Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Research Article **DOI: 10.26479/2023.0904.01**

FORMULATION AND EVALUATION OF DRUG-DRUG COCRYSTALS TO IMPROVE BIOPHARMACEUTICAL PROPERTIES OF DRUG(S)

Arpana Patil[1]*, Nitin Khandagale[1], Vishal Zambre[2]

1. Department of Pharmaceutics, Smt. Kashibai Navale College of Pharmacy, Kondhwa, (Bk), Pune.
2. Department of Pharmaceutical Chemistry, Smt. Kashibai Navale College of Pharmacy, Kondhwa, (Bk), Pune.

ABSTRACT: Drug - drug co-crystallization is proposed as a new method to improve the solubility and hence the bioavailability of drugs. The drug-drug cocrystals batches of atorvastatin and aspirin were successfully synthesized by neat grinding (NG) , liquid assisted grinding (LAG) and solvent evaporation (SE) method. The FDC were selected based on their ability to form hydrogen bonding by molecular docking. The docking outcome indicated the possibility of 1 hydrogen bond between both drugs and cocrystals were optimized for its physicochemical characterization. The physicochemical properties were characterized by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and powder X-ray diffractometry. Permeability of the cocrystals were evaluated by using everted gut sac method. Compared to pure Atorvastatin, Aspirin the drug- drug cocrystal displayed a 10 , 2 -fold increase in solubility and a 2-fold increase in dissolution profile. Improved permeability of the drug is attributed to drug – drug interaction. This study showed the utility of the co-crystallization approach to improve bioavailability of both drugs. Further in this study sublingual tablet dosage form was made and in vitro dissolution study was performed.

Keywords: Drug-Drug Cocrystal, Solubility, Bioavailability**,** Molecular docking.

Article History: Received: June 28, 2023; Revised: July 06, 2023; Accepted: July 20,2023.

Corresponding Author: Dr. Arpana R. Patil

Associate Professor, Department of Pharmaceutics, Smt. Kashibai Navale College of Pharmacy, Kondhwa, Pune – 411048. Email Address: drarpanarpatil@gmail.com

1.INTRODUCTION

Pharmaceutical co-crystallization is a feasible approach to modify and enhance physical and chemical properties of drugs such as solubility, dissolution rate, permeability, stability and compressibility without altering their pharmacological activity. Cocrystal consists of two or more neutral molecular components in a crystal lattice with well- defined stoichiometric ratio. Formation of cocrystal mainly depends on functional group of APIs and co-formers to allow for the formation of hydrogen bonds or other weak type of interactions, mainly hydrogen bonding. The basis for co-formers selection is its ability to form non - covalent interactions especially hydrogen bonds with an APIs. There are various approaches proposed for the selection of co-formers such as supramolecular synthon approach, Hansen solubility parameter, pKa based, lattice energy calculation, hydrogen bonding propensity and molecular docking. Atorvastatin is the HMG CoA reductase inhibitor which acts as lipid lowering agent and it belongs to BCS class II having low solubility and high permeability.[1],[2],[3] Atorvastatin undergoes rapid absorption when taken orally, with an approximate time to maximum plasma concentration (T_{max}) of 1–2 h. The absolute bioavailability of the medication is about 14%, but the systemic availability for HMG-CoA reductase activity is approximately 30%. Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability. Aspirin, also known as acetylsalicylic acid (ASA), is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce pain, fever, and/or inflammation, and as an antithrombotic. Aspirin is also used long-term to help prevent further heart attacks, ischaemic strokes, and blood clots in people at high risk. It belongs to BCS class I having high solubility and high permeability. Atorvastatin's poor aqueous solubility is one of the main arising problems in drug research and development because about 40% of the new available marketed immediate release oral drugs are practically insoluble. Dissolution rate of the drug is critically determined by its water solubility. The limited aqueous solubility limits the dissolution rate, absorption and bioavailability of orally administered drugs. In such situation, there is need to augment the dose of drug in order to achieve the therapeutic drug concentration in blood. Crystal engineering enhances the solubility and dissolution rate of drug by a number of ways depending upon the molecular characteristics of active pharmaceutical ingredients and crystallization process.[4],[5] To overcome the problems associated with the solubility and hence the bioavailability drug-drug cocrystals approach is used in which the atorvastatin is screened with aspirin by molecular docking and hydrogen bonding propensity and negative binding energy is checked and as per the docking results the combination is finalized for the further study. Drug-drug cocrystals could offer potential advantages of synergistic and/or additive effects enhanced solubility and dissolution of at least one component, enhanced bioavailability possible stabilization of unstable components through intermolecular interactions.[6],[7],[8],[9].

2. MATERIALS AND METHODS

Materials:

Atorvastatin calcium was kindly gifted by Ajanta pharmaceuticals Ltd. Aspirin was purchased from Research Lab Fine Chem Mumbai ,All required solvents and excipients were purchased from Research Lab Fine Chem, Mumbai. Molecular docking was performed by using Auto Dock vina software.

Methods:

The Atorvastatin calcium and Aspirin were selected based on the fixed dose combination available in market and checked for their potential to form hydrogen bonding to form cocrystal based on number of hydrogen bond formation and bond energy.

Hardware and Programs:

A personal computer equipped with Intel Core i5 2.5 GHz processor DRAM 8 GB was used in this work. Open Babel GUI 2.2.3 was the program used for the initial preparation of the ligands and Auto Dock software was used for the docking process.

Molecular Docking:

2D structures of FEX (PubChem CID: 63002) and its co-formers in. mol formats were downloaded from https://pubchem.ncbi.nlm.nih.gov. All. mol files of the molecules were converted into. pdb files by employing Open Babel GUI 2.2.3. The files were then opened in Auto-Dock 4.2.3 and converted into. Pdbqt files by adding polar hydrogen and Kollman charges. The. pdbqt files were converted into. pdbqt by calculating their torsion angles and were ready to be used for docking. Docking was done with each co-former and the parameters observed were the type and energy (Ei) of interactions.

Preparation of Drug-drug Cocrystal:

Cocrystals of Atorvastatin calcium prepared with Aspirin as co-former were developed using three methods; neat grinding method , liquid assisted grinding method and solvent evaporation.

1) Solvent evaporation:

Solvent evaporation method was performed to synthesize the drug-drug cocrystals using petri-plate and methanol as a solvent. An equimolar ratio of both APIs ratios (1: 1, 1: 2 , 1: 3 & 1: 4) dissolved in methanol and kept to evaporation at room temperature for 3-4 days.[10],[11]

2) Neat grinding method:

Neat grinding method was employed for the preparation of ATOR:ASP cocrystals. Drug and co-former were weighed, mixed in different molar ratios (1: 1, 1: 2 , 1: 3 & 1: 4) and grounded well in mortar and pestle for 50 minutes to form cocrystals.

3) Liquid assisted grinding:

In liquid assisted grinding method, ATOR and ASP were weighed, mixed in different molar ratios (1: 1, 1: 2 , 1: 3 & 1: 4) using drops of methanol prior to the grinding process. The mixture was

grounded well in mortar and pestle for 40 minutes to form cocrystals.

Characterization of cocrystals:

The prepared cocrystal in the present research work was preliminary confirmed by comparing results of scanning electron microscopy (SEM), infra-red (IR) spectroscopy, differential scanning calorimetry (DSC) and x-ray diffraction (XRD) crystallography of developed cocrystals with ATOR and ASP as a co-former. In-vitro dissolution and ex-vivo permeation studies were also carried out to ascertain the drug release.

