IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
September 2019 Vol.:16, Issue:2

Bioavailability Improvement Approaches of Atorvastatin: A Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

NAGESH C*[1], PRASHANTH KUMAR HN[1], HARISH M[1], SANDIP MURTALE[1], JEET BAHADUR MOKTAN [1], ANKIT ACHARYA 1, VINAY C H[2]

1.DEPARTMENT OF PHARMACEUTICS, SRI ADICHUNCHANAGIRI COLLEGE OF PHARMACY, ADICHUNCHNAGIRI UNIVERSITY, B G. NAGAR - 571448- KARNATAKA

2.DEPARTMENT OF PHARMACEUTICS, D.R KARIGOWDA COLLEGE OF PHARMACY HASSAN KARNATAKA -573 -201

Submission: 29 August 2019
Accepted: 5 September 2019
Published: 30 September 2019

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Atorvastatin calcium, Solid dispersion, particle size reduction.

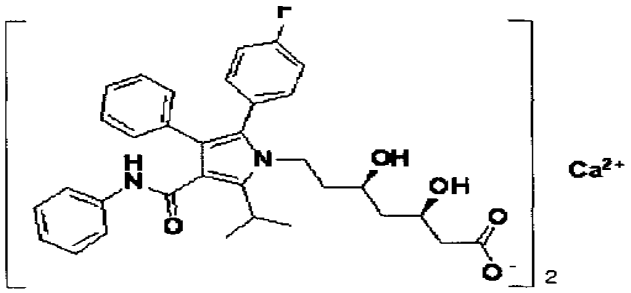
ABSTRACT

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin (ATR) is an inhibitor of 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase (1). This enzyme catalysis the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. According to the biopharmaceutical classification, Atorvastatin belongs under Class II (low solubility and high permeability) Our main objective of this study is to review the work carried out to improve the bioavailability of Atorvastatin Calcium (2). Various approaches such as solid dispersion, Nanosuspension, Cosolvency, were reviewed on this using hydrophilic polymers. and in this article, we discussed patents related to atorvastatin and we reviewed the analytical methods of atorvastatin (3).

INTRODUCTION

Atorvastatin is a selective competitive inhibitor of *HMG CoA reductase*. Atorvastatin reduces total cholesterol, Low-Density Lipoproteins (LDL) cholesterol in patients with mixed dyslipidemia. It also decreases the Very Low-Density Lipoproteins (VLDL)-cholesterol and triglyceride(4). Atorvastatin inhibits the rate-limiting enzyme that converts 3-hydroxy-3-methyl glutaryl coenzyme A to mevalonate, an originator of sterols, containing cholesterol(5). By preventing de novo cholesterol synthesis, they reduce the intracellular source of cholesterol Atorvastatin calcium ([R-(R*, R*)] – 2 - (4fluorophenyl) - β, γ-dihydroxy-5-(1-methyl ethyl)3-phenyl-4- [(phenylamino) carbonyl]-1Hpyrrol- 1heptanoic acid) is hemi-calcium salt.

Chemical structure of atorvastatin



Atorvastatin is very slightly soluble in water, phosphate buffer, at pH 7.4 and acetonitrile. Freely soluble in methanol. The intestinal permeability of atorvastatin is high at the physiological intestinal pH of (6 – 6.5). However, it is reported that the absolute bioavailability of atorvastatin is 12% after a 40 mg oral dose(6). Therefore, it is vital to design effective methods to boost oral bioavailability atorvastatin. (7) Then various methods are adapted to increase the solubility.

Various Methods to Increase Solubility

1)Chemical Modification	2) Physical Modifications	3) Other Methods
1. Salt Formation	1. Particle size reduction	1) Supercritical fluid method
2. Co-solvency	2. Modification of the crystal habit	2) Spray freezing into liquid and Lyophilization
3. Co-crystallization	3. Complexation	3) Evaporative precipitation into an aqueous solution
4. Hydrotropic	4.Solubilization by surfactants	4) Solvent evaporation method
5. Solubilizing agent	5. Drug dispersion in carriers	5) Hot-melt extrusion
6. Nanotechnology	a. Solid solution	6) Electrostatic spinning method
	b. Eutectic mixtures	7) Direct capsule filling
	c. Solid dispersion	8) Polymeric Alteration
		9) High- Pressure Homogenization
		10) Lyophilization technique
		11) Inclusion Complexes:
		a. Kneading Technique
		b. Co-precipitation
		c Neutralization
		d. Co-grinding
		e. Spray-Drying Method
		f. Microwave Irradiation Method

Chemical modification: narrate the modification, addition or removal, between chemical reaction, of any of a variety of substances or organic compounds(8).

