CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1184375

Available online at: http://www.iajps.com *Review Article*

SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT STRATEGIES FOR EFFECTIVE DELIVERY OF POORLY WATER SOLUBLE DRUGS BY NANO FORMULATIONS AND SOLID DISPERSIONS

Rayapolu Ranga Goud[1*], Gunnala Krishnaveni[2], Girija Prasad Patro[1]

1. NATCO Research Centre, Hyderabad – 500018, Telangana State, India.
2. Mallareddy Institute of Pharmaceutical Sciences, Hyderabad, Telangana State, India.

Abstract:

For the ancient few years, there has been a substantial research done on diverse methodologies for poorly water soluble and lipophilic drugs. More in modern times voluminous molecules cannot be distributed due to low solubility. Now a day frequently, particulate vesicle systems such as nanoparticles, liposomes, microspheres, niosomes, pronisomes, ethosomes, and proliposomes have been used as drug carriers. Drug delivery designates the technique and methodology to conveying medications or drugs. Nanoparticles have been refining the beneficial effect of drugs and minimize the side effects. Basically, Nanoparticles have been arranged by using various techniques as such dispersion of preformed polymers, polymerization of monomers and ionic gelation or coacervation of hydrophilic polymer. Nano particulate formulation approaches could be applied instead as alternative. As in the case of solid dispersions, efficacious permeation of these generally rather difficult to develop approaches into commercial drug product development has taken. This review tries to gives viewpoint for both Nano particulate and solid dispersion technologies.

Keywords: *Nanoparticles, solid dispersions, coacervation, polymerization, drug delivery.*

Corresponding author:

Rayapolu Ranga Goud,
NATCO Research Centre,
Hyderabad – 500018,
Telangana State, India.
E-mail id: ranga.goud@gmail.com

QR code

Please cite this article in press as Rayapolu Ranga Goud et al., ***Solubility and Bioavailability Enhancement Strategies for Effective Delivery of Poorly Water Soluble Drugs by Nano Formulations and Solid Dispersions****, Indo Am. J. P. Sci, 2018; 05(02).*

INTRODUCTION:

The word "Nano" itself denotes as one thousand times smaller than the micro scale, it was occasionally associated with the electronics industry [1]. Nanotechnology is success established at several levels [2]. Their distinctive size dependent things make these materials superior and indispensable in many areas of human activity [3]. The nanomaterial's are most advanced at present, both in scientific knowledge and in commercial uses [4-7]. According to United States of Environmental Protection Agency (USEPA) and National Nanotechnology Initiative (NNI) of the USA, nanotechnology is research and technology development at the atomic, molecular, or macromolecular levels; and the capability to manipulate an atomic scale [8]. They can be metal (gold, silver, copper etc.,), mineral, polymer based or a combination of constituents [9-12]. The water solubility of a drug is a necessary thing that plays significant part in absorption after oral administration. It is directs the opportunity of parenteral direction and also beneficial in retaining and trying of drug properties during design and improvement of drugs [13-14]. Drug solubility is balance measure but the dissolution rate at which solid drug or dosage form passes into solution is an important [15-16]. In drug innovation, the numeral of insoluble drug candidates has improved in latest years, nearly 70% of drugs viewing poor water solubility [17-18]. Solid dispersions have fascinated great interest on current resources of an enlightening the dissolution rate and hence the bioavailability of a range of hydrophobic drugs [19-21]. The excessive interest in improving drug delivery approaches and outstanding to an emergent number of poorly soluble drug candidates has been widely discussed [22-29]. Because of following reasons solid dispersions and Nano particulate based preparations had been an essentially in the attention only of academia but not for pharmaceutical industry [30-31]:

- Deficiency of appropriate industrial and investigative description tools
- Exclusive technologies maintained by a small number of corporations
- Insufficiency of high-ranking management support to capitalize in more precarious machineries
- Lack of understanding to apply the provisions in drug development
- Meta-stable nature

Among countless practices for solubility enrichment, physical modifications of drugs and products such as dropping the unit size and altering crystal pattern are common methodologies to rise drug solubility [32-34]. Apart from conventional micronizing procedures, particle knowledge now deals with various particle and nanoparticle engineering procedures as promising methods for improving drug solubility [35-37].