Scanning electron microscopy:

The surface morphology of pure ATOR, ASP and optimized batch were examined using a scanning electron microscope (Nova Nano SEM 450). The powder sample was directly sprinkled over the double-sided adhesive tape that was attached to an aluminium stub that had been coated with platinum (about 5 nm thick) and made electrically conductive by keeping them in a vacuum for 100 s at 30 W. To examine the surface properties, samples were examined using a scanning electron microscope, and micrographs were captured at various magnifications.[12],[13]

Infrared spectroscopy:

Infrared spectroscopy was employed to determine the possible interaction between drug and co-former. The samples were dispersed in KBr pellet and scanned using PerkinElmer IR spectrophotometer between 4000 - 400 cm^{-1} with resolution of 4 cm^{-1}. [14],[15]

Differential Scanning Calorimetry (DSC):

DSC was performed on calorimeter (DSC-60, Shimadzu, Japan) instrument having software TA-60 and an empty standard aluminium pan were used as reference. DSC scans were recorded at heating rate of 10 ^{o}C / min in temperature range 30-300 ^{o}C, DSC measurements were carried out on prepared ATOR:ASP cocrystal.

X-ray diffraction (XRD) study:

Powder X-ray diffraction pattern of pure ATOR, ASP and cocrystal batch was investigated using (Bruker D8 Advance Diffractometer) instrument. The instrument was supplied with a fine focus X-ray tube and each sample was placed on to a goniometer head that was motorized to permit spinning of the sample during data acquisition.

Ex - vivo permeation study using everted gut sac method:

To understand the absorption mechanism of ATOR, ASP and ATOR-ASP cocrystal, everted gut sac studies using goat intestinal segment were performed. The small intestine with jejunum part was identified, segment was then isolated and transferred to a petri dish containing phosphate buffer 6.8 medium where it was thoroughly cleaned. The cleaned intestine was carefully everted using a glass rod and the jejunum section of the everted intestine was then cut into 3 cm pieces. One end was tied with a thread and from another end dissected butterfly needle was inserted and tied to form a gut sac. 2 mL phosphate buffer pH 6.8 was filled into the gut sac through the inserted dissected

butterfly needle. At a time, equal to zero, the everted intestinal sac was incubated in the predetermined volume (50 ml) of experimental test solution. The experimental solution was continually aerated and maintained at 37 ^{o} C. At predetermined time intervals (0, 15, 30, 45, 60), sample solution (0.5ml) was withdrawn from the sac and diluted up to 5 ml to carry out UV spectrophotometric analysis. The volume in the gut sac was maintained at 2 ml with phosphate buffer 6.8, each time after the sampling was carried out at respective time intervals. The % drug permeation was determined to calculate the n-fold increase in permeability.[16],[17],[18]

In- vitro dissolution study:

In-vitro study was performed by using USP type II dissolution apparatus with rotation speed of set to 100 rpm. About 900 mL of phosphate buffer pH 6.8 at 37 ± 0.5 °C was used as a dissolution media. At predetermined time intervals 1 mL samples were withdrawn, filtered through 0.45 µm membrane and 1 mL blank dissolution medium was added for replenishing of the dissolution medium. The amount of dissolved drug was determined at 246.4 nm and 276.6 nm using a UV spectrophotometer.[19],[20]

3. RESULTS AND DISCUSSION

Screening of fixed dose combination:

In the process of co-crystallization identifying the most promising co-former is a significant step as well as a critical task to impart the desired properties to the cocrystal. The traditional experimental approaches for the screening of co-former include solvent evaporation, dry grinding, liquid assisted grinding, solution crystallisation, cooling crystallisation, antisolvent addition, and slurry crystallisation. There is little reliable data regarding the outcome of the crystallisation reaction in experimental procedures, which primarily rely on hit-or-miss co-former selection. Unexpected results of co-crystallization investigations include solvates, hydrates, salts, and eutectics. In addition, it is not realistic to conduct experimental techniques for a large group of co-formers since they require a lot of time and resources, are expensive economically, and require a lot of resources.[21],[22],[23] With the development of robust and sophisticated computing systems, it is now possible to carry out in-silico co-former screening tests to quickly identify the optimal co-former from a large library of various compounds. The Cambridge Structural Database (CSD) is a vast collection of various chemicals that provides insights into the crystal structures of molecules, predicts expected intermolecular interactions, and enables knowledge-based cocrystal creation. There are other various methods reported to be efficient such as conductor like screening model for real solvents (COSMO-RS), molecular electrostatic potential surfaces (MEPS), lattice energy calculations and Hansen solubility parameter (HSP) etc. for the pre - screening of co-formers. Co-former selection methods also included the supramolecular synthon approach, the pKa-based method, the computation of the lattice energy, the hydrogen bond propensity, and molecular docking.

Molecular docking is a type of computational modelling that makes it easier to anticipate the preferred binding orientation of one molecule (such as a ligand) to another (such as a receptor) when they interact to form a stable complex. The strength and stability of complexes, as well as their energy profile (such as their binding free energy), can all be predicted using information on the bound molecules' preferred orientation. Auto-Dock, GOLD, Le-Dock and Flex X etc. are various soft-wares used for molecular docking.[24],[25],[26] The virtual screening of co-former (ASP) for formulating co-crystal with ATOR was done by molecular docking.(Fig.No.1) Auto Dock software was used for docking, the type of interaction and binding energy between the drug and the co-former was the two parameters observed for the selection of the co-former. Co-former selected for molecular docking was Aspirin as it is available with the Atorvastatin calcium Fixed dose combination.[27],[28],[29]