Salt Formation: Salt formation is the most usually and successful method of increasing solubility and dissolution rate of acidic and basic drugs(9). Physicochemical principles of salts solubility are presented with special references to the influence of the pH-solubility profile of acidic and basic drugs on the salt formation and dissolution(10).

This Patent Number **WO 2011/089559 Al** Invention provides an improved process for the preparation of Atorvastatin of formula (I) or its salts, preferably hemi calcium salts with purity greater than 99.5% using salts of Atorvastatin such as N, N dicyclohexylethylene diamine salt of Atorvastatin and novel polymorph of Atorvastatin sodium salt. This invention

also provides a process for preparation said salts with increased purity and good yield. The novel salt stated to the present development is useful in the preparation of atorvastatin calcium.

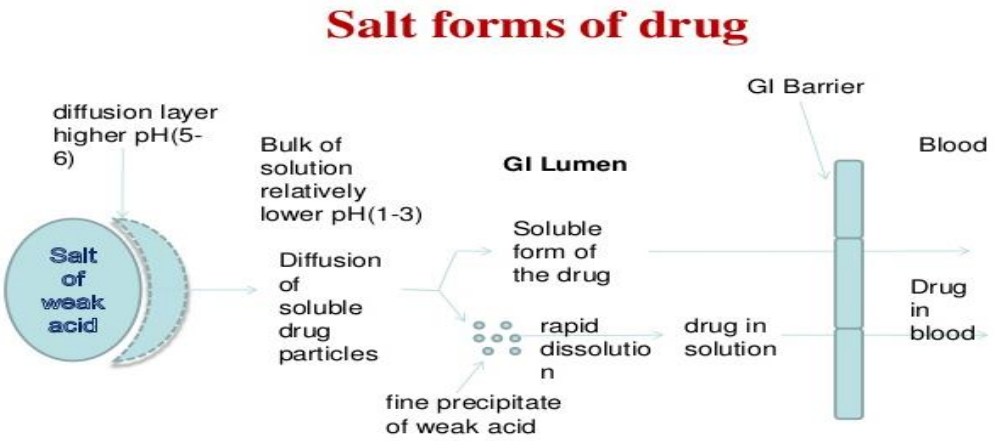


Fig: Dissolution and absorption of an acidic drug administered in a salt form

Cosolvency: is one of the most obtain approaches for improving the solubility of poorly aqueous soluble drugs in pharmaceutical liquid formulations(11). Cosolvents are the mixtures of miscible solvents often used to water which can significantly change in the solubility of poorly aqueous soluble drugs Weakly electrolytes and nonpolar molecules frequently have poor water solubility(12). 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(12)**.**

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%.

Co-crystallisation: is a comparatively new solid form of active pharmaceutical ingredient that offers an alternative(13) platform in improving physicochemical properties of active pharmaceutical ingredients Cocrystal is defined as a stoichiometric multicomponent system connected by non-covalent (14)interactions where all the components neutral and solid under ambient conditions(15).

D. Gozali *et. al.* They have found that Atorvastatin calcium aspartame co-crystal shows better dissolution profile (91.62 % in 60 minutes) than Atorvastatin without cocrystals shows (73.54 % in 60 minutes). The characteristic peaks of ATC and aspartame were gone, although new peaks appeared after the slurry process.

Physical modifications: often aim to increase the surface area(8), solubility and wettability of the powder particles and therefore typically focus on particle size(16).

Particle Size: An important factor for control the dissolution rate is the particle size of the drug(17). The dissolution rate is directly proportional to the effective surface area of the drug which may be increased by physically reducing the particle size(18). Faster initial dissolution rates obtained by grinding or milling the drug can often be attributed to both an increase in the surface area as well as changes in surface morphology that lead to a higher surface free energy(19).

