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CO-AMORPHOUS DISPERSIONS OF AMLODIPINE AND ATORVASTATIN: PREPARATION, CHARACTERIZATION, STABILITY EVALUATION AND FORMULATION

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ABSTRACT

The aim of present research was to prepare co amorphous system of amlodipine besylate (AML) and atorvastatin calcium (ATR) by different methods and to evaluate stability of drugs when tablets were stored at room condition and under controlled condition. The co amorphous system was prepared by three different methods viz rotary flash evaporation, solvent evaporation under room condition and by melt quenching technique. Solubility studies were carried out with co amorphous forms and physical mixture of AML and ATR. The optimized formula from our previous study[1] was considered and total eight formulations were prepared employing either physical mixture or co amorphous forms of AML and ATR. Formulation blend was compressed into tablet by direct compression method using cross povidone or sodium starch glycolate as superdisintegrant. All the three methods have resulted in co amorphous precipitation of active ingredients with increase in their solubility and *in vitro* drug release from the tablet formulations. Pre and post compression studies were satisfactory for all the formulations. Tablets were found to be stable (12 months at room condition and 6 months at 40℃ ± 2℃ and 75% ± 5% RH).

KEYWORDS: Co-amorphous Amlodipine besylate, Co-amorphous Atorvastatin calcium, melt quenching, rotary flash evaporation, solvent evaporation, stability studies.

INTRODUCTION

Amlodipine besylate (AML) and Atorvastatin calcium (ATR) are the most commonly prescribed drugs for combination therapy of hypertension coexisting with hyperlipidemia. This combination is bioequivalent to Amlodipine besylate and Atorvastatin calcium given alone and does not modify the efficacy of individual agent. Combination therapy has increased patient acceptance with reduced tablet weight, number of pill and cost of treatment.[2,3,4,5,6]

Amlodipine besylate and Atorvastatin calcium belong to BCS class II (exhibit low solubility and high permeability). Solubility enhancement can be achieved by drugs amorphization. However, being a high energy form it usually tends to recrystallize, necessitating new formulation strategy to stabilize amorphous drugs. Polymeric amorphous solid dispersion (PASD) is one of the widely investigated strategies to stabilize amorphous drug, with major limitations like limited polymer solubility and hygroscopicity. Co amorphous system (CAM) is a promising alternate to PASD. CAMs are multi component single phase amorphous solid systems made up of two or more small molecules that may be a combination of drugs or drug and excipients. Excipients explored for CAM preparation include amino acids, carboxylic acids, nicotinamide and saccharine. Advantages offered by CAM include improved aqueous solubility and physical stability of amorphous drug, with a potential to improve therapeutic efficacy.[6]

Numerous lab scale methods are reported for preparation of CAM which can be categorized as thermal (melt quenching) and non-thermal(solvent evaporation and milling) methods. Various properties of drug and excipients like thermal stability, melting point and crystallization tendency influence the selection of preparation method.[6]

In previous research work we were successful in getting co amorphous form of amlodipine besylate (AML) and Atorvastatin calcium (ATR) by rotary flash evaporation technique. We were also able to formulate a stable fast disintegrating tablet of co amorphous system. In continuation, as a comparative study in the present work we have decided to prepare co amorphous forms of AML-ATR by methods such as solvent evaporation and melt quenching techniques. The stability studies of the prepared tablets were extended to a period of 12 months (room condition) and 6 months (controlled condition).

The aim of present research was to prepare co amorphous system of amlodipine besylate (AML) and

atorvastatin calcium (ATR) by different methods and to evaluate stability of drugs when tablets were stored at room condition and under controlled condition.

MATERIALS AND METHOD

Materials: Amlodipine besilate (AML) and Atorvastatin calcium (ATR) were gift samples from Dr. Reddy's Laboratories limited, Telangana (India). Other materials were purchased as follows. Sodium starch glycolate, Magnesium stearate and sodium hydroxide pellets by S.D.Fine Chemical Limited, Mumbai. Crospovidone, Microcrystalline cellulose, and Colloidal silicate from Sigma-Aldrich Corporation, Bengaluru. Potassium dihydrogen phosphate and Potassium bromide (IR grade) by Merck, Mumbai.

Methods

Determination of λmax

Absorption maximum for AML and ATR was determined using UV spectrophotometer by scanning the solution of dug in phosphate buffer pH 6.8 between 200-400 nm.

Calibration curve for AML and ATR

Calibration curve for both the drugs were prepared using phosphate buffer pH 6.8. Absorbances of serially diluted (4-24µg/ml) solutions were measured using UV spectrophotometer at 365 nm for AML and 241 nm for ATR against a suitable blank.

Melting point

Melting point of AML and ATR was determined by capillary method. Small amount of drug was filled in a capillary tube sealed at one end and placed in melting point apparatus. The temperature at which drug melts was recorded. This was repeated three times and average value was recorded.

Solubility studies

The solubility studies were performed using phosphate buffer pH 6.8 by dissolving pure drugs and co amorphous system obtained by all the three method. Saturated solutions were obtained by agitating at a speed of 200 rpm on a rotary shaker for 24 hrs. After 24 hrs, filtered and suitably diluted solutions were analyzed for concentration of AML and ATR using UV spectrophotometer respectively at 365 nm and 241 nm.

FT-IR Study

To study compatibility among the ingredients FTIR study was carried out. 10 mg of sample (pure drug/physical mixtures of crystalline drugs and excipients /physical mixture of co amorphous precipitate and excipients) and 400 mg of KBR were taken and triturated in a mortar. A small amount of the triturated sample was taken into a pellet maker and was compressed at a 10 kg/cm^{2}hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm-1 to 600 cm-1 in FT-IR spectrophotometer (Shimadzu FTIR-8700). The spectra obtained were compared and interpreted for the functional group peaks.[7,8]

Preparation of amorphous precipitate of AML-ATR binary system

Rotary flash evaporation method: Co-amorphous system of AML and ATR were prepared by solvent evaporation technique using methanol as a solvent. A total of 15 g in 10 g of atorvastatin calcium and 5 g of amlodipine besilate were mixed homogeneously and then dissolved in 200 ml methanol. The solvent was evaporated under reduced pressure at 40 °C. The residual solvent left after evaporation was then removed completely by placing the sample under vacuum for 2 days inside desiccator containing CaCO3. The precipitates were stored in desiccator until its use in the formulation.[9,10,11]

Solvent evaporation under room condition: The process is similar to rotary flash evaporation. However, methanol was removed completely by exposing the solution at room temperature for 48 hrs. In brief a total of 1.5 g in 1 g of atorvastatin calcium and 0.5 g of amlodipine besilate were mixed homogeneously and then dissolved in 20 ml methanol.[6]

Melt quenching method: Since the M.P of ATR is higher than AML, former was melted first (1 g). Afterwards AML (0.5g) was added to the cooled melted ATR and heated together until everything was melted. Mixture was stirred till homogeneous; resultant was directly chilled in the freezer. Co amorphous system was sieved through 100 mesh and stored in desiccators.

X-ray powder diffractometry (XRPD)

X-ray powder diffraction patterns were obtained using Rigakuminiflex 600 X-ray diffractometer (Rigaku Co., Tokyo, Japan) for pure AML, ATR, physical mixture of drugs and Co-amorphous form of AML-ATR prepared by different methods. Instrument was operated at 600 watts (X-ray tube), with a fixed tube current of 15 mA and a voltage of 40 kV. The diffracted X-ray beam was monochromated by a graphite monochromator and a standard scintillation counter was used as the detector. Diffraction intensities were measured by fixed time step scanning method in the range of 0–50° (2θ).[12]

Preparation of tablets containing physical mixture of ATR and AML and Co-amorphous AML-ATR by Direct compression

Either physical mixture of drugs or co amorphous AML-ATR, superdisintegrantand other excipients were passed through #80 for further processing. Physical mixture of drugs/ co amorphous binary system, superdisintegrant and MCC were initially mixed in a mortar using pestle for 5 min. To the premixed blend, colloidal silicate was added and mixed for 10 min. After lubricating the blend was compressed into tablets using 8 mm flat faced bevel edged punches. The tablets were compressed keeping the hardness constant.

List of materials and quantities used in different formulations.

Ingredient	Quantity/unit dose (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
*AMR-ATR binary mixture	15	15	15	15	15	15	15	15
Sodium starch glycolate	15	--	15	--	15	--	15	--
Crospovidone	--	15	--	15	--	15	--	15
Microcrystalline cellulose	165	165	165	165	165	165	165	165
Colloidal silicate	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3

Weight of the tablet was maintained constant (200 mg)

*F1 and F2 contained physical mixture of AML (5mg) and ATR (10mg), remaining formulations contained co amorphous precipitate of AML-ATR (AML 5 mg & ATR 10mg).
F3 and F4 co amorphous precipitate prepared by rotary flash evaporation, F5 and F6 by solvent evaporation under room condition and F7 and F8 by melt quenching technique.

Pre – compression parameters.[13,14,15]
Pre – compression parameters like bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose were performed to all the formulations

Post – compression parameters.[7,14,17,18,19]
Thickness: Diameter and thickness of the tablets were measured using Vernier calipers. It is measured in mm.