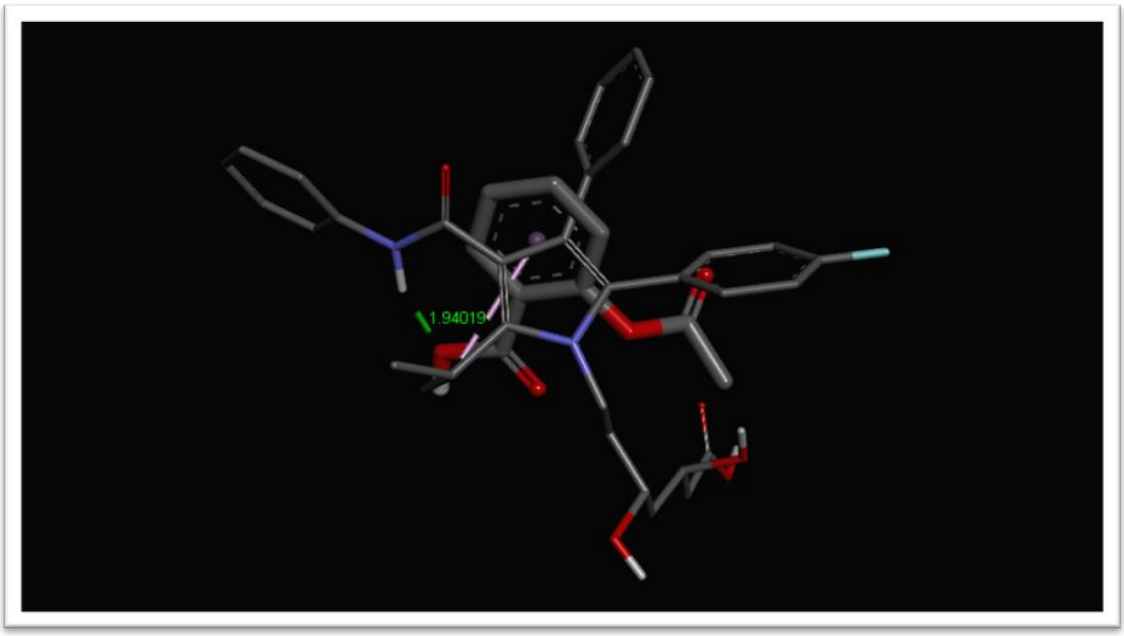

Fig.No.1: Docking Outcome Of Atorvastatin Calcium With Aspirin

The molecule ATOR contains 6 hydrogen bond donors and 12 hydrogen bond acceptors hence it is possible to form cocrystals with Aspirin, the result of virtual screening of co-former for molecular docking was shown below which revealed that Aspirin able to form non-covalent interactions with ATOR. Aspirin showed 1 hydrogen bond formation as well as II-II stacking interaction with ATOR with binding energy - 4.2 Kcal/mol.

Scope of Drug-Drug Cocrystal (DDC):

Cocrystal containing both the components as Active pharmaceutical ingredient (API's) is called "drug-drug cocrystal". DDC offers a feasible approach to overcome the problem related with conventional combination of drugs. Additionally, it has the potential to be used as solid forms for the administration of dual drug therapy and can alter the physicochemical properties of parent drugs. In comparison to other drug combination technologies, DDC may enhance the physicochemical

characteristics of relevant APIs, such as improved dissolution of at least one component, increased bioavailability, enhanced stability of unstable components, and support in lifecycle management of existing products. Today, many major diseases (such as infectious diseases, HIV/AIDS, cancer, diabetes, and cardiovascular disorders) are treated by using a combination of multiple drugs, which confidently pushes out monotherapy (aimed at a definite receptor). The use of cost-effective and multi-target fixed-dose drug combinations (FDC) can significantly decrease the pill load without adding to the risk of adverse events or drug resistance, enhancing patient compliance by optimizing disease management.[11],[30],[31],[32] Employing multi-component crystals with more than one active pharmaceutical ingredient, such as salts, complexes, and cocrystals, is an alternate method of using drug combinations. The pharmaceutical industry pays the most attention to cocrystals among all the multicomponent systems discussed since the US Food and Drug Administration (FDA) has introduced regulatory standards as a result of increased patent portfolios. Unfortunately, the majority of cocrystal investigations are devoted to the supramolecular synthesis of API-based cocrystals and crystal engineering. For instance, the [sulfadimidine + aspirin] cocrystal, which can be thought of as an antibacterial and NSAID therapeutic medication, has not had its pharmaceutical qualities assessed.[33],[34],[35],[36] Another example is a two-component crystal containing gentisic acid (NSAID) and piracetam (a nootropic medication), for which no research has been done outside those examining the role of the synthons in the cocrystal formation. In terms of their potential usage in the pharmaceutical sector, drug cocrystal research is far less intensive. Creating drug-drug cocrystals of commercially available drugs may result in a shorter development time (including clinical trials) than that required to create new chemical entities because cocrystals do not require structural alteration of the APIs.[37],[38],[39]

Scanning electron microscopy (SEM):

As depicted in SEM micrograph (Fig 2), pure ATOR revealed crystals with an irregular size with columnar and rod-like shapes (Fig 2a) whereas pure ASP crystals were in irregular sizes and flat rod shapes (Fig 2b). Fig 2c & 2d shows granular and cuboidal shaped crystals with irregular size for developed co-crystal of ATOR with ASP (1:4).

Fourier Transform Infrared Spectroscopy (FTIR):

In IR spectroscopy, shift of the IR absorption bands of the functional groups of starting drug and co-former is generally used to examine the formation of cocrystals, polymorphs, salts, solvates or the formation of new solid between drug and conformer. Fig.No.3 shows FTIR spectra for pure ATOR, ASP, and ATOR-ASP cocrystal batches. (Fig.3a)FTIR spectrum of Atorvastatin Calcium showed a strong absorption band at 3362 cm^{-1},in the region of 2970 cm^{-1} ,1649 cm^{-1} and at 1241 cm^{-1} which is attributed to broad N–H stretching , C-H stretching , C=O stretching and C-N stretching and 1215 cm^{-1} , 1578 cm^{-1}, 1549 cm^{-1}, 1157 cm^{-1} , 1315 cm^{-1} , 842 cm^{-1}, 745 cm^{-1}, 692 cm^{-1} C-F stretching , C=C stretching , C-O stretching , C-N stretching , C-H bending and

deformation were observed.

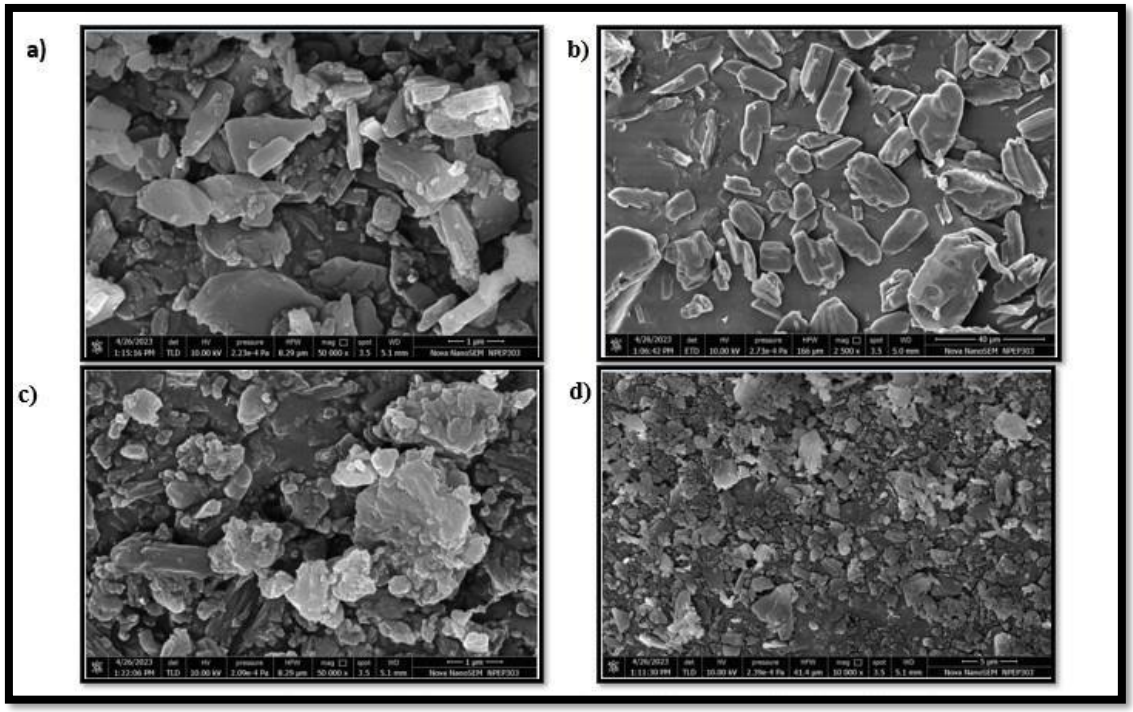

Fig.No.2: SEM Micrographs Of A) Atorvastatin Calcium B) Aspirin And Cocrystals Batches