Nanosuspension: A Nanosuspension is defined as very finely dispersed solid drug particles in an aqueous or organic vehicle for either oral and topical use or parenteral and pulmonary administration(20). The particle size distribution of the solid particles in nanosuspension is usually less than one micron with an average particle is ranging between 200 and 600nm(21). It has several advantages such as**,** it can be applied for the poorly water-soluble drugs, Rapid dissolution and tissue targeting can be achieved by intravenous route of administration, Oral administration of nanosuspension provide rapid and improved bioavailability, Long term physical stability due to the presence of stabilizers. Nanosuspensions can incorporate into tablets, pellets, hydrogel(22).

Arun K *et. al.*: Atorvastatin calcium were successfully prepared by high-pressure homogenization and were evaluated for its physicochemical properties. The physicochemical characterization showed that crystalline atorvastatin was converted to amorphous form and exhibited enhanced dissolution rate and high saturation solubility due to its amorphous nature, in comparison with crystalline atorvastatin. The increase in drug dissolution rate and solubility can be expected to have a significant impact on the oral bioavailability of the drug. This study demonstrated the usefulness of the high-pressure homogenization technique as a method of enhancing the dissolution of poorly soluble drug-like Atorvastatin calcium.

PREPARATION OF NANOSUSPENSION

BOTTOM-UP TECHNOLOGY: Means that one starts from the molecular level, and moves via molecular association to the formation of a solid particle. Classical precipitation techniques by reducing the solvent quality, for example, by pouring the solvent into a nonsolvent or changing the temperature or a combination of both(23).

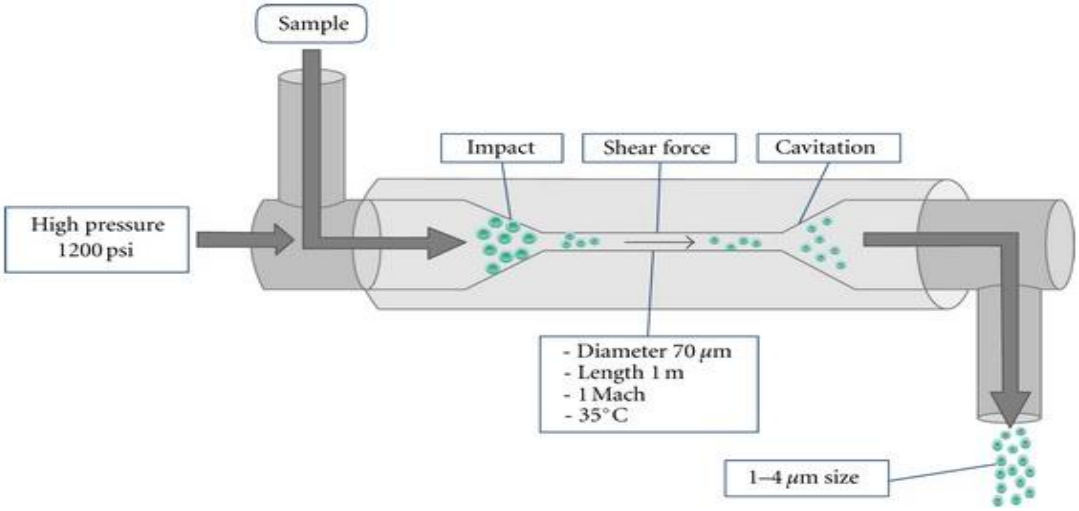
(1) PRECIPITATION METHOD) Drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent for precipitation.in the water-solvent mixture the solubility is low and the drug precipitates. precipitation has also been coupled with high shear processing(24).

TOP-DOWN TECHNOLOGY: Top-Down approaches refers to slicing or successive cutting of bulk material to get nano-sized particles(25).

PREPARATION OF WET MILLING: Milling chamber is charged with the milling media water or suitable buffer, drug, and stabilizer. Milling media are rotated at a very high shear rate(26).