Weight variation of tablets: The average weight of 20 tablets was determined by individually weighing the tablets. By comparing the individual weights to the average weight, tablet weight variation was determined.

Hardness of tablets: Tablet was placed between the holding anvil and the piston connected to the direct force reading gauge of tester (Pfizer tester). Force was applied to the anvil and the crushing strength (Kg/cm^2) that just causes the tablet to break was recorded.

Friability: Pre weighed tablet sample was placed in the friabilator, which was then operated for 100 revolutions. The tablets were then dusted and reweighed to check the loss in its weight. The friability was calculated using the formula

% friability= 100 X (initial tablet weight- final tablet weight)/initial tablet weight.

Drug content: Drug content was determined by crushing the tablet in a glass mortar and pestle, and extracting the drugs in phosphate buffer pH 6.8 with continuous shaking on a rotary shaker for 24 hrs. The drug content in each extracted fluid was assayed using a UV spectrophotometer at 365 nm and 241 nm against a suitable blank respectively for AML and ATR.

Disintegration Time: The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet is placed in each of the 6 tubes of the basket. A Disc was added to each tube, and experiment done by using Phosphate buffer pH 6.8 maintained at 37±2 °C as immersion liquid. Assembly raised and lowered between 30 cycles. The time taken for tablet to complete disintegration with no palpable mass remaining in the apparatus was measured was recorded in seconds.

Water absorption ratio: A piece of tissue paper folded twice was placed in a small Petri dish Containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

R = (Wa-Wb/Wa)X100
Where,
Wa = Weight of tablet after water absorption
Wb = Weight of tablet before water absorption

Wetting Time: In wetting time a piece of tissue paper folded twice was placed in small petri dish (internal diameter = 6.5cm) containing 10mL of 5% amaranth solution, a tablet was placed on the paper, and the time for complete wetting was measured. Three trails for each batch were performed and standard deviation was also determined.

***In-Vitro* Drug Release:** The *in-vitro* dissolution studies were carried out for the formulations using USP apparatus type II (Paddle type). The dissolution medium used was 900 ml of phosphate buffer of pH 6.8 for 30 mins. The temperature was maintained at 37 °C ± 0.5 °C and the stirring rate was 50 rpm. 5ml of samples were withdrawn at intervals of 5 minutes till 30th minutes; the same volume was replaced with freshly prepared pH 6.8 phosphate buffer. The samples were measured by UV Spectrophotometer at 365 nm and 241 nm against blank for AML and ATR respectively. The release studies were conducted in triplicate and the mean values were plotted versus time.

Storage and aging study: Storage and aging study was carried out to evaluate the stability of formulations.Tablets containing co amorphous AML-ATR were stored for 12 months at room condition and at controlled conditions of relative humidity (RH) &

temperature (RH 75% ± 5%, 40°C ± 2 °C) for 6 months. At the end of 4, 6 and 12 months tablets stored at room condition and at the end of 2, 4 and 6 months tablets stored at controlled conditions were evaluated for physical properties and *in vitro* drug release.[20]

RESULT AND DISCUSSION

Determination of λmax

The λmax of ATR was found to be 241 nm. The AML exhibits two λmax at 239 nm and 365 nm. Both the peaks were distinct but in order to avoid the absorbance interference of ATR with AML and visa-versa, 365nm was selected as λmax for the analysis of formulation.

Calibration curve for AML and ATR

The values of regression coefficient were found to be 0.9994 and 0.9998 for AML and ATR respectively which showed linear relationship between concentration and absorbance. The standard calibration cures of both AML and ATR were obeyed Beer's law at the given concentration range of 4 to 24 µg/ml in phosphate buffer of pH 6.8.

Melting point

The melting point of AML and ATR was found to be in the range of 178-179 °C and 159.2-160.7°C respectively.

Solubility studies

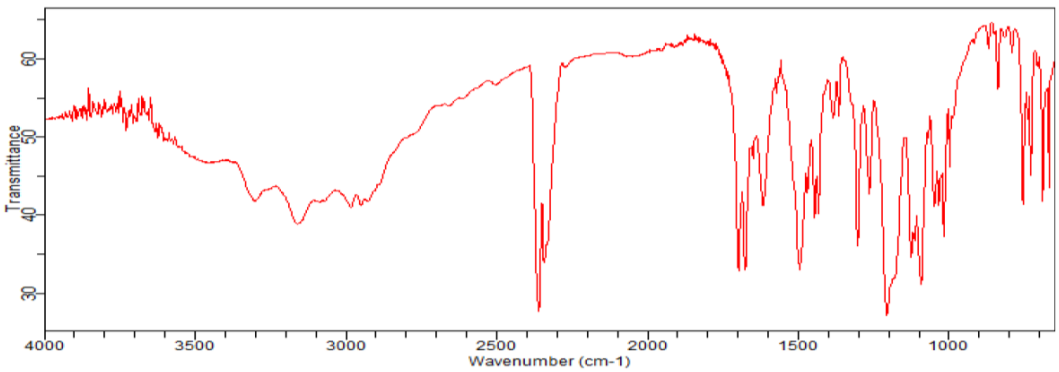
Solubility of pure drugs and prepared co-amorphous systems are given below.

Physical form of AML	Solubility (µg/ml)	Physical form of ATR	Solubility (µg/ml)
Crystalline solid	357.61	Crystalline solid	100.14
Co-amorphous form (RFE)	498.24	Co-amorphous form (RFE)	189.53
Co-amorphous form (SE)	532.72	Co-amorphous form (SE)	192.48
Co-amorphous form (MQ)	584.4	Co-amorphous form (MQ)	197.65

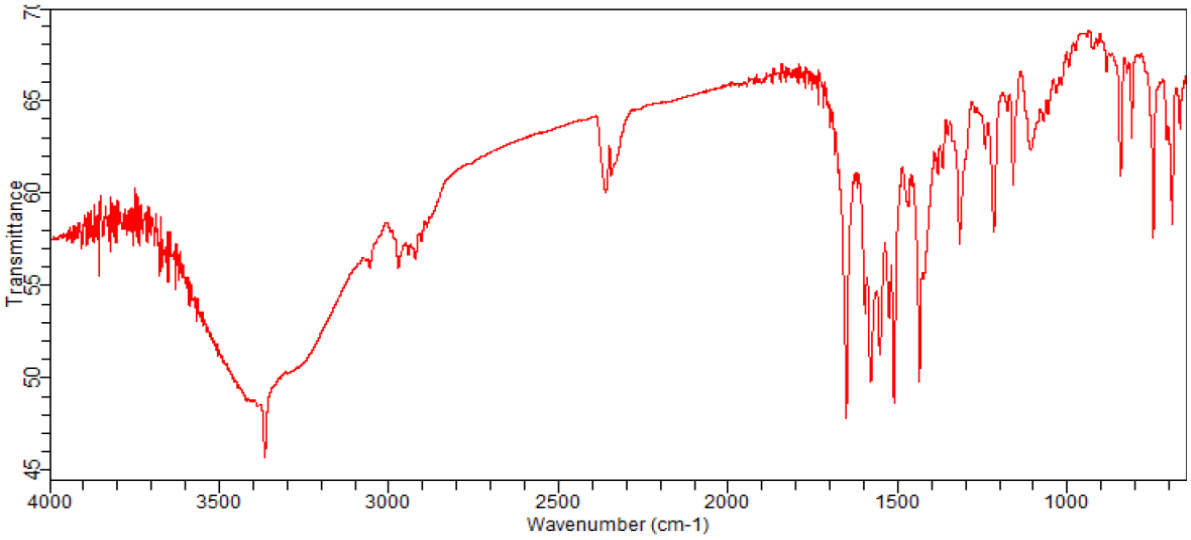
The saturation solubility of crystalline AML and ATR in phosphate buffer (pH 6.8 at 37 °C) was found out to be 357.61 µg/ml and 100.14 µg/ml, respectively. Enhancements in the saturation solubility of the individual component as compared to their crystalline counterparts were reported in the binary amorphous systems.