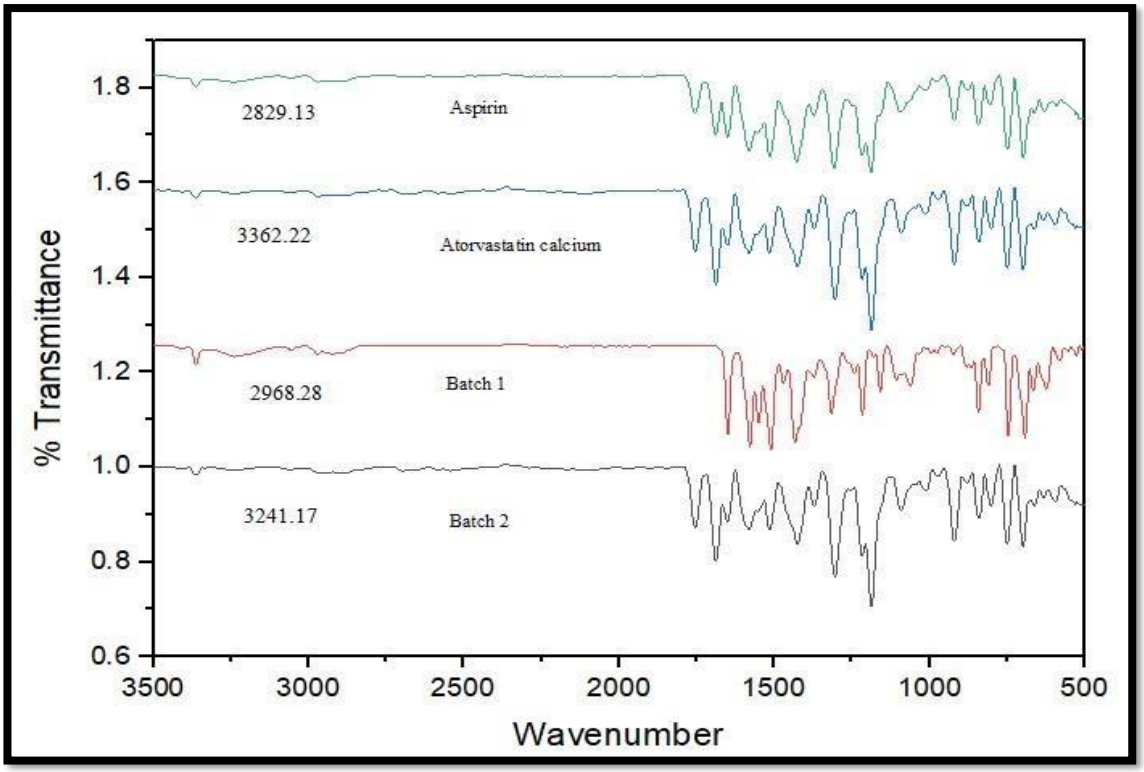

Fig.No.3: FTIR Spectrum A) Atorvastatin Calcium B) Aspirin And Cocrystals Batches

(Fig 3b) The broad absorption peak of ASA that spans from approximately 3250 to 2500 cm−1 contains stretching modes of the O–H group from the acid, CH3 group attached to the ketone, and C–H bonds located on the benzene ring. C=O stretching was assigned to the peaks observed at

1749 cm−1 for the ester and 1679 cm−1 for the carboxy group. (Fig 3c) FTIR spectrum of Batch 1 showed shift of the characteristic peaks of aspirin from 2829 cm^{-1} to 2862 cm^{-1} . This confirmed the formation of hydrogen bond as well as covalent bonding between drugs. . (Fig 3d) FTIR analysis of cocrystal batch 2 showed slight peak shift corresponding to O–H carboxylic acid stretch of Aspirin from 2829 cm^{-1} to 3277 cm^{-1}, indicating hydrogen bonding between Atorvastatin calcium and Aspirin which facilitates cocrystal formation.

Differential Scanning Calorimetry (DSC):

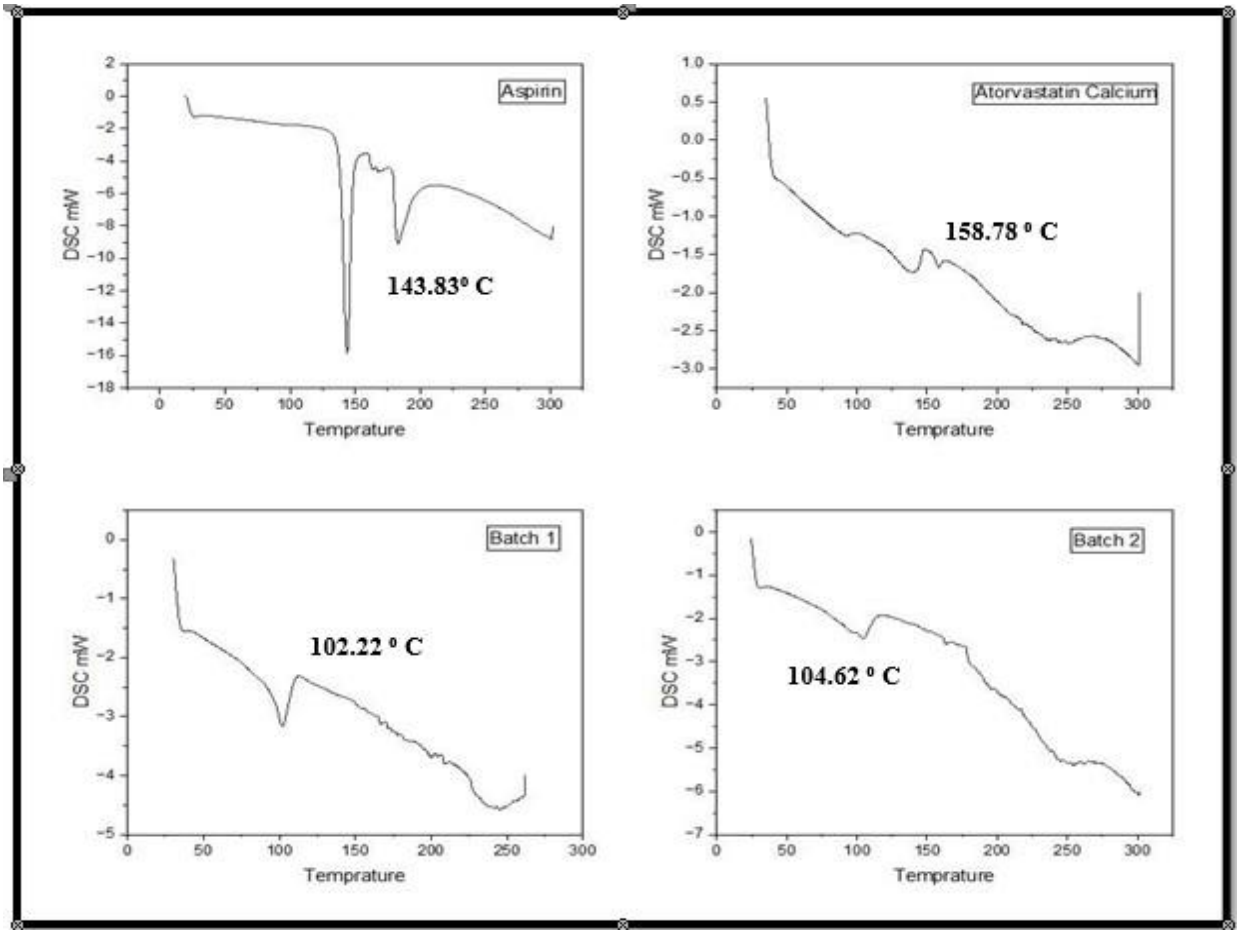

Fig.No.4: DSC Thermographs Of A) Atorvastatin Calcium B) Aspirin And Cocrystals Batches

