, drug dispersion in carriers like eutectic mixtures, solid solutions, and crystal habit modification like polymorphs, amorphous form, and cocrystallization. Recently, the latter gained considerable interest and the Food and Drug Administration issued draft guidance on pharmaceutical cocrystals (PCs), defining a PC to be composed of an active pharmaceutical ingredient (API) and

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an appropriate coformer. The cocrystals (Cs) are formed based on several types of interactions such as hydrogen bonding, π-staking, or Van der Waals forces.[2]

Therefore, PCs offer an opportunity to address the challenges of low solubility and other properties of APIs with relatively low cost. In addition, Cs provides additional manufacturing attributes and advantages not only necessarily related to therapeutic outcomes but also may promote commercialization of the API. These technical properties include one or more of the following advantages; improved flow properties and compressibility, better drying, lower hygroscopicity, enhanced dissolution, and greater stability.[3]

Atorvastatin calcium (ATC) is a model for PWS drugs belonging to Class II of the Biopharmaceutics Classification System. The drug is a competitive, reversible inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis.[4] In a previous publication,[5] the enhancement of the dissolution rate of ATC by cocrystallization method was highlighted, using glucosamine (GluN) and nicotinamide (NIC) as coformers, applying the solvent drop grinding (SDG) and solvent evaporation (SE) method at 1:1, 1:3, and 1:10 drug-coformer molar ratios. The data indicated higher solubility values for GluN- and NIC-Cs; 35 and 50 µg/mL, respectively, compared with the raw ATC (26 µg/mL). Furthermore, the dissolution rate of ATC from the Cs was >90% after 5 min, compared to 41% for the untreated ATC. The promising results encouraged further formulation and stability studies of the developed Cs as a tablet dosage form. The oral route of administration remains the most convenient for patients and is the simplest, safest means of drug administration, and painlessly administered with comparably low costs.[6]

Therefore, the aims of the present work were (a) to formulate the developed ATC-Cs into tablets employing the direct compression (DC) technique; (b) to investigate the quality attributes of the developed tablets, such as disintegration, dissolution, active content, as well as drug-excipients interactions by gas chromatography-mass spectroscopy (GC-MS), differential scanning calorimetry (DSC), etc.; (c) to compare the dissolution rate of the optimum developed tablets with a marketed tablet (Lipitor®); and (d) to study the effect of storage, under different conditions, on the *in vitro* characteristics of the Cs and the developed tablets.

MATERIALS AND METHODS

Chemicals and reagents

Methanol, acetonitrile, and methanol HPLC grade (Merck, Germany); ATC trihydrate, GluN HCl (Zhengzhou Sigma Chemical Co., Ltd., China); NIC (Hubei Ocean Biotech Co., Ltd., China); croscarmellose sodium (Ac-Di-Sol®) and microcrystalline cellulose (Avicel PH200®) (FMC, Belgium); DC isomalt (Galen IQ 720, TM) (Fluka, Switzerland), magnesium stearate and talc (Sigma-Aldrich, USA); and potassium phosphate monobasic (Loba Chemie, India). All other chemicals were analytical reagent grade.

Preparation of ATC-Cs by SDG and SE method

In this study, two techniques for cocrystal preparation were compared, namely, the SDG and the SE to prepare ATC-Cs with GluN and NIC as coformers (1:3 drug: conformer molar ratios).[5] Table 1 summarizes the codes assigned to each cocrystal formulation. The therapeutic dose of atorvastatin varies between 5 mg and 40 mg and frequently prescribed dose for adults is 10 mg; therefore, in the present study, 10 mg dose was selected.[7]

Preparation of ATC-Cs by SDG

The method of preparation was adopted from a previously reported work[8] and detailed previously in research work from this lab.[5] In brief, predetermined concentrations of the drug and each coformer (GluN and NIC) were mixed and ground in a mortar for 20 min; subsequently, few drops of 25% methanol/H_2O were added to about 100 mg of the solid mixture while grinding.[8] Then, the powder was passed through a 250 µm sieve and stored in a closed glass vial inside a desiccator.

Table 1: Codes of ATC-GluN and ATC-NIC cocrystals in various molar ratios

Coformer used	Method	Drug:coformer ratio	Code
GluN	SDG method	1:1	GL1
		1:3	GL2
		1:10	GL3
	SE method	1:1	GS1
		1:3	GS2
		1:10	GS3
	Physical mixture	1:1	GP1
		1:3	GP2
		1:10	GP3
NIC	SDG method	1:1	NL1
		1:3	NL2
		1:10	NL3
	SE method	1:1	NS1
		1:3	NS2
		1:10	NS3
	Physical mixture	1:1	NP1
		1:3	NP2
		1:10	NP3

ATC-GluN: Atorvastatin calcium-glucosamine, ATC-NIC: Atorvastatin calcium-nicotinamide, SDG: Solvent drop grinding

Preparation of ATC-Cs by SE method

Likewise, in the SDG, calculated amounts of ATC and NIC (1:3 molar ration, respectively) were used. In this case, the drug and the coformer were dissolved in 100 ml methanol, and subsequently stirred for 5 min and left for slow evaporation for 3 days at room temperature (RT). The samples were stored also in a desiccator until further investigations.[5]

Preparation of ACT and coformers physical mixtures (PMs)

To investigate the simple mixing effect of each of the tested coformers, PMs were prepared by mixing the drug and the coformer in a mortar until a homogenous mixture was obtained. The PMs were collected, sieved through 250 μm sieve, and stored in vials in a desiccator at RT till further use, Table 1.

Methods of drug analysis and validation

UV spectrophotometer was used in this study for the determination of ATC content in different powder preparations, studies, and dissolution rate studies.

A standard solution of ATC in methanol (20 μg/mL) was scanned in the entire UV range to determine the maximum wavelength of absorbance (λmax) of the drug (246 nm).

Furthermore, series of standard solutions were prepared by taking aliquots of stock solution in methanol (20 μg/mL) and diluted with water/phosphate buffer pH 6 to obtain the concentration in the range of 6–20 μg/mL. The absorbance values of the resulting solutions were measured at 246 and 284 nm for GluN-and NIC-containing Cs, respectively, since NIC possesses no significant absorbance at 284 nm, thereby avoiding potential interference with the readouts.[9]

On the other hand, the ultra-fast liquid chromatography (UFLC) method was used in this study as a stability-indicating method for the determination of ATC content in the ATC-Cs, F1-F5 tablets, and in the PMs. In this method, a system consisting of UFLC pump equipped with a PDA detector (Shimadzu, Japan) was used. The data were acquired and processed using Shimadzu LC Solutions software. Pre-filtered samples (10 μL) were injected into a Shim-pack XR-ODS column (3.0 mm I.D., 30 mm L, 2.2 mm particle size) maintained at 37°C. The mobile phase system consisted of acetonitrile and water (80:20 v/v) and was run in isocratic mode at a flow rate of 0.1 mL/min. The run time was 10 min/injection and the elute was monitored at 246 and 284 nm. The standard stock solution of ATC was prepared as mentioned above. A series of standard solutions were prepared by taking aliquots of the stock solution and diluted with the mobile phase to obtain concentrations in the range of 5–25 μg/ml. Standard calibration curves of ATC were constructed in the mobile phase at 246 nm and 284 nm.

Both the applied UV spectrophotometry and UFLC were tested for linearity, precision, accuracy, and sensitivity. The validation of UV spectrophotometry and UFLC method used was in compliance with the recommendations of the International Conference on Harmonization (ICH).[10] The analytical methods were validated for linearity (6–20 μg/mL), repeatability, precision (intra-day and inter-day), accuracy, limit of quantitation, and limit of detection.[11]

Evaluation of the physicochemical properties of ATC-Cs and the PMs

The homogeneity of the drug within the ATC-Cs was assessed by UV spectrophotometry before carrying out further investigations. The dissolution study was performed in triplicate. Further, the Cs were studied in terms of the relevant physicochemical properties, including Fourier-transform infrared (FT-IR), DSC, and powder X-ray diffraction (PXRD) as described previously.[5] All raw materials under investigation (ATC, GluN, and NIC, and their mixtures/Cs) were passed through 250 μm sieve before each further experiment.

FT-IR

Infrared spectra of ATC, GluN, and NIC were obtained employing Thermo Scientific Nicolet iS50 FT-IR (USA) using attenuated total reflectance sampling station. Scans were recorded at a resolution of 0.5 cm^{-1}.

DSC

DSC thermograms of the samples were traced using Netzsch DSC 204 F1, Phoenix, USA at a heating rate of 10°C/min over a temperature range of 20–500°C with nitrogen purging.

PXRD

The PXRD analysis of the powder samples was undertaken using an X-ray diffractometer (Bruker D8 ADVANCE, Germany) equipped with a Lynxeye detector, as indicated previously.[5] The intensity of the reflected radiation is recorded, and the data were then analyzed for the reflection angle to calculate the interatomic spacing (d value).

Mass analysis (GC-MS)

The analysis was undertaken using high-resolution GC-MS (DFS Thermo, USA) under the same conditions described previously.[5]

Dissolution rate study

The dissolution rate was studied using USP apparatus II (paddle method), employing 500 mL of phosphate buffer pH 6.[12] The equivalent of 10 mg ATC was sprinkled into

the dissolution flask at 50 rpm and at 37 ± 1°C for 30 min. The samples were filtered using 0.45 µm filters and the absorbance was determined using UV spectrophotometer at 246/284 nm.[5] The dissolution rate test was performed in triplicates.

Formulation of ATC-Cs into tablets by DC

Direct compression was used to prepare tablets from the best Cs powders (GL2 and NL2), based on the best dissolution results. The excipients were selected to ensure that the tableting operation can run satisfactorily and to ensure compliance with set pharmacopeial quality attributes, including powder flow properties, tablet weight variation, disintegration time, and dissolution rate.