FT-IR Study

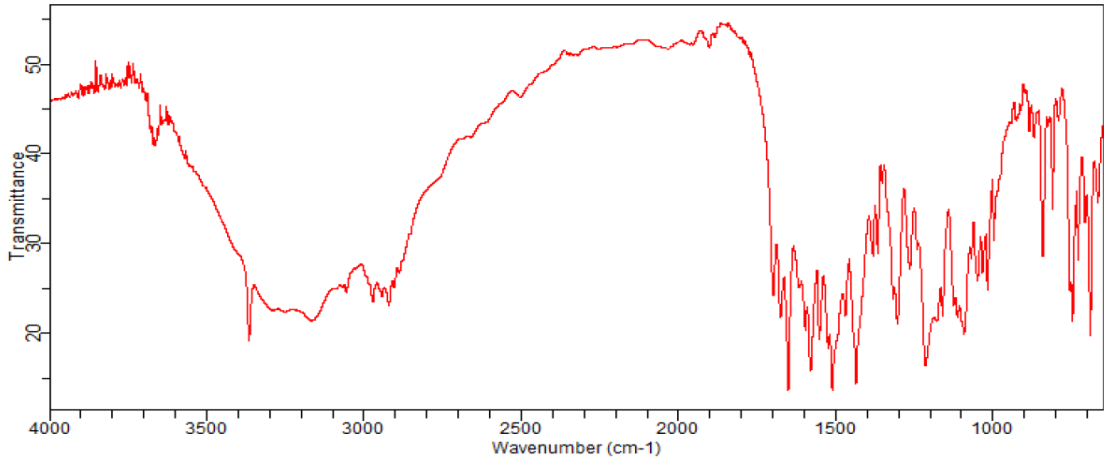
AML showed strong peaks at 3297, 3158-2982, 1676, 1614-1493, 1207, 1095, 995, and 755-730 cm-1 which are attributes N-H stretching, C-H stretching, C=O stretching, aromatic C=C stretching, C-O stretching and S=O stretching, C-O-C stretching, C-Cl stretching, and aromatic C-H bending respectively. Whereas for ATR at 3381, 2992-2900, 3670, 3055, 1662, 1595-1531, 1157, 1213, 1224 and 843-753 cm-1 for N-H stretching, C-H stretching, free O-H stretching, O-H stretching, C=O stretching, aromatic C=C stretching, C-N stretching, C-O stretching, C-F stretching, and aromatic C-H bending. In order to detect the interaction between the ingredients, the individual spectrum of each drug was compared with the spectrums that of physical mixture of AML-ATR, Co-A AML-ATR with formulation blend. FT-IR spectroscopic studies revealed the compatibility among the ingredients.



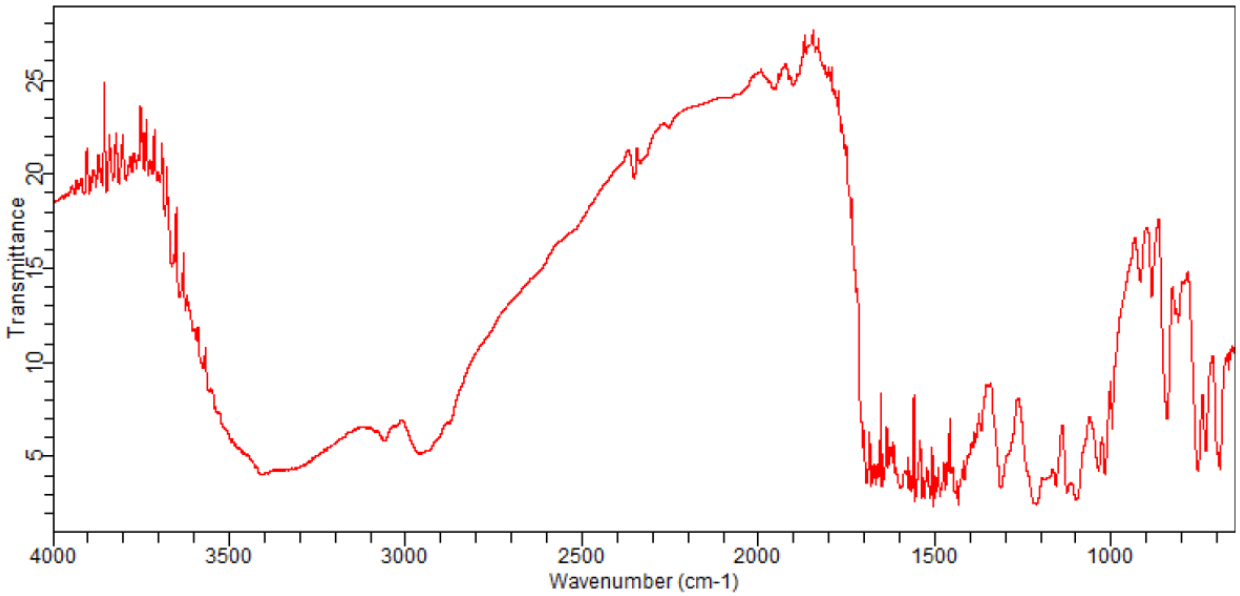
FTIR spectrum of Amlodipine besilate



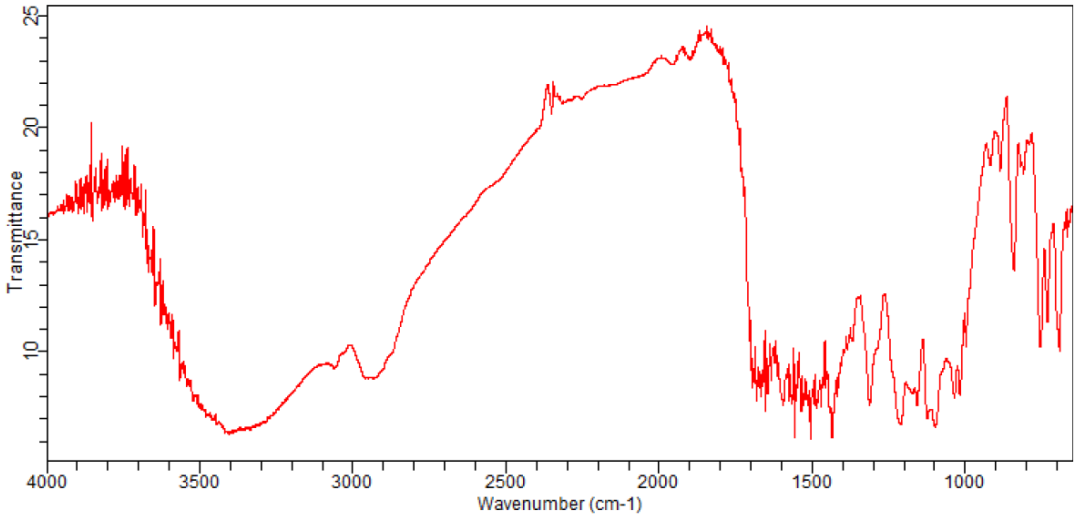
FTIR spectrum of Atorvastatin calcium



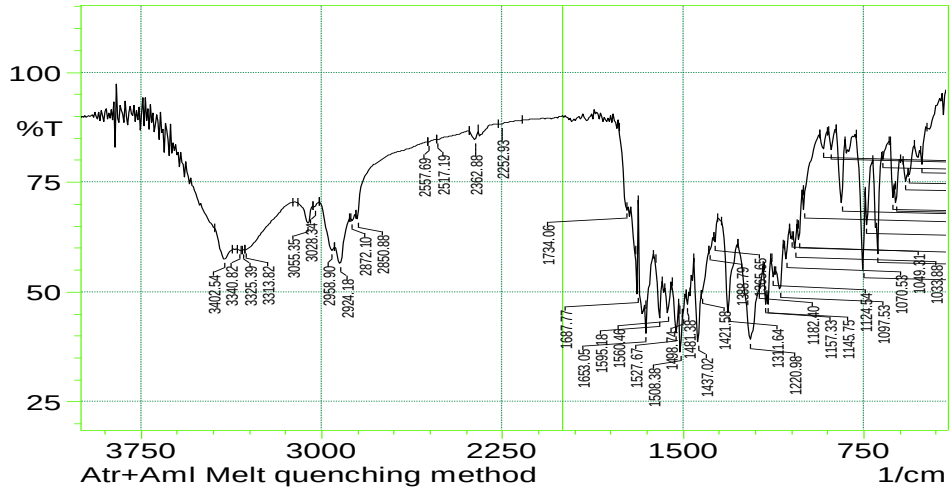
FTIR spectrum of physical mixture of Amlodipine besilate and Atorvastatin calcium with formulation blend



FTIR spectrum of Co-amorphous AML-ATR with formulation blend (Rotary Flash Evaporation method)



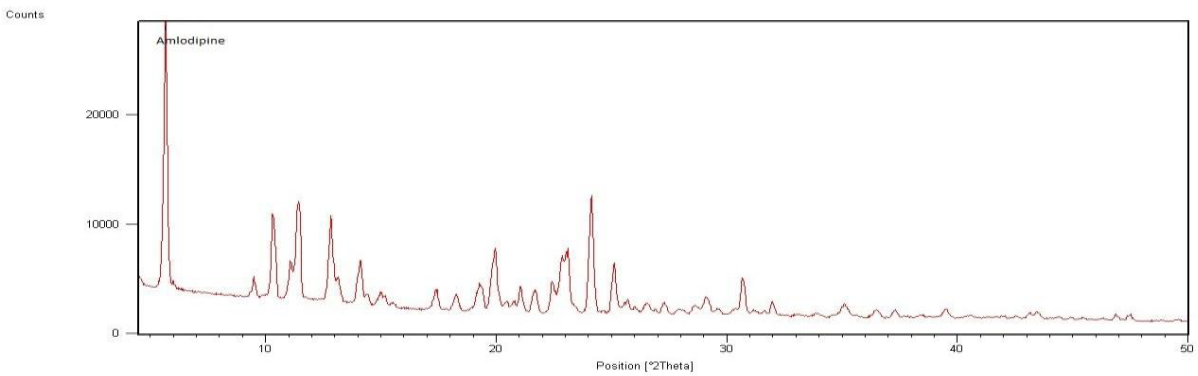
FTIR spectrum of Co-amorphous AML-ATR with formulation blend (Solvent Evaporation method)