This assessment effort principally on several particle machineries, from conventional size reduction approaches to current novel procedures that can be used for formulating drugs with reduced aqueous solubility. [38-40].

Approaches to make nanoparticulate products

Nanotechnology carries idea, that the assembly can be ranked and measured in specific ways. There are two diverse methodologies to constructing products with Nano measure features and attributes:

1. Bottom-up technologies
2. Top-down technologies

1. ***Bottom-up technologies:*** This method is directly related to the chemicals industry. It starts with very small components, frequently single particles or even molecules, and gathers these building block units into longer structures obviously the domain of chemistry. In these cases the drug normally dissolves in a solvent composed with stabilizer. The drug solution is precipitated e.g. through a nozzle into an anti-solvent.

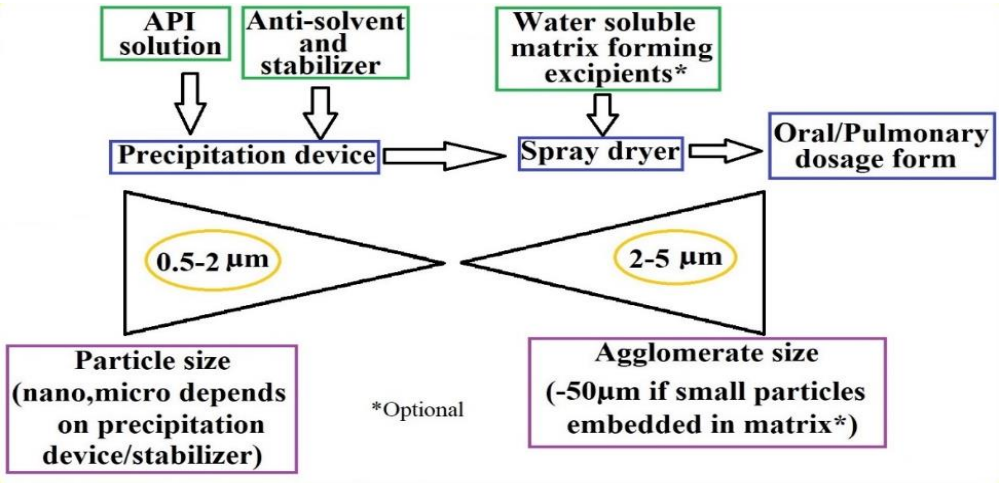

Fig. 1: Schematic representation of manufacturing flow for a bottom-up process

2. ***Top-down technologies***: Mechanical energies affected on crystal construction and which lead to crystal destruction. Limited or complete amorphisation or polymorph alteration can happen.

Note: In both methods surfactants or polymers stabilized the nanoparticles. The top down technologies particularly the ball milling process has led to prosperous promotions of different products and applications broadly designated in patents [41-43]. In this process characteristically the drug suspended in its micronized form in an aqueous medium to simplify the Nano milling. The milling chamber (sizes from 300 ml to 60L) contains raw suspension and grinding medium. The fluid is pumped through a media separator and back again into the milling chamber. A motor driven mechanical agitator shaft bears the impeller and runs high shear agitation up to several thousand rpm. Mill and outside recirculation vessel are jacketed to control the temperature sufficiently (e.g. 5-10°C inlet temperature).