Before compression of the tablets, ATC-Cs and the selected excipients were mixed together to explore compatibility and exclude drug-excipients interaction. Therefore, pre-formulation and drug-excipients compatibility studies were performed to ensure the above quality properties, and the results obtained directed the way and method of formulation. Finally, the prepared tablets were evaluated *in vitro* according to the US Pharmacopeia specifications[13] and their stability was tested under different storage conditions over 12 months.

Preparation of ATC-tablets

Selected functional excipients were utilized in the tablets formulations, including microcrystalline Cellulose (Avicel PH 200®), croscarmellose sodium (Ac-Di-Sol®), DC isomalt (Galen IQ 720), magnesium stearate, and talc. Five batches, each tablet containing 10 mg ATC (F1-F5), were prepared; F2 and F4 containing two types of ATC-Cs (GluN and NIC as coformers, respectively), F3 and F5 are the corresponding PMs to F2 and F4, respectively, in addition to the untreated ATC raw material (F1) [Table 2]. ATC and the excipients were passed through 40 meshes sieve and mixed together through geometric dilution to ensure uniform distribution of the drug throughout the resulting powder mix.

Each batch was manufactured by DC technique at constant pressure on a single punch tablet machine (Erweka AR 401, Germany) to produce rounded tablets with concave surface, 400 mg each. The resultant tablets were kept in airtight containers and stored at RT in a desiccator until further studies.

Evaluation of the pre-compression parameters of the powder mix

Before compression, the flow properties of the powder mixtures were estimated by determining the angle of repose, Hausner's ratio, and Carr's compressibility index.[5,14]

Evaluation of the post-compression parameters of the prepared tablets

The post-compression parameters of the prepared tablets were determined according to the official Pharmacopoeial specifications[13] which include the following tests: Hardness, thickness, friability, disintegration time, weight variation, and drug content uniformity.[15]

Tablet hardness

Monsanto tester (Campbell Electronics, India) was used to determine the hardness of ten randomly selected tablets. Results were expressed as mean values ± SD.

Tablet thickness

Vernier Caliper (Aerospace, China) was used to measure the thickness of ten randomly selected tablets. Results were expressed as mean values ± SD.

Tablet friability

Ten tablets were randomly selected, accurately weighed and placed in the drum of a tablet friability test apparatus (Erweka TAR 20, Germany). The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted, and accurately weighed. The percent weight loss was calculated.[16]

The friability in terms of % weight loss = $[(W1-W2)/W1] \times 100$, where W1 is the weight of tablets before the test and W2 is the weight of tablets after the test.

Table 2: Composition and codes for ATC tablet formulations*

Ingredients	Amounts per tablet(mg)					% ingredient used				
	F1	F2	F3	F4	F5	F1	F2	F3	F4	F5
ATC	10	14.7	14.7	13.2	13.2	2.5	3.67	3.67	3.3	3.3
Avicel PH 200	175	175	175	175	175	43.75	43.75	43.75	43.75	43.75
DC isomalt	175	170.3	170.3	171.8	171.8	43.75	42.58	42.58	42.95	42.95
Ac-Di-Sol	28	28	28	28	28	7	7	7	7	7
Talc	8	8	8	8	8	2	2	2	2	2
Mg-stearate	4	4	4	4	4	1	1	1	1	1
Total	400	400	400	400	400	100%	100%	100%	100%	100%

*F1=Raw ATC (untreated), F2=(ATC:GluN cocrystals 1:3), F3=(ATC:GluN, Physical mixture 1:3), F4=(ATC:NIC cocrystals 1:3), F5=(ATC:NIC, Physical mixture 1:3). ATC: Atorvastatin calcium, NIC: Nicotinamide

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed. Results are expressed as mean values ± SD.

Disintegration time

Disintegration of six tablets was determined using a tablet disintegration tester (Erweka ZT 34, Germany) with small plastic discs to ensure immersion of the dosage units completely. The entire basket-rack assembly was immersed in a vessel containing water as the disintegration medium at 37 ± 0.5°C.

ATC content uniformity

Ten tablets were individually crushed and each was transferred into a 100 ml standard flask. The drug was dissolved with 10 ml methanol and made up to a volume with 80% acetonitrile/water. Then, 1.5 ml of the solution was diluted with 10 ml of the mobile phase (ACN: water [80:20 v/v]) to get a concentration of about 15 µg/ml. The solution was sonicated for 15 min and filtered through 0.45 T PTFE filters and loaded in glass vials in an autosampler tray and measured for actual drug content using UFLC. The same conditions of UFLC were used as mentioned above.

Dissolution rate of the formulated tablets (in vitro drug release)

The dissolution study was performed as mentioned before under ATC-Cs powder, with the same dissolution media and same dissolution conditions. All the results were expressed as mean ± SD and analyzed by one-way ANOVA test.

Stability studies

Stability testing of ATC-Cs powder

All stability studies were carried out according to the ICH guidelines.[17] The selected ATC-Cs, along with their PMs and the raw ATC powder, were stored at 40 ± 2°C/75 ± 5% RH and at room temperature (RT) (22–25°C) for 6 months. Samples were withdrawn every 2 months. In addition, the same samples were evaluated for drug content, dissolution rate, FT-IR, PXRD, MS, and DSC after 6 months using the same conditions mentioned previously.[5] The drug content was determined by UFLC by taking samples containing the equivalent of 5 mg of ATC and dissolving in a suitable quantity of methanol (about 50 ml). Then, 1.5 ml of the solution is diluted to 10 ml with the mobile phase (ACN:water [80:20 v/v]) to get a concentration of 15 µg/ml, followed by sonication for 15 min. The samples were filtered through 0.45 TPTFE filters and loaded in glass vials in an autosampler tray for drug content analysis.

Stability testing of the formulated ATC tablets

Drug-excipient compatibility using DSC, FT-IR, and PXRD

After mixing each of ATC/Cs /PMs with the tablet excipients, the compatibility was directly tested for drug-excipient interactions using DSC, FT-IR, and PXRD, according to the briefly described above and detailed published methods.[5] Samples from all prepared tablets (F1-F5) were stored at 40 ± 2°C/75 ± 5% RH and at RT for 12 months. These tablets were also tested for any drug-excipient interactions after 6 months through DSC, FT-IR, and PXRD techniques, as described before for the fresh samples. The powder of the crushed tablets was used for the analyses.

Drug content and dissolution rate

Samples of all prepared tablets were stored at 40 ± 2°C/75 ± 5% RH and at RT for 12 months. The samples were withdrawn and evaluated for drug content after 1, 2, 3, and 12 months. In addition, after 3 and 12 months, all tablet formulations were evaluated for the dissolution rate. The dissolution conditions were the same as used for the powder Cs. The drug content was determined by UFLC, as mentioned above under ATC-Cs.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22 software. The results were expressed as the mean ± SD and the *t*-test was used to analyze the differences between samples. A value of $P < 0.05$ was considered significant. In addition, the model-independent similarity factor (f2) approach[18] which is a relatively simple and widely accepted method for comparing dissolution profiles, was used to compare dissolution rate results of the prepared tablets F2 and F4, with the marketed product (Lipitor®).

RESULTS AND DISCUSSION

The physicochemical characteristics of the drug, Cs, and the PMs were initially investigated before starting the tablets manufacture. The data will be presented hereafter under the results of the stability studies of the developed tablets.

Formulation of ATC tablets

Tablets can be produced by granulation either through dry or wet granulation or by DC. DC was used in this study because heat and water are not involved, and this can improve product stability and minimize the impact of manufacturing condition on the integrity of the already formed cocrystal. In addition, drug dissolution might be faster owing to fast tablet disintegration into primary drug particles.[19] Tablet production by DC involves only two operations in sequence, powder mixing, and tableting.

Effect of cocrystallization on pre-compression parameters

Powder flow of tablet granulation is an important property in tablet manufacture, which is influenced by many interrelated

factors.[20] Therefore, in our study, the pre-compression parameters of the prepared powders of ATC and other excipients, including angle of repose (θ), bulk density, tapped density, Hausner's ratio, and Carr's compressibility index,[21] were evaluated for the five tested formulations (F1-F5) as shown in Table 3.

The angle of repose (θ) is used in several branches of science to characterize the flow properties of solids.[13] The value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive.[20] From the present angle of repose results, it is clear that the flowability of ATC was improved in F2 and F4, which contain ATC-Cs. The untreated ATC formulation (F1) showed θ value of 36.5°, where F2 and F4 showed lower θ values, 32.5° and 30.7°, respectively. F4 formulation that contains ATC-NIC Cs showed better flow with a smaller angle of repose than F2 formulation which contains ATC-GluN cocrystals. The formulations F3 and F5, which contain PMs of the drug and the coformers, also showed smaller θ values, 32.74° and 32.87° for F3 and F5, respectively, when compared to F1 (36.5°).

In recent years, the compressibility index[21] and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index is an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials.[13] According to the theory, the less compressible materials are more flowable. A material having values of <20–30% is defined as the free-flowing material.[22] Looking into our results, F2 and F4 showed enhanced flow properties, where Hausner's ratio decreased from 1.31 (ATC) to 1.26 in both F2 and F4 and Carr's compressibility index was reduced from 23.75% (ATC) to 20.41% and 20.83% in F2 and F4, respectively. Accordingly, F4 exhibited better compressibility and minimal porosity and showed the smallest values for both parameters; Hausner's ratio and Carr's compressibility index (1.26 and 20.83%, respectively). Furthermore, the observed Hausner's ratio and Carr's compressibility index for F3 and F5 were reduced, in comparison with F1. On the other hand, F1 exhibited correspondingly the largest values for Hausner's ratio and Carr's compressibility index (1.31 and 23.75%, respectively). In addition, the presence of the coformers with ATC in the PMs could also improve the drug flow properties but to a lesser extent. Therefore, all ATC blends were considerably good to formulate the tablets by DC technique.

Effect of cocrystallization on post-compression parameters and dissolution rate of the prepared tablets

The formulated tablets F1-F5 were evaluated for hardness, thickness, friability, uniformity of weight, disintegration time, drug content uniformity, and *in vitro* drug release [Table 4].

