Preparation and Characterization of Nanoparticles for Solubility and Dissolution Rate Enhancement of Meloxicam

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Abstract

The aim of the present work was to enhance dissolution of poorly water-soluble meloxicam by preparing stable nanoparticles. Meloxicam nanoparticles were produced by combining antisolvent precipitation and high pressure homogenization approaches in presence of selected stabilizers and converting into dry powders by spray-drying. The physicochemical properties of drug and its nanoparticles were characterized by SEM, XRD, FT-IR, DSC as well as measuring the particle size and in-vitro drug dissolution. The DSC and XRD results indicated that the antisolvent precipitation process led to the amorphization of meloxicam. An increase in the stability of the nanoparticles was also assured by the sufficient adsorption of the stabilizers onto the drug surface. Meloxicam nanoparticles increased the saturation solubility of drug almost fourfold. The in vitro studies at Q_{5min} showed a marked increase in the drug release from just 7% (raw drug) to 82% (Meloxicam nanoparticles). The combining of both the methods was a promising method to produce uniform and stable nanoparticles of meloxicam with remarkable improvement in dissolution rate due to an increased solubility by the effect of increased surface area and change to amorphous form of the drug.

Keywords: Meloxicam, Nanoparticles, Stabilizers, Sonication, Homogenization, Spray Drying.

1. Introduction

A majority of drugs developed and used today suffer from poor oral bioavailability due to poor aqueous solubility and/or low dissolution rate (Chen et al, 2004 and Zimmermann et al, 2007). One of the main focuses of pharmaceutical technology today is developing novel strategies to enhance the solubility of poorly water-soluble drugs. Nanosuspensions are a promising strategy for improving the dissolution rate and oral bioavailability of poorly water soluble drugs by reducing the particle size and/or transforming drugs from a crystalline to an amorphous state (Leuner & Dressmann, 2002; Patravale et al, 2004; Rabinow, 2004 and Kesisoglu et al, 2007). In addition there is generally a reduction in the variability of fed-fasted state bioavailability with nanosuspensions formulation (Rabinow, 2004 and Kesisoglu et al, 2007.). In the present time, an increasing attention has focused on nanosuspensions as observed by a speedy increase in the number of reports on this particular area (Chen et al, 2008; Fakes et al, 2009; Lai et al, 2009; Cerdeira et al, 2010; Pardeike & Müller, 2010 and Shegokar et al, 2010).

There are two common methods to prepare drug nanosuspensions: precipitation method (bottom-up) and disintegration method (top-down) (Rabinow, 2004). The bottom up technology involves dissolving drug in a solvent which is then added to non-solvent to precipitate the crystals. The top down approach relies on mechanical attrition to render large crystalline particles into nanoparticles. The ‘Technology’ includes Media Milling (Nanocrystals®), High Pressure Homogenization in water (Dissocubes®, High Pressure Homogenization in nonaqueous media (Nanopure®) and combination of...
Meloxicam (MLX) is a nonselective, nonsteroidal, anti-inflammatory drug (NSAID) with preferential inhibition of cyclo-oxygenase-2 (COX-2) over COX-1 (Fahmy, 2006). MLX does not have documented cardiovascular toxicity at doses of less or equal to 15 mg/day which are recommended for the treatment of rheumatoid arthritis and osteoarthritis. Meloxicam has been shown to be useful in the symptomatic treatment of painful osteoarthritis (arthrosis, degenerative joint disease), symptomatic treatment of rheumatoid arthritis, symptomatic treatment of ankylosing spondylitis, and symptomatic treatment of the signs and symptoms of osteoarthritis including pain, stiffness, and inflammation (Laurent & Annette, 2000 and Hanft et al, 2001).

The drug is available in tablet dosage form and is practically insoluble in water and peak blood plasma level reaches between 5 to 6 hours after oral administrations. Because meloxicam is practically insoluble in water, attaining sufficient bioavailability of this drug is problematic. Prior art methods of increasing the bioavailability of meloxicam include increasing its solubility by forming a cyclodextrin complex of the drug (Henke et al, 2000) or by forming a salt of meloxicam with an inorganic or organic base (Henke et al, 2002).

Nanoparticulate formulations can be prepared for oral administration for treatment of, for example, migraine headaches. The use of oral nanoparticulate formulations also provides much faster onset of action as compared to conventional orally dosed meloxicam formulations (Cooper et al, 2010).