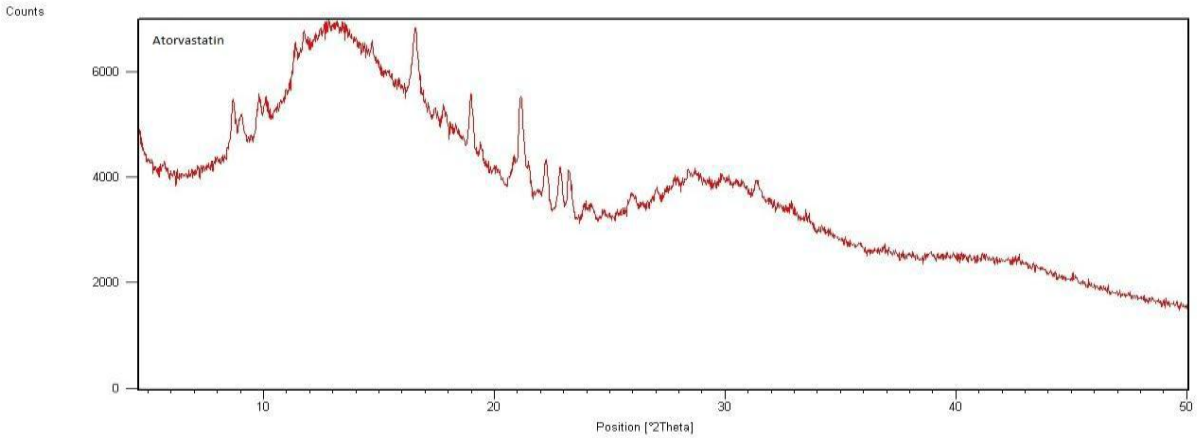
FTIR spectrum of Co-amorphous AML-ATR with formulation blend (Melt quenching method)

X-ray powder diffractometry (XRPD)

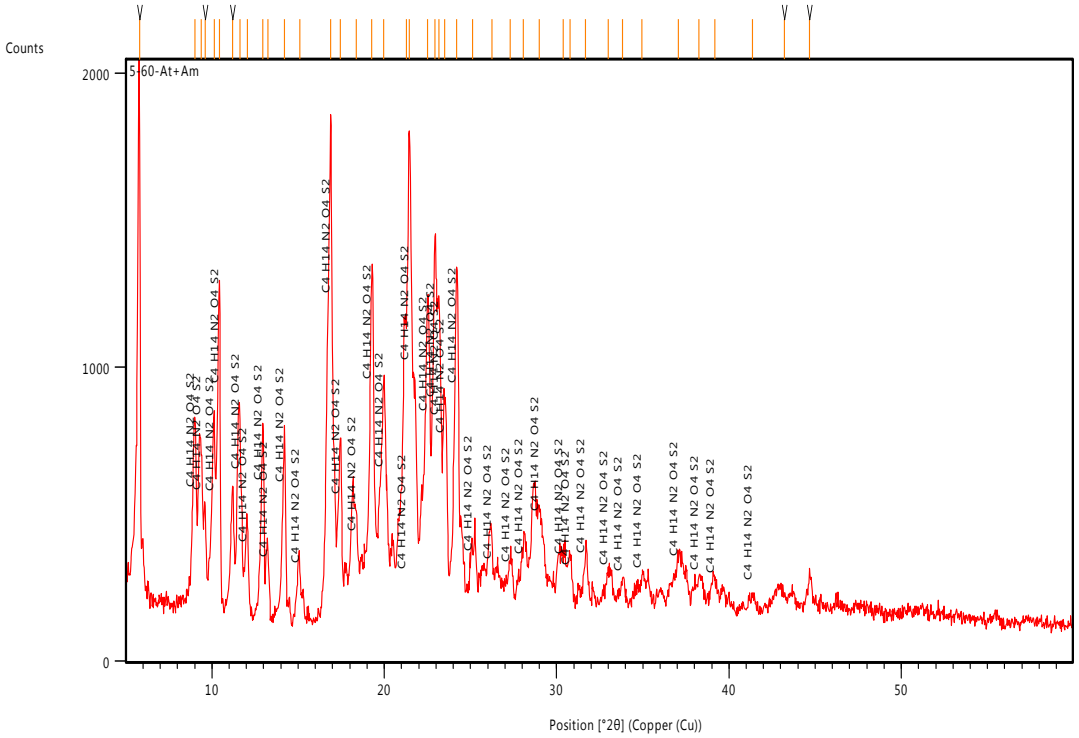
To characterize the presence of amorphous material, XRPD is considered as a gold standard method. XRPD does not detect the presence of amorphous form per say but instead detects the absence of crystallinity in the samples. Absence of crystallinity can be confirmed by spotting the halo pattern in the diffractogram. Crystalline AML, ATR and their physical mixtures show number of peaks in diffractogram, which confirms the crystalline nature of drugs and their physical mixture. For the precipitated amorphous samples, the XRPD patterns show the typical halo (absence of crystalline peaks) suggesting amorphousness.



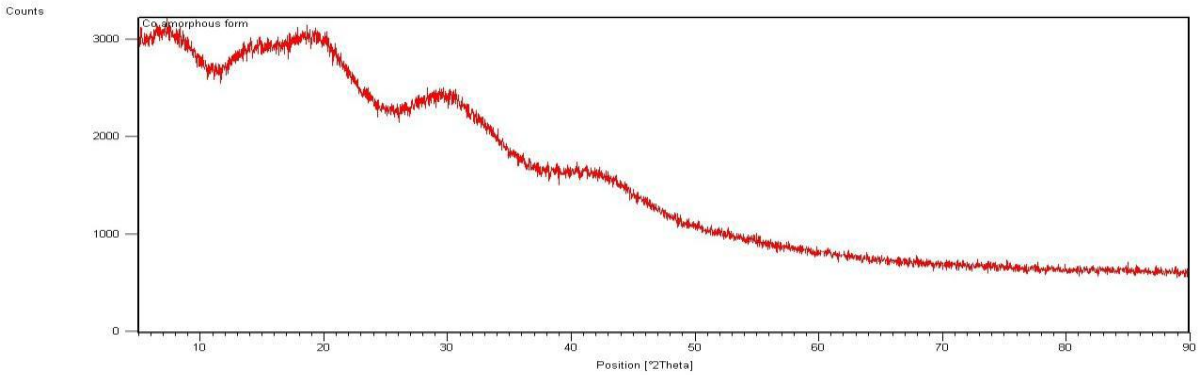
X-ray powder diffractometer of Amlodipine



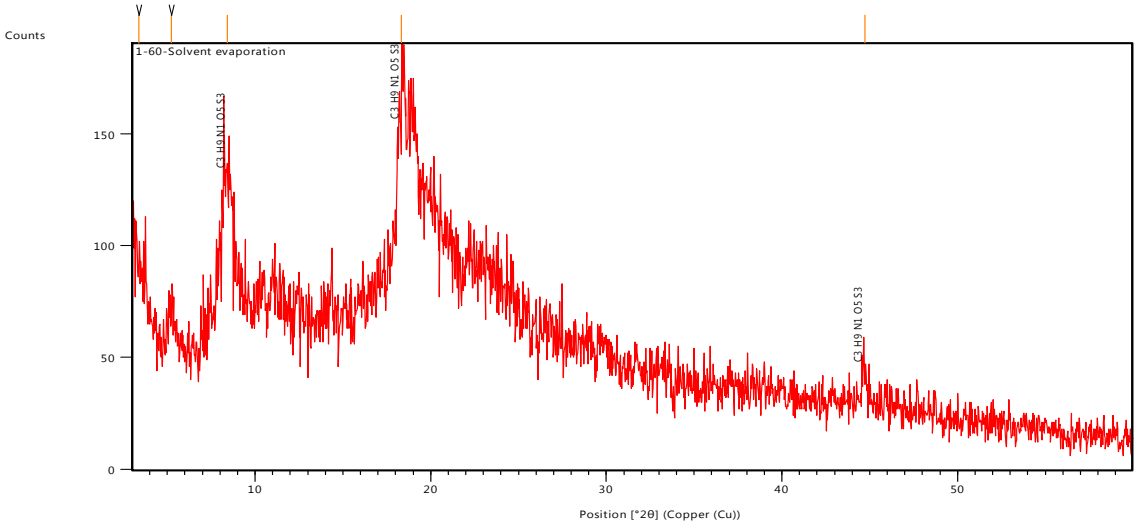
X-ray powder diffractometer of Atorvastatin.