The drug content in the tested tablet formulations varied between 98.6% and 99.62%. Tablet weight varied between 400.50 and 401.38 mg. A little variation was allowed in the weight of a tablet, according to USP 2015, where maximum ± 5% limit of deviation is acceptable if the average tablet weight is more than 324 mg. The results of the tested formulations indicated that all tablets met the official weight variation requirements.

Thickness, hardness, and friability of all formulated tablets were also evaluated. Thickness of the tablets was important for the uniformity of tablet size. It was in the range 5.64–5.69 mm. The hardness test was performed to provide a measure of tablet strength. The resistance of tablet toward chipping or breakage under conditions of storage, transportation, and

Table 3: Summary of powder flow characterization of the five formulas

Pre-compression parameter	F1	F2	F3	F4	F5
Angle of repose	36.5°	32.5°	32.74°	30.7°	32.87°
Bulk density (g/ml)	0.427	0.435	0.412	0.425	0.419
Tapped density (g/ml)	0.56	0.546	0.532	0.537	0.537
Hausner's ratio	1.31	1.26	0.29	1.26	1.28
Carr's compressibility index (%)	23.75	20.41	22.45	20.83	22

Table 4: Post-compression parameters of prepared tablets

Post-compression parameter	F1	F2	F3	F4	F5
Average wt. (mg), *n*=20	401.38±1.84	401.02±1.45	400.79±1.08	400.50±1.04	400.81±0.83
Thickness (mm), *n*=10	5.68±0.01	5.65±0.03	5.69±0.02	5.64±0.01	5.66±0.01
Hardness (kg/cm^2), *n*=10	6.5±0.02	6.6±0.01	6.2±0.08	6.7±0.05	6.5±0.06
Friability (% w/w), *n*=10	0.26±0.13	0.49±0.31	0.5±0.02	0.24±0.1	0.3±0.07
Disintegration time (s), *n*=6	99±0.25	95±0.14	23±0.33	69±0.2	32±0.09
Drug content uniformity (%), *n*=10	99.62±0.38	98.99±0.19	98.83±0.98	99.5±0.52	98.6±0.28

handling before usage depends on its hardness. The average hardness results of F1-F5 were 6.5 ± 0.02, 6.6 ± 0.01, 6.2 ± 0.08, 6.7 ± 0.05, and 6.5 ± 0.06 kg/cm^2, respectively.

Friability is related to the property of tablet hardness; therefore, it is important to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. Friability below 1% is considered acceptable.[20] All the formulations were found within the limit and mean values were in the range of 0.24–0.5%, which indicates a good mechanical resistance of the tested tablets.

In addition, all tablets were tested for *in vitro* disintegration time, which should be not more than 15 min.[13] The *in vitro* disintegration times of the formulated tablets were between 23 ± 0.33 and 99 ± 0.25 s, which met the official USP specifications. Tablets containing untreated ATC (F1) exhibited a longer disintegration time (99 ± 0.25 s). The presence of hydrophilic coformers within the ATC-Cs and as PMs could explain the reduction of disintegration time as a result of better wettability or/and decrease in the crystallinity of the drug. These results are in compliance with the results of Etman *et al*., where tablets containing co-ground mixtures of meloxicam with PEG 6000 disintegrated rapidly when compared to tablets that contain meloxicam alone.[23]

Finally, the dissolution rates of the five tablet formulations with the innovator tablet (Lipitor®) as a reference were compared in Figure 1. The dissolution data showed that F2 and F4, which contain ATC-Cs, exhibited a higher dissolution rate than F1 that contains the untreated ATC. More than 91% of drug was released from F4 formulation and more than 82% was released from F2 in the first 20 min. In comparison, the innovator tablet showed more than 88% drug release after the same time. The drug release from F1 was the least (63.65%), although it showed good tablet integrity and disintegration time. ANOVA test showed that there was no significant difference between F2, F4, and the innovator tablet (Lipitor®). In addition, the model-independent similarity factor (f2) approach showed that the prepared tablets F2 and F4 are equivalent to the marketed product (Lipitor®). The difference factor (f1) and the similarity factor (f2) were 3.73 and 71.18 in F2 and 7.71 and 55.32 in F4. According to the guidelines issued by many regulatory authorities, F1 values up to 15 (0–15) and F2 values >50 (50–100) ensure the "sameness" or "equivalence" of the two profiles.[18]

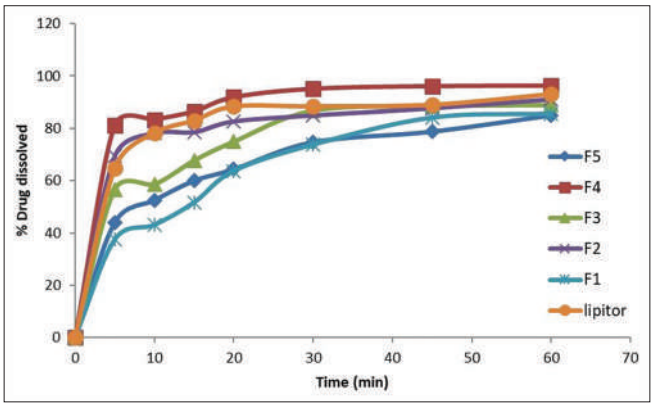

Figure 1: Dissolution rate profiles of the formulated tablets with Lipitor® tablets

Stability study

Stability is an integral part of formulation development and it is important in ensuring safety and efficacy of drug products. A drug should be stable and maintain its quality until its expiration date. It is important to assess the effect of temperature and humidity on the stability of drug and *in vitro* drug release rate and in turn the future *in vivo* performance. It helps to generate information for predicting the shelf life of the product and recommended storage conditions. Accordingly, the stability of ATC in the prepared powder Cs and the formulated tablets were performed at RT and at 40°C ± 2°C/75 ± 5% RH.

Stability of the drug in the Cs

The drug content in the ATC-Cs during the stability period is summarized in Table 5. No significant changes were observed in ATC content after 6 months of storage at RT and at 40°C ± 2°C/75 ± 5% RH and the values were within the limits of drug content specified by British Pharmacopeia (between 85% and 115% of the average content).[24] These results indicated good stability for 6 months, where all preparations were chemically stable, indicating superior compatibility between the drug and the chosen coformers.

Dissolution rate studies

The dissolution data of all freshly prepared samples and after 6 months' storage at RT and at 40°C ± 2°C/75 ± 5% RH were compared [Figure 2]. No significant difference ($P > 0.05$) in the dissolution data of the untreated ATC, GP2, and NP2 at 60 min ($P = 1$, 0.316, and 0.137, respectively). On the other hand, there was a significant difference ($P < 0.05$) in the dissolution rate data of GL2 and NL2 ($P < 0.001$). Tukey test revealed that the dissolution rate data of the freshly prepared samples and after 6 months at RT differ significantly from dissolution rate data of GL2 and NL2 at 40°C ± 2°C/75 ± 5% RH after 6 months. From the dissolution results, it is obvious that the dissolution results of GL2 and NL2 decreased after storing the samples 6 months at 40°C ± 2°C/75 ± 5% RH, although no significant difference in the ATC content of GL2 and NL2 after storage. The reason may be attributed to the instability of the weak intermolecular hydrogen bonding between the drug and the coformers under these conditions, and hence leading to dissociation of the Cs to the individual components.

These results are in accordance with MS, PXRD, and DSC analysis findings. This is consistent with data

Table 5: Summary of the drug content (±SD) for cocrystal powder preparations after different time intervals at RT and at 40°C/75% RH

Time interval for stability test of different preparations	Drug content (%) ±SD (ATC)		Drug content (%) ±SD (GL2)		Drug content (%) ±SD (GP2)		Drug content (%) ±SD (NL2)		Drug content (%) ±SD (NP2)	
	40°C±2° C/75±5% RH	RT	40°C±2° C/75±5% RH	RT	40°C±2° C/75±5% RH	RT	40°C±2° C/75±5% RH	RT	40°C±2° C/75±5% RH	RT
At the beginning	100.44±0.23		99.98±0.12		100.02±0.31		100.3±0.22		99.98±0.19	
After 2 moths	100.2±0.23	100.44±0.29	98.8±0.16	99.78±0.33	99.84±0.31	100±0.22	100 ±0.27	100.16±0.12	99.76±0.44	99.98±0.30
After 4 months	99±0.17	100.38±0.38	99.2±0.28	99.76±0.32	98.2±0.26	99.96±0.2	99.2±0.12	100±0.16	99±0.13	99.948±0.11
After 6 months	98.8±0.1	100.2±0.18	99±0.25	99.7±0.11	98±0.27	99.6±0.19	98.4±0.12	99.98±0.18	98±0.23	99.93±0.42

ATC: Atorvastatin calcium, SD: Standard deviation

reported by other researchers, where many Cs dissociate during storage, particularly in high-humidity and high-temperature environments.[25] Eddleston *et al*. found that at high humidity storage condition (98% RH), the Cs formed between caffeine and theophylline with a series of dicarboxylic acids partially dissociated and this dissociation was driven by the partial dissolution of the acid. They also found that partial dissociation occurs under all humidity conditions.[26]

FT-IR spectroscopy analysis

The FT-IR analysis was carried out before and after storing the samples at RT and at 40°C/75% RH for 6 months [Figure 3]. It is clear from the spectra that no change took place after stability tests, where all characteristic peaks of ATC, specifically at 3670.52, 3368.85, 3212.23, 3055.18, 2971.48, 1650.07, 1578.01, 750.6, and 690.64 cm^{-1} appeared in all ATC spectra. Similarly, all characteristic peaks of the drug in the freshly prepared GL2, GP2, NL2, and NP2 appeared in FT-IR spectra after stability tests at RT and at 40°C/75% RH, nevertheless with decreased intensity. In addition, after storage at RT, the resultant peaks of all FT-IR spectra of all tested preparations became broader due to water absorption.