DSC has been used to screen and confirm the formation of cocrystals based on the differences in thermal behaviour of drug, conformer and their cocrystal in molar rations. DSC thermograms for ATOR, ASP and cocrystal batches are showed in Fig.4. (Fig 4a) showed a sharp endothermic peak at 158.78 ° C demonstrating the crystalline nature of the drug. A sharp endothermic peak was also observed for Aspirin at 143.83 ° C indicating the crystalline nature of drug (Fig. 4b). The Batch 1 thermograms (Fig. 4c) showed a sharp endothermic peak at 102.22 ° C which is distinct from an individual peak of both components and might be related to the cocrystal formation. In (Fig.4d) The DSC thermogram of Batch 2 showed a sharp endothermic peak at 104.62 ° C which is distinct from an individual peak of both components and might be related to the cocrystal formation.

Powder X-ray diffractometry (PXRD):

As depicted in Fig 5a & 5b, PXRD diffractograms of pure ATOR and pure ASP showed several sharp intense between of 2θ 10-40, respectively.

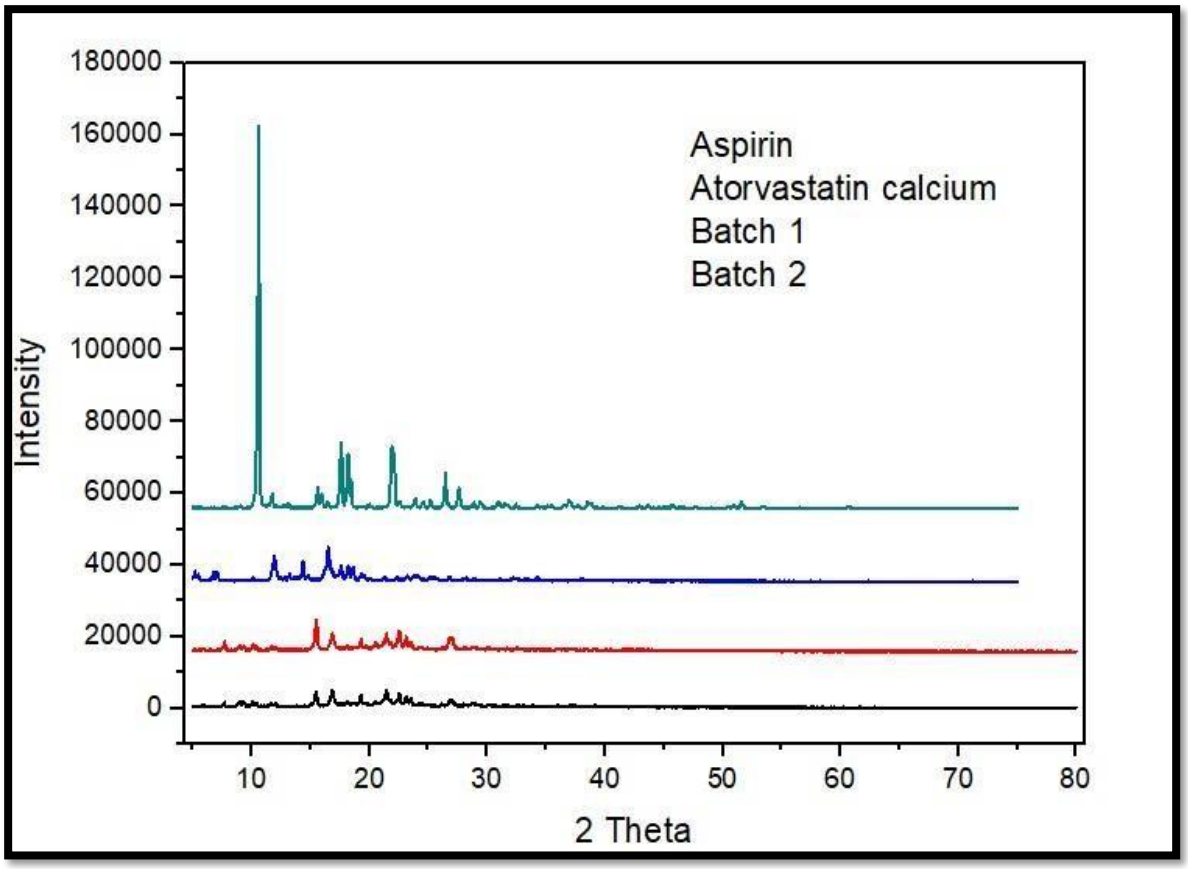

Fig.No.5: PXRD graphs of a) Atorvastatin calcium b) Aspirin and cocrystals batches

Fig.5a) The sharp peaks at 12.10, 15.10, 16.92, 18.22, 18.78, 19.36, 21.52, 22.60, 23.20, 23.62, 24.36, 26.26, 27.34, 28.20, 29.04, 30.20, 31.78, 33.18, 33.90, 37.16 and 39.24 degrees indicated the crystallinity of the drug. Fig. 5b whereas pure Aspirin showed several sharp intense between 10-40 2θ. The sharp peaks at 14.06, 15.58, 16.72, 18.14, 20.60, 21.48, 22.60, 23.18, 24.96, 26.98, 28.88, 29.56, 30.20, 31.44, 32.62, 33.84, 34.46, 35.96, 36.54, 37.48, 39.26, and 40.50 degrees indicated the crystalline nature of Aspirin.Fig.5c) PXRD of batch 1 showed several sharp peaks with characteristic peaks reported at 15.50, 16.88, 18.14, 19.30, 21.46 and 22.54 degrees which were relevant to both the components in the prepared cocrystal batch indicating the retention of crystallinity of cocrystal prepared. Fig.5d) PXRD of batch 2 showed several sharp peaks with characteristic peaks reported at 15.48, 16.86, 18.84, 19.28, 21.76 and 23.14 degrees which were relevant to both the components in the prepared cocrystal batch indicating the retention of crystallinity of cocrystal prepared.