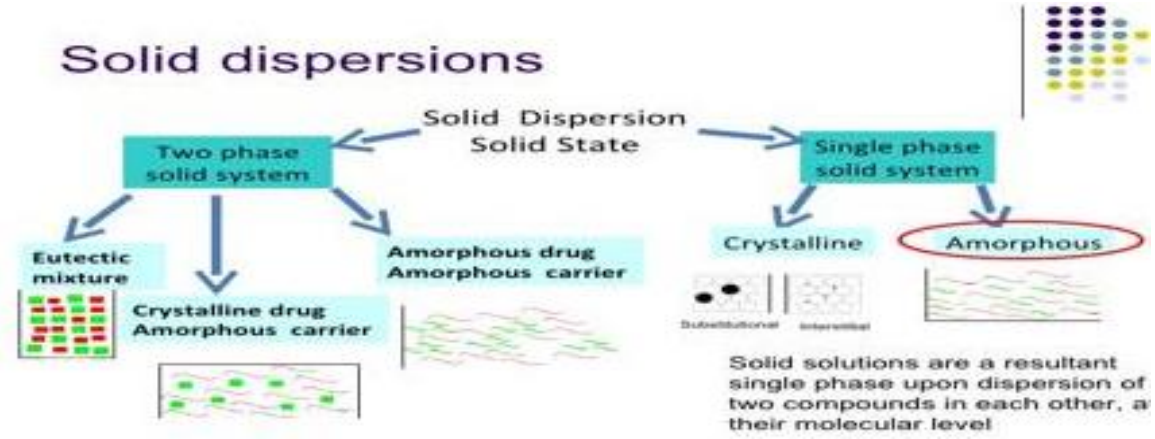
HIGH-PRESSURE HOMOGENIZATION: It is one of the most widely used methods for preparing nanosuspensions of many poorly aqueous soluble drugs.it involves three steps.

- Firstly, drug powders are dispersed in a stabilizer solution to form pre-suspension.
- Secondly, the pre-suspension homogenized in high-pressure homogenizer at low pressure for premilling.
- Finally homogenized at high pressure for 10 to 25 cycles until the nano-suspensions of the desired size are formed(27).



- **SOLID DISPERSION:** There are various techniques for solubility improvement. Solid dispersion is one of the best approaches for solubility enhancement(28). The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug(29). The matrix can be either crystalline or amorphous; basically, amorphous is having good solubility than crystalline substance because no energy is required to break up the crystal lattice of a drug during dissolution process(30). Drug solubility and wettability may be increased by surrounding hydrophilic carriers. And it is also having several advantages such as It increases bioavailability, Fast absorption, Patient compliance, no shaking, no gritty particles are observed(31).

- **Lakshmi N *et. al.*** Conclusion of atorvastatin was found to be the prepared solid dispersions were increased to various characterizations. for them, FTIR studies show there was no degradation of the drug. The solubility and dissolution studies showed there is a possibility of improved solubility of Atorvastatin Calcium through solid dispersion with Polyethylene glycol 6000. A maximum increase in dissolution rate was obtained with Atorvastatin Calcium: PEG 6000 solid dispersion with a weight ratio of 1:3 (drug: carrier). PEG 6000 dispersion by dropping method showed a faster dissolution rate when compared with that of pure drug and physical mixtures. Finally, it can be concluded that solid dispersion by dropping method for Atorvastatin Calcium using hydrophilic polymers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.



PREPARATION OF SOLID DISPERSION

1) HOT MELT METHOD OR FUSION METHOD: In this method, the physical mixture of a drug & water-soluble carrier was heated directly until it melted(32). The melted mixture was then cooled & solidified rapidly in the ice-bath under vigorous stirring the final solid mass was compressing, pulverized & sieved, which can be compressed into tablets with the help of tableting agents(33).

2) SOLVENT EVAPORATION METHOD: In this method, the physical mixture of the drug and carrier is dissolved in a common solvent(34)which is evaporated until a clear, solvent-free film is left. The film is further dried to constant weight(35).

3) MELTING SOLVENT METHOD: The melting or fusion method, first proposed by (Sekiguchi and Obi 1961) involves the preparation of a physical mixture of a drug and a water-soluble carrier and heating it directly until it melted the melted mixture is then solidified rapidly in an ice-bath under vigorous stirring(36). The final solid mass is crushed, pulverized and sieved.

4) KNEADING METHOD: Drug & carrier weighed they are mixed, use motor & pestle to reduce the size of both drug & carrier. Water-methanol mixture 3:1 ratio was added to the above mixture(37). The solution was mixed well and the slurry was collected by filtration and dried in a hot-air oven for 2hrs at 500C. Then dried mass was collected further dried in desiccated for 12hrs. Then the solid dispersion passed to sieve no:80 to obtained uniform particle size(38).

5) MELT EXTRUSION METHOD: The drug or carrier mix is typically processed with a twin-screw extruder(39). The drug/carrier mix is simultaneously melted, homogenized and

then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed.