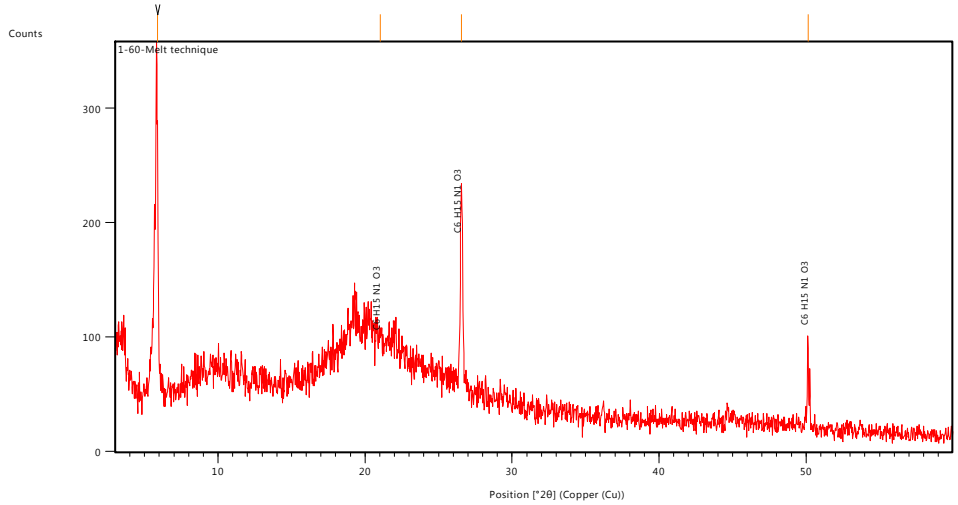
X-ray powder diffractometer of Amlodipine and Atorvastatin physical mixture.



X-ray power diffractometer of Co-amorphous AML-ATR (Rotary flash evaporation method).



X-ray power diffractometer of Co-amorphous AML-ATR (Solvent evaporation method).



X-ray power diffractometer of Co-amorphous AML-ATR (Melt quenching method).

Physical evaluation of co amorphous precipitate and tablets

Formulations were prepared by co amorphous precipitates obtained by three different methods, rotary flash evaporation, solvent evaporation and melt quenching. Tablets were prepared using sodium starch glycolate or cross povidone as superdisintegrants.

The prepared tablets showed a friability of < 1% and hardness was in the range of 5.42-6.89 kg/cm^2. Drug content of all the formulations was in the range of 99.01±0.7 to 101.3±0.4% (AML) and 96.83±0.5 to 102.2±0.45% (ATR). The weight variations among the prepared tablets were in pharmacopoeial limits. Angle of repose for co amorphous precipitates was found to be in the range of 25.43 to 27.73 degrees, indicating a good flow character of the precipitates.

Wetting time, water absorption ratio (%) and disintegration time

Formulation code	Wetting time (sec)	Water absorption ratio (%)	Disintegration time (sec)
F1 (PM- SSG)	16.6±0.721	50.2±0.655	23.66±0.59
F2 (PM-CP)	15.23±0.20	51.56±0.45	21.10±0.75
F3 (RFE-SSG)	14.56±0.737	58.06±0.404	18.06±0.21
F4 (RFE-CP)	12.56±0.602	59.03±0.25	15.53±0.55
F5 (SE-SSG)	12.93±0.650	58.56±0.50	17.93±0.70
F6 (SE-CP)	11.73±0.404	59.26±0.41	15.05±0.31
F7 (MQ-SSG)	13.97±0.650	53.96±0.25	17.06±0.25
F8 (MQ-CP)	12.43±0.55	56.1±0.264	16.60±0.40

Tablets containing CP wetted and disintegrated rapidly than that containing SSG. Also, % water absorption was greater in CP tablets than SSG tablets. However, co amorphous dispersion tablets showed shorter wetting and disintegration time and higher % water absorption than tablets containing physical dispersion.

***In-Vitro* Drug Release**

Tablets containing co amorphous AML-ATR showed higher drug release than that containing physical mixture of AML and ATR. It remained same irrespective of method used in the preparation of co amorphous binary mixture. Among the methods, drug release was high with rotary flash evaporation than solvent evaporation and melt quenching. (Figure 1-4)

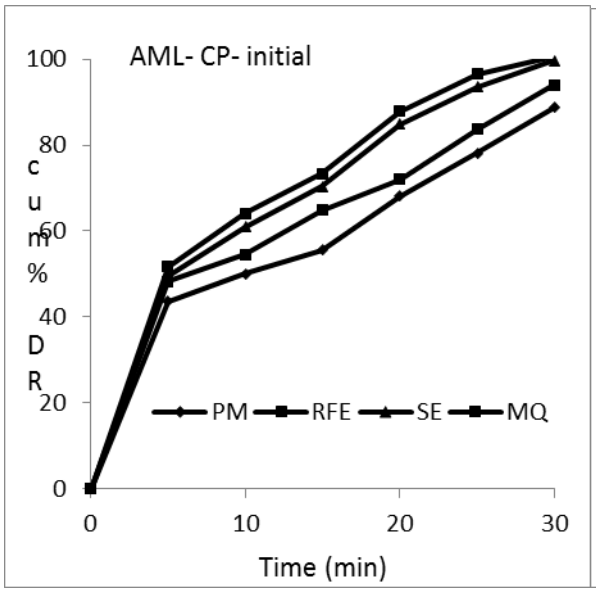


Figure 1:

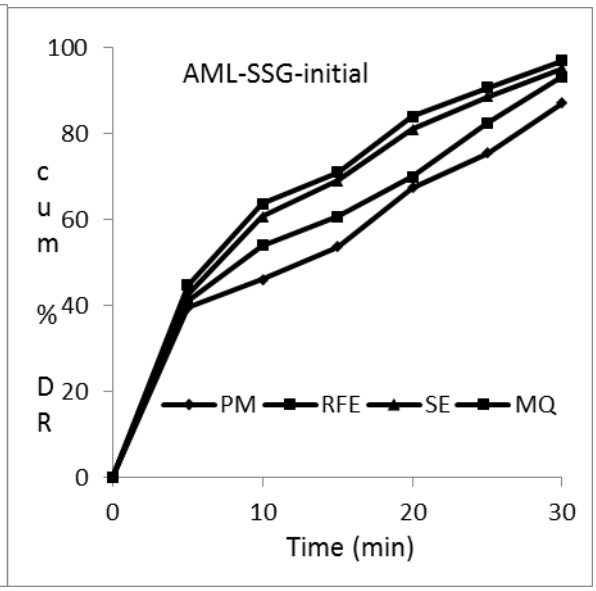


Figure 2:

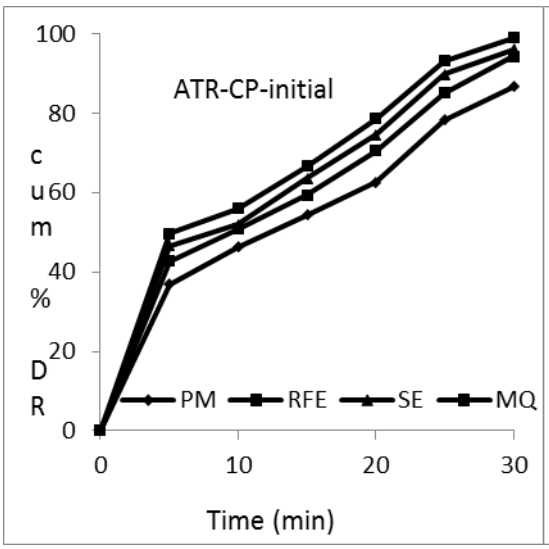


Figure 3:

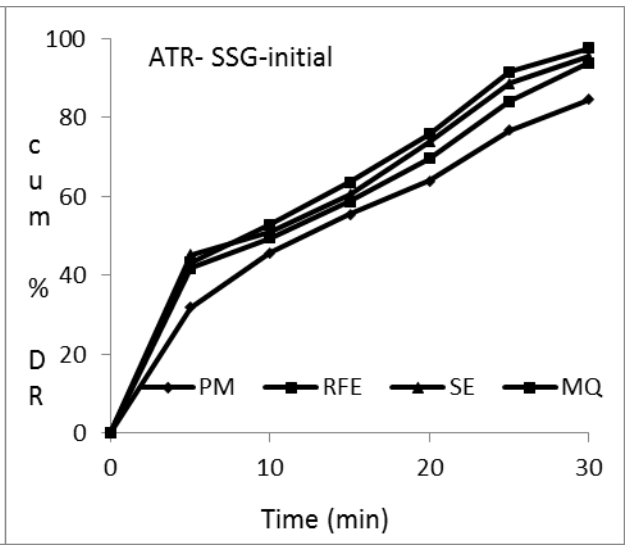


Figure 4:

Storage and aging study

Hardness of the stored tablets was in the range of 5.87-6.27 kg/cm^2. Drug content of all the formulations was in the range of 98.52±0.4 to 102.8±0.8% (AML) and 97.65±0.7 to 101.6±0.3% (ATR). No major changes were observed with respect to *in vitro* dissolution pattern for tablets stored at room condition (Figure 5-16) or at controlled condition (Figure 17-28) during the stated storage period.