Permeability study for developed cocrystal:

ATOR:ASP cocrystals:

Permeability study for prepared cocrystals of ATOR:ASP (1:4) batch prepared by solvent evaporation was carried out in Phosphate buffer pH 6.8 as a media. Time vs % drug permeated graph was plotted.(Fig.No.5) The permeability of both the drugs is increased for Aspirin and Atorvastatin calcium from 13.65 % & 8.74 % to 22.61 % & 11.20 % . The increase for Atorvastatin calcium is 1.28 fold and for Aspirin is 1.66 fold.[33],[36]

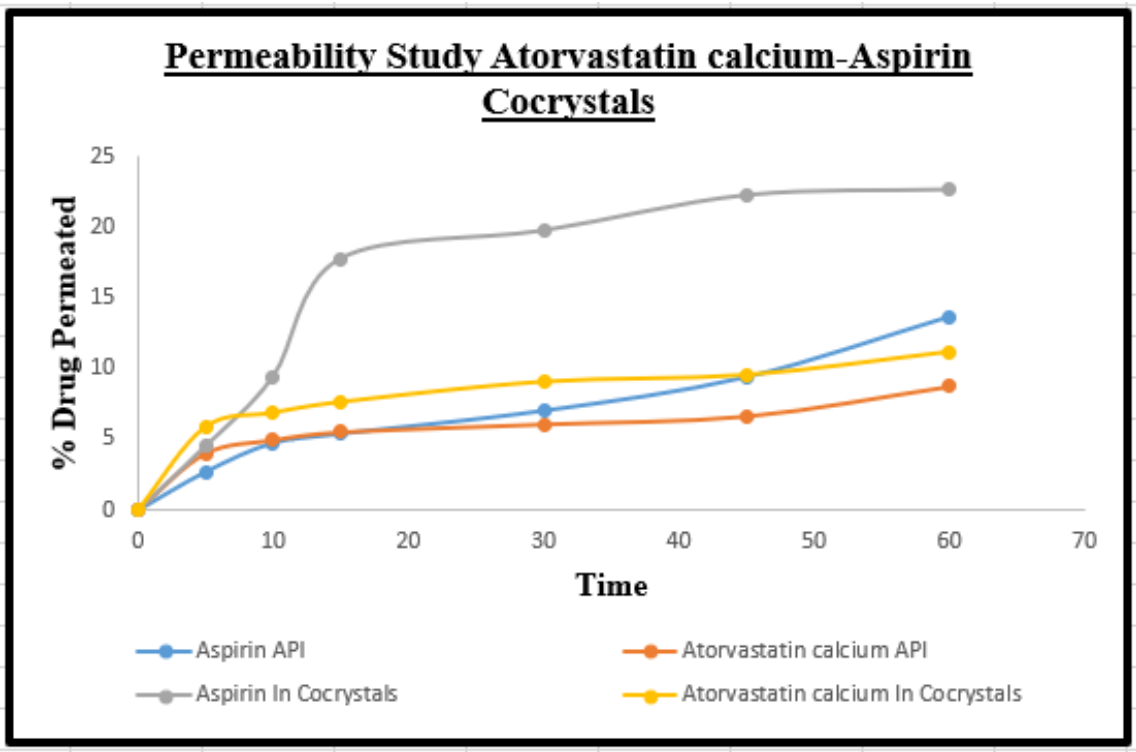

Fig.No.6: Ex-Vivo Permeability Study Of A) Atorvastatin Calcium B) Aspirin And Cocrystals Batches

In-vitro dissolution study of developed ATOR:ASP cocrystal tablets:

From permeability study observations and benefits of ATOR:ASP, cocrystal batch prepared using in 1:4 ratio by solvent evaporation method was further selected for in vitro drug release study.

To conduct in-vitro dissolution study, prepared cocrystals were developed into a tablet using direct compression method. These developed tablets showed hardness 3.2 kg/cm^2, friability of 0.664% with disintegration time of 50 sec. In-vitro dissolution study was performed to compare release of ATOR and ASP from prepared cocrystals and release study is graphically presented in Fig.6 & 7. In-vitro release profile of prepared ATOR:ASP cocrystal was compared with pure ATOR ,ASP as well as marketed formulation. The % drug release of pure ATOR, ASP, marketed tablet of ATOR & ASP and prepared cocrystal tablet was found to be 54.46 %, 62.88 % , 60.10 % ,70.01 % and for cocrystal tablet 94.60 % & 95.13 % respectively at the end 60 min.

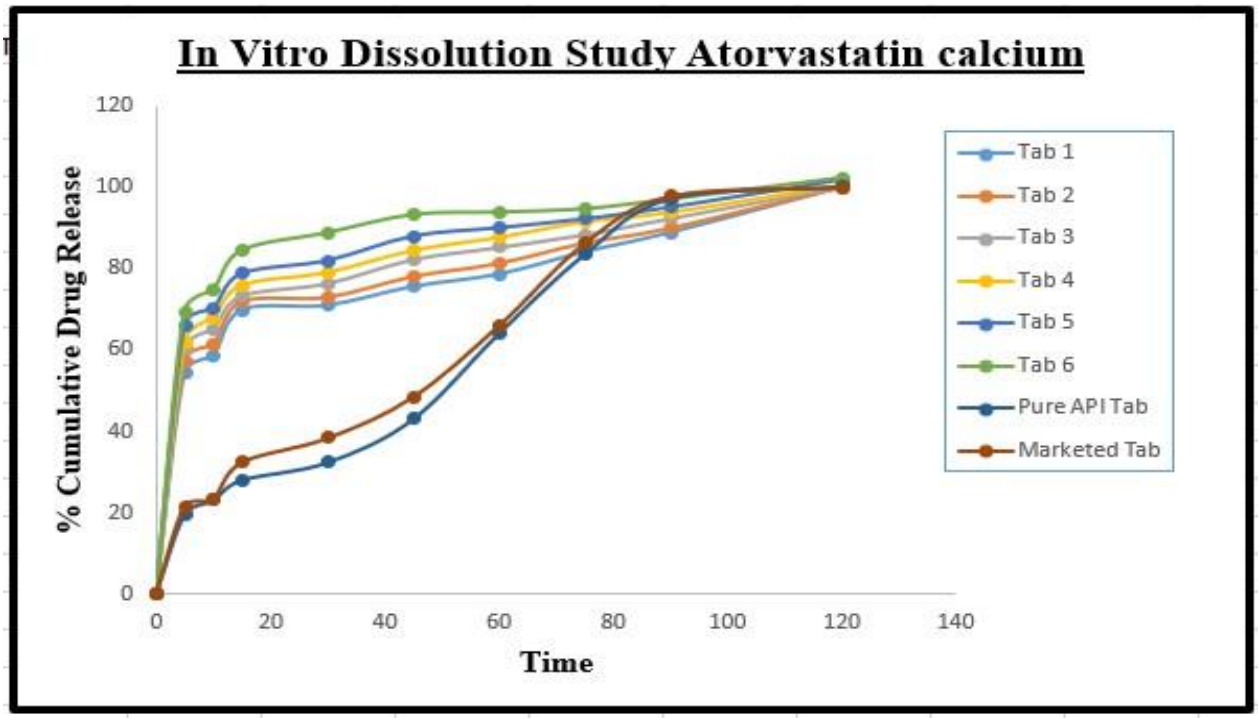

Fig.No.7: In Vitro Dissolution Study Of Atorvastatin Calcium API Tab, Marketed Tab And Cocrystals Tablets