The aim of this study was to prepare and investigate the properties and mechanism of enhancement of dissolution and oral bioavailability of the stable meloxicam nanoparticles. Although MLX nanoparticles can be prepared by antisolvent precipitation under sonication, the PSD of MLX particles was broad. Thus we made an attempt on using antisolvent precipitation followed by HPH. The physicochemical properties of MLX nanoparticles were investigated. In addition, improvement on in-vitro drug dissolution of nanoparticles was studied.

2. Materials and Methods

2.1. Materials

Meloxicam was obtained as a gift sample from Acme Pharma, Gujarat, India. HPMC E5 and SDS was a kind gift from Cadila Pharma, Gujarat, India. DMF was purchased from S.D. Fine Chemicals Ltd., Ahmedabad, India. All other ingredients were of analytical or pharmaceutical grade.

2.2. Methods

2.2.1. Preparation of Meloxicam Nanosuspensions

Briefly, accurately weighed MLX was dissolved in 10 ml DMF to form organic solution of drug. Specified quantities of HPMC and SDS were dissolved in 200 ml water to anti-solvent system. Both solutions were passed through a 0.45 µm filter (Gelman Laboratory, Mumbai, India). The organic solution was then injected into anti-solvent solution cooled to below 8°C in an ice-water bath and kept under sonication condition. Low temperature (below 8°C) was maintained through out the process using an ice-water bath which controlled the precipitation rate. The treatment was done with an ultrasonic probe sonicator (FS-5, Frontline limited, Mumbai, India.) at ultrasonic power input of 300 W for 20 time length. The probe with a tip diameter of 8 mm was immersed 10 mm in the liquid resulting in the wave traveling downwards and reflecting upwards. The batches were coded with ‘S’ to stand for sonicated batch. The suspensions were kept under vacuum at room temperature for 2 hours to remove DMF.

Further, MLX suspensions were homogenized by HPH (high pressure homogenizer), using an ATS AH100D homogenizer (ATS Engineer Inc. China) at 500 bar for 15 cycles to obtain the final product. The temperature of the suspensions was maintained at -10°C during the process using a circulating ethanol bath (DL-1005, Ningbo Scientz Biotechnology Co., Ltd, China). The batches were coded with ‘SH’ to stand for sonicated and homogenized batch. The sonicated suspension and also homogenized suspension was evaluated for the particle size distribution. This was done to assure the need of incorporation of homogenization stage in the preparation of nanoparticles.

2.2.2. Conversion of Liquid Nanosuspension to Dry Nanosuspension

Different methods are available like lyophilization, spray drying, vacuum drying, evaporation by heating but we are preferred spray drying because it requires less time and energy compared to lyophilization. Solid state formulations are having long term stability compared to liquid state. So, stable batches of preliminary trial were tried to convert in a powder by spray drying technology. A spray dryer (LU-222 ADVANCED lab spray drier, Labultima, India) was used to convert MLX liquid nanosuspensions into dry powders. The inlet air temperature was 105°C. The aspirator was operated at 0.6 m³/min and the pump was set at 4 ml/min. 200 ml MLX nanosuspensions was not diluted before spray-drying and no protectant was added.
2.3. Characterization of MLX Nanoparticles

2.3.1. Particle Size

The average diameter of Meloxicam nanosuspensions was determined by photon correlation spectroscopy (PCS) (Zeta-sizer Nano ZS, Malvern Instruments, UK) at room temperature. Nanosuspension was added to the sample dispersion unit (deionized water) and stirred at 2000 rpm with magnet in order to reduce the inter-particulate aggregation and laser obscuration range was maintained between 10-20%. The samples were adequately diluted with deionized water and placed in an electrophoretic cell. The particle size was measured after performing the experiment in triplicates.

2.3.2. Scanning Electron Microscopy (SEM)

The morphologies of raw MLX and nano-sized MLX were examined using a scanning electron microscope (JEOL JSM-7001F, Japan) operated at an accelerating voltage of 15 kV and a secondary detector. Freshly prepared MLX nanosuspensions and dispersions of raw MLX were deposited on a glass slides following the evaporation of solvent.

2.3.3. X-ray Powder Diffraction (XRD)

X-ray powder diffraction measurements were carried out on samples using a diffractometer (X’Pert MPD Model, Phillips, Holland). The results were recorded over a range of 0–40° (2θ) using the Cu-target X-ray tube and Xe-filled detector. The operating conditions were: voltage 40 kV; current 30 mA; scanning speed 1/min.

