The Electronic Conference on Pharmaceutical Sciences
ECPS'2011

sciforum
e-conferences

www.sciforum.net

Communication

Nanocrystalline Solid Dispersions of Indomethacin with Hydrophilic Polymers

Ajay Dantuluri[1], Sameer Modi[1] and Arvind Bansal[1,*]

[1] Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), S.A.S.Nagar; Punjab – 160 062. INDIA.

* Author to whom correspondence should be addressed; **Phone:** +91 172 2214682, **Fax:** +91 172 214692, **Email:** akbansal@niper.ac.in

Abstract

Nanocrystalline solid dispersions (NCSDs) of Indomethacin were prepared by antisolvent precipitation followed by spray drying, using hydrophilic polymers like polyvinyl pyrrolidine (PVP K30), hydroxyl propyl methyl cellulose (HPMC E15) and polyvinyl alocohol (PVA) in the ratio of 90:10 w/w. Methonolic solution of Indomethacin was added to aqueous polymeric solution to obtain nano-crystals of Indomethacin, and was spray dried to obtain NCSDs. Crystallite size of Indomethacin in dispersion was measured using by Scherrer equation, which uses powder X-ray diffraction peak broadening of nano-crystallites over micro-crystallites. The average crystallite size of Indomethacin in dispersions was lowest in PVA dispersion followed by HPMC E15 and PVP K30. NCSDs showed considerably higher dissolution rate over crystalline solid dispersions and "as received" Indomethacin in water. NCSDs released 80 - 90% of Indomethacin within 10 min in comparison to 25-50% in case of crystalline solid dispersion and < 5% incase of "as received" Indomethacin. Higher dissolution efficiency of nanocrystalline solid dispersions could be attributed to the nano-size of Indomethacin crystallites, and crystal growth inhibition role of polymers. Influence of viscosity and drug-excipient miscibility (solubility parameter), of polymers used in the present study, on the crystallite size is discussed.

Keywords: Nanocrstalline, Scherrer equation, crystallite size, nanoprecipitation

Introduction

With increasing incidence of poorly-soluble drugs entering the drug discovery pipeline, search for dissolution enhancement techniques is of major interest for the formulation scientist. Of various dissolution enhancement techniques, size reduction to increase the interfacial surface area has attracted lot of attention in recent past.[1,2] Size reduction, especially, nanonization is done either by top-down approach or bottom-up approach.[3] Most common and widely used technique for size reduction is by milling methods such as spiral jet milling. In addition, media milling technology and the high pressure homogenization were used for size reduction of many model drugs. These techniques, however, suffer certain drawbacks such as need of high energy. Moreover, the product obtained after such high energy input has electrostatic charge and broad particle size distributions. In the last decade, supercritical fluid-based technologies have been widely investigated to obtain submicron sized drug particles.[4] However, these methods are difficult to control and scale up. Bottom-up approach, anti-solvent method is also utilized to prepare nanosized drug particles. In this method, the drug is first dissolved in the solvent and the formed solution is quickly poured to the anti-solvent. Currently, aqueous solutions containing some surfactants are used as the anti-solvent.[5] The stabilizers presented in the aqueous are sorbed on the formed drug particles to inhibit crystal growth. This technique has advantage of being easy and rapid process. However, there might be some disadvantages such as the contamination of drug particles by surfactants sorbed on the surface of the drug particles. Instead, use of hydrophilic polymers in the place of surfactants has extra advantage of enhancing the dissolution rate besides stabilizing the nanoparticles by preventing the crystal growth. The objective of this study was to produce nanocrystalline solid dispersions of indomethacin and investigate the role of polymer in process of precipitation. In this method, solvent was organic solvent and antisolvent was aqueous polymeric solution. Spray drying was used for drying the suspensions. In the present work, we investigate nanoprecipiatation in aqueous polymeric solution, followed by spray drying, as a technology for enhancing dissolution of poorly soluble drugs. Indomethacin was selected as model compound to establish the efficiency of the technology.

Materials and Methods

Materials

Indomethacin (γ-form), received as a gift sample from Jubilant Organosys Ltd., was used as the model drug. Povidone K-29/30 (PVP) (ISP Technologies, INC, USA), Methocel E5 premium LVEP (HPMC)

(Colorcon Asia Pvt. Ltd., India), Poly(vinyl alcohol) (PVA) (Sigma-Aldrich, Inc., Germany) were the polymers used for preparing solid dispersions. All other solvents used are HPLC grade.