PXRD analysis

The PXRD patterns of the untreated drug, prepared Cs GL2 and NL2, in addition to their PMs GP2 and NP2 were examined after storing the samples at RT and at 40°C/75% RH [Figure 4]. After storing the samples at RT, their PXRD patterns showed no significant change, where all characteristic peaks exhibited almost the same intensity in comparison with the freshly prepared samples. On the other hand, storage conditions at 40°C/75% RH affected the PXRD patterns of the prepared Cs GL2 and NL2, and their PMs GP2 and NP2. After storage at 40°C/75% RH, the newly observed peak in fresh GL2 was shifted from 38.635° (intensity = 97.2%) to 35.487° (intensity = 25.5%), whereas in NL2 its newly formed peak of the freshly prepared sample disappeared. Although all the peaks of freshly prepared GL2 and NL2 were detected in the diffractograms after storage at 40°C/75% RH, yet the peak intensities of all preparations were less. These results come in compliance with MS analysis and dissolution rate results, where significant reduction in dissolution rate was observed in these preparations after storing at 40°C/75% RH. The disappearance of newly formed peaks, due to cocrystal formation, in the freshly prepared GL2 and NL2 may be explained by instability of hydrogen bonds under these storage conditions. Trask *et al*. came to the same conclusion, where the storage of theophylline-caffeine Cs at high humidity (98% RH) leads to dissociation of the Cs, and this was monitored by PXRD. The reported PXRD pattern of the cocrystal after storage at this high humidity condition showed reflections corresponding to theophylline only, indicating that full cocrystal dissociation occurred because

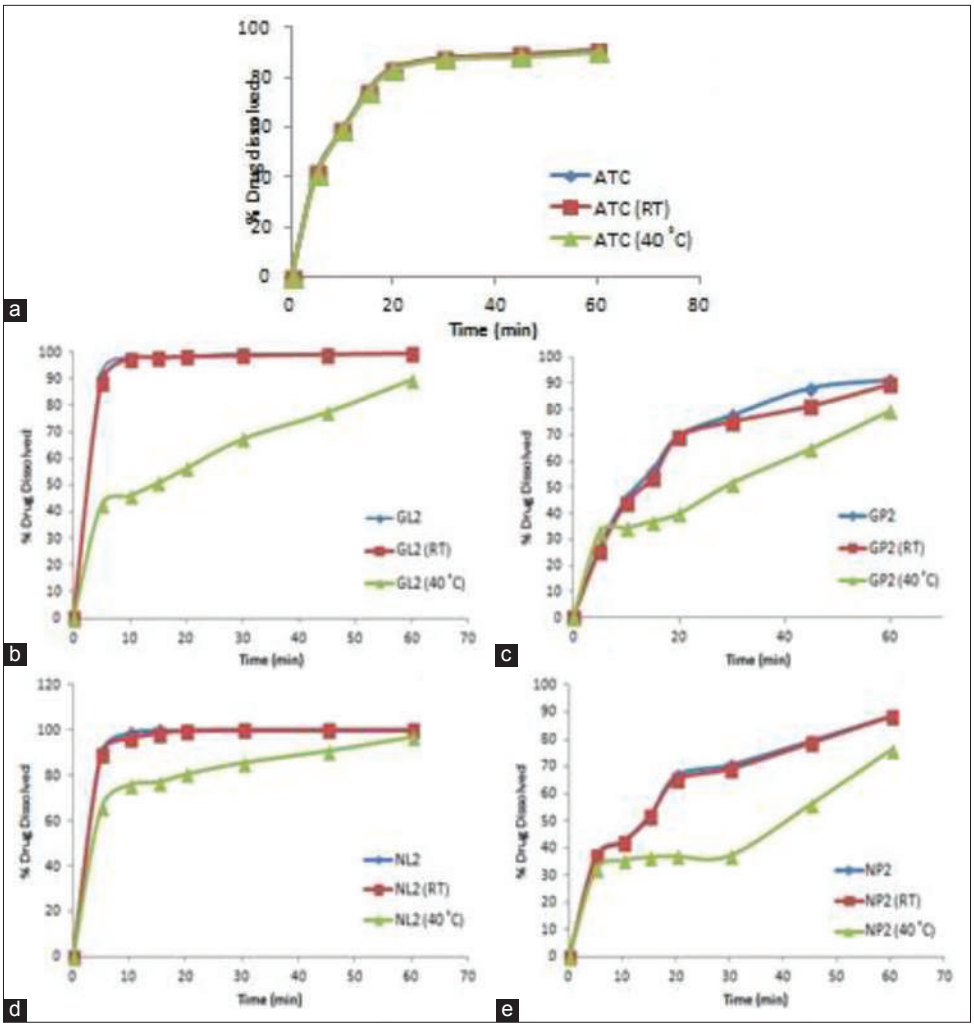

Figure 2: Dissolution profiles of freshly prepared and aged samples after 6 months at room temperature and at 40°C ± 2°C/75 ± 5% RH; untreated ATC (a), ATC-GluN cocrystals (1:3) (b) and the physical mixtures (c), ATC-NIC Cs (d), and the physical mixture (1:3) (e)

of the dissolution of the more soluble conformer.[27] The PXRD pattern of the PM GP2 and NP2 showed that all peaks that were observed in the freshly prepared GP2 and NP2 appeared again with decreased intensity and some of ATC peaks disappeared that were there in the freshly prepared PMs. The decrease in peak i=ntensity of all preparation may be explained by decreased crystallinity due to the storage conditions.

DSC analysis

The results of DSC analysis of ATC, GL2, GP2, NL2, and NP2 was carried out after storing the samples at 40°C/57% RH and at RT for 6 months are shown in Figure 5. The heat of fusion (ΔH) and the peak melting temperatures of the Cs and their PMs after stability tests were calculated and summarized in Table 6. ATC exhibited a single melting endothermic peak at 167.7°C and 166.4°C at RT and 40°C/57% RH, respectively, indicating its melting point. Freshly prepared GL2 and NL2 preparations showed single sharp peaks at 170.2°C and 191.2°C, respectively. After 6 months at RT, both also showed single sharp peaks at 171.2°C and 190.3°C, respectively. These results indicated that these Cs were stable at RT after 6 months. The DSC analysis of PMs GP2 and NP2 at RT demonstrated two endothermic peaks at 160.4°C and 210.9°C and at 176°C and 197.4°C, respectively, which correspond to the melting points of ATC and the coformer.

After storing the samples at 40°C/57% RH for 6 months, the DSC thermogram of GL2 pointed out the appearance of two melting endothermic peaks of at 164.3°C and 208.9°C, corresponding to the melting points of ATC and GluN. NL2 exhibited three melting endotherms at 164.2°C, 171.6°C, and 183.5°C. Endothermic peaks at 164.2°C and 171.6°C are corresponding to ATC and NIC melting points, while the third peak at 183.5°C corresponds to the cocrystal melting point. These results revealed that GL2 and NL2 Cs dissociated to ATC and the respective coformer, which may be explained by the weak intermolecular hydrogen bonding between the drug and the coformers at 40°C ± 2°C/75 ± 5% RH. With regard to NL2, the appearance of the peak at 183.5°C after 6 months at 40°C ± 2°C/75 ± 5%

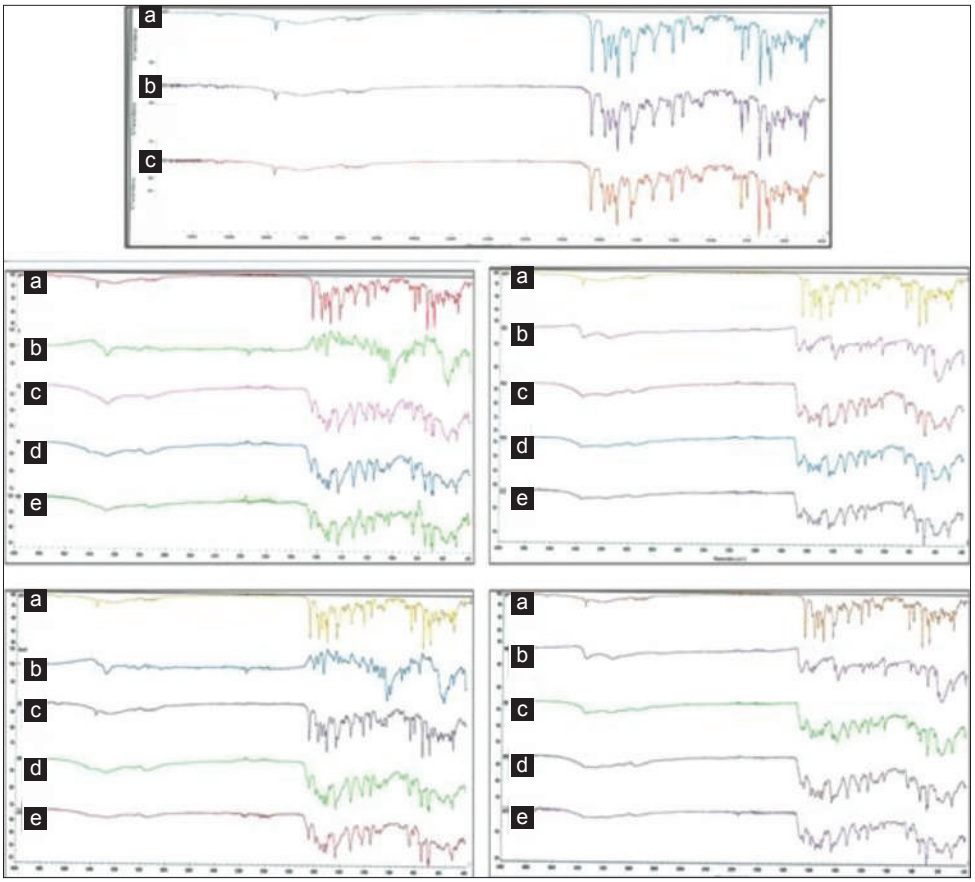

Figure 3: FT-IR spectra of freshly prepared and aged samples after 6 months at room temperature and at 40°C ± 2°C/75 ± 5% RH; (i) Fresh ATC (a), after 6 months at RT (b), and at 40° (c); (II-V) fresh ATC (a), coformer (b), cocrystal/physical mixture (c), and after 6 months at RT (d), and at 40°C (e)

