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Review Article

# Performance Enhancement of Water Insoluble Drugs Using Novel Formulation Technique

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**ABSTRACT**
With increasing poorly water soluble drugs in pharmaceutical industry, nanosized formulations is a growing strategy in increasing the solubility of poorly water soluble drugs. Nanosized formulations are prepared by bottom up, top down, top down and bottom up, and spray drying. The advantages of using nanoparticles as a drug delivery system include increased dissolution rate, increased rate of absorption, increased oral bioavailability, rapid effect, improved dose proportionality, reduction in required dose.

**Key words:** Nanoparticles, Oral Bioavailability, Absorption, Solubility

## INTRODUCTION

The number of poorly water-soluble drugs in pharmaceutical industry is steadily increasing. About 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from chemical synthesis are poorly water-soluble[1]. Absorption of drugs from gastrointestinal tract needs concentration gradient of the drug across the membrane which in turn is dependent on drug release from its pharmaceutical form and its dissolution into gastrointestinal fluids. The solubility-dissolution behaviour of a drug is frequently the rate-limiting step to absorption of drugs from the gastrointestinal tract. Consequently poorly water soluble drugs exhibit poor oral bioavailability (BCS class II drugs). Poor aqueous solubility has always been a very challenging obstacle as it is, together with membrane permeability, an essential factor in the limitation of a drug's bioavailability following oral administration[2]. Since an increasing number of newly developed drug candidates in pre-clinical development phases present poor water-solubility characteristics, there is a great need for formulation approaches to overcome this factor.

Historically poorly-water soluble compounds were viewed as highly risky development candidates[3]. In the past, the overwhelming consensus was that poorly-water soluble drug candidates would be problematic to develop and there would be numerous post launch issues prompting clinicians to prescribe such medications cautiously and when available, alternative therapies to improve compliance, efficacy and safety would be prescribed. To address this need, a significant amount of attention over the years has been focused on formulation strategies for this class of molecule which includes molecules in BCS classification II (poorly soluble and highly permeable) and Class IV (poorly soluble and impermeable). According to an FDA survey conducted between 1995 and 2002, only 9% of the new drug entities belonged to BCS class-I category (high solubility-high permeability), majority of new drug candidates (approximately more than 40%) have poor aqueous solubility which leads to low bioavailability. By adopting different strategies, such as complexation with cyclodextrin, solid dispersion, cryogenic techniques[4], floating granules[5] and self-emulsifying drug delivery system, solubility-dissolution profile and thereby bioavailability of drugs can be improved[6].

Out of the many ways to increase a product's solubility/dissolution rate characteristics with the aim of enhancing its oral bioavailability, drug formulation as nanoparticles has received much-increased interest over the last decade. The hypothesis behind dissolution rate enhancement, considering drug particle size reduction to nanometer range, lies primarily in a much-increased effective surface area (Noyes-Whitney) presented by the resulting drug nanoparticles. Nanoparticles are defined as particulate dispersion or solid particles with size range of 10- 1000nm.The drug is dissolved, entrapped, encapsulated or attached to nanoparticle matrix. Depending upon method of preparation nanoparticles, nanospheres or nanocapsule can be obtained. The advantages of using nanoparticles as a drug delivery system include increased dissolution rate, increased rate of absorption, increased oral bioavailability, rapid effect, improved dose proportionality, reduction in required dose. The two existing technologies used for nanoparticles preparation are bottom up and top down. Bottom up technologies start from the molecules which are dissolved and precipitated then by adding the solvent to a non-

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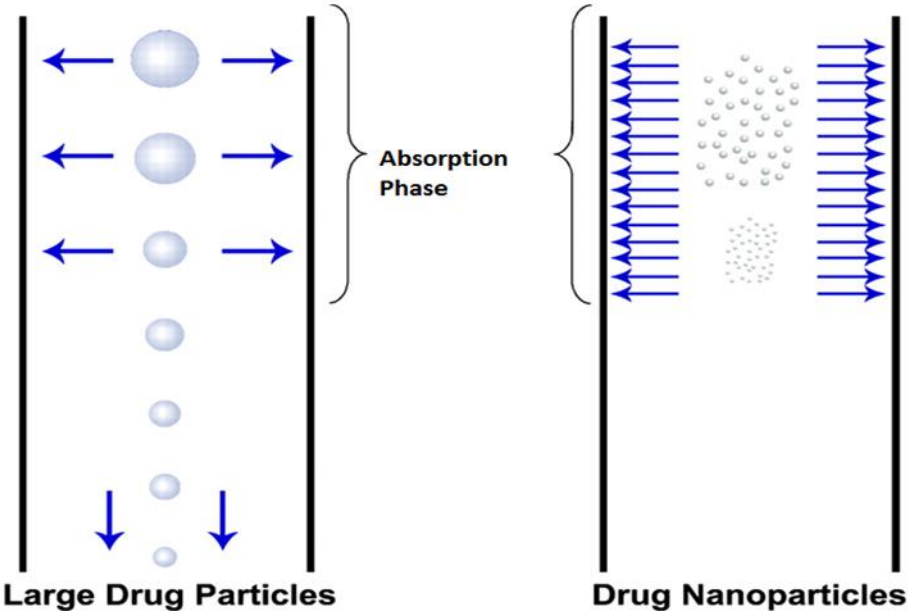