Methods

Preparation of nanocrystalline solid dispersions

Nanocrystalline indomethacin-polymer dispersions were prepared by nanoprecipitation followed by spray drying. Nanoprecipitation was caused by addition of methanol solution of Indomethacin (60 mcg/ml) into 0.1% w/w polymeric aqueous solutions. Polymeric solution was continuously stirred at 1700 rpm throughout the process. After complete addition of methanolic solution, stirring was continued for 30 min, after which the suspension was spray dried. The suspension was spray dried using laboratory spray dryer (Labultima spray dryer, India), using the following process parameters

- Feed Rate: 3 ml/min
- Atomization Pressure: 0.95 kg.sq.cm
- Inlet Temperature: 120°C
- Vacuum: 120 mm of WC
- Outlet Temperature: 60°C

The nanocrystalline solid dispersions obtained were collected and stored in P_2O_5 desiccator at ambient conditions.

Preparation of crystalline solid dispersions

Crystalline solid dispersions were prepared in the same way as nanocrystalline solid dispersions, to compare the dissolution profiles. .

Dissolution

A USP/NF paddle method was used at a rotational speed of 100 rpm. Elga water was used as dissolution medium (900ml). It was equilibrated to 37.0 ± 0.5 °C before dissolution. 100mg equivalent Indomethacin of different dispersions was added to dissolution apparatus (Electrolab USP-24, India). Samples were collected at 10, 20, 30, 40, 50, 60, 90 and 120 min, filtered through 0.22 µ filter, and UV absorbance was measured. The dissolution profiles were constructed by plotting the cumulative percent drug released against time.

Analytical Methods

U.V Spectroscopy

Spectrophotometric analyses were performed using a scanning ultraviolet–visible spectrophotometer (Specord 200, Analytikjena Solutions, UK). Calibration plot was obtained in Elga water for the dissolution studies (267 nm, 0.002–0.0020 mg/ml). Six concentrations and three replicates were used for the plotting calibration curve. Linear regression analysis indicated no significant deviations from linearity (R^2=0.999) when intercept was zero.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using Mettler Toledo 821eDSC (Mettler Toledo, Switzerland) operating with Stare software version 2.5.1. Temperature axis and cell constant were calibrated using indium. The samples were analyzed under nitrogen purging (80 ml/min) in pin-holed aluminum pans at a heating rate of 20°C/min over a temperature range of 25 to 220°C.

Powder X-ray Diffraction (PXRD)

PXRD patterns were recorded at room temperature using Bruker's model D8 Advance Diffractometer (Karlsruhe, West Germany) equipped with a compensating slit, using Cu K radiation at 40 kV and 40 mA passing through nickel filter with divergence slit (0.5°), antiscattering slit (0.5°) and receiving slit (1 mm). Samples were scanned over a range of 2Ɵ values from 3° to 40° at a scan rate of 0.01°/ 4 sec. Obtained diffractograms were analyzed with DIFFRACplus EVA (ver. 9.0) diffraction software.

Viscosity Determination

Viscosities of aqueous polymeric solutions were determined using Brookfield viscometer (DV III) with UL adaptor spindle. 250 rpm of spindle was used to attain torque of 10 %. Recordings were noted after 30 sec. All the measurements were done at ambient conditions (20 °C).

Results and Discussion

Results

Solid-form Characterization

PXRD and DSC results indicate the presence of Indomethacin as crystalline form in the nanocrystalline solid dispersions. PXRD pattern of (figure 1) of nanocrystalline solid dispersions prepared using various polymers (PVP K30, HPMC E15 and PVA) did not vary noticeably. However,

the DSC scans (figure 2) showed presence of transitions other than melting, that can be attributed to the differential melting behaviour of indomethacin in presence of polymers and interaction between indomethacin and polymer. In the presence of PVP K30, the melting point of Indomethacin decreased drastically. This indicates that drug has highest interaction with PVP K30, followed by HPMC E15 and PVA.

Figure 1 DSC overlay of nanocrystalline solid dispersions (a.) Indomethacin-PVP K30 dispersion, (b.) Indomethacin – HPMC E15 dispersion and (c.) Indomethacin – PVA dispersion