Table 6: The peak temperature and heat of fusion (ΔH) of ATC, freshly prepared cocrystals, and their physical mixtures and after different storage conditions

	ATC		GL2		GP2		NL2		NP2	
	Peak temp. (°C)	ΔH (J/g)	Peak temp. (°C)	ΔH (J/g)	Peak temp. (°C)	ΔH (J/g)	Peak temp. (°C)	ΔH (J/g)	Peak temp. (°C)	ΔH (J/g)
Freshly prepared	167.8	100.02	170.2	72.92	156.6 212.2	10.89 170.24	191.2	16.77	111.3 187	103.46 23.27
At room temp.	167.7	102.18	171.2	46.51	160.4 210.9	8.04 87.39	190.3	23.27	176 197.4	23.21 10.25
At 40°C/57% RH	166.4	116.97	164.3 208.9	51.45 49.68	162 210.7	37.35 67.87	164.2 171.6 183.5	50.54 59.22 35.33	104.7 177	19.33 18.65

RH indicates that these Cs are more stable than GL2 Cs. These results were in compliance with the dissolution rate results after 6 months at 40°C ± 2°C/75 ± 5% RH of GL2 and NL2. Although lower dissolution rate was observed, yet NL2 Cs exhibited better results than GL2. In addition, the following MS results also support our DSC findings. The DSC thermograms of the PMs GP2 and NP2 revealed the appearance of 2 endothermic peaks at 162°C and 210.7°C and at 104.7°C and 177°C, respectively, corresponding to the melting points of ATC and the coformer.

The enthalpy data summarized in Table 6, show a dramatic decrease of energy in all tested mixtures, including the Cs and their PMs, compared to the pure ATC. These findings give evidence for pronounced interactions between ATC and the currently tested coformers (GluN and NIC). The decrease in ΔH values reported for the mixtures reflects a lower degree of crystallinity, which is usually encountered in drug-coformer interactions.[28] NL2 enthalpic data showed more reduction in enthalpy, compared to GL2 in freshly prepared samples and also after stability tests. These results further

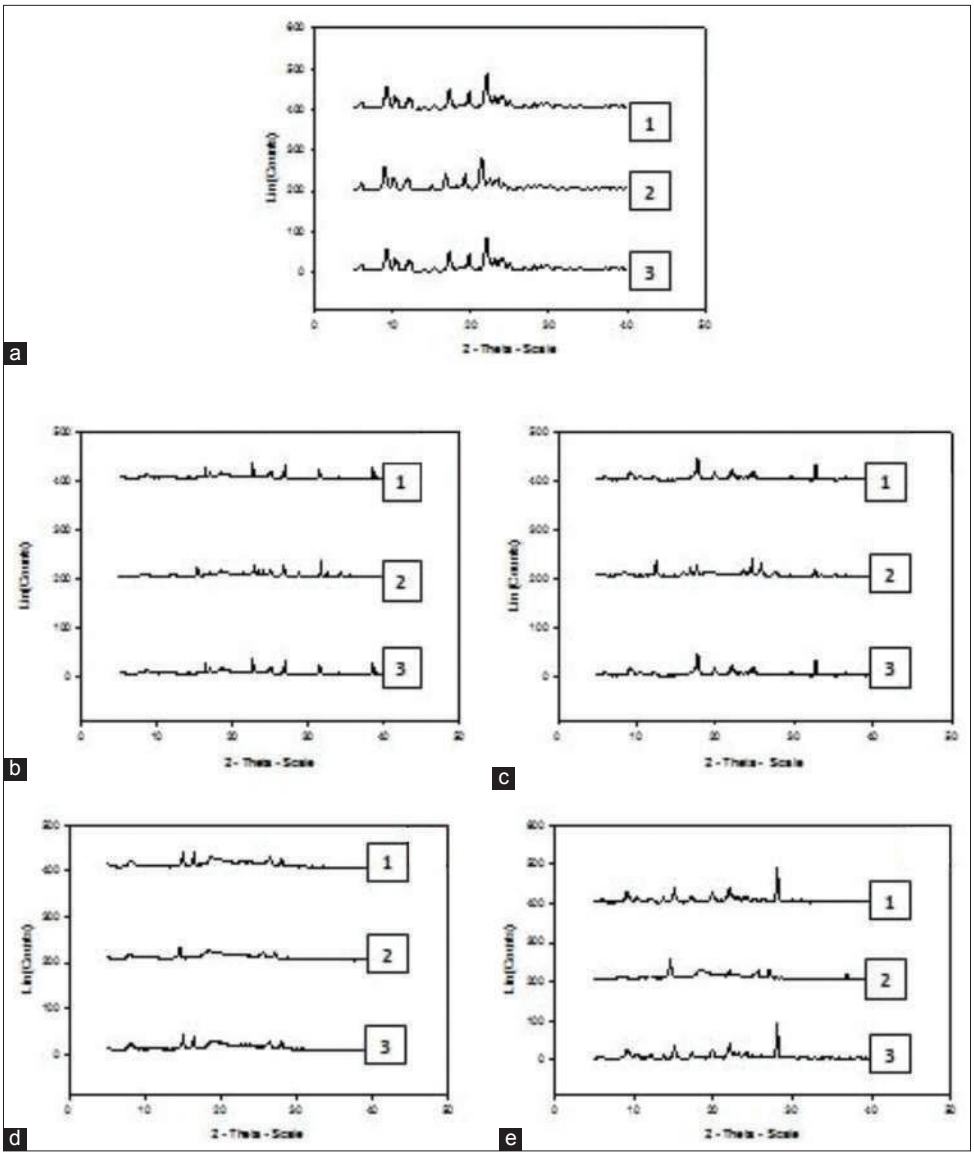

Figure 4: PXRD pattern of freshly prepared (1) and aged samples after 6 months at RT (2) and at 40°C ± 2°C/75 ± 5% RH (3): Untreated ATC (a), ATC-GluN cocrystals 1:3 molar ratio (b) and the physical mixtures (c), ATC-NIC Cs 1:3 molar ratio (d), and the physical mixture (1:3 molar ratio) (e)

support the explanation of the dissolution results indicating the superiority of NL2 Cs to enhance the dissolution rate of ATC more than GL2.

GC-MS analysis

The data mass spectral of the different samples after 6 months' storage at 40°C ± 2°C/75 ± 5% RH are presented in Figure 6. MS analysis of GL2 product indicates the absence of ion mass signal at m/z 523.1 and the appearance of mass signals for the drug and the coformer (GLU-N) at m/z 306.3 and 214.1, respectively. This finding indicates the dissociation of the molecular complex (ATC-GluN) to free atorvastatin and GluN. Similarly, the ion mass signal for the drug and the coformer NIC appeared at m/z 306.3 and 122, respectively, in addition to the ion mass signal for NL2 complex at m/z 430.3. The mass analysis of the PM GP2 indicated that the drug is present as simple mixtures without any interaction with the coformer, where only the mass signals at 306.3 and 214.2 for the PMs of GP2 were observed. Similarly, the mass signals for drug and coformer depicted at 306.2 and 122 for the PMs of NP2, as shown in Figure 6. These results indicate that intermolecular hydrogen bonding between the drug and the coformers was unstable for 6 months at 40°C ± 2°C/75 ± 5% RH.

Stability study of the formulated tablets

The results of the stability study of the cocrystal tablet formulations (F2 and F4) revealed excellent resistance of the prepared tablets to storage at RT and at 40°C ± 2°C/75 ± 5% RH for a period of 12 months without showing any significant change in drug content and absence of any

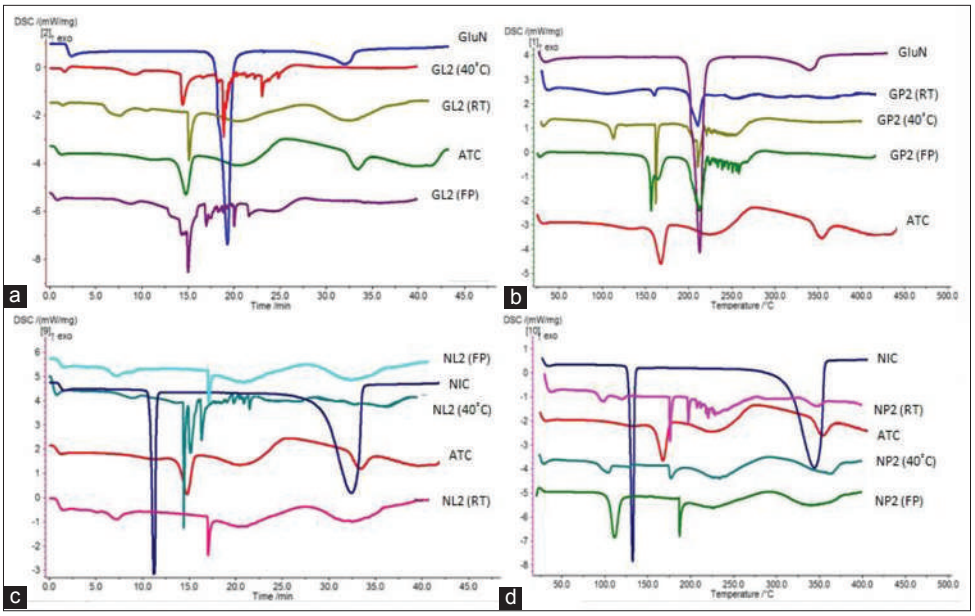

Figure 5: DSC thermograms of the fresh samples (FP) and after storage for 6 months at different storage conditions: ATC-GluN cocrystals (a), ATC-GluN physical mixture (b), ATC-NIC cocrystals (c), ATC-NIC physical mixture (d)