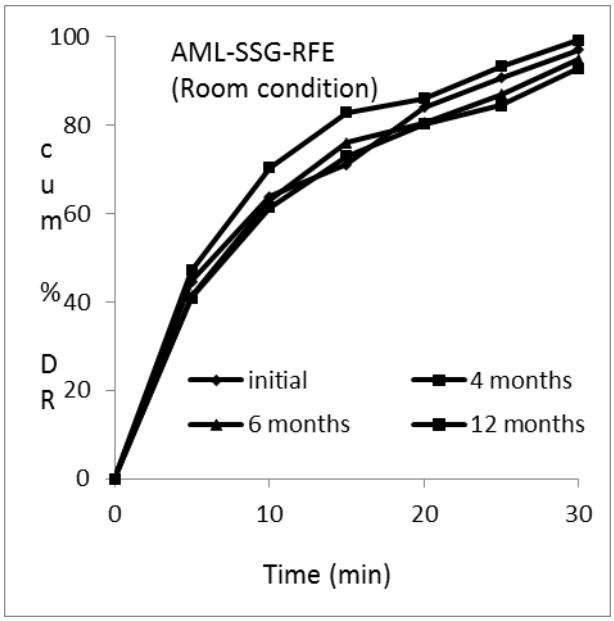


Figure 5:

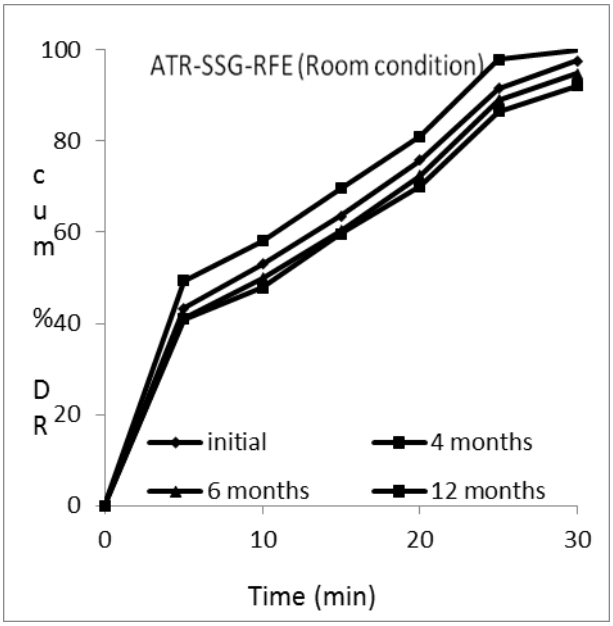


Figure 6:

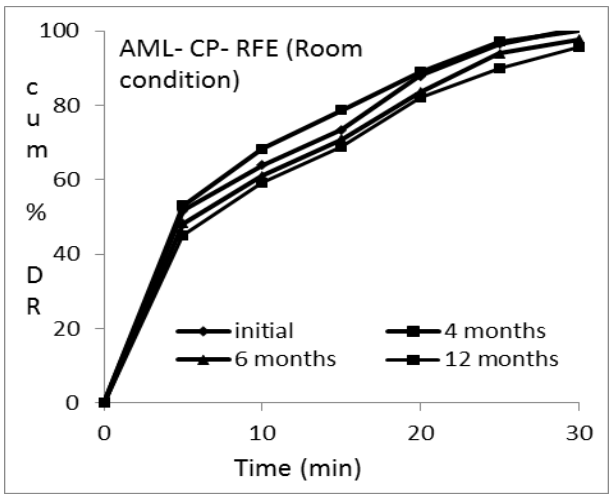


Figure 7:

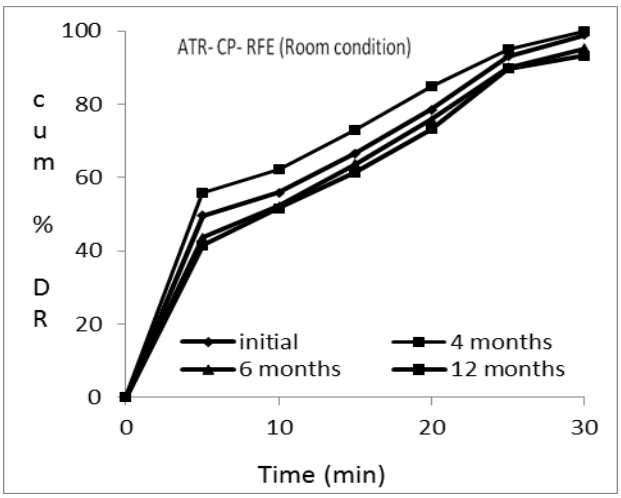


Figure 8:

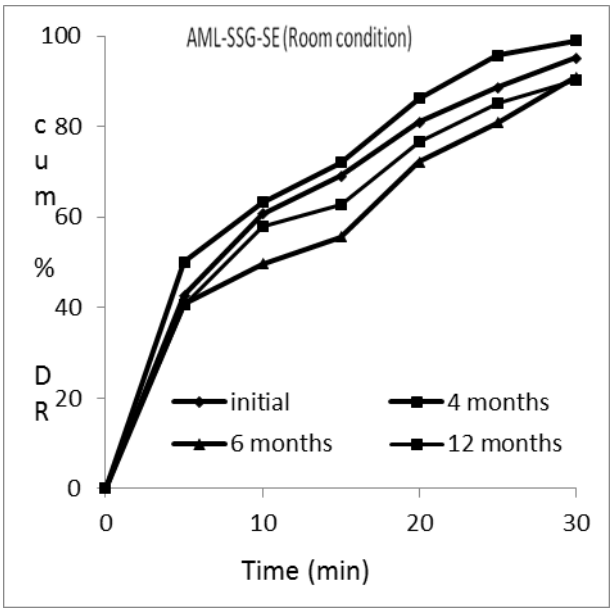


Figure 9:

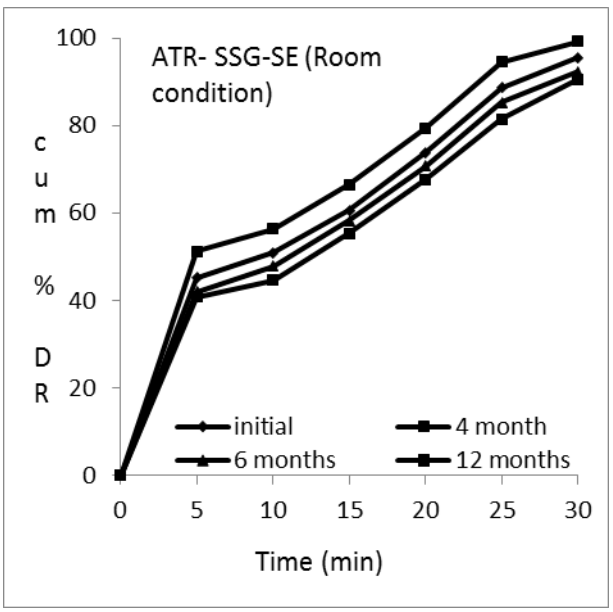
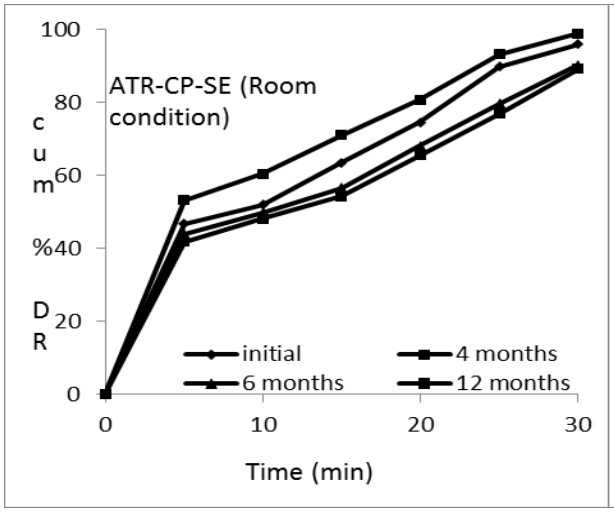


Figure 10:



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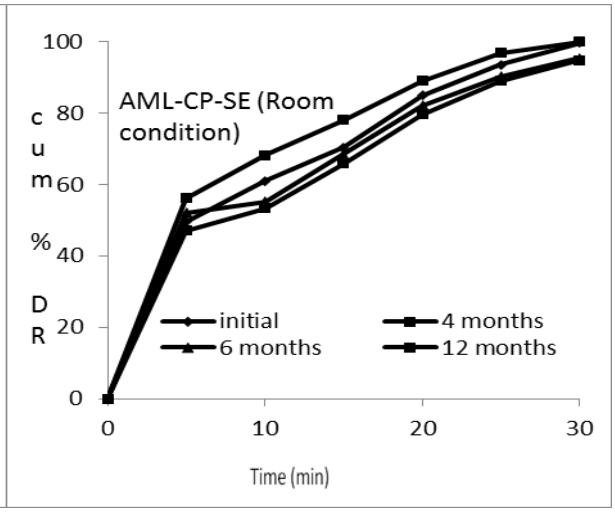

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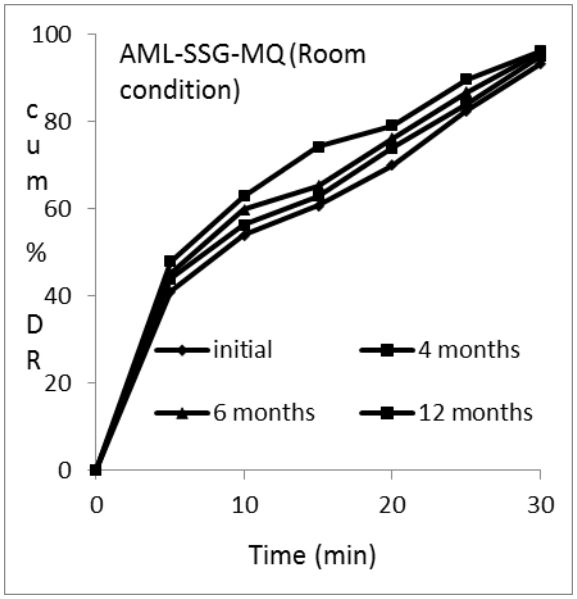