solvent. Various techniques involved are coacervation, ionic gelation, solvent evaporation method, spontaneous emulsification or solvent diffusion method, polymerization, supercritical fluid technology. Top down technologies are disintegration methods, e.g. various types of wet milling.

Advantages of Nanoparticles

- Increased rate of absorption due to enhanced solubility results in increased oral bioavailability
- Improved dose proportionality,
- Reduction in required dose,
- Reduction in fed/fasted variability,
- Rapid, simple and cheap formulation development
- Possibility of high amounts (30-40 %) of drug loading,
- Increased reliability. Usually side effects are proportional to drug concentration, so decreasing the concentration of active drug substances leads to an increased reliability for patients.
- Improved stability. They are stable systems because of the use of a stabilizer that prevents reaggregation of active drug substances during preparation.
- Applicability to all routes of administration in any dosage form. Oral administration is possible in the form of tablets, capsules, sachets or powder; preferably in the form of a tablet.

Nanoparticle preparation methods: Today, implemented preparation methods of nanocrystal formulations can be classified as "bottom up", "top-down", "top down and bottom up" and "spray drying".

Bottom up Technology: Bottom up" technology relies on precipitation. The principle of this method is based on the dissolution of the active drug substance in an organic solvent which is then added into a nonsolvent (miscible with the organic solvent). In the presence of stabilizers, thereafter, the nanocrystals are precipitated. Basic advantage of the precipitation technique is that it is simple and has a low cost. Also, scale up is simple in this method.

- Examples of products manufactured by the precipitation method are hydrosols and Nanomorph$^{TM}$, which are developed by Sucker and Soliqs/Abbott respectively.

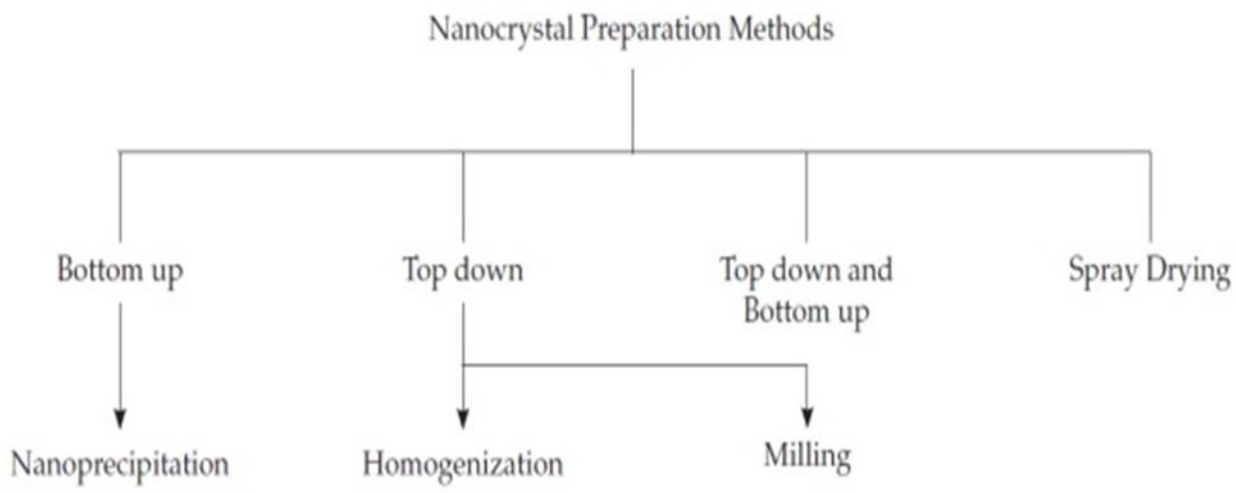
Top down: Top down" technology can be applied by either homogenization or milling. In the milling method; pearl, bead or ball mills can be utilized to prepare a nanocrystal formulation. In this method, the active drug substance and the stabilizer are dispersed in the dispersion medium, and this mixture is then put into a grinder chamber. Balls are rotated at a very high speed and particle size of the drug gets smaller until nanocrystals are obtained. Nanocrystals of drugs; such as N-[[4-(5-Bromo-2-pyrimidinyloxy)-3-chlorophenyl]amino] carbonyl]-2–nitrobenzamide, naproxen, cilostazol, paclitaxel, 3,9-bis(N,N dimethylcarbamoyloxy)-5Hbenzofuro[3,2-c] quinoline-6-one have been prepared by this method and highly improved bioavailability values were obtained.