2.3.4. Differential Scanning Calorimetry (DSC) Analysis

DSC scans of the powdered samples of meloxicam drug; HPMC E5, SDS and formulation mixtures were studied using DSC- Shimadzu 60 with TDA trend line software. All samples were weighed (8-10 mg) and heated at a scanning rate of 20°C/min under dry air flow (100 ml/min) between 50°C and 300°C.

2.3.5. FTIR Spectroscopy

The pure drug meloxicam and a mixture of it with the polymer HPMC E5 and SDS were mixed separately with IR grade KBr. The powder blends were scanned over a wave number range of 500 to 4000 cm⁻¹ in FTIR 8400S model instrument.

2.3.6. Drug Content

Drug content of Liquid nanosuspension formulation was carried out by taking 1ml of formulation and diluting with phosphate buffer pH 6.8 and the absorbance was measured at 363 nm in UV spectrophotometer. Drug content of dry nanosuspension formulation was carried out by taking powder formulation (weigh equivalent to 5mg of drug) in Phosphate buffer pH 6.8, shaken well and the absorbance was measured at 363 nm with significant dilution in UV spectrophotometer. There was not any interference of other excipients on the absorbance at 363 nm.

2.3.7. Saturation Solubility

Saturation solubility is a compound-specific constant only depending on the temperature and the properties of the dissolution medium. However, below a size of approximately 1–2µm, the saturation solubility is also a function of the particle size. Saturation solubility of plain drug (MLX) and dry nanosuspension formulations were carried out in distilled water for which 5 mg of drug and dry nanosuspensions (weigh equivalent to 5 mg of drug) in 2 ml distilled water were taken separately and were allowed to be stirred in an isothermal shaker (37.0 ± 1.0°C) for 24h. The stirred samples were further taken in test tubes and centrifuged (Remi) at 1000 rpm for 15 minutes. The supernatants were collected and filtered through 0.22µm nylon membrane filter (Gelman Laboratory, Mumbai, India), diluted with Phosphate buffer and absorbance was measured at 363 nm using UV-Visible spectrophotometer. The solubility was measured at 25°C. Every sample was analyzed in triplicate and the mean values and standard deviations were reported.

2.3.8. In-Vitro Dissolution Study

The dissolution profiles of plain drug, dry nanosuspension formulations and marketed formulations (tablet and suspension) were determined in a dissolution tester (TDT-06P Tablet Dissolution Rate Test App Electro, Lab, Mumbai) by USP apparatus II in 900ml phosphate buffer pH 6.8. The dissolution media were maintained at 37±0.5°C with a paddle rotation speed at 50 rpm. The amount of drug used was equivalent to 15 mg. At specified time intervals (5, 10, 15, 20, 25 30 60, 90 and 120 minutes.) 5ml of dissolution media were withdrawn and replaced with an equal volume of the fresh medium to maintained at 37°C to maintain a constant total volume. Samples were filtered through a 0.22µm nylon membrane filter (Millipore, Bedford, MA) and assayed for drug content spectrophotometrically at 363 nm using UV-1700, Shimadzu Corporation, Japan UV/Vis double beam spectrophotometer after appropriate dilution with phosphate buffer pH 6.8. Cumulative percentage of drug dissolved in the preparations was calculated using calibration equations. Dissolution tests were performed in three vessels per formulation (n = 3).
3. Results and Discussion

The method selected for the preparation of initial suspension was antisolvent precipitation under sonication. Here, dimethyl formamide (DMF) was selected as the solvent (the only solvent in which MLX is freely soluble) while water was selected as the antisolvent. MLX nanoparticles were successfully prepared by the combination of antisolvent precipitation and HPH. As can be seen from Table 1, there was a vast difference in the particle size distribution of the raw drug and the sonicated product. Also, a smaller particle size and narrower PSD of MLX nanoparticles was obtained by the combination of antisolvent precipitation under sonication and HPH than that prepared only by sonication. Actually, the reproducibility of particle size of MLX nanoparticles under sonication was poor. It is evident that the uniformity of MLX particle size is significantly improved after homogenization (Table 1), which should be more beneficial to enhance the stability of MLX nanoparticles. The dry powder with nano-sized MLX exhibited good uniformity, the drug content was above 98% and the yield of dry powder was close to 70 %.