PATENTS RELATED to ATORVASTATIN CALCIUM

Patent Number	Title	Inventors
US7488750B2	Crystal forms of atorvastatin 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.
EP1562583A1	The present invention relates to Atorvastatin Calcium Form VI or hydrates thereof and a process for preparing it	Manmohan Singh, Baldev Morepen, Jujhar Morepen.
Us7361772B2	Process for the production of atorvastatin calcium	JoyMathew, Madhavan, Sridharan, SambasivamGanesh, Tom Thomas puthiaparampil.
US7732623B2	The polymorphic form of atorvastatin calcium	Ari Ayalon, Michal Levinger, Sofia Roytblat, Valerie Niddam, Revital Lifshitz, Judith Aronhime.
US7994343B2	Process for the production of atorvastatin calcium in amorphous form	Yatendra Kumar, Saridi MadhavaDileepkumar, Swargam Satyanarayana.
US20070032665A1	The present invention relates to a process for the preparation of atorvastatin calcium crystalline Form I.	SrinivasGudipati,Srinivas Katkam,Satyanarayana Komati.

Research work on Atorvastatin:

Sr. No	Topic	Reference
1	Amorphous solid dispersion with increased gastric solubility in tandem with oral disintegrating tablets: a successful approach to improve the bioavailability of **Atorvastatin**(40)	Jumah Masoud M *et.al*.2015.
2	Preparation and characterization and in vivo evaluation of amorphous **Atorvastatin** calcium nanoparticles using supercritical antisolvent (SAS) process(24)	Min-so-Kim-*et.al*. 2008
3	Enhanced Bioavailability of **Atorvastatin** Calcium from Stabilized Gastric Resident Formulation(41).	Furquan Nazimuddin Khan *et.al*.2011
4	Dissolution Improvement of **Atorvastatin** Calcium using Modified Locust Bean Gum by the Solid Dispersion Technique(38)	Dharmila P *et.al* 2013
5	chitosan-based **atorvastatin** nanocrystals effect of cationic charge on particle size, formulation stability, and in-vivo efficacy(19).	Kurakula M *et.al* 2015
6	Dissolution enhancement of **Atorvastatin calcium** by co-grinding technique(42).	Prabhu.P *et.al* 2015
7	Coamorphous **Atorvastatin Calcium** to Improve its Physicochemical and Pharmacokinetic Properties(43)	Shayanfar. A. *et.al* 2013
8	Enhanced Bioavailability and Dissolution of **Atorvastatin Calcium** from Floating Microcapsules using Minimum Additives(44)	Nazimuddin.F.*et.al*.2011
9	custom fractional factorial designs to develop **Atorvastatin** self-nano emulsifying and nanosuspension delivery systems – enhancement of oral bioavailability(4).	Fahima M *et.al*.2015
10	The studies of PLGA nanoparticles loading **atorvastatin calcium** for oral administration in vitro and in vivo.(41)	Zhenbao L *et.al*.2016
11	Self-nano emulsifying drug delivery system (SNEDDS) for oral delivery of **atorvastatin formulation** and bioavailability studies(45).	Venkatesh M. *et.al*.2013
12	Preparation, Evaluation, and Optimization of **Atorvastatin** Nanosuspension Incorporated Transdermal Patch(46).	Subramanian.S *et.al*.2016
13	Formulation and Evaluation of Solid dispersion of **Atorvastatin Calcium**(47)**.**	Monika S *et.al*.2013
14	Micronization of **atorvastatin calcium** by antisolvent precipitation process(31).	Hai-Xia Z. *et.al*.2009

HPLC METHOD OF ANALYSIS:

Sr. 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	20minute	Indian pharmacopeia 2018 volume 2 page No 1287.
2	Kromasil	Acetonitrile and Orthophosphoric acid 0.1%(48)	246nm	1.5ml	20µl	4.98minute	Elasdig.H *et.al*.2015
3	C18 column	Acetonitrile and Orthophosphoric acid(49)	245nm	1.5m	100µl	25 minute	Beta S *et.al*.2006
4	C18 column	Phosphate buffer and methanol(50)	247nm	1ml	20µl	4.02minute	Gulam.M *et.al*.2010
5	c18 column	Acetonitrile and Ammonium Acetate buffer, Tetrahydrofuran(51)	248nm	1.0ml	100µl	25 minute	Sidika E.*et.al*2003

