Review Article

Approaches to Improve Atorvastatin Calcium Bioavailability: A Review

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ABSTRACT

Poor bioavailability is one among major challenges faced by the pharmaceutical drugs in the dosage form development. Atorvastatin (AST) is one among such challenging drugs facing poor bioavailability due to poor solubility. The objective of this article is to review the literature published in the selected search engines about the solubility / bioavailability enhancement of AST. Literature was searched in the four databases Science direct, PubMed, Google scholar, and BASE engine. Seventy-one articles related to atorvastatin formulations were selected from which 26 articles related to bioavailability enhancement were discussed. Further, various method of estimation of AST alone and in formulations were also compiled. Results: researches that the bioavailability could be improved by several methods including solid-dispersion co-crystallization, Microspheres, solid lipid nanoparticles, co-solvency, and nanosuspension, self-nano emulsifying drug delivery system (SNEEDS). Further, simple UV and HPLC methods could be used for the estimation of AST alone and in combination.

Keywords: Solid dispersion, Nano emulsion, solid-lipid nano-particles, Co-solvency.

INTRODUCTION

Hyperlipidaemia is a disorder of lipid metabolism produced by height of plasma concentration of the diverse lipid and lipoprotein fractions, which are the source of cardiac disease.[1] It is defined as increase serum Triglycerides [TG], Very low-density lipoproteins [VLDL], Low density lipoproteins [LDL] and High-density lipoproteins [HDL] which are responsible for different problems like: Atherosclerosis, heart attack, coronary artery syndrome, stroke, myocardial infarction and pancreatitis.[2] this problem can be treated by antihyperlipidemic drugs.[3]

Synthesis pathway of cholesterol

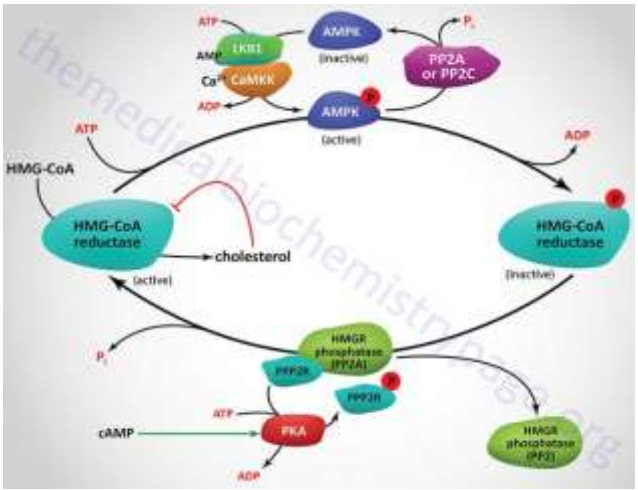

Figure 1: Synthesis pathway of cholesterol

Atorvastatin calcium is one of the most popular medicine for the treatment of hyperlipidaemia. Atorvastatin calcium (ATC) can inhibit 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzymes that catalyse the conversion of HMG-CoA to mevalonate. Atorvastatin calcium (ATC)is BCS Class II drug with low aqueous solubility and high permeability.[4] Oral bioavailability of atorvastatin calcium (ATC)is very low (only 14%). The low oral bioavailability of atorvastatin calcium is caused by low aqueous solubility and high hepatic first-pass metabolism. Various Efforts are needed to enhance dissolution rate and oral bioavailability of atorvastatin calcium (ATC).[5]

Chemistry of Atorvastatin

Atorvastatin was first synthesized in 1985 by Dr. Bruce Roth and approved by the FDA in 1996. It is a Penta substituted pyrrole formed by two contrasting moieties with an achiral heterocyclic core unit and a 3,5-dihydroxypentanoyl side chain identical to its parent compound. Unlike other members of the statin group, atorvastatin is an active compound and therefore does not require activation.[6]

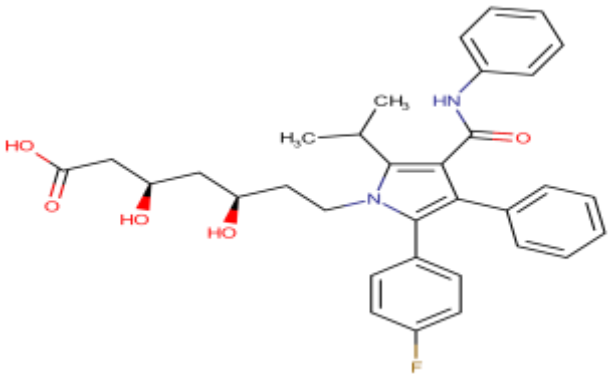

Figure 2: Structure of atorvastatin

Solubility

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response.[7] Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like, solid dispersion, Nanoparticles, salt formation, particle size reduction, co-crystallization, use of surfactant, complexation, microspheres and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.[8] Atorvastatin has very low aqueous solubility and its results in low oral bioavailability (12%).