The other "top down" method is homogenization. One of the preparation methods of nanocrystals is homogenization by ultrasonication. Ultrasonic probes are used to decrease the particle size in liquid or solid dispersed phase. Ultrasonic homogenization is quite effective for reducing the size of hard and soft particles. Homogenization by ultrasonication is based on high frequency mechanical vibrations. Another homogenization method is high pressure homogenization in which two types of homogenizers, namely, microfluidizers and piston gap homogenizers are used. Here, the main goal is to reduce particle size with high pressure homogenization. Piston gap homogenization is performed in water (DissoCubesR), water mixtures or nonaqueous media (NanopureR)

Nanotechnology & Nanoformulations Based Delivery:

Gels Formulation Using Nanoparticles

Low molecular weight heparin nanoparticles transdermal gel: Loira-Pastoriza *et al;* (2012) used a commercial suspension of nanoparticles (Eudragit(®) RS 30D) to manufacture a gel for topical application. Gels were prepared by mixing a polycationic polymer (Eudragit(®)




RS 30D) and a low molecular weight heparin (LMWH), an antithrombotic agent. Gels formed spontaneously at a ratio of 1:1 as a result of electrostatic interactions between the polyanionic drug and the polycationic polymer. The amount of heparin incorporated into the gel matrix was determined. The release kinetics of LMWH from the gel were also studied. Regardless of the LMWH used in the formulation, a biphasic release profile was observed. Accordingly, a burst effect was observed. Afterwards, the release rate became steady. The penetration of the LMWH through the dermal barrier was also investigated.

Rofecoxib Gel Formulation: Malay k Das *et al;* (2007) developed topical gel formulations of rofecoxib. The effects of polymer composition on the rate of drug release from the gel formulations were examined through cellulose membrane mounting on a Keshary-Chien diffusion cell. The effects of initial drug concentration and viscosity on the permeation rate of rofecoxib from the gel formulations were evaluated using rat epidermis at 37-0.5ºC. The anti-inflammatory activity of the rofecoxib gel formulation was evaluated using the rat hind paw edema model. The gel formulation consisting of 4% w/w sodium alginate-Carbopol 940 at 3:1 ratio was found to be suitable for topical application based on in vitro evaluation and ex vivo permeation studies.

Aceclofenac gel using different polymers: Patel *et al;* (2010) developed a gel formulation of aceclofenac using four types of gelling agents: carbopol, hydroxypropyl methyl cellulose (HPMC), carboxymethylcellulose sodium (Na CMC) and sodium alginate. Effect of penetration enhancer (propylene glycol) on the release has been studied. The gels were evaluated for physical appearance, rheological behavior, drug release and stability. The drug release from all gelling agents through a standard cellophane membrane was evaluated using Keshary-Chien diffusion cell. All gels showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value.

Topical delivery of antifungal drug ketoconazole: Najmuddin *et al;* (2010) Designed and evaluated gels for topical delivery of water insoluble antifungal agent ketoconazole with an aim to increase its penetration through skin and thereby its flux. The solubility of ketoconazole is increased by complexation with ß-cyclodextrin were prepared by solvent evaporation technique with 1:1 and then incorporated into gels. The complex was characterized by infrared spectroscopy. Ketoconazole gel formulations were made with different polymers like carbopol 940, hydroxyl propyl methyl cellulose, methyl cellulose, and sodium carboxymethylcellulose, containing various permeationenhancers namely sodium lauryl sulphate (0.5-1.0%) and dimethyl sulfoxide (5-20%) in different proportions. The formulated gels were evaluated for various physicochemical parameters like, drug content, pH, viscosity, spreadability, extrudability, in-vitro drug release. The in-vitro drug release study were carried out using pH 7.4 phosphate buffer, All the formulated topical preparations showed pH in the range of 6.5 to 7.4, and also showed good spreadability, extrudability. The carbopol 940 with 15% of dimethyl sulfoxide (KCD3) showed best in-vitro drug release 98.07% at the end of 6 hrs.