### Table 1. Particle Size Distribution of Raw Meloxicam or Meloxicam in Nanosuspension Samples in Water

<table>
<thead>
<tr>
<th>Samples</th>
<th>d (µm)</th>
<th>10%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw MLX</td>
<td>24.75 ±2.54</td>
<td>46.39±7.37</td>
<td>188.52±27.33</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>0.111±0.04</td>
<td>0.259±0.03</td>
<td>4.111±0.93</td>
<td></td>
</tr>
<tr>
<td>SH</td>
<td>0.102±0.03</td>
<td>0.212±0.04</td>
<td>0.285±0.07</td>
<td></td>
</tr>
<tr>
<td>SHD*</td>
<td>0.098±0.01</td>
<td>0.178±0.02</td>
<td>0.273±0.02</td>
<td></td>
</tr>
<tr>
<td>SHD**</td>
<td>0.132±0.03</td>
<td>0.241±0.01</td>
<td>0.289±0.01</td>
<td></td>
</tr>
</tbody>
</table>

* Particle size after spray drying  
** Particle size after 2 months of storage

Additionally, the nanosuspension (batch SHD) was stored in a refrigerator (4°C) for two months. There was no obvious increase in particle size of batch which suggested that stability of MLX nanoparticles was also obtained. Stabilization of the nanosuspension was linked to absorption of HPMC E5 on the surface of MLX nanocrystals, owing to the absence of layered structure (Wu et al, 2011). A combination of HPMC E5 and SDS (2:1, w/w) was the most successful of all the stabilizing agents investigated as far as the formation of MLX suspensions were concerned. The results indicated that HPMC E5 and SDS played a key role in inhibiting the growth of MLX nanoparticles. The above results demonstrated that the combination of antisolvent precipitation under sonication and HPH offered a better and more promising method of producing MLX nanoparticles.

3.1. Study of Stabilizer Concentration

Further, the effect of the stabilizer concentration on the particle size ranging from 0.1, 0.15, 0.3 to 0.6% w/v was investigated. The ratio of the two stabilizers i.e. HPMC E5 and SDS; was kept constant i.e. 2:1 w/w. When the stabilizer concentration was 0.1%, the mean particle size was about 750 nm. This can be increased easily on storage and become unstable. As the stabilizer concentration increased to 0.15%, the mean particle size was dramatically reduced to 183 nm and particle growth can be controlled well by stabilizers. A further increase in the stabilizer concentration, the particle size was not markedly reduced which indicated that the drug particle surface was already sufficiently covered by the stabilizer molecules.

3.2. Study of Different Homogenization Pressure and Cycle Number

The study of the effect of different homogenization pressure and cycle number was done to get optimized process parameters for the homogenization step of the production. The homogenization pressure was increased from 300, 500, 700 to 900 bar gradually at 15 cycles. The study of cycle was done with three different numbers i.e 10, 15 and 20 cycles (Müller & Junghanns, 2006). The particle size of MLX nanoparticles at different pressures is shown in Figure 1.

The particle size of large particles was reduced as the pressure increased from 300 to 500 bar (15 cycles) but the particle size was not markedly reduced at a higher homogenization pressure (700–900 bars). The number of cycles had a greater influence on PSD in comparison with the particle size when the pressure was constant. Once it was clear to have homogenization pressure of 500 bar, further study was carried out with different number of cycles (10, 15, and 20 cycles) at this pressure. When the number of cycles were 15 the PSD is narrower compared to that at 10 cycles. Also, a further increase in the number of cycles had no significant difference in PSD. Thus, in this method uniform and small MLX particles can be produced at low homogenization pressure (500 bar). It indicated that a very high pressure and a large number of cycles were not needed so, the drug damage caused by the high energy generated.

3.3. The Morphology of MLX Nanoparticles

The SEM images are showed in Figure 2. It can be seen that the raw drug particles existed as micro crystals (Figure 2a). However, MLX nanoparticles obtained by the combination of antisolvent precipitation and HPH were spherical with a narrow PSD in the presence of a combination of HPMC and SDS (2:1 w/w) (Figure 2b). It was clearly seen that stabilizers were adsorbed onto the
drug particle surface inhibiting particle growth and thus making the nanoparticles stable. With the formation of spherical particles it can be expected to improve powder properties of MLX, such flow ability and compressibility. The images also revealed that these agglomerates or particle assemblies were composed of a large number of individual nanoparticles.

and spray-dried powder of MLX nanosuspensions along with that of HPMC E5 and SDS are displayed in Figure 3. The raw MLX is crystalline and exhibited crystalline peaks at 20 values from 10 to 30°, indicating crystalline nature of MLX. The MLX/stabilizer physical mixture also showed the characteristic crystalline diffraction peaks of MLX. However, the characteristic crystalline peaks disappeared in the pattern of prepared nanoparticles producing a halo and diffused pattern typical of an amorphous material revealing that the crystallinity of MLX was decreased dramatically.