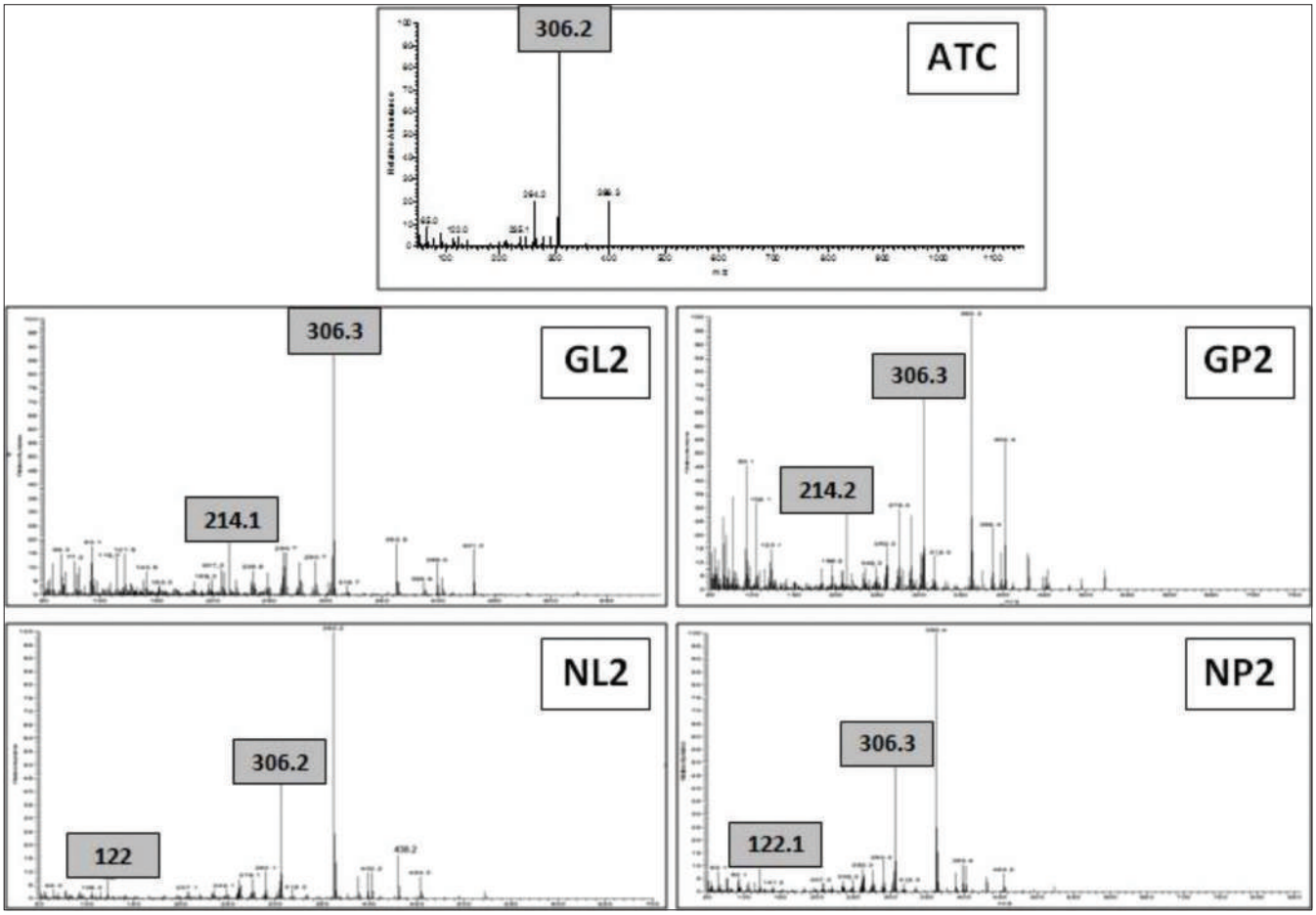

Figure 6: MS spectra after 6 months' storage at 40°C/75% RH: Untreated drug (ATC), ATC-GluN cocrystals (GL2), ATC-GluN physical mixture (GP2), ATC-NIC cocrystals (NL2), and ATC-NIC physical mixture (NP2)

degradation products, as evidenced by UFLC. These tablets also maintained a high dissolution rate profile after the adopted stability tests at RT only, but not at 40°C ± 2°C/75 ± 5% RH, as will be discussed below.

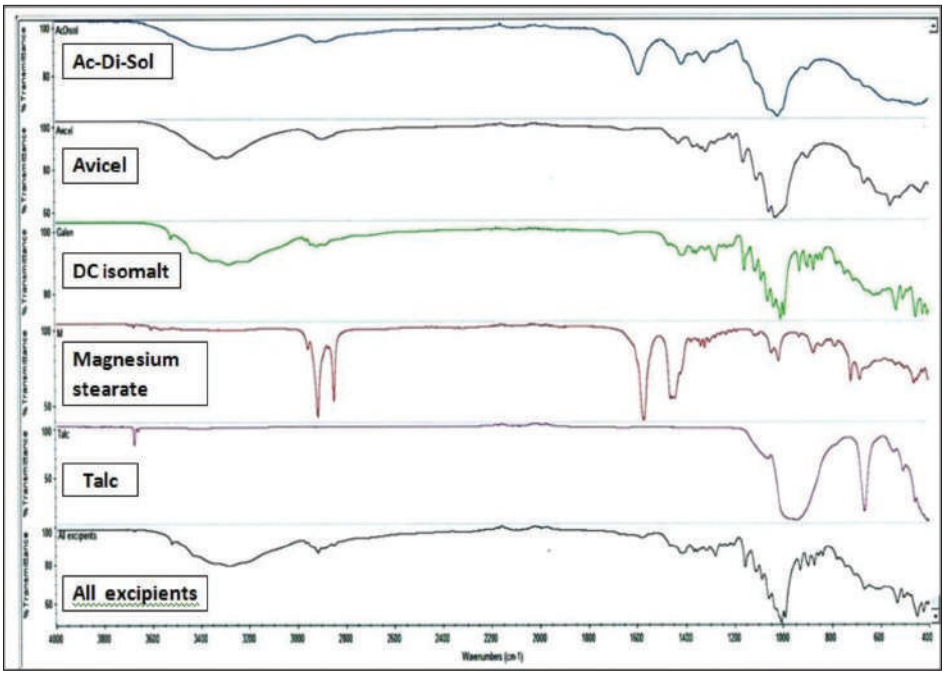

Figure 7: FT-IR spectra of each excipient and a mixture of all excipient without ATC

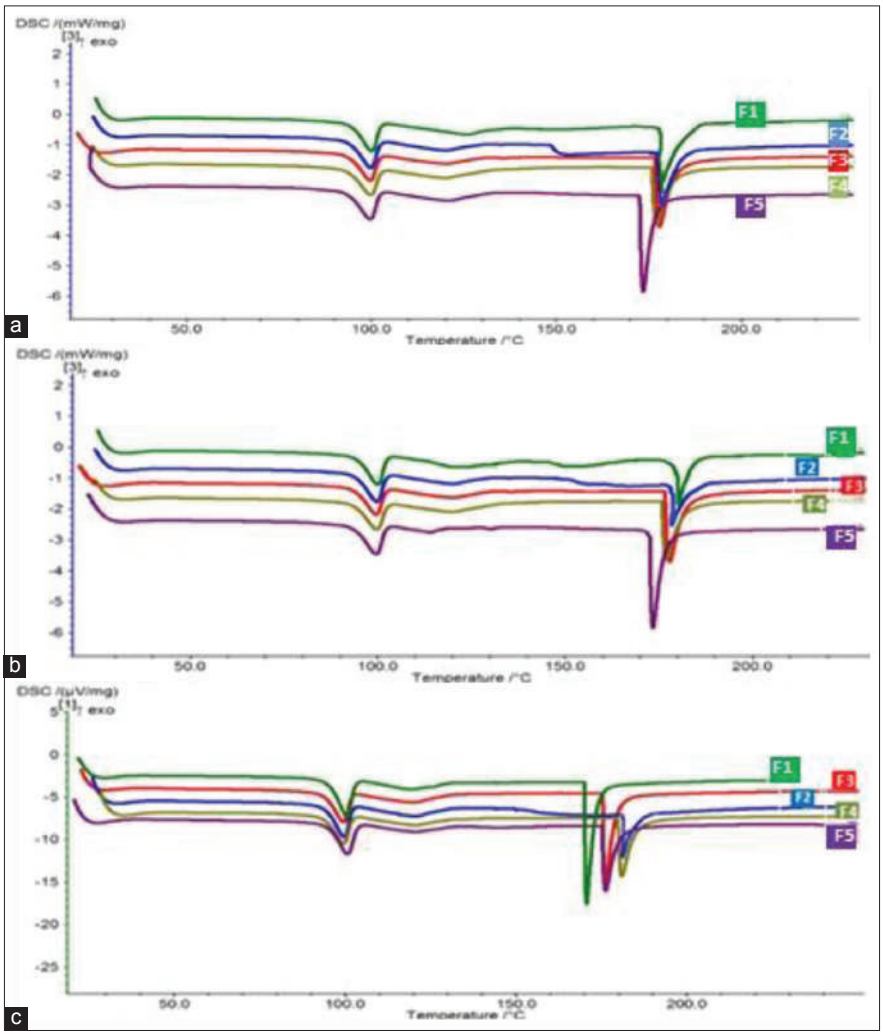

Figure 8: DSC thermograms of freshly prepared tablet formulations (a), after 6-month storage at room temperature (b), and at 40°C/57% RH (c)

Table 7: Summary of the drug content during the stability study of the tablet formulations at RT and at 40°C/75% RH