High-pressure Homogenization

Mueller et al., evaluated high-pressure homogenization. A macro suspension comprising an aqueous surfactant is pressures through a small gap of 20-30 μm with a piston. The streaming velocity of fluid dramatically improved by pushing the material through the gap. The static pressure drops behind the gap, water starts to boil. Implosion of the resulting water gas bubbles generates very tough cavitation forces that main to mechanical damage of the crystals [44]. One of the very significant features of nanoparticles is that they characteristically have the affinity to re-agglomerate due to growing status of attractive inter particulate for Vander Waal forces in the 'nm' range. Another phenomenon Ostwald ripening is based on an imbalance between the higher saturation concentration in the vicinity of very small particles and lesser concentrations close to longer particles [45-46].

To overcome these phenomena, nanoparticles can be divided by fostering repulsive forces among them or keeping them apart via steric interference by adsorbing polymeric stabilizers such as hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), povidone (PVK K 30) and copolymers like pluronic F68 or F127 (see figure 3)

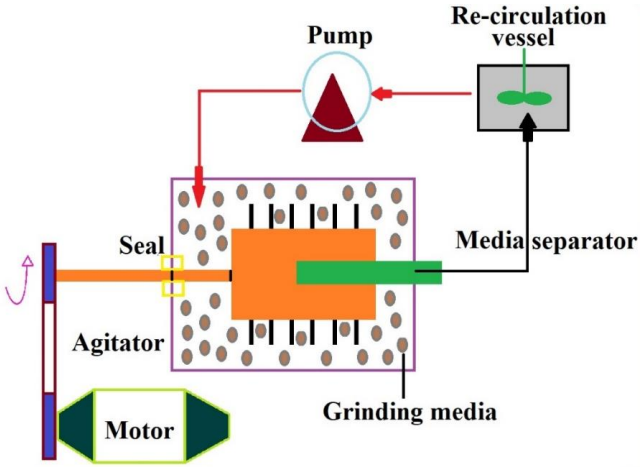

Fig. 2: Schematic representation simplified scheme of a ball milling technology

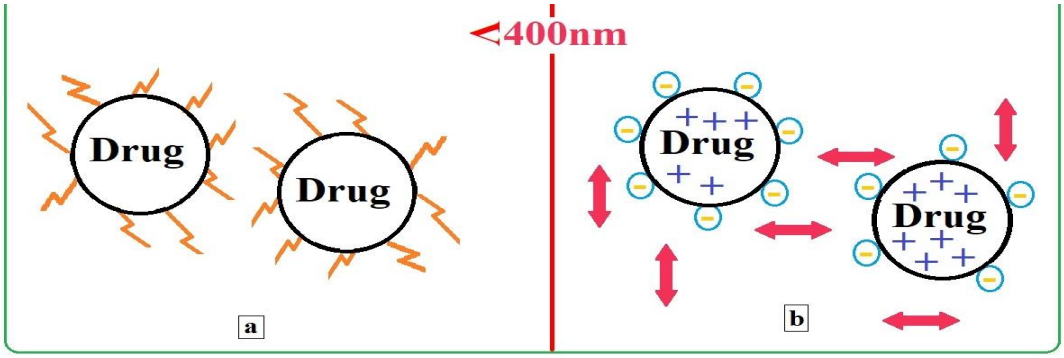

Fig. 3: Stabilization of drug nanoparticles: steric hindrance (a) and repulsive electrostatic forces (b)

Recently Deng *et al.*, described another stability phenomenon by as gel relaxation and shortly after wet milling particle cluster formation has been observed with dramatic morphology changes under the scanning electron microscopy (SEM): With the particle growth up to a maximum a significant viscosity rise has been measured dramatically when the Nano suspension was standing for more than 24 hours. By modifying milling conditions (i.e., milling time, concentration of surfactants etc.) the extent of this phenomenon could be reduced. Adsorption of positively or negatively charged particles at the charged drug surface leads to an electrical double layer and specific electrical charge of drug nanoparticle which is decreasing with increasing distance from nanoparticle surface. The potential at the boundary plane is expressed as `zeta potential` measured in mV units and it should be typically at least 30 mV [47].