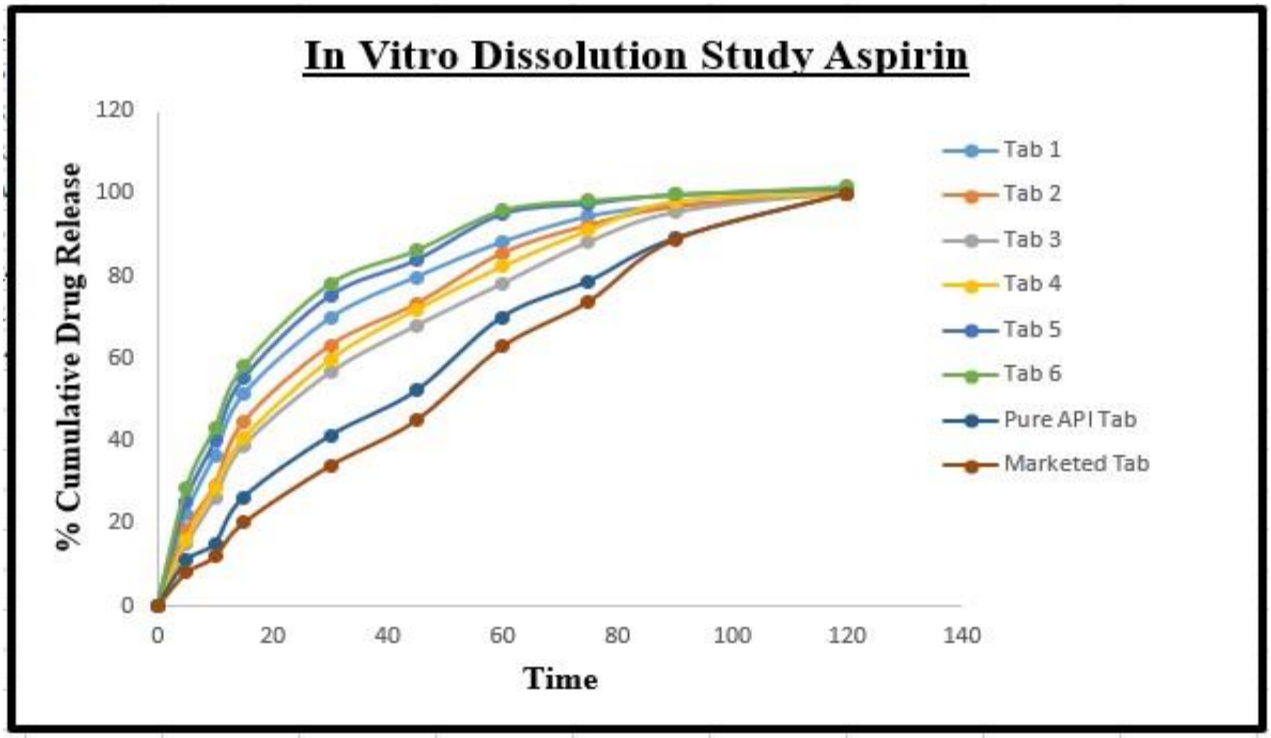

Fig.No.8: In Vitro Dissolution Study Of Aspirin API Tab, Marketed Tab And Cocrystals Tablets

The study indicates that drug release from tablet containing ATOR:ASP cocrystal was complete at the end of 60 min and though the ATOR belong to BCS Class II and ASP belong to BCS Class I incomplete release was observed from pure drug. It was observed that the drug release of ATOR &

ASP was improved by formulating cocrystal tablet.[37],[40]

Summary:

ATOR is a BCS Class II drug having low solubility. The drug of concern undergoes extensive first pass metabolism and causes its low oral bioavailability. Drug– Drug cocrystals of ATOR:ASP were successfully prepared to make use of ASP as a co-former to increase solubility of ATOR by using molecular docking analysis. Cocrystals of ATOR:ASP (1:1, 1:2 1:3 & 1:4) were successfully prepared using neat grinding, liquid assisted grinding and solvent evaporation methods. Based on outcome of permeability study, batch 1:4 was selected as an optimized batch which exhibits 1.28-fold increase in permeability for ATOR and for ASP it is 1.66 fold. FTIR, SEM, DSC and PXRD study outcome confirmed the formation of cocrystal. Drug–Drug cocrystal sublingual tablet was prepared using direct compression method which showed complete drug release at the end of 60 min.

4. CONCLUSION

In conclusion, the co-crystallization of Anti-hyperlipidemic drug Atorvastatin calcium with Aspirin used as a conformer was successfully prepared using Solvent evaporation (SE) method. The resulting cocrystal was characterized by FTIR, SEM, DSC and PXRD. Compared to the original API ATOR– ASP cocrystal displayed superior tableting performance. The permeability and dissolution profile of ATOR– ASP cocrystal showed, 1.74 fold and 1.513 fold increase in drug release and 1.28-fold and 1.66 fold increase in permeability to that of pure ATOR and ASP. The result of this study suggests that co-crystallization with Aspirin offers a valuable way to improve physicochemical properties of Atorvastatin calcium.

ACKNOWLEDGEMENT

Not Applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

REFERENCES

1. Kara DD, Rathnanand M. Cocrystals And Drug–Drug Cocrystals Of Anticancer Drugs: A Perception Towards Screening Techniques, Preparation, And Enhancement Of Drug

Properties. Vol. 12, Crystals. MDPI; 2022. 12-17

2. Sekhon BS. Drug-Drug Co-Crystals. Vol. 20, DARU, Journal Of Pharmaceutical Sciences. 2012.4-7
3. Mohite P, Mane P. Drug-Drug Cocrystals: Opportunities And Challenges [Internet]. Vol. 9. 2021. Available From: Www.Ijcrt.Org : 2-8
4. Taraka SKK, Pasala PK, Sahoo RK, Laddha UD, Khairnar SJ, Bendale AR, Et Al. Atorvastatin Ascorbic Acid Cocrystal Strategy To Improve The Safety And Efficacy Of Atorvastatin. Pharmacia. 2022;69(2):295–302.
5. Al-Kazemi R, Al-Basarah Y, Nada A. Atorvastatin Cocrystals: Tablet Formulation And Stability. Vol. 14, Asian Journal Of Pharmaceutics; 3-7.
6. Desiraju GR. Crystal And Co-Crystal. Vol. 5, Crystengcomm. 2003. P. 466–7.
7. Desiraju GR. Crystal Engineering, Crystals And Crystallography. Vol. 5, Iucrj. International Union Of Crystallography; 2018. P. 660.
8. Desiraju GR. Reflections On The Hydrogen Bond In Crystal Engineering. Cryst Growth Des. 2011 Apr 6;11(4):896–8.
9. Saha S, Desiraju GR. Acid···Amide Supramolecular Synthon In Cocrystals: From Spectroscopic Detection To Property Engineering. J Am Chem Soc. 2018 May 23;140(20):6361–73.
10. Thorat Ys, Gonjari Id, Hosmani Ah. Solubility Enhancement Techniques: A Review On Conventional And Novel Approaches. Ijpsr [Internet]. 2011;2(10). Available From: Www.Ijpsr.Com
11. Kara DD, Rathnanand M. Cocrystals And Drug–Drug Cocrystals Of Anticancer Drugs: A Perception Towards Screening Techniques, Preparation, And Enhancement Of Drug Properties. Vol. 12, Crystals. MDPI; 2022.
12. Darwish S, Zeglinski J, Krishna GR, Shaikh R, Khraisheh M, Walker GM, Et Al. A New 1:1 Drug-Drug Cocrystal Of Theophylline And Aspirin: Discovery, Characterization, And Construction Of Ternary Phase Diagrams. Cryst Growth Des. 2018 Dec 5;18(12):7526–32.
13. Inam M, Wu J, Shen J, Phan CU, Tang G, Hu X. Preparation And Characterization Of Novel Pharmaceutical Co-Crystals: Ticagrelor With Nicotinamide. Crystals (Basel). 2018 Sep 1;8(9).
14. Kumar Bandaru R, Rout SR, Kenguva G, Gorain B, Alhakamy NA, Kesharwani P, Et Al. Recent Advances In Pharmaceutical Cocrystals: From Bench To Market. Vol. 12, Frontiers In Pharmacology. Frontiers Media S.A.; 2021.4-23
15. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating Cocrystals: A Review Of Pharmaceutical Cocrystal Preparation Routes And Applications. Vol. 18, Crystal Growth And Design. American Chemical Society; 2018. P. 6370–87.