U.V Spectroscopic Analysis

Sr. No.	Absorbance	Beer'Range	Standard Deviation	Coefficient of Variance	Reference
1	246 nm	5-25µg/ml	0.1604	0.02573	Kailash.P *et*.al(52)
2	246.5nm	5-30µg/ml	0.896	0.9992	Baldha.R.*et*.al(53)
3	245nm	8-24µg/ml	0.742	0.671	Dhable.N.*et*.al(54)

SUMMARY

By this article, we conclude that The BCS II drug of atorvastatin calcium was successfully prepared by using conventional methods. such as solid dispersion, Particle size reduction, Complexation, Nanosuspension, etc**.** Solubility was increased significantly as compared to pure drug and we also reviewed Hplc method analysis and UV determinations.

REFERENCES

1. Deveswaran R, Madhavan V, Vittal Gv, Basavaraj B, Bharath S. Formulation and characterization of ketoprofen liquisolid compacts by Box-Behnken design. Int J Pharm Investig. 2012;2(3):150.
2. Rodde MS, Divase GT, Devkar TB, Tekade AR. Solubility and bioavailability enhancement of poorly aqueous soluble atorvastatin: In vitro, ex vivo, and in vivo studies. Biomed Res Int. 2014;2014.
3. Wagh H, Salunkhe KS, Chavan MJ, Hundiwale JC, Asti A, Pere U. A Review on Techniques to Improve Solubility of Poorly Soluble Drugs. World J Pharm Pharm Sci. 2018;7(7):254–67.
4. Ahmed O, Hashem F, Al-Sawahli M, Nasr M. Custom fractional factorial designs to develop atorvastatin self-nanoemulsifying and nanosuspension delivery systems – enhancement of oral bioavailability. Drug Des Devel Ther. 2015;3141.
5. Mehta S, Joseph NM, Feleke F, Palani S. Improving Solubility of Bcs Class Ii Drugs Using Solid Dispersion: a Review. J Drug Deliv Ther. 2018;4(3):7–13.
6. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23–24):1068–75.
7. Sareen S, Joseph L, Mathew G. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012;2(1):12.
8. Chaudhary A, Nagaich U, Gulati N, Sharma V, Khosa R, Partapur M. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J Adv Pharm Educ Res. 2012;2(1):32–67.
9. Serajuddin ATM. Salt formation to improve drug solubility. Adv Drug Deliv Rev. 2007;59(7):603–16.
10. Savjani KT, Gajjar AK, Savjani JK. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm [Internet]. 2012;2012(100 mL):1–10. Available from: https://www.hindawi.com/archive/2012/195727/
11. Kharwade M, Mahitha K, Subrahmanyam CVS, Babu PRS. Cosolvency – An Approach for the Solubility Enhancement of Lornoxicam. 2012;5(8):4204–6.
12. Nayak AK, Panigrahi PP. Solubility Enhancement of Etoricoxib by Cosolvency Approach. 2012;2012.
13. Wicaksono Y. Cocrystal of Atorvastatin Calcium-Malonic Acid. 2017;(August).
14. Wicaksono Y, Wisudyaningsih B, Siswoyo TA. Enhancement of solubility and dissolution rate of atorvastatin calcium by co-crystallization. Trop J Pharm Res. 2017;16(7):1497–502.
15. Nekui, Venus. Sadeghi, Masoumeh Sakh. No Title Comparison of Spiritual Intelligence, Psychological Hardiness in Patients with Coronary Artery Disease and Healthy People. International Conference on New Horizons in Humanities. 1394; 8 (9): 3768–75.
16. Savjani KT, Gajjar AK, Savjani JK. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm [Internet]. 2012;2012:1–10. Available from: https://www.hindawi.com/archive/2012/195727/
17. Salazar J, Müller RH, Möschwitzer JP. Combinative Particle Size Reduction Technologies for the Production of Drug Nanocrystals. J Pharm. 2014;2014:1–14.
18. Schiffter HA, Lee G. Single-droplet evaporation kinetics and particle formation in an acoustic levitator. Part 2: Drying kinetics and particle formation from microdroplets of aqueous mannitol, trehalose, or catalase. J Pharm Sci. 2007;96(9):2284–95.
19. Kurakula M, El-Helw AM, Sobahi TR, Abdelaal MY. Chitosan based atorvastatin nanocrystals: Effect of cationic charge on particle size, formulation stability, and in-vivo efficacy. Int J Nanomedicine. 2015;10:321–34.
20. R. Santosh Kumar* M. Nanosuspensions - a Promising Novel Drug Delivery System. Indo Am J Pharm Sci. 2018;05(4):1478–84.
21. Patel HM, Patel BB, Shah CN, Shah DP. Nanosuspension technologies for delivery of poorly soluble drugs - A review. Res J Pharm Technol. 2016;9(5):625–32.
22. Kumar KV. Preparation and Solid State Characterization of Atorvastatin Nanosuspensions for Enhanced. 2009;1(4):1725–30.
23. Amsa P, Tamizharasi S, Jagadeeswaran M, Sivakumar T. Preparation and solid state characterization of simvastatin nanosuspensions for enhanced solubility and dissolution. Int J Pharm Pharm Sci. 2014;6(1):265–9.
24. Zhang HX, Wang JX, Zhang ZB, Le Y, Shen ZG, Chen JF. Micronization of atorvastatin calcium by antisolvent precipitation process. Int J Pharm. 2009;374(1–2):106–13.