Solubility of Atorvastatin calcium

Atorvastatin completely soluble in methanol very slightly soluble in water, and sparingly soluble in ethanol, acetonitrile.

Methods to improve Bioavailability

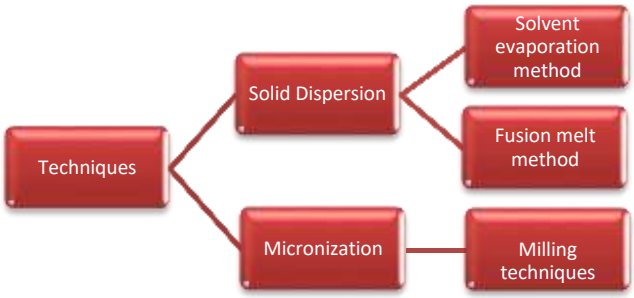

Figure 3: Different technique to improve Bioavailability.

SOLID DISPERSION

Solid dispersions can be defined as the dispersion of one or more active pharmaceutical ingredient in a solid carrier. It is an efficient technique to improve dissolution and bioavailability.[9] Solid dispersions can be prepared by various methods such as solvent evaporation, hot melt extrusion, fusion method, kneading method, spray drying, freeze drying, supercritical fluid methods-precipitation method, dropping method.[10]

Solid dispersions of AST were prepared by lyophilization utilising skimmed milk as a carrier by Ankush et.al. Six formulations along with corresponding physical mixtures were prepared with different drug carrier ratios. Solubility was increased to 33 folds in 1:9 drug carrier ratio when compared to pure drug. *In vitro* dissolution release studies showed of 83.69% as compared to 22.7% for the pure drug.[11] Then formation of a solid dispersion formulation was confirmed by differential scanning calorimetry and x-ray diffraction studies. The ideal drug to carrier ratio of 1:9 increased solubility almost 33-fold as compared to pure drug. *In vitro* drug release studies.

Raihan Sarkar *et.al*. prepared Solid dispersions of AST were prepared by Solvent and physical mixing method. Physical mixtures (PMs) of AST and hydrophilic polymer Kollicoat IR and PVK 30 were prepared at 1:0.5, 1:1 and 1:2 ratios. Melt Solvent method was used to prepare solid dispersion of AST, PVK 30 and kollicoat IR at 1:2 ratio. Solid dispersions were characterized by differential scanning calorimetry, scanning electron microscopy and dissolution tests. Characterization studies exhibited that solid dispersion of AST prepared by Melt Solvent methods showed better dissolution compared to Physical mixing and pure AST due to the conversion of AST into a less crystalline and/or amorphous form. The order of dissolution enhancement was Kollicoat IR > PVK30 in solid dispersions as well as in physical mixtures. Improvement of dissolution was considerably greater in solid dispersions prepared by Melt solvent method than in physical mixtures.[12]

In another study by Shikha Aggarwal *et.al*, Solid dispersions of AST were prepared and evaluated using Modified gum karaya.[13] Physical mixtures along with solid dispersions of drug and polymer was prepared using three methods kneading, solvent evaporation and solvent wetting method in 5 different ratios (1:1,1:3,1:5,1:7,1:9). Among the three methods used AST calcium solid dispersions prepared by kneading method in 1:3 ratio showed most promising results in terms of percent yield, percent drug content, solubility of solid dispersions in phosphate buffer pH 6.8, X ray diffraction studies, Differential Scanning Calorimetry, SEM and In vitro release studies These solid dispersions they were selected to prepare tablets A techniques revealed remarkable increase in the solubility compared to the pure AST calcium. The solubility analysis demonstrated increase in the solubility of drug observed with ATR-AMG ratio 1:1 by lyophilisation technique.[14] During In Vitro study result shows that the SD prepared using the Lyophilisation method containing 1:1 ATR-AMG ratio displays faster dissolution rates compared with those prepared using the other that is 98.8±0.09% drug release within 90 min.[15]