16. Eedara BB, Veerareddy PR, Jukanti R, Bandari S. Improved Oral Bioavailability Of Fexofenadine Hydrochloride Using Lipid Surfactants: Ex Vivo, In Situ And In Vivo Studies. Drug Dev Ind Pharm. 2014;40(8):1030–43.
17. Luo Z, Liu Y, Zhao B, Tang M, Dong H, Zhang L, Et Al. Ex Vivo And In Situ Approaches Used To Study Intestinal Absorption. Vol. 68, Journal Of Pharmacological And Toxicological Methods. 2013. P. 208–16.
18. Shah I, Vyas J. Role Of P-Gp Inhibitors On Gut Permeation Of Metformin: An Ex-Vivo Study. Int J Pharm Pharm Sci. 2022 Oct 1;18–23.
19. Li J, Hao X, Wang C, Liu H, Liu L, He X, Et Al. Improving The Solubility, Dissolution, And Bioavailability Of Metronidazole Via Cocrystallization With Ethyl Gallate. Pharmaceutics. 2021 Apr 1;13(4).
20. Al-Kazemi R, Al-Basarah Y, Nada A. Dissolution Enhancement Of Atorvastatin Calcium By Cocrystallization. Adv Pharm Bull. 2019;9(4):559–70.
21. Desiraju GR. Crystal Engineering, Crystals And Crystallography. Vol. 5, Iucrj. International Union Of Crystallography; 2018. P. 660.
22. Desiraju GR. Reflections On The Hydrogen Bond In Crystal Engineering. Cryst Growth Des. 2011 Apr 6;11(4):896–8.
23. Desiraju GR. The Hydrogen Bond. A Bond For Life. Crystallogr Rev. 2020 Jan 2;26(1):64
24. Dhibar M, Chakraborty S, Basak S, Pattanayak P, Chatterjee T, Ghosh B, Et Al. Critical Analysis And Optimization Of Stoichiometric Ratio Of Drug-Coformer On Cocrystal Design: Molecular Docking, In Vitro And In Vivo Assessment. Pharmaceuticals. 2023 Feb 1;16(2).
25. Surov AO, Ramazanova AG, Voronin AP, Drozd K V., Churakov A V., Perlovich GL. Virtual Screening, Structural Analysis, And Formation Thermodynamics Of Carbamazepine Cocrystals. Pharmaceutics. 2023 Mar 3;15(3):836.
26. Mangesh B, Sumedh P, Sumedh M, Pradhan B. Scientific Coformer Screening, Preparation And Evaluation Of Fenofibrate Tartaric Acid Cocrystal. Journal Of Drug Delivery And Therapeutics [Internet]. 2019;9(4):406–10. Available From: Http://Jddtonline.Info
27. Desiraju GR. Approaches To Crystal Structure Landscape Exploration. Vol. 73, Acta Crystallographica Section B: Structural Science, Crystal Engineering And Materials. International Union Of Crystallography; 2017. P. 775–8.
28. Desiraju GR. Co-Crystals. Preparation, Characterization And Applications . Edited By C. B. Aakeröy And A. S. Sinha. Royal Society Of Chemistry, Monographs In Supramolecular Chemistry No. 24, 2018, Hardcover, Pp. 342. Price GBP 159.00. ISBN 978-1-78801-115-0 . Acta Crystallogr B Struct Sci Cryst Eng Mater. 2019 Oct 1;75(5):914–5.
29. Desiraju GR. Crystal Engineering: Structure, Property And Beyond. Vol. 4, Iucrj. International Union Of Crystallography; 2017. P. 710–1.

30. Thakuria R, Sarma B. Drug-Drug And Drug-Nutraceutical Cocrystal/Salt As Alternative Medicine For Combination Therapy: A Crystal Engineering Approach. Vol. 8, Crystals. MDPI AG; 2018.
31. Samie A, Desiraju GR, Banik M. Salts And Cocrystals Of The Antidiabetic Drugs Gliclazide, Tolbutamide, And Glipizide: Solubility Enhancements Through Drug-Coformer Interactions. Cryst Growth Des. 2017 May 3;17(5):2406–17.
32. Maity DK, Paul RK, Desiraju GR. Drug-Drug Binary Solids Of Nitrofurantoin And Trimethoprim: Crystal Engineering And Pharmaceutical Properties. Mol Pharm. 2020 Dec 7;17(12):4435–42.
33. Balimane P V, Chong S, Morrison RA. Current Methodologies Used For Evaluation Of Intestinal Permeability And Absorption.
34. Dai XL, Li S, Chen JM, Lu TB. Improving The Membrane Permeability Of 5-Fluorouracil Via Cocrystallization. Cryst Growth Des. 2016 Aug 3;16(8):4430–8.
35. Schimpel C, Teubl B, Absenger M, Meindl C, Fröhlich E, Leitinger G, Et Al. Development Of An Advanced Intestinal In Vitro Triple Culture Permeability Model To Study Transport Of Nanoparticles. Mol Pharm. 2014 Mar 3;11(3):808–18.
36. Dixit P, Jain DK, Dumbwani J. Standardization Of An Ex Vivo Method For Determination Of Intestinal Permeability Of Drugs Using Everted Rat Intestine Apparatus. J Pharmacol Toxicol Methods. 2012 Jan;65(1):13–7.
37. Hassan Nada A, Zaghloul A, Alsoraj M, Nada A, Zaghloul AA, Al-Soraj M, Et Al. Comparative Ex Vivo And In Vitro Permeation Kinetics Of Tocopherol In Liquid Formulations [Internet]. Vol. 12, Asian Journal Of Pharmaceutics. Available From: Https://Www.Researchgate.Net/Publication/325146283
38. Godbole AM, Somnache SN, Thakker SP, Iliger SR, Joshi AS, Patel B V. Formulation And In-Vitro Evaluation Of Sublingual Tablets Of Ondansetron Hydrochloride Using Coprocessed Excipients. Indian Journal Of Pharmaceutical Education And Research. 2014;48(4):7–17.
39. Atia NN, Tawfeek HM, Rageh AH, El-Zahry MR, Abdelfattah A, Younis MA. Novel Sublingual Tablets Of Atorvastatin Calcium/Trimetazidine Hydrochloride Combination; HPTLC Quantification, In Vitro Formulation And Characterization. Saudi Pharmaceutical Journal. 2019 May 1;27(4):540–9.
40. Atia NN, Tawfeek HM, Rageh AH, El-Zahry MR, Abdelfattah A, Younis MA. Novel Sublingual Tablets Of Atorvastatin Calcium/Trimetazidine Hydrochloride Combination; HPTLC Quantification, In Vitro Formulation And Characterization. Saudi Pharmaceutical Journal. 2019 May 1;27(4):540–9.