Proniosomal gel of celecoxib: M. Intakhab Alam *et al;* (2010) developed a low dose proniosomal gel containing celecoxib for the treatment of osteoarthritis. All the prepared formulations were subjected to physicochemical evaluations and anti-inflammatory studies. The entrapment was > 90%. The vesicle shape was determined with the help of transmission electron microscopy. The vesicle size, size distribution, and polydispersity studies were performed using photon correlation spectroscopy. Anti-inflammatory studies were performed using the rat hind-paw oedema induced by carrageenan (1% w/v). The selected proniosomal gel (N1LE3) produced 100% inhibition of paw oedema in rats up to 8 h after carrageenan injection. It produced 95% and 92% inhibition after 12 h and 24 h, respectively.

Nanoparticles Using Milling Techniques:

Nanoparticles of ibuprofen: Plakkot *et al;* (2011) reduced particle size of ibuprofen using comminution which resulted in production of crystalline particles with average diameter of approximately 270 nm. Physical stability studies showed that the nano-suspension remained homogeneous with slight increases in mean particle size, when stored at room temperature and under refrigerated storage conditions 2–8 ◦C for up to 2 days. Powder

containing crystalline drug was prepared by spray-drying ibuprofen nano-suspensions with mannitol dissolved in the aqueous phase. Dissolution studies showed similar release rates for the nano-suspension and powder which were markedly improved compared to a commercially available drug product. Ibuprofen nano-particles could be produced rapidly with smaller sizes achieved at higher suspension concentrations. Particles produced in water with stabilisers demonstrated greatest physical stability, whilst rapid dissolution was observed for the nano-particles isolated in powder form.

Nanosuspension Based Technology:

Hydrocortisone nanosuspension: S.M. Ali *et al;*(2011) produced nanosuspension Hydrocortisone drug using microfluidic nanoprecipitation i.e bottom-up technique of drug nanonization. For comparison, a second nanosuspension was prepared by top-down wet milling procedures..Nanosuspensions of approximately 300 nm particle size were produced. X-ray diffraction and differential scanning calorimetry revealed that drug maintained its crystalline structure upon milling, while predominant amorphous particles were generated after precipitation. Ocular bioavailability of nanosuspensions was assessed in albino rabbits using hydrocortisone solution as a control. The precipitated and milled nanosuspension achieved comparable AUC 0–9h values of 28.06±4.08 and 30.95±2.2, respectively, that were significantly ($P>0.05$) higher than that of control solution (15.86±2.7). After 2 months storage at room temperature, the milled hydrocortisone nanosuspension showed good stability with no discernable changes in particle size, whereas the particle size of the precipitated nanosuspension increased to 440 nm.

Piroxicam Nanocrystals: Lai *et al;*(2011) prepared orally disintegrating tablets (ODT) using nanocrystal formulations in order to optimise dissolution properties of lipophilic, poorly soluble drug piroxicam. Different nanocrystal formulations were prepared using a high pressure homogenisation technique and poloxamer 188 as stabiliser. The XRPD and FTIR studies demonstrated that the homogenisation process led to a polymorphic transition from form I (bulk commercial Piroxicam) to form III and monohydrate form of the nanocrystals. All ODT formulations prepared using nanosuspensions showed a higher dissolution rate compared with the ODT prepared with the coarse piroxicam drug. Since the solubility of the different PRX polymorphic forms increased only slightly from bulk piroxicam (form I) to monohydrate, form II and form III, conclusion was drawn that the improvement in piroxicam dissolution rate is mainly caused by the increased surface-to-volume ratio due to the submicron dimension of the drug particles.