Another study by Emanual.*et.a*l, Solid dispersions of AST with different polymers such as PEG 6000, PVP K-30 and HPMC K3LV were studied. Saturation solubility study exhibited the ability of PEG 6000, PVP K-30 and HPMC K3LV to form solid dispersions with AST. Various Methods for preparation of solid dispersions include solvent evaporation, fusion, kneading and microwave irradiation fusion method. and these Solid dispersions were characterized for dissolution study, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) Fourier transform infrared spectroscopy (FTIR), and X-Ray diffraction (XRD) to confirm conversion of crystalline ATR

to amorphous form in solid dispersions. Then immediate release tablets prepared using solid dispersions (ATR- PEG 6000) showed 99.19%, solid dispersions (ATR- PVP K30) showed 99.12% and solid dispersion (ATR- HPMC K3LV) showed 99.09% drug release within 30 minutes.[16]

Dharmila *et.a*l, were prepared solid dispersions by using modified locust bean gum in modified solvent evaporation method. And other mixtures were also prepared by physical mixing, co-grinding, and the kneading method. The locust bean gum was exposed to heat for modification. The prepared solid dispersions and other mixtures were evaluated for equilibrium solubility studies, content uniformity, FTIR, DSC, XRD, in vitro drug release, and in vivo pharmacodynamic studies. The equilibrium solubility was increased in the solid dispersions (in a drug: polymer ratio of 1:6) and other mixtures such as the co- grinding mixture (CGM) and kneading mixture (KM). Maximum dissolution rate was perceived in the solid dispersion batch SD3 (50% within 15 min) with maximum drug release after 2 hours (80%) out of all solid dispersions.[14]

Co-crystallization

Cocrystal is a comparatively new solid form of active pharmaceutical ingredient that offers an alternative platform in improving physicochemical properties of active pharmaceutical ingredients Cocrystal is defined as a stoichiometric multi- component system connected by non-covalent interactions where all the components neutral and solid under ambient environments.[17] Cocrystal can be constructed through interaction hydrogen bonding, pi- stacking, and van der Waals forces, A pharmaceutical cocrystal is composed of an API and an appropriate coformer as carboxylic acids and amides Co-crystallization of active pharmaceutical ingredient is an opportunity for enhancement of important physiochemical properties of an active pharmaceutical ingredient without changing its molecular structure.[18]

Yudi Wicaksono *et.al*, were Examined the formation of AST calcium co-crystal to improve its solubility by using equimolar ratio with nicotinamide (INA) was carried out by slow solvent evaporation method using methanol. solid obtained was identified by powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and then further evaluated for solubility and dissolution. and finally results showed that dissolution rate of ACINA co-crystal was 2-3 times faster than that of pure AST calcium.[19]

Microspheres are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability or stability and to target drug to specific sites.[20] Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. Eudragit polymers are a series of acrylate and methacrylate polymers available in different ionic forms. Eudragit S100 is insoluble in aqueous media, but they are permeable and have pH dependent release profile.[21]

Kotame et.al microspheres were prepared by solvent evaporation method using Eudragit S -100 polymer, polyvinyl alcohol used as the droplet stabilizer. The prepared spherical crystals were characterized for their micromeritic properties as well by Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) showed the crystalline nature of drug in a final stage. The in vitro release studies were performed in pH 1.2 (0.1 N HCl) for 60 min. and showed increased entrapment efficiency in the particles.[22]

Multiple-unit floating microcapsules of AST calcium (ATC) were developed Furquan Nazimuddin KHAN et.al., to expand the gastric residence time of the drug, as ATC has maximum rate of absorption in the upper GI tract. Floating microcapsules were prepared by Emulsion-solvent evaporation technique through incorporation of dioctyl sodium sulphosuccinate (DSS) as a dissolution enhancer. The microcapsules were characterized for shape, size, drug entrapment efficiency, stability and in-vitro drug dissolution rate and were subjected to SEM, DSC and PXRD studies. The ATC-loaded floating microcapsules were spherical in shape and had the particle size of about 28.10 µm and drug-loading efficiency of about 96.55 %. The floating microspheres containing DSS had significantly higher drug dissolution rates than those without DSS. The best formulation, AT4, consisting of Ethyl cellulose, DSS and Poly Ox®, had a maximum drug dissolution rate of 97.86 %, as compared to pure drug.[23]

Solid Lipid Nanoparticles

Lipid nanoparticles with a solid matrix, such as solid lipid nanoparticles (SLN), are an alternative nanoparticulate carrier system to polymeric nanoparticles,[24] liposomes and o/w emulsions Aqueous SLN dispersions are composed of a lipid which is solid both at body and room temperature, being stabilized by a suitable surfactant.[25]