Solid dispersion formulations

Typically an oversaturated solution is generated, bearing the threat of fast recrystallization or precipitation. Solid dispersions is preferably based on an amorphous and molecular dispersion of a poorly soluble drug in a carrier matrix which allows to improve dissolution of the drug in water or in physiological media since no crystal lattice energy needs then to be overcome. Three different generations of solid dispersions can be differentiated [48].

1st generation solid dispersions (1960s) using crystalline carriers like fructose, urea, mannitol etc., are lead to improvement of wettability, but again require energy to break up the crystalline structures of the carrier

2nd generation solid dispersions (1970s) using polymeric carriers like poly vinyl alcohol (PVA), hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), ethyl cellulose (EC), poly ethylene glycol (PEG). Due to lone partial miscibility (heterogeneous mixtures of amorphous solutions in polymer) carrier and un-dissolved in small microcrystalline particles

3rd generation solid dispersions (1990s until now): These are modern systems, typically the drug is kept in an amorphous (or Nano crystalline) state and during dissolution no crystal structures need to be damaged up. By addition of surfactants (inulin, lauroyl macrogol glycerides or glyceryl behenate) increase bioavailability of solid dispersions.

Manufacturing technologies of solid dispersions

Classical methods of preparing solid dispersion formulations are:

- Melting method (melt extrusion)
- Solvent evaporation techniques.

The melting processes at high temperatures (>> 100°C), which may lead to thermal degradation of the drug. Melt extrusion has offered an attractive, solvent-free solution to extrude thermoplastic materials (polymers) together with dissolved drugs homogeneously at much lower temperatures than the melting point of the drug and the softening temperature of the polymer. Timpe *et al*, explained more detailed about solvent based manufacturing procedures for solid dispersions [49]. Melt extrusion processes are compared against a solvent co-precipitation [50]. Characteristically for melt extrusion processes drug substances are extruded together with a polymer at high temperatures in a twin extruder to dissolve the drug in the molten polymeric carrier matrix. The mechanical shear forces applied during extrusion represent apart from the high temperature. Twin screw extruders comprise apart from shearing elements heating and cooling segments and allow for short residence times and reduced heating stress due to the continuous mass flow. Manufacturing processes are typically developed on a drug material and carrier specific basis [51]. Homogeneity of the extrudates should be carefully checked; application of confocal Raman spectroscopy described [52].

Physical stabilization principles of solid dispersions

Solid dispersions can principally be stabilized by following methods

Thermodynamic stabilization: The drug concentration is kept below the saturation solubility e.g. in the polymeric carrier matrix.

Kinetic stabilization: In case of less soluble drugs in the polymer, the viscosity of the resulting solid dispersion typically expressed via the glass transition temperature Tg - should be sufficiently high (recommend 40 – 50 K above the intended storage temperature) [54-55].

Screening of solid dispersions

Solid dispersion formulations can be analysed with different analytical techniques regarding

- *In vitro* performance in water, physiological media (simulated gastric fluid (SGF), Fasted State Simulated Intestinal Fluid (FaSSIF), fasted and fed state intestinal bio relevant Media (FeSSIF) etc.) [56-58].
- ***Physical stability:*** Powder X-Ray Diffractometer and Diffractogram (XRPD), Differential Scanning Calorimetry (DSC)/ Scanning Electronic Microscope (SEM), Gas Chromatography (GC) etc., [59].

CONCLUSIONS:

Nowadays, special drug delivery systems are becoming more and most important with the increasing number of poorly soluble drugs. In early, Nano based formulations have gained strong interest now in cases where drugs depict only marginal solubility in lipid and surfactant

excipients and polymers, making development of a self-emulsifying drug delivery system (SEDDS) or Self micro emulsifying drug delivery system (SMEDDS) or solid dispersion nearly impossible and extra research is essential to optimally develop these boosted formulations with improved performance under real *in vivo* conditions.