Indomethacin Nanosuspension: Verma *et al;*(2011) prepared Indomethacin nanosuspensions with small molecule stabilizers (sodium lauryl sulfate (SLS) and Dowfax 2A1 (DF)) and a polymeric stabilizer (hydroxypropyl methyl cellulose (HPMC)). Two different drug: stabilizer ratios were used to evaluate the effect of micellar solubilized drug. The Ostwald ripening potential of nanosuspensions was evaluated by subjecting them to various stress conditions (temperature (15, 25, 35 and 45 ◦C), thermal cycling, and mechanical shaking) for three months. The mean particle size increased in all SLS and DF formulations stored under different stress conditions. No effect of micellar solubilized drug on the Ostwald ripening rate was observed. In the case of HPMC formulations only those stored at higher temperatures (35 or 45 ◦C) exhibited an increase in mean particle size. The increase in size in the HPMC formulation stored at 45 ◦C was attributed to dehydration of the HPMC chains and subsequent loss of protection of the nanoparticles. The cube of the mean particle diameter versus time plot was determined to be non-linear for all formulations exhibiting Ostwald ripening. Therefore, according to the Lifshitz, Slyozov and Wagner theory the process was not diffusion controlled. The most probable mechanism for Ostwald ripening was surface nucleation controlled.

Itraconazole nanosuspension:-Beirowski *et al;*(2010) Six different drug nanosuspensions containing itraconazole as a drug model were studied using freeze–thaw experiments and a full factorial design to reveal major factors for the stabilization of drug nanosuspensions and the corresponding interactions. In contrast to previous reports, the freezing regime showed no significant influence on preserving the original particle size distribution, suggesting that the concentrations of both the steric stabilizer and the cryoprotective agent are optimized. Moreover, was realized that the combined effect of steric stabilizer and cryoprotectant clearly contribute to nanoparticle stability

Erdenbrugh *et al;*(2009) prepared Solid dispersions by co-spray-drying of TPGS-stabilized itraconazole nanosuspensions with Aerosil®200, followed by heat treatment of the powders. The itraconazole/Aerosil®200 weight ratios amounted to 50/50, 30/70, 40/60 and 20/80. The itraconazole content of the powders was close to the expected value, with relative errors between 0.3% and 7.8%. X-ray powder diffraction (XRPD),solid state NMR (SSNMR) and differential scanning calorimetry (DSC) evaluation on the powders revealed the formation of amorphous itraconazole and the absence of glassy itraconazole. Dissolution of the powderswas enhanced compared to crystalline and glassy itraconazole (a 2-dimensional structured form of itraconazole). However, no clear trend could be observed between drug loading and dissolution performance of the solid dispersions. Upon storage, conversion to crystalline itraconazole was observed for the 50/50 powder based on XRPD, SSNMR and DSC measurements.

Oridonin nanosuspension: Lei Gao *et al*;(2007) made stable nanosuspension with an increased drug saturation solubility and dissolution velocity. The homogenization procedure was optimized in regard to particle size and long-term stability. The characteristics of the oridonin nanosuspension, such as particle size, size distribution, shape, and zeta potential, were evaluated following the water removal. The solubility and dissolution experiments were performed to verify the obvious improvement of the dissolution behavior compared with commercial oridonin. Crystalline state evaluation before and following the

formulation was performed through differential scanning calorimetry (DSC) and powder X-ray (PXRD).

Naproxen nanosupension: Chen *et al;*(2006) flocculated aqueous suspensions of crystalline naproxen nanoparticles, formed by antisolvent precipitation, were with sodium sulfate, filtered, and dried to form redispersible powders for oral delivery. The particles were stabilized with polyvinylpyrrolidone (PVP K-15) and/or poly(ethylene oxide-*b*-propylene oxide-*b*-ethylene oxide) (poloxamer 407). The yield of the drug in the powder was typically 92–99%, and the drug loading was reproducible to within 1–2%. The filtration process increased the drug loading by up to 61% relative to the initial value, as unbound surfactant was removed with the filtrate. Upon redispersion of the dried powder, the average particle size measured by light scattering was comparable to the original value in the aqueous suspension prior to flocculation, and consistent with primary particle sizes observed by scanning electron microscopy (SEM). For 300-nm particles, up to 95% of the drug dissolved in 2 min. The dissolution rate was correlated linearly with the specific surface area calculated from the average particle diameter after redispersion.

Solid Lipid Nanoparticles (SLN):

**Repaglinide SLN**: Rawat, M. K *et al;* (2011) developed prolonged release binary lipid matrix-based solid lipid nanoparticles (SLN) of repaglinide (RG) for oral intestinal delivery and to improve the bioavailability of RG. SLN were designed by using glycerol monostearate and tristearin as lipid core materials and Pluronic-F68 as stabilizer.