Panakanti Pavan Kumar *et.al,* Reported the formulation of AST (ATRS) loaded solid lipid nanoparticles by hot homogenization followed by ultrasonication technique, and optimization of formulation and process parameters to formulate preferred SLN dispersions. The effects of composition of lipid materials, surfactant mixture and sonication time on particle size, PDI, zeta potential, drug entrapment efficiency, and in vitro drug release behaviour were examined. The mean particles size, PDI, zeta potential and entrapment efficiency of optimized formulation (A5) was found to be 50.0± 6.12 nm, 0.08±0.011,10.40± 4.68mV, 88.7± 6.08 % respectively. To describe the state of drug and lipid modification in ATRS loaded solid lipid nanoparticles, differential scanning calorimetry analysis was performed.[26]

Cosolvency: is one of the most obtain approaches for improving the solubility of poorly aqueous soluble drugs in pharmaceutical liquid formulations Cosolvents are the mixtures of miscible solvents often used to water which

can significant change in the solubility of poorly aqueous soluble drugs Weakly electrolytes and nonpolar molecules frequently have poor water solubility.[27] Their solubility usually can be increased by the addition of water miscible solvent in which the drug has good solubility. And the solvents used to increase solubility are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute.[28]

Geetha Lakshmi et.al, They have found the co-solvent evaporated mixtures of the drug with MCC & HPMC was prepared in ratios of 1:1 and 1:2 using Rotary evaporation technique All solid dispersions of drug with MCC and HPMC were showed increases in the solubility in the range of Drug showed MCC (1:1) 79.7 %Drug: HPMC (1:1) 86.4% Drug: MCC (1:2) 91.8 %Drug: HPMC (1:2) 98.3%.[29]

Nanosuspension

Nanosuspensions are important carriers to develop novel drug formulations. Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages.[30] Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability. Stability and bioavailability of the drugs can be improved by the Nanosuspension technology.[31]

To improve the solubility and dissolution characteristics of a poorly soluble drug AST calcium Arun Kumar *et.al,* used nanosuspension technology. Nanoparticles were identified in terms of size and morphological characteristics. Saturation solubility and dissolution characteristics were examined and compared with the commercial drug. Crystallinity of the drug was also evaluated by performing thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to denote eventual transformation to amorphous state during the homogenization process. Through this study it has been showed that were highly increased in comparison with commercial drug by the enhancement of intrinsic dissolution rate and the reduction of particle size, resulting in an increased specific surface area.[32]

SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS)

Self-nanoemulsifying drug delivery systems (SNEDDS) are anhydrous homogenous liquid mixtures consisting of oil, surfactant, drug and coemulsifier or solubilizer, which instinctively form oil-in-water Nano emulsion of approximately 200 nm or less in size upon dilution with water under gentle stirring.[33] The physicochemical properties, drug solubilization capacity and physiological fate considerably control the selection of the SNEDDS components. SNEDDS can improve oral bioavailability of hydrophobic drugs by several mechanisms.[34]

self-nano emulsifying drug delivery system (SNEDDS) for oral delivery of AST was performed by Venkatesh Miryala *et.al,* they were used various surfactants to enhance the bioavailability and surfactants were screened for emulsification stability and they did comparison studies with marketed product the results were significantly increases the dissolution rate (99.65%) in 90 minutes.[35]

polymorphism is the ability of solid materials to exist in two or more crystalline forms with different arrangements or conformations of the constituents in the crystal lattice. these polymorphic forms of a drug differ in the physicochemical properties like dissolution and solubility chemical and physical stability, flowability and hygroscopicity.[36] These forms also differ in various important drug outcomes like drug efficacy, bioavailability, and even toxicity, polymorphic studies are important as a particular polymorph can be responsible for a particular property which might not be exhibited by any other form.[37]

AST CALCIUM PATENT RELATED POLYMORPHISM

Table 1: AST calcium patent related polymorphism.

Sl. No.	Patent Number	Title	Inventors
01	EP1562583A1	The present invention relates to AST Calcium Form VI or hydrates thereof and a process for preparing it	Manmohan Singh, Baldev Morepen, Jujhar Morepen.
02	US7488750B2	Crystal forms of AST hemi-calcium and processes for their preparation as well as novel processes for preparing other forms	Judith Arnhem, Ramy Bio-Rad's, Valerie Niddam, Revital Lifshitz, Shlomit Wizel.
03	Us7361772B2	Process for the production of AST calcium	Joy Mathew, Madhavan, Sridharan, Sambasivam Ganesh, Tom Thomas puthiaparampil.
04	US7732623B2	Polymorphic form of AST calcium	Ari Ayalon, Michal Levinger, Sofia Roytblat, Valerie Niddam, Revital Lifshitz, Judith Aronhime.
05	US7994343B2	Process for the production of AST calcium in amorphous form	Yatendra Kumar, Saridi MadhavaDileepkumar, Swargam Satyanarayana.
06	US20070032665 A1	The present invention relates to a process for the preparation of AST calcium crystalline Form I.	Srinivas Gudipati, Srinivas Katkam, Satyanarayana Komati.