REFERENCES:

1. Loeve S. About a Definition of Nano: How to Articulate Nano and Technology. HYLE – International Journal for Philosophy of Chemistry, 2010; 16 (1): 3-18.
2. Mazzola L. Commercializing nanotechnology. Nat Biotechnology. 2003; 21(10): 1137-43.
3. Salata OV. Applications of nanoparticles in biology and medicine, J Nano-biotechnology. 2004; 2: 3.
4. Rajiv S, Santosh S and Sugandha S. Nanotechnology: The Future Medicine, J Cutan Aesthet Surg. 2010; 3(1): 32–33.
5. Erika D, Jarpslav F, Tomas B, Peter B, Peter K and Jan T. Nanotechnology in glycomics: applications in diagnostics, therapy, imaging, and separation processes. Med Res Rev., 2017; 37 (3): 514-626.
6. Hari Krishna S, Michael PE, Hui M, Andrew YW, Shuming N, and Lily Y. Development of multifunctional nanoparticles for targeted drug delivery and non-invasive imaging of therapeutic effect. Curr Drug Discov Technol, 2009; 6(1): 43–51.
7. Pelaz B. et al., Diverse Applications of Nano medicine. ACS Nano, 2017; 11(3): 2313-2381.
8. U.S. Environmental Protection Agency, Office of the Science Advisor, Science Policy Council, Nanotechnology White Paper, EPA 100/B-07/001, Feb-2007; Washington: DC 20460.
9. Speshock JL, Murdock RC, Braydich-Stolle LK, Schrand AM, and Hussain SM. Interaction of silver nanoparticles with Tacaribe virus. Journal of Nano biotechnology, 2010; 8:19–27.
10. Alonso A, Macanas J, Davies GL and Gun'ko YK. Environmentally-safe polymer-metal Nano composites with most favourable distribution of catalytically active and biocide nanoparticles in Advances in Nano composite Technology, Intech, Rijeka, Croatia, 2011; 176–200.
11. Rana S and Kalaichelvan PT. Ecotoxicity of Nanoparticles. ISRN Toxicology, 2013; 2013: 1-12.
12. Louis D. Formulation and evaluation of Nano crystals of a lipid lowering agent. Iran J Pharm Res., 2016; 15(1): 71–82.
13. Prakash K et al., Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian Journal of Pharmaceutical Sciences, 2014; 9 (6): 304-316.
14. Damoiseaux R. et al., No time to lose—high throughput screening to assess nanomaterial safety. Nano scale, 2011; 3: 1345-1360.
15. Breitenbach J. Drug delivery, a tool for improved products: Kaletra® tablets, presentation at informa life sciences conference. Strategies to Enhance Solubility and Drug Absorption, 2007, Brussels.
16. Miller M.A et al., Antibody nanoparticle dispersions formed with mixtures of crowding molecules retain activity and *in vivo* bioavailability. J Pharm Sci., 2012; 101(10): 3763–3778.
17. Sandeep K and Vijay Kumar N. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B., 2015; 5(5): 442–453.
18. Ndidi CN et al., Fabrication, modelling and characterization of multi cross-linked methacrylate co-polymeric nanoparticles for oral drug delivery. International Journal of Molecular Sciences, 2011; 12(9): 6194-225.
19. Singh N and Sarangi MK. Solid Dispersion - a Novel approach for enhancement of bioavailability of poorly soluble drugs in oral drug delivery system. Global journal of Pharmacy and pharmaceutical Science, 2017; 3 (2): 001-008.
20. Patel BB, Patel JK, Chakraborty S and Shukla D. Revealing facts behind spray dried solid dispersion technology used for solubility enhancement. Saudi Pharmaceutical Journal, 2015; 23(4): 352-365.
21. Sanjay V and Rudraraju VS. A systematic approach to design and prepare solid dispersions of poorly water-soluble drug. AAPS Pharm SciTech., 2014; 15(3): 641–657.
22. Serajuddin ATM. Solid dispersion of poorly water-soluble drug: early promises, subsequent problems, and recent breakthroughs. Pharm. Sci., 1999, 88: 1058-1066.
23. Karavas E, Georgarakis E, Sigalas MP, Avgoustakis K and Bikiaris D. Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug-polymer interactions, Eur J Pharm Biopharm, 2007; 66(3): 334-47.
24. Fahr A and Liu X. Drug delivery strategies for poorly soluble drugs, Expert Opin. Drug Deliv., 2007; 4(4): 403 – 416.
25. Ahmed MAA and Al-Remawi MM. Freeze dried quetiapine - nicotinamide binary solid dispersions: A new strategy for improving physicochemical properties and *ex vivo* diffusion. Journal of Pharmaceutics, 2016; 2016: 1-11.
26. Gehan B, Mahdi M and Rania AB. Improvement of solubility and dissolution properties of clotrimazole by solid dispersions and inclusion complexes. Indian J. Pharm. Sci., 2011, 73 (5): 517-526.