25. Anwar M, Warsi MH, Mallick N, Akhter S, Gahoi S, Jain GK, et al. Enhanced bioavailability of nano-sized chitosan-atorvastatin conjugate after oral administration to rats. Eur J Pharm Sci [Internet]. 2011;44(3):241–9. Available from: http://dx.doi.org/10.1016/j.ejps.2011.08.001
26. Shid RL, Dhole SN, Kulkarni N, Shid SL. Nanosuspension: A review. Int J Pharm Sci Rev Res. 2013;22(1):98–106.
27. Siya M, Sinai Kunde D, Bhilegaonkar S, Godbole AM, Pankaj Gajre M. Biopharmaceutical Classification System: A Brief Account. Int J Res Methodol. 2015;1(1):20–46.
28. Argade PS, Magar DD, Saudagar RB. Solid Dispersion: Solubility Enhancement Technique for poorly water soluble Drugs. J Advcanced Pharmarcy Educ Res. 2013;3(4):427–39.
29. Choudhary A, Rana AC, Aggarwal G, Kumar V, Zakir F. Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability. Acta Pharm Sin B [Internet]. 2012;2(4):421–8. Available from: http://dx.doi.org/10.1016/j.apsb.2012.05.002
30. Bobe KR, Subrahmanya CR, Suresh S, Gaikwad DT, Patil MD, Khade TS, et al. Formulation and evaluation of solid dispersion of atorvatstatin with various carriers. Int J Compr Pharm. 2011;02(01):1–6.
31. N TM. Solubility Enhancement of Atorvastatin Calcium by Using Microwave Assisted Solid Dispersion Preparation Method. 2015;4(1):51–6.
32. Ashour EA, Majumdar S, Alsheteli A, Alshehri S, Alsulays B, Feng X, et al. Hot melt extrusion as an approach to improve solubility, permeability and oral absorption of a psychoactive natural product, piperine. J Pharm Pharmacol. 2016;989–98.
33. Nikghalb LA, Singh G, Singh G, Kahkeshan KF. Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs. J Appl Pharm Sci. 2012;2(10):170–5.
34. McGinity, O'Donnell. Preparation of microspheres by the solvent evaporation technique. Adv Drug Deliv Rev [Internet]. 1997;28(1):25–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10837563
35. Aggarwal S, Gupta GD, Chaudhary S. Solubility and dissolution enhancement of poorly aqueous soluble drug atorvastatin calcium using modified gum karaya as carrier: In vitro-In vivo evaluation. Int J Drug Deliv. 2012;4(3):341–65.
36. Value SJRI, Roy AK, Mondal S, Bera T. Available online http://www.ijddr.in Covered in Official Product of Elsevier , The Netherlands ATP generation in Leishmania donovani amastigote form Full Length Research Manuscript Full Length Research Manuscript. 2013;5(2):354–61.
37. Khadka P, Ro J, Kim HH, Kim I, Kim JT, Kim HH, et al. Solubility and Dissolution Enhancement of Gliclazide. Int J Pharm Chem Anal [Internet]. 2015;2(3):462–75, 14 pp. Available from: http://www.ijpbs.com/download.php?file=ijpbsadmin/upload/ijpbs_52730eb5983cf.pdf&iid=462
38. Panghal D, Nagpal M, Thakur GS, Arora S. Dissolution improvement of atorvastatin calcium using modified locust bean gum by the solid dispersion technique. Sci Pharm. 2014;82(1):177–91.
39. Backensfeld T, Keitel S, Bodmeier R, Hu S. Melt extrusion ± an alternative method for enhancing the dissolution rate of 17 b -estradiol hemihydrate. Eur J Pharm Biopharm. 2000;49:237–42.
40. Salmani JMM, Lv H, Asghar S, Zhou J. Amorphous solid dispersion with increased gastric solubility in tandem with oral disintegrating tablets: A successful approach to improve the bioavailability of atorvastatin. Pharm Dev Technol. 2015;20(4):465–72.
41. Li Z, Tao W, Zhang D, Wu C, Song B, Wang S, et al. The studies of PLGA nanoparticles loading atorvastatin calcium for oral administration in vitro and in vivo. Asian J Pharm Sci [Internet]. 2017;12(3):285–91. Available from: http://dx.doi.org/10.1016/j.ajps.2016.08.006
42. Prabhu P, Patravale V. Dissolution enhancement of atorvastatin calcium by co-grinding technique. Drug Deliv Transl Res. 2016;6(4):380–91.
43. Shayanfar A, Ghavimi H, Hamishehkar H, Jouyban A. Coamorphous atorvastatin calcium to improve its physicochemical and pharmacokinetic properties. J Pharm Pharm Sci. 2013;16(4):577–87.
44. Khan FN, Dehghan MHG. Enhanced bioavailability and dissolution of Atorvastatin calcium from floating microcapsules using minimum additives. Sci Pharm. 2012;80(1):215–28.
45. Venkatesh M, Mallesh K. Self-Nano Emulsifying Drug Delivery System (Snedds) for Oral Delivery of Atorvastatin- Formulation and Bioavailability Studies. J Drug Deliv Ther. 2013;3(3):131–42.
46. Preparation, evaluation, and optimization of atorvastatin nanosuspension incorporated transdermal patch. Asian J Pharm. 2016;10(4):S487–91.