**Fenofibrate SLN**: Hanafy *et al;* (2007) study the bioavailability of the poorly soluble fenofibrate following oral administration was investigated in rats. Four formulations were tested: a nanosuspension type DissoCube®, one solid lipid nanoparticle (SLN) preparation and two suspensions of micronized fenofibrate as reference formulations, one suspension in sirupus simplex and a second in a solution of hydroxyethyl-cellulose in physiological saline.

**REFERENCE**


1. Lipinski, C.2002. Poor aqueous solubility – an industry wide problem in drug discovery. Am. Pharm. Rev. 5: 82–85.
2. Heimbach, T., D. Fleisher and A. Kaddoumi. 2007. Overcoming poor aqueous solubility of drugs for oral delivery. In Prodrugs. pp. 157–215, Springer.
3. Krishnaiah Y.S.R., 2010 Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs, J. Bioequivalence Bioavailability. 2: 28–36.
4. Purvis T., M. E. Mattucci, M. T. Crisp, K. P. Johnston, R. O. Williams. 2007. Rapidly Dissolving Repaglinide Powders Produced by the Ultra-Rapid Freezing Process. AAPS Pharm sci. 8(3):1-9.
5. Badawi A.A, H. M. El-Laithy, R K. El Qidra, H.E. Mofty and M. E. Dally.2008 Archives of Pharmacal Research 31(8): 1040-1049.
6. Giliyar C., D.T. Fickstad, S. Tyavanagimatt, 2006. Challenges and opportunities in oral delivery of poorly-water soluble drugs, Drug Deliv. Technol. 6: 57–63.
7. Loira-Pastoriza C., A. Sapin-Minet, R. Diab, JL. Grossiord, P. Maincent. 2012. Low molecular weight heparin gels based nanoparticles for topical delivery, Int J Pharm. 2012 Apr 15;426(1-2) 256-62.
8. Das M.K. 2007. Design, development and evaluation of, Rofecoxib gel, Acta Poloniae Pharmaceutica n Drug Research, Vol. 63 No. 5:461-467
9. Patel J. 2011. Formulation And Evaluation of Topical Aceclofenac Gel Using Different gelling Agent, Int. J. Drug Dev. & Res., 3 (1): 156-164
10. Najmuddin, A.A. Mohsin, T. Khan, V. Patel, S. Shelar. 2011. Formulation and evaluation of solid dispersion incorporated gel of ketoconazole, RJPBCS Vol, 1 (2):407
11. Alam MI., S. Baboota,K. Kohli, J. Ali, A. Ahuja. 2010. Pharmacodynamic evaluation of proniosomal transdermal therapeutic gel containing celecoxib, ScienceAsia 36: 305–311
12. Plakkot S., P. York, M. Saunders,B. Sulaiman.2011. Comminution of ibuprofen to produce nano-particles for rapid dissolution, International Journal of Pharmaceutics 415: 307– 314
13. Lai F.,E. Pini,G. Angioni ,ML. Manca, J. Perricci, C. Sinico, A.M. Fadda. 2011. Nanocrystals as tool to improve piroxicam dissolution rate in novel orally disintegrating tablets, European Journal of Pharmaceutics and Biopharmaceutics 79: 552–558
14. Verma S., S. Kumar, R. Gokhale, D. J. Burgess. 2011. Physical stability of nanosuspensions: Investigation of the role of stabilizers on Ostwald ripening, International Journal of Pharmaceutics. 406:145–152.
15. Eerdenbrugh B V., R. M. Martensb, L. Froyen, J. V. Humbeeck, P. Augustijns,G. V.Mooter. 2009. Itraconazole/ TPGS/Aerosil®200 solid dispersions Characterization, physical stability and in vivo performance, European Journal of Pharmaceutical Sciences 38:270–278.
16. Chen M., Gao L., Zhang, T. Zheng and S. Wang. Preparation and Characterization of an Oridonin nanosuspension for Solubility and Dissolution Velocity Enhancement, Drug Development and Industrial Pharmacy, 33:1332–1339.
17. Rawat M. K., A. Jain and S. Singh. 2011. In-vivo and cytotoxicity evaluation of repaglinide-loaded binary solid lipid nanoparticles after oral administration to rats. Journal of Pharmaceutical Sciences, 100: 2406–2417.
18. Hanafy A, S. Langguth,G. Vergnault, P. Grenier, M. Tubic Grozdanis, T. Lenhardt, P. Langguth. 2007. Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions of micronized drug, Advanced Drug Delivery Reviews, Volume 59, Issue 6,10: 419-426