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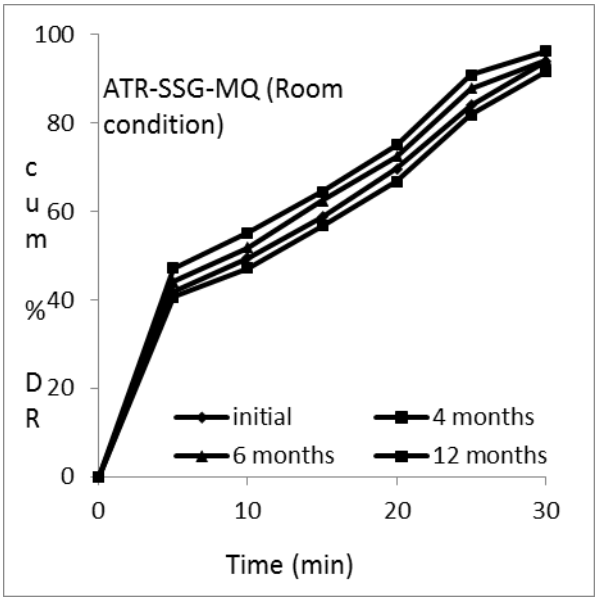

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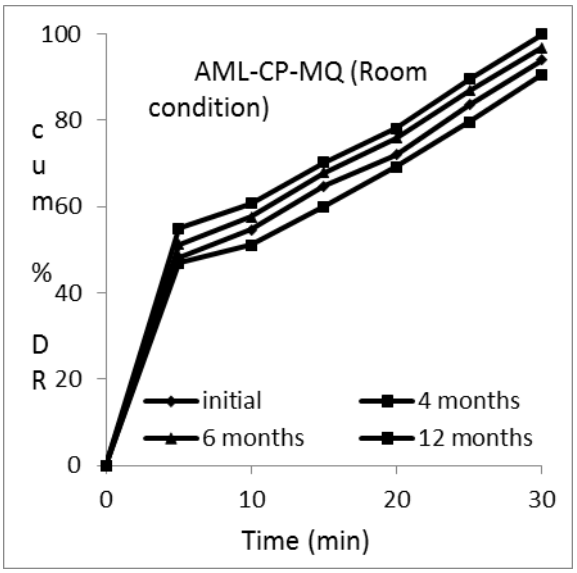

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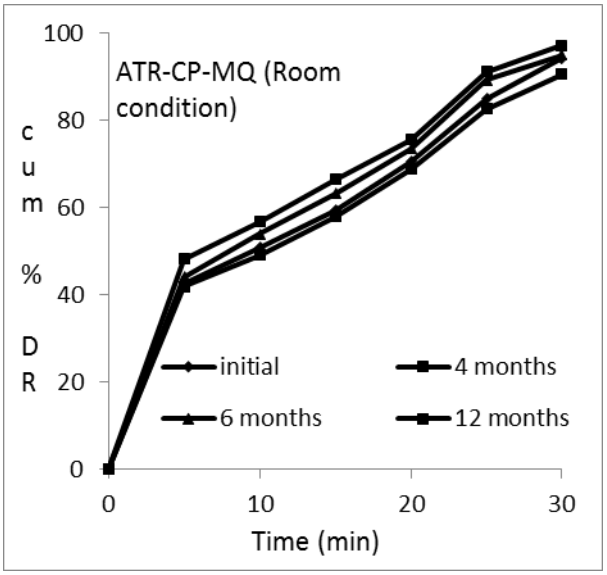

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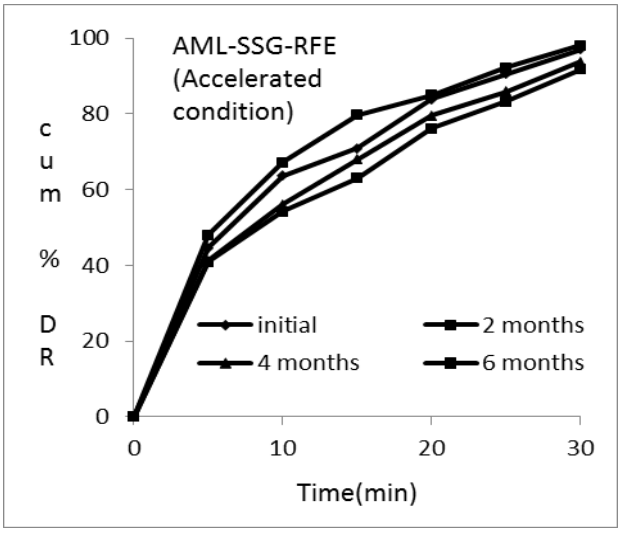

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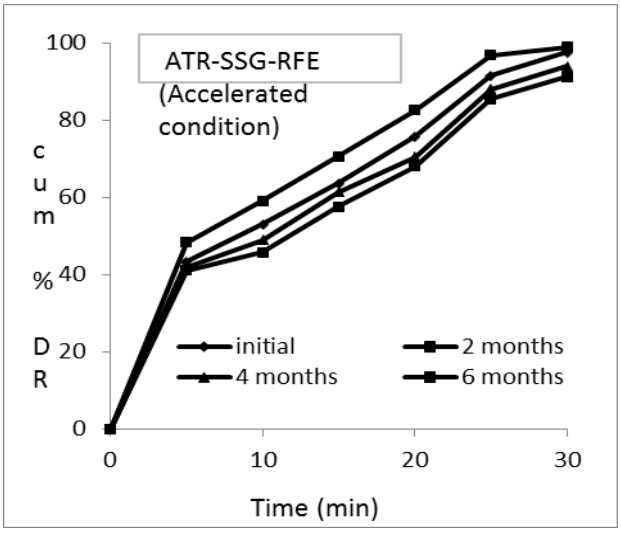

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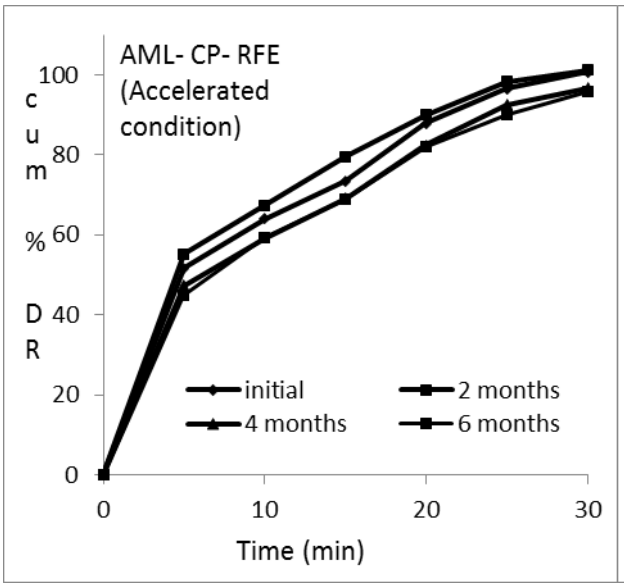

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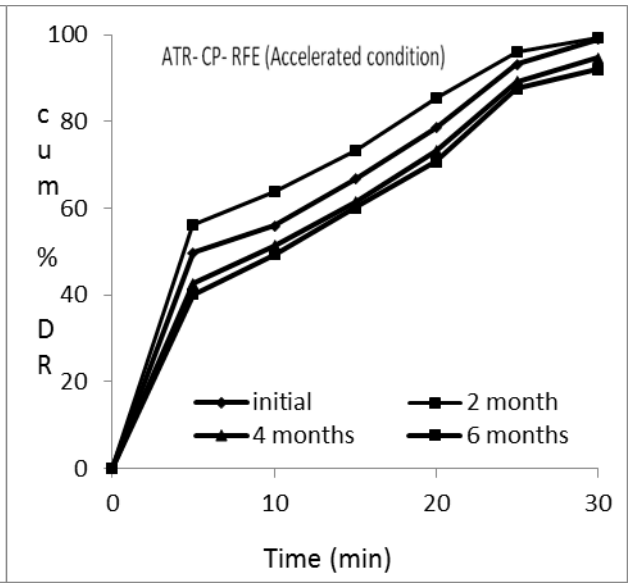