47. Sharma M, Garg R, Gupta GD. Formulation and Evaluation of Solid Dispersion of Atorvastatin Calcium. J Pharm Sci Innov. 2013;2(4):73–81.
48. Satyadev TNVSS, Ch B, Sundar BS. Pelagia Research Library Development and validation of high performance liquid chromatographic method for the determination of Dolutegravir in human plasma. Der Pharm Sin [Internet]. 2015;6(4):65–72. Available from: http://pelagiaresearchlibrary.com/der-pharmacia-sinica/vol6-iss4/DPS-2015-6-4-65-72.pdf
49. Stanisz B, Kania Ł. Validation of HPLC method for determination of atorvastatin in tablets and for monitoring stability in solid phase. Acta Pol Pharm - Drug Res. 2006;63(6):471–6.
50. Mustafa G, Azeem A, Ahmad FJ, Khan ZI, Shakeel F, Talegaonkar S. Stability-indicating RP-HPLC method for analysis of atorvastatin in bulk drug, marketed tablet and nanoemulsion formulation. J Chil Chem Soc. 2010;55(2):184–8.
51. Ertürk S, Aktaş ES, Ersoy L, Fiçicioğlu S. An HPLC method for the determination of atorvastatin and its impurities in bulk drug and tablets. J Pharm Biomed Anal. 2003;33(5):1017–23.
52. Prajapati KP, Bhandari a. Spectroscopic Method For Estimation of Atorvastatin Calcium in Tablet Dosage Form. Indo Glob J Pharm Sci. 2011;1(4):294–9.
53. Baldha RG, B PV, Bapna M. Simultaneous Spectrophotometric Determination of Atorvastatin Calcium and Ezetimibe in Tablet Dosage Form Simultaneous Spectrophotometric Determination of Atorvastatin Calcium and Ezetimibe in Tablet Dosage Form. 2015;(January).
54. Dhabale PN, Gharge ds. simultaneous spectrophotometric estimation of atorvastatin and fenofibrate in bulk drug and dosage form by using simultaneous equation method. 2010;2(1):325–8.