Time interval	Drug content (%) ± SD (F1)		Drug content (%) ± SD (F2)		Drug content (%) ± SD (F3)		Drug content (%) ± SD (F4)		Drug content (%) ± SD (F5)	
	40°C ± RT		40°C ± RT		40°C ± RT		40°C ± RT		40°C ± RT	
Zero	99.27±0.20		98.67±0.10		98.53±0.30		99.20±0.22		98.33±.29	
1 moths	99.13±0.21	99.2±0.23	98.6±0.11	98.67±0.31	98.33±0.30	98.4±0.2	99.07±0.21	99.2±0.12	98±0.32	98.2±0.31
2 months	99±0.11	99.07±0.32	98.4±0.21	98.53±0.31	98±0.21	98.27±0.1	98.8±0.13	99±0.11	97.87±0.11	98.2±0.1
3 months	98.67±0.1	99±0.12	98.13±0.21	98.47±0.1	97.67±0.21	98.27±0.15	98.67±0.11	98.93±0.11	97.8±0.2	98.07±0.32
12 months	98.12±0.25	98.52±0.18	98.00±0.11	98.21±0.17	97.60±0.13	98.1±0.18	98.6±0.12	98.88±0.31	97.78±0.19	98.00±0.22

RT: Room temperature

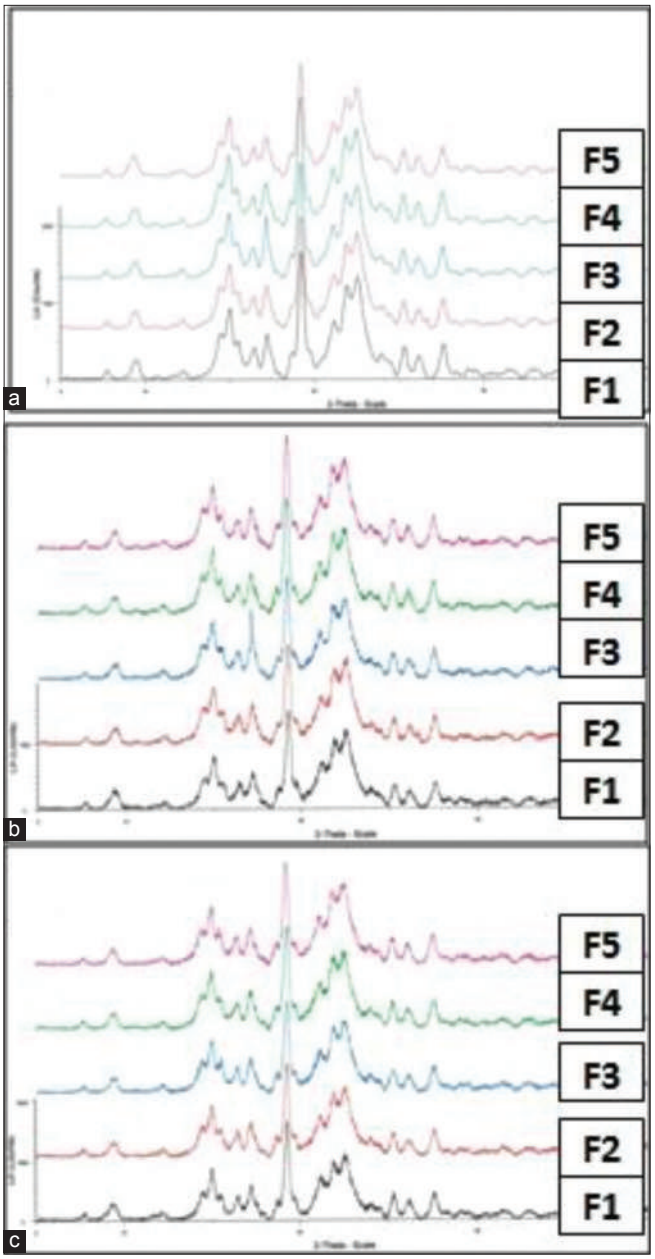

Figure 9: PXRD patterns of freshly formulated tablets (F1-F5) (a), after 6 months' storage at room temperature (b), and at 40°C/75% RH (c)

Effect of storage conditions on the drug-excipient compatibility

To ensure drug-excipient compatibility, FT-IR, DSC, and PXRD were used at the end of the stability tests at RT and at 40°C/75% RH. No incompatibility was found in all tablet formulations.

The analysis by FT-IR spectroscopy was done on the individual excipients and also their mixture and the results are depicted in Figure 7. In addition, FT-IR spectroscopy analysis of the formulated tablets after the stability test was done (data not shown, Supplementary Figure). No change was observed after stability test at RT and at 40°C/75% RH

for the FT-IR spectra of the prepared tablets, which declared no interaction took place between the components of the formulated tablets, including the drug, coformers, and the excipients.

DSC analysis of the five formulations was carried out after storing the samples at RT and at 40°C/75% RH for 6 months [Figure 8B and C]. DSC curves of the five formulations after 3 months at RT and at 40°C/75% RH were very similar to the DSC curves of freshly prepared tablets [Figure 8A], where no significant difference occurred in the DSC curves of all formulations before and after stability.

The analysis of PXRD patterns of the excipients and freshly prepared tablets was performed and the results are shown in Figure 9. The PXRD patterns for tablets were overlapped with the excipient patterns. All PXRD patterns after stability at RT and at 40°C/75% RH were similar to PXRD patterns of the freshly prepared formulations [Figure 9A-C], which again ensures no interaction occurred between the components of the tablets.

Effect of tablet compression on drug content and dissolution rate

The drug content of ATC in tablet formulations during stability tests is summarized in Table 7. Obviously, no significant change from the initial values was observed in ATC content after 12 months of storing the five formulations at RT and at 40°C ± 2°C/75 ± 5% RH. The drug content was within the pharmacopeial specifications[24] which indicate good chemical stability of the formulated tablets after 12 months under such storing conditions. These findings point out good drug stability in our formulations, in contrary to the previous report where 5 tablet brands showed degradation at all storage conditions.[29] On the other hand, Wankhede *et al*., 2010 achieved the formulation and stabilization of amorphous atorvastatin in tablets prepared using the dry granulation method by roller compaction.[30]

The release data of the five tablet formulations are graphically summarized in Figure 10. The release profiles of F1, F2, and F4 formulations after 3 months were similar

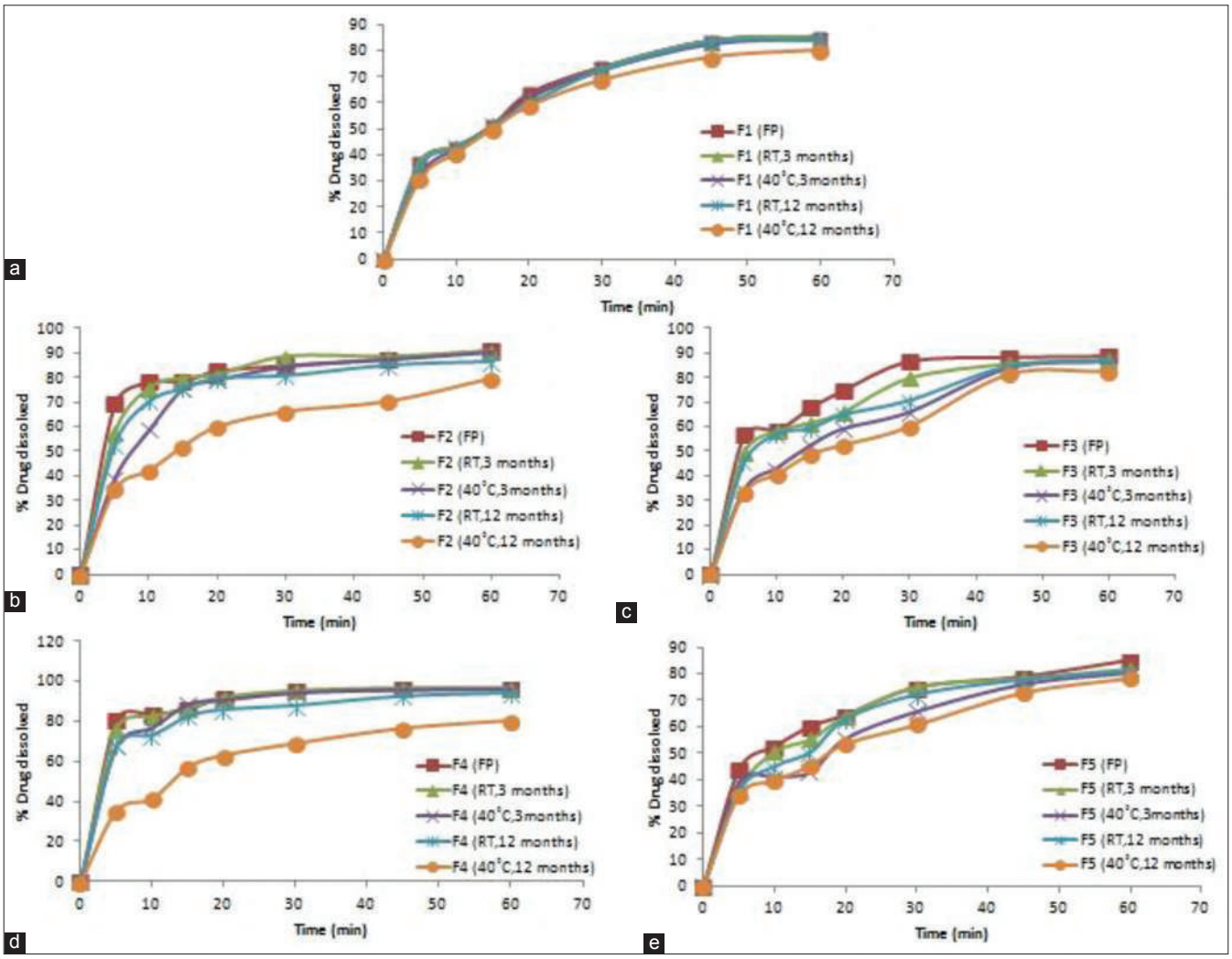

Figure 10: Dissolution profiles of freshly prepared (FP) tablets (F1-F5) and after 3 and 12 months at room temperature (RT) and at 40°C ± 2°C/75 ± 5% RH

as that of the fresh tablets. In regard to F3 and F5, the *in vitro* release studies at 40°C/75% RH were slightly reduced when compared to their freshly prepared formulations [Figure 10]. The marked stability and superior dissolution rate of F2 and F4 formulations, even after 3 months of the accelerated stability study, could be mainly due to the stability of intermolecular hydrogen bonding between ATC and the coformers. This assumption leads to a decrease in the drug mobility and maintains the drug-coformer association, which prevents drug molecules aggregation and also protects the drug from interaction with other excipients during the production process and throughout the shelf life.