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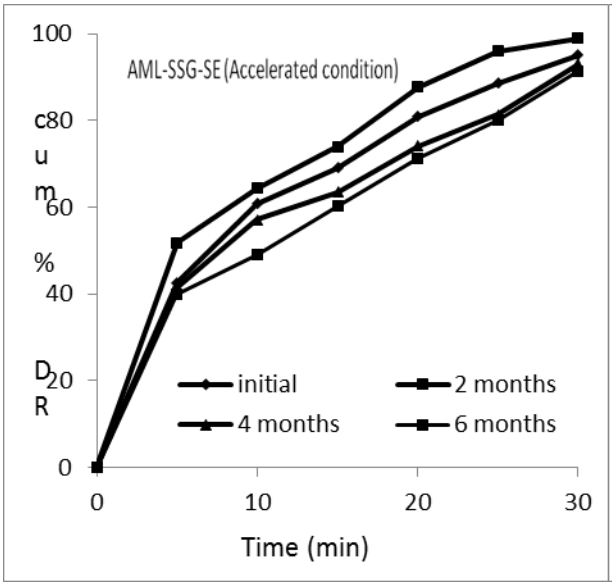

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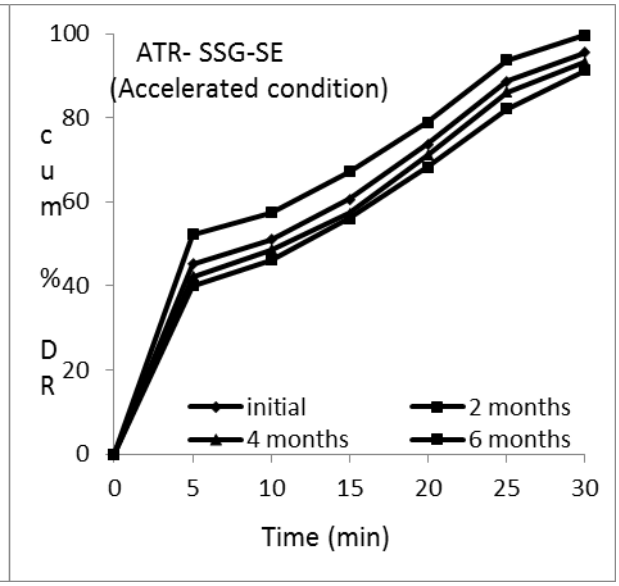

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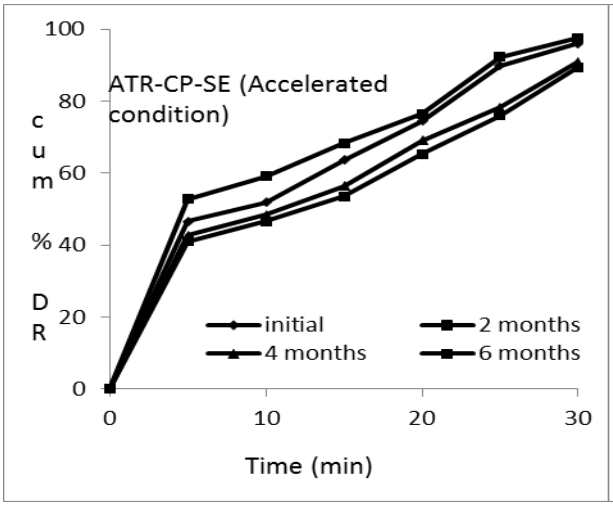

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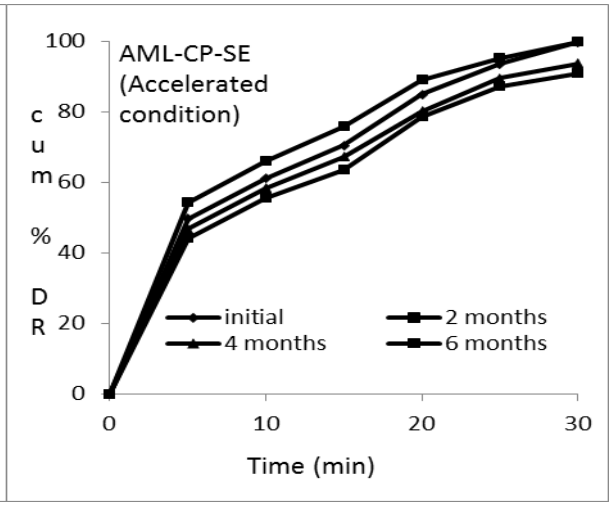

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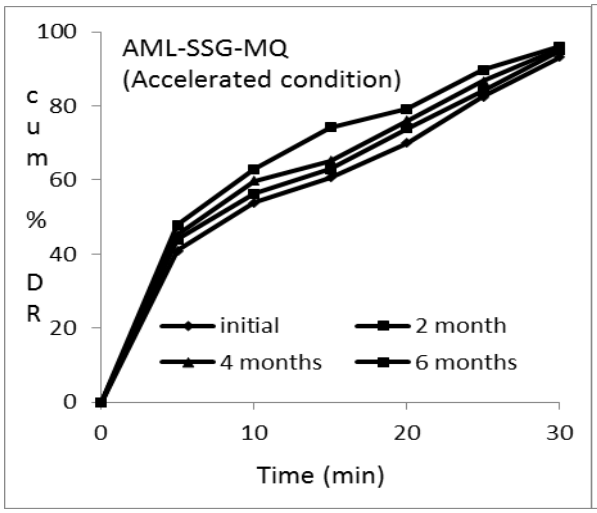

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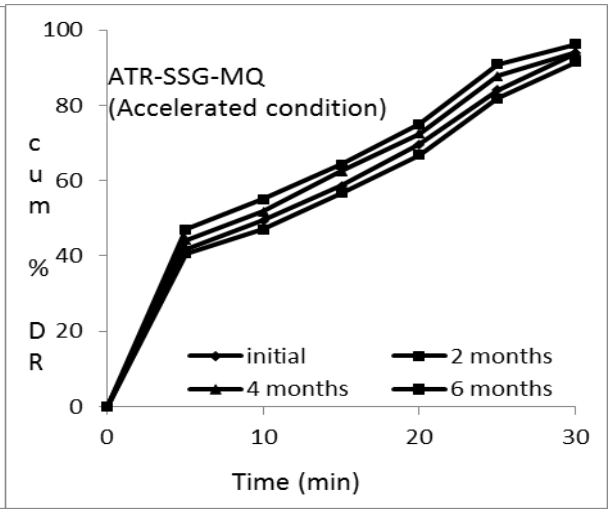

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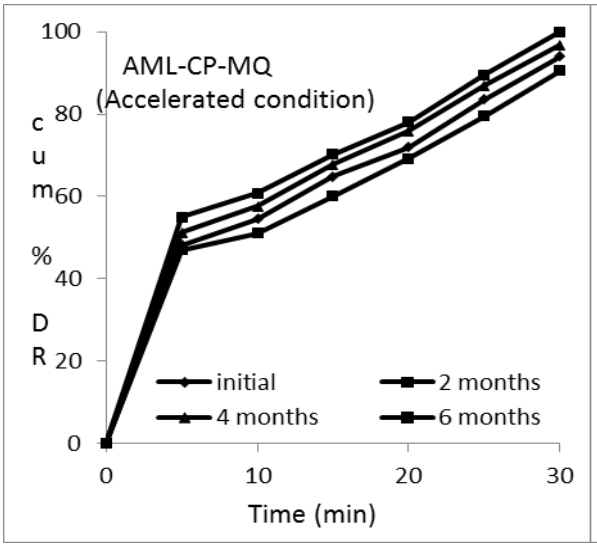

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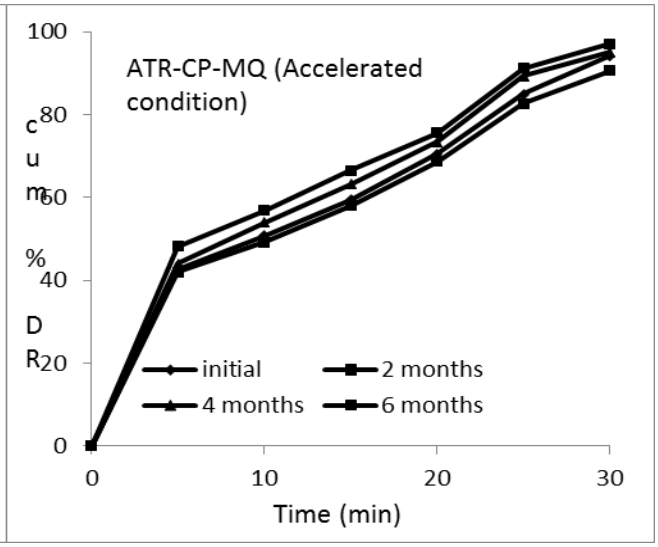

Figure 28:

CONCLUSION

Both AML and ATR were successfully converted into amorphous form by rotary flash evaporation, solvent evaporation under room condition and melt quenching techniques. The amorphous form was confirmed by detection of halo pattern in XRPD studies. All the methods of amorphization have resulted in increased solubility of BCS class II drugs. Compatibility among

the API's and API's with formulation blend was established by FTIR studies. Irrespective of method of amorphization, cumulative % drug released was higher from amorphous formulations in comparison to their crystalline counterparts. Tablets containing amorphous drugs prepared by rotary flash evaporation wetted and disintegrated quickly and released higher amounts of drugs than tablets containing amorphous drugs prepared by solvent evaporation under room condition than that of melt quenching. However, drugs maintained their stability in amorphous state in their final formulation under the tested conditions.

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