27. Jiannan Lu et al., Solid-state Characterization of Felodipine-Soluplus® amorphous solid dispersions. Drug DevInd Pharm. 2016; 42(3): 485–496.
28. Abhisekh D, Amit Kumar N, Mohanty B and Panda S. Solubility and dissolution enhancement of etoricoxib by solid dispersion technique using sugar carriers. International Scholarly Research Notices, 2011; 2011: 1-8.
29. Sanjay V and Rudraraju VS. Wetting Kinetics: an alternative approach towards understanding the enhanced dissolution rate for amorphous solid dispersion of a poorly soluble drug. AAPS Pharm SciTech., 2015; 16(5): 1079–1090.
30. Timpe C. Strategies for formulation development of poorly water-soluble drug candidates – a recent perspective. American Pharmaceutical Review, 2007; 10(3): 104 – 109.
31. Timpe C. Drug solubilisation strategies applying Nano particulate formulation and solid dispersion approaches in drug development. American Pharmaceutical Review, 2010; 13(1): 1-14.
32. Deng Z, Xu S and Li S. Understanding a relaxation behaviour in a nanoparticle suspension for drug delivery applications. International Journal of Pharmaceutics, 2008; 351: 236–243.
33. Bibi FC et al., A Menthol-Based Solid Dispersion Technique for Enhanced Solubility and Dissolution of Sulfamethoxazole from an Oral Tablet Matrix. AAPS Pharm SciTech., 2015; 16(4): 771–786.
34. Mahmoudi ZN, Upadhye SB, Ferrizzi D, Rajabi-Siahboomi AR. *In vitro* characterization of a novel polymeric system for preparation of amorphous solid drug dispersions. AAPS J., 2014; 16(4): 685–697.
35. Vyas A and Gidwani B. Technologies to counter poor solubility issues: A review. Research J. Pharm. and Tech., 2013; 6(11): 1258-1270.
36. Viraj VK and Pravin DC. Effectiveness of spray congealing to obtain physically stabilized amorphous dispersions of a poorly soluble thermo sensitive API. AAPS Pharm SciTech., 2014; 15(6): 1370–1377.
37. Yajun L, Gino MS, Keun-joong L, Annette B and Dennis HL. Modulating drug release and enhancing the oral bioavailability of torcetrapib with solid lipid dispersion formulations. AAPS Pharm SciTech., 2015; 16(5): 1091–1100.
38. Ketan TS, Anuradha KG and Jignasa KS. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm., 2012; 2012: 1-10.
39. Hou P, Ni J, Cao S, Lei H, Cai Z, Zhang T, Yu F, Tan Q. Preparation and evaluation of solid dispersions of a new antitumor compound based on early-stage preparation discovery concept. AAPS Pharm SciTech., 2013, 14(2):629-638.
40. Hemlata P, Roshan VT and Michael AR. Hot Melt Extrusion: from Theory to application in pharmaceutical formulation. AAPS Pharm SciTech., 2015; 17(1).
41. Liversidge GC, Cundy KC, Bishop J and Czekai D. 1991. Surface modified drug nanoparticles, US Patent No. 5145684.
42. Liversidge GC and Conzentino P. Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats, Int. J. Pharm., 1995; 125: 309–313.
43. Liversidge GC and Cundy KC. Particle size reduction for absolute oral bioavailability of nanocrystallinedanazole in beagle dogs, Int. J. Pharm., 1995; 127: 91–97.