When the data of dissolution results of all prepared tablet formulations before and after 12 months' storage were compared, the freshly prepared F2 and F4 and the aged tablets at RT were higher and differ significantly from those at 40°C. The lower dissolution rates were observed due to partial dissociation of the prepared Cs due to the weak intermolecular hydrogen bonding between ATC and the coformers at elevated temperature.

CONCLUSION

In brief, a novel solid-state structural modification of atorvastatin raw material was investigated to obtain alternative forms of atorvastatin possessing higher dissolution profiles to improve drug therapy and/or reduce commonly associated side effects. The developed ATC-Cs were successfully incorporated into tablet formulations by DC.

In addition, the stability of ATC in the prepared Cs and the formulated tablets were performed at RT and at 40°C ± 2°C/75 ± 5% RH and the results did not reveal significant changes in drug content, as well as the absence of any degradation products. However, after 6 months' storage at 40°C ± 2°C/75 ± 5% RH, partial dissociation occurred of the prepared original Cs due to the instability of the weak intermolecular hydrogen bonding between the drug and the coformers under these conditions. The tablets maintained the enhanced dissolution rate power of the original Cs. In addition, the prepared tablets showed satisfactory results for various physicochemical tests such as hardness, thickness, weight variation, and *in vitro* dissolution study. Among all the tablet formulations, F4 was the best in terms of pre-compression and post-compression parameters.

Furthermore, ATC in all tablet formulations was compatible with the selected excipients and coformers used in the study, pointing out no drug-excipient interactions. Further *in vivo* study is foreseen to confirm the expected higher bioavailability as a result of the enhanced dissolution rate and to establish a good *in vitro*/*in vivo* correlation.

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REFERENCES

1. Daniel E, Kevin P, Robert O. Optimizing the formulation of poorly water-soluble drugs. In: Williams RO, Watts AB, Miller DA, editors. Formulating Poorly Water Soluble Drugs. 1st ed. New York, USA: Springer Science and Business Media; 2012.
2. Kumar A, Kumar S, Nanda A. A review about regulatory status and recent patents of pharmaceutical co-crystals. Adv Pharm Bull 2018;8:355-63.
3. Hoffman M, Lindeman JA. Co-crystals: Commercial opportunities and patent considerations. In: Johan W, Luc Q, editors. Pharmacutical Salts and Co-crystals. United Kingdom: Royal Society of Chemistry; 2012.
4. Lennernas H. Clinical pharmacokinetics of atorvastatin. Clin Pharmacokinet 2003;42:1141-60.
5. Al-Kazemi R, Al-Basarah Y, Nada A. Dissolution enhancement of atorvastatin calcium by cocrystallization. Adv Pharm Bull 2019;9:559-70.
6. York P. The design of dosage forms. In: Aulton ME, editor. Pharmaceutics the Science of Dosage Form Design. 2nd ed. United Kingdom: Churchill Livingstone; 2002.
7. Talegaonkar S, Mustafa G, Akhter S, Iqbal ZI. Design and development of oral oil-in-water nanoemulsion formulation bearing atorvastatin: *In vitro* assessment. J Dispers Sci Technol 2010;31:690-701.
8. Friščić T, Jones W. Benefits of cocrystallisation in pharmaceutical materials science: An update. J Pharm Pharmacol 2010;62:1547-59.
9. Shayanfar A, Ghavimi H, Hamishehkar H, Jouyban A. Coamorphous atorvastatin calcium to improve its physicochemical and pharmacokinetic properties. J Pharm Pharm Sci 2013;16:577-87.
10. Huber L. Good Laboratory Practice and Current Good Manufacturing Practice. Germany: Hewlett-Packard; 2002.
11. Papadoyannis NI, Samanidou FV. Validation of HPLC instrumentation. Liq Chromatogr Relat Technol 2004;27:753-83.
12. Machado JC, Lange AD, Todeschini V, Volpato NM. Development and validation of a discriminative dissolution method for atorvastatin calcium tablets using *in vivo* data by LC and UV methods. AAPS PharmSciTech 2014;15:189-97.

13. The United State Pharmacopeial Convention. US Pharmacopeia 38 National Formulary 33. Maryland, USA: The United State Pharmacopeial Convention; 2015.
14. Banker GS, Anderson NL. Tablets. In: The Theory and Practice of Industrial Pharmacy. Bombay, India: Varghese Publishing House; 1987.
15. Salam WA, Dumitru L. Enhancement of solubility and dissolution rate of different forms of atorvastain calcium in direct compression tablet formulas. Farmacia 2009;57:290-300.
16. Furquan NK, Mohamed HG. Enhanced bioavailability of atorvastatin calcium from stabilized gastric resident formulation. AAPS PharmSciTech 2011;12:1077-86.
17. ICH Stability Guidelines. Available from: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html. [Last accessed on 2020 Oct 09].
18. Diaz DA, Colgan ST, Langer CS, Bandi NT, Likar MD, Van Alstine L. Dissolution similarity requirements: How similar or dissimilar are the global regulatory expectations? AAPS J 2016;18:15-22.
19. Aulton ME. Tablets and compaction. In: Aulton ME, editor. Pharmaceutics the Science of Dosage Form Design. 2nd ed. United Kingdom: Churchill Livingstone; 2002.
20. Rajesh K, Rajalakshmi R. Formulation and evaluation of bilayer liquisolid tablets of atorvastatin calcium and felodipine. Int Res J Pharm 2013;4:138-45.
21. Carr RL. Evaluating flow properties of solids. Chem Eng 1965;72:163-8.
22. Babu GS, Venkatadri D, Kumar DV, Kumar ND, Malathy PS. Preparation and evaluation of atorvastatin calcium porous tablets by sublimation technique. J Glob Trends Pharm Sci 2014;5:2139-44.
23. Etman M, Shekedef M, Nada A, Ismail A. *In vitro* and *in vivo* evaluation of tablets containing meloxicam-PEG 6000 ball-milled co-ground mixtures. J Appl Pharm Sci 2017;7:31-9.
24. British Pharmacopoeia. Stationarey Office on Behalf of the Medicines and Healthcare Products Regulatory Agency (MHRA). London, UK: British Pharmacopoeia; 2015.
25. Izutsu K, Koide T, Takata N, Ikeda Y, Ono M, Inoue M, *et al*. Characterization and quality control of pharmaceutical cocrystals. Chem Pharm Bull (Yokyo) 2016;64:1421-30.
26. Eddleston M, Thakuria R, Aldous B, Jones W. An investigation of the causes of cocrystal dissociation at high humidity. J Pharm Sci 2014;103:2859-64.
27. Trask A, Motherwell W, Jones W. Physical stability enhancement of theophylline via cocrystallization. Int J Pharm 2006;320:114-23.
28. Nada AH. Evaluation of ball-mill ground mixtures of hydrophilic carriers and phenytoin. Alex J Pharm Sci 1997;11:29-34.
29. Jakaria M, Chowdhury TA, Bhuiyan DI, Arifujjaman, Mamur A. Effect of acid, base and heat on five brands of atorvastatin tablet available in Bangladesh. J Sci Innov Res 2014;3:598-601.
30. Wankhede SV, Krishnaprasad M, Manjunath SY, Debnath S. Formulation and stabilization of atorvastatin tablets. J Chem Pharm Res 2010;2:548-54.

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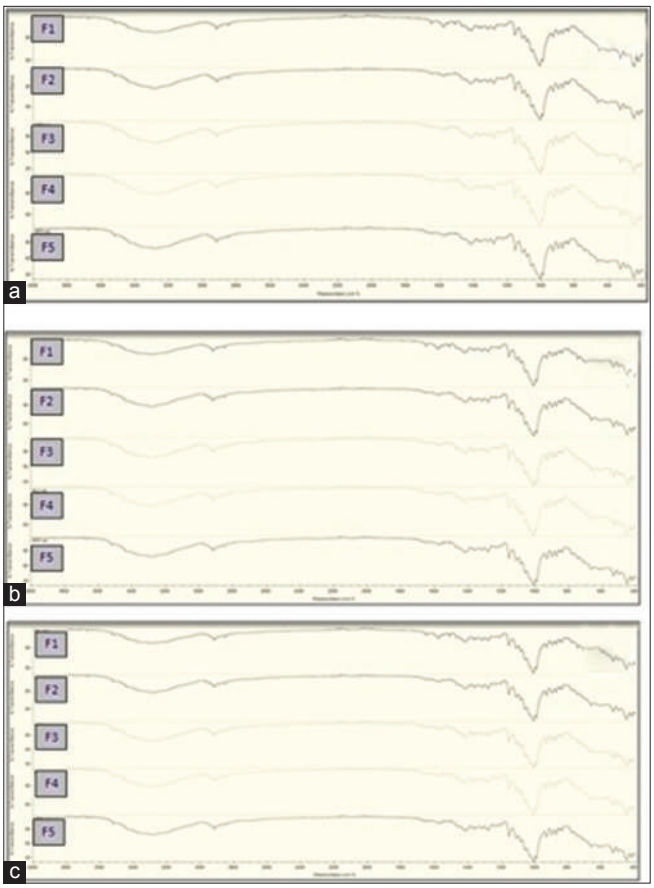
SUPPLEMENTARY FIGURE



Supplementary Figure: FT-IR spectra of the tablets (F1-F5): Freshly prepared (a), and after 6 months at room temperature (b) and 40˚C/75%RH (c)