LIST OF AST FORMULATIONS:

Table 2: List of AST formulations.

1	Amorphous solid dispersion with increased gastric solubility in tandem with oral disintegrating tablets: a successful approach to improve the bioavailability of **AST**	Jumah Masoud M *et.al*.2015.[38]
2	Preparation and characterization and in vivo evaluation of amorphous **AST** calcium nanoparticles using super critical antisolvent (SAS) process	Min-so-kim-*et.al*. 2008.[39]
3	Enhanced Bioavailability of **AST** Calcium from Stabilized Gastric Resident Formulation	Furquan Nazimuddin Khan *et.al.*2011.[40]
4	Dissolution Improvement of **AST** Calcium using Modified Locust Bean Gum by the Solid Dispersion Technique	Dharmila P *et.al* 2013.[41]
5	chitosan based **AST** nanocrystals effect of cationic charge on particle size, formulation stability, and in-vivo efficacy	Kurakula M *et.al* 2015.[41]
6	Dissolution enhancement of **AST calcium** by co-grinding technique	Prabhu.P *et.al* 2015.[42]
7	Coamorphous **AST Calcium** to Improve its Physicochemical and Pharmacokinetic Properties	Shayanfar. A. *et.al* 2013.[43]
8	Enhanced Bioavailability and Dissolution of **AST Calcium** from Floating Microcapsules using Minimum Additives	Nazimuddin.F.*et.al.*2011.[40]
9	custom fractional factorial designs to develop **AST** self-nanoemulsifying and nanosuspension delivery systems – enhancement of oral bioavailability	Fahima M *et.al.*2015.[44]
10	The studies of PLGA nanoparticles loading **AST calcium** for oral administration in vitro and in vivo.	Zhenbao L *et.al.*2016.[45]
11	Self-nano emulsifying drug delivery system (SNEDDS) for oral delivery of **AST formulation** and bioavailability studies	Venkatesh M. *et.al.*2013.[46]
12	Preparation, Evaluation, and Optimization of **AST** Nanosuspension Incorporated Transdermal Patch.	Subramanian.S *et.al*.2016.[47]
13	Formulation and Evaluation of Solid dispersion of **AST Calcium.**	Monika S *et.al*.2013.[48]
14	Micronization of **AST calcium** by antisolvent precipitation process	Hai-Xia Z. *et.al*.2009.[49]

U.V SPECTROSCOPIC ANALYSIS:

Table 3: U.V Spectroscopic analysis

S.no	Absorbance	Beer's Range	Standard Deviation	Regression Coefficient	Reference
1	246 nm	5-25µg/ml	0.1604	0.02573	Kailash.P *et*.al.[50]
2	246.5nm	5-30µg/ml	0.896	0.9992	Baldha.R.*et*.al.[52]
3	245nm	8-24µg/ml	0.742	0.671	Dhable.N.*et*.al.[53]

HPLC METHOD OF ANALYSIS:

Table 4: HPLC method of analysis

Sl. no.	Column	Mobile phase	Spectro-photometer set	Flow Rate	Injection Volume	Retention Time	References
1	Octadecylsilane bonded to porous silica (5µm)	Acetonitrile and Tetrahydrofuran	246 nm,	1.8ml	20µl	20min.	Indian pharmacopoeia 2018 volume 2 page No 1287.
2	Kromasil	Acetonitrile and Orthophosphoric acid 0.1%	246nm	1.5ml	20µl	4.98min	Elasdig.H *et.al.*2015.
3	C18 column	Acetonitrile and Orthophosphoric acid	245nm	1.5m	100µl	25 min.	Beta.S *et.al.*2006
4	C18 column	Phosphate buffer and methanol	247nm	1ml	20µl	4.02min.	Gulam.M *et.al*.2010
5	c18 column	Acetonitrile and Ammonium Acetate buffer, Tetrahydrofuran	248nm	1.0ml	100µl	25 min.	Sidika E.*et.al.*, 2003.[17]

CONCULSION

Here we are conducting that different approaches to Improve bioavailability according to our literature survey the solid-dispersion, microspheres, solid-lipid nano particles, and nano suspensions, SNEDDS are the major techniques to improve the bioavailability and in this article reviews analytical method for AST calcium and list of the AST calcium (ATC) formulations related to bioavailability and polymorphism of patent related of ATC and there are still more techniques not attempted to improve bioavailability such as complexation, hydro trophy, particle size reduction, and there are some future aspects are there to improve bioavailability by using natural polymers.

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