44. Mueller RH, Jacobs C and Kayser O. Nano suspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future. Advanced Drug Delivery Reviews, 2001; 47: 3–19
45. Shweta G, Rajesh K, Narendra C, Ambikanandan M and Abdelwahab O. Systematic Approach for the formulation and optimization of solid lipid nanoparticles of efavirenz by high pressure homogenization using design of experiments for brain targeting and enhanced bioavailability. Biomed Research International, 2017; 1-18.
46. Corzo MM, Mohan M, Dunlap J and Harte F. Effect of ultra-high pressure homogenization on the interaction between bovine casein micelles and ritonavir. Pharm Res., 2015; 32(3):1055-71.
47. Rantanen J and Khinast J. The Future of Pharmaceutical Manufacturing Sciences. Journal of Pharmaceutical Sciences, 2015; 104 (11): 3612–3638.
48. Vasconcelos T. Solid dispersions as strategy to improve solubility/dissolution of poorly soluble drugs (Presentation), 2nd enhanced solubility and bioavailability IQPC Conference, Frankfurt, 2009.
49. Timpe C, Diederich A and Kalb O. A novel solvent-based fluidized bed wet granulation process for solid dispersions. Am. Pharm. Review, 2008; 11(4): 75 – 81
50. Dong ZA, Chatterji A, Sandhu H, Choi DS, Chokshi H and Shah N. Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. Int. J Pharm, 2008; 335:141-149.
51. Xu, H et al., Preparation of evodiamine solid dispersions and its pharmacokinetics. Indian Journal of Pharmaceutical Sciences, 2011; 73(3): 276-281.
52. Breitenbach J et al., Confocal Raman spectroscopy: analytical approach to solid dispersions and mapping of drugs, Pharm. Res. 1999; 16: 1109- 1113.
53. Yu L. Amorphous pharmaceutical solids: preparation, characterization and stabilization, Adv. Drug Deliv. Rev., 2001; 48 (1): 27 – 42.

54. Jeon IY and Baek JB. Nano composites derived from polymers and inorganic nanoparticles. Materials, 2010; 3: 3654-3674.
55. Sivacharan K and Rajesh Kumar G. Pharmacokinetic aspects and in vitro *in vivo* correlation potential for lipid-based formulations. Acta Pharmaceutica Sinica B, 2014; 4(5):333–349.
56. Margareth M. Dissolution media simulating fasted and fed states. Dissolution Technologies, 2004: 16.
57. Jadi RK, Bomma R and Sellappan V. Development of a new single unit dosage form of propranolol HCl extended release non-effervescent floating matrix tablets: *In vitro* and *in vivo* evaluation. Journal of Applied Pharmaceutical Science, 2016; 6 (5): 112-118.
58. Jadi RK, Tatikonda A, Veera Reedy PR and Venisetty RK. Design and Characterization of Pregabalin Swellable Core Osmotic Pumps. International Journal of Pharmaceutical Research and Allied Sciences, 2016; 5(3): 8-15.
59. Togaru V, Venisetty RK, Bakshi V and Jadi RK. Formulation development and *in vitro* evaluation of propranolol hydrochloride extended release matrix tablets. Emergent Life Sciences Research, 2017; 3(1): 38-47.