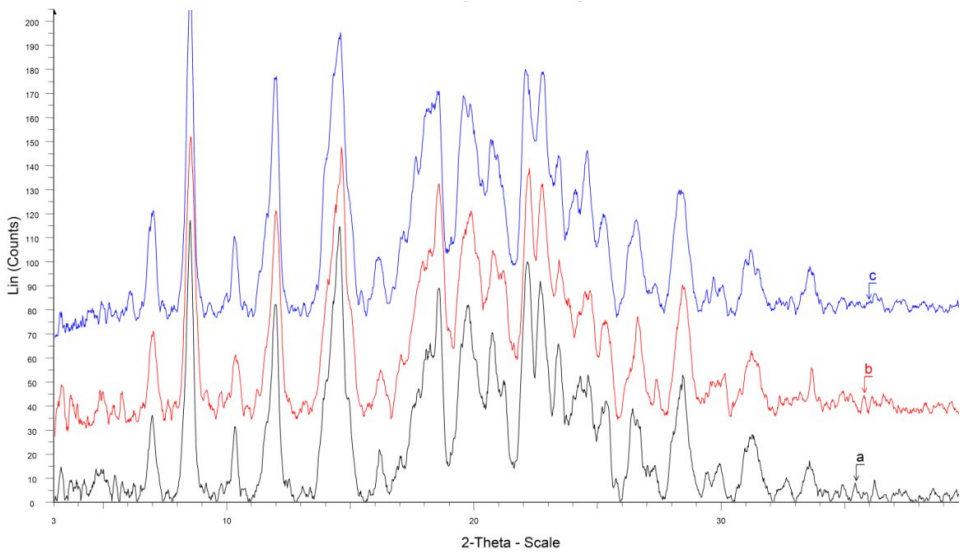
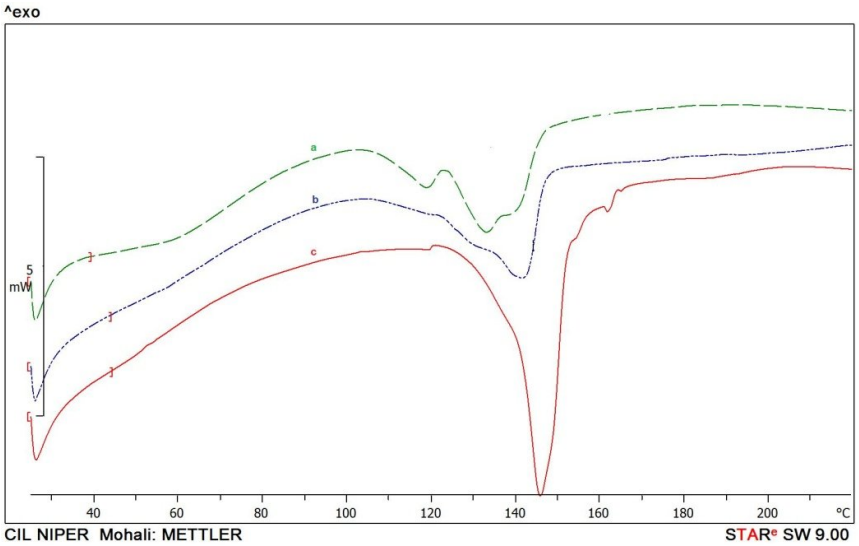


Figure 2 DSC overlay of nanocrystalline solid dispersions (a.) Indomethacin-PVP K30 dispersion, (b.) Indomethacin – HPMC E15 dispersion and (c.) Indomethacin – PVA dispersion



Average crystallite size of Indomethacin in nanocrystalline solid dispersions was calculated based on PXRD peak broadening using the Scherrer equation

$$\tau = \frac{K\lambda}{\beta_\tau \cos\theta}$$

where τ is the mean crystallite dimension, K is a constant of 0.9, λ is the X-ray wavelength (1.542 nm), β_τ is the line broadening value due to crystal size reduction, i.e., the full- width-at-half-maximal (FWHM) difference in radian at a certain Bragg angle (Θ), between a nanocrystalline sample and the micron-sized drug crystals. Table 1 depicts the average crystallite size of nanocrystalline solid dispersions.

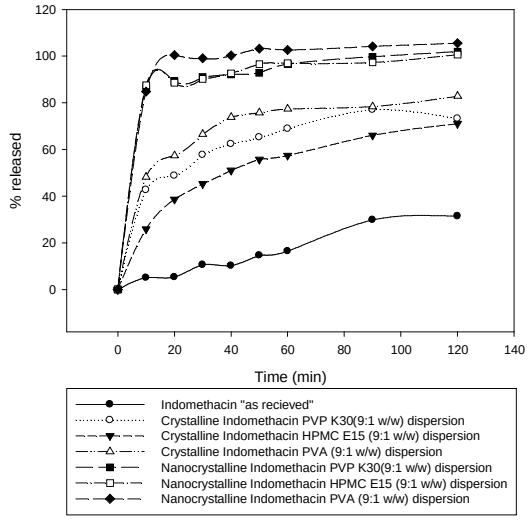
Table 1 Average crystallite size of Indomethacin in nanocrystalline dispersions

Dispersion	**Average Crystallite Size (nm)**
Indomethacin : PVP (9:1 w/w)	85.24
Indomethacin : HPMC (9:1 w/w)	51.93
Indomethacin : PVA (9:1 w/w)	47.17

Dissolution

Nanocrystalline solid dispersions have shown significant dissolution enhancement compared to crystalline solid dispersions and "as received" indomethacin. Figure 3 depicts the comparative dissolution profile of nanocrystalline solid dispersions, crystalline dispersions and indomethacin "as received". Nanocrystalline solid dispersions released more than 85 % in 10 min where as crystalline solid dispersions release varied from 25 to 50 % depending on the polymer used in the dispersion. Indomethacin PVA crystalline dispersion released 48 % compared to 42 % release in PVP dispersion and 26 % in HPMC dispersion. Indomethacin "as received" released only 5 %. This indicated the role of polymers in modulating the dissolution of indomethacin by possibly affecting the interfacial tension.

Figure 3 Comparative dissolution profiles of nanocrystalline solid dispersions, crystalline dispersions and Indomethacin "as received"



Discussion

Role of polymer on crystallite size

As depicted in the Table 1, PVA produced smallest crystallites followed by HPMC E15 and PVP K30. As per the classical nucleation theory, supersaturation is the cause for nucleation, followed by crystal growth. When drug solution is added to antisolvent, supersatuartion is achieved momentarily and is followed by nucleation. The nuclei of critical radius grow into crystals. Size of the crystals is dependent upon extent of nucleation and crystal growth. In the present study, all the process parameters that can influence size of the crystals like solvent: antisolvent ratio, concentration of indomethacin in solvent, stirring, temperature etc., were kept constant to investigate the role of polymer on the crystallite size. Polymers, by virtue of their high molecular weights, increase the viscosity of the solutions. Viscosities of 0.1 % PVP K30, HPMC E15 and PVA aqueous solutions, as determined by Brookfield viscometer, were 1.9, 2 and 2.15 cps respectively. As, the viscosity of PVA solution is high the diffusion of Indomethacin molecules from the solution into growing nuclei is restricted more, as compared to that in case of HPMC E15 and PVP K30.

Role of polymer on dissolution enhancement

Dissolution profiles of crystalline solid dispersions indicated the solubilising efficiency of polymer. As depicted in figure 3, PVP K30 has improved the dissolution efficiency of crystalline Indomethacin more as compared to PVA and HPMC E15. This indicates the PVP K30 contributes positively to the dissolution enhancement but not towards smaller crystallite size.

Conclusion

In the present work, a technique for dissolution enhancement was proposed and established using a model poorly soluble drug, indomethacin. Nanocrystalline solid dispersions of Indomethacin with hydrophilic polymers, PVP K30, HPMC E15 and PVA, are prepared using nanoprecipitation followed by spray drying. Methanol and aqueous polymeric solutions are used as solvent and antisolvent respectively. Presence of Indomethacin in nano-size range in all dispersions has enhanced the dissolution significantly compared to crystalline dispersions. Viscosity of antisolvent was found to be influencing the crystallite size.

Acknowledgement

Ajay Kumar Raju Dantuluri acknowledges Department of Biotechnology (DBT, New Delhi, India) for providing senior research fellowship (Grant Ref. No. BT /PR10084 /NNT /28 /98 /2007).

References

1. Mosharrafand, M., Nystrom, C. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. *Int. J. Pharm*. **1995**, 122, 35–47.
2. Muller, R.H., Jacobs, C., Kayser, O. Nanosuspensions as particulate drug formulations in therapy rationale for development and what we can expect for the future. Adv. *Drug Deliv. Rev.* 2001, 47, 3–19.
3. Dateand, A.A., Patravale, V.B. Current strategies for engineering drug nanoparticles. *Curr. Opin. Colloid Interf.***2004**, 9, 222–235.
4. Jun, S.W., Kim. M.S., Jo, G.H., Lee. S., Woo. J.S., Park. J.S., and Hwang. S.J. Cefuroxime axetil solid dispersions prepared using solution enhanced dispersion by supercritical fuids. *J. Pharm. Pharmcol.*, **2005**, 57, 1529-1537.
5. Paiphansriri. U., Tangboriboonrat. P., and Landfester. K., Polymeric nanocapsules containing an antseptic agent obtained by controlled nanoprecipitation onto water-in-oil miniemulsion droplets. *Macromol. Biosci*., **2006**, 6, 33-40.