3.5. DSC Study

235.54° C in the formulation are due to the formation of the peaks of both the excipients. The peak of drug seems to have shifted slightly though it is still prominent. Thus, it was found from these results that the drug and the polymers are compatible with each other. From the results of DSC graph (Figure 4) it is seen that the drug shows a sharp peak at 265.73° C. The DSC graph of mixture shows the drug peak at 265.45° C.

3.4. X-Ray Diffraction

During the preparation of nanosuspensions, three different processes—antisolvent precipitation under sonication, HPH and spray-drying were involved. According to many reports, they all have the possibilities that decrease the degree of crystallinity of drug compounds or transform the drug crystals to its amorphous form (Müller et al, 2001). Therefore, it is significant to investigate the effect of the above three processes on the physical state of MLX. The solid powders were characterized by XRD. The patterns obtained of raw MLX, MLX/stabilizer physical mixture
3.6. FTIR Study

Figure 5 shows the spectrum of MLX, HPMC E5, SDS, physical mixture, and optimized formula of nanosuspension compared in the range of 4000–500 cm⁻¹. In the present study, the interaction between MLX and stabilizers (HPMC and SDS) resulted in noticeable changes in the FT-IR spectra. The spectrum of MLX displayed characteristic peaks at 3291.3 and 1622.02 cm⁻¹ (N-H stretching), 1591.16 cm⁻¹ (C-O stretching), 1163 (S=O stretching) and 1615.27 cm⁻¹ (C=N stretching). In the case of HPMC E5, a sharp absorption at 3471.63 cm⁻¹ was due to the free O-H stretching. In the spectrum of batch SHD, the peaks of N-H stretching were much weaker resulting in a relatively broad absorption band. At the same time, the free O-H stretching band was observed to shift to a slightly lower wave number (3361.69 cm⁻¹). These changes indicated the possibility of hydrogen bonding between the N-H group of MLX and the O-H group of HPMC E5 (Raghavan et al., 2003 and Li et al., 2007). The characteristic peaks in the low frequency region were almost unchanged in the spectrum of batch SHD. The spectra peaks of drug are almost unchanged in the optimized formula of nanosuspension which indicates that the overall symmetry of molecule is not significantly affected. The spectrum of physical mixture was equivalent to the spectrum of the drug and stabilizers indicating no interaction occurring in physical mixing.

3.7. Saturated Solubility

Table 2 shows the saturation solubility of raw MLX and prepared nanoparticles. The results of the solubility study indicated that pure MLX possesses a very low solubility in water (4.4 ± 0.05 µg/mL). In this study, the aqueous solubility of MLX was improved greatly. The saturation solubility of nano-sized MLX (21.84 µg/mL) was four times greater than that of raw MLX (4.4 µg/mL). The reduction of the particle size of MLX to nano scale increased surface area and enhanced hydrophilicity were responsible for the significantly increased saturation solubility.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Saturated Solubility (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLX</td>
<td>4.4 ± 0.50</td>
</tr>
<tr>
<td>PM</td>
<td>5.83 ± 0.62</td>
</tr>
<tr>
<td>Batch SHD</td>
<td>21.84 ± 0.78</td>
</tr>
</tbody>
</table>

3.8. In Vitro Drug Release

The dissolution rates of raw MLX, physical mixture and SHD were studied to check the extent of drug solubility in media in each case. Nano-sized MLX displayed a dramatic increase in the rate and extent of dissolution in comparison with raw MLX especially during the initial stage (first 5
min). SHD exhibited 82.59% drug dissolution within 5 min whereas only 7.43% of raw MLX dissolved during the same period. After 10 min, SHD was almost dissolved completely but only 17.39 % of raw MLX had dissolved owing to its crystalline nature and larger crystal size. The dissolution profile of PM was all the more similar to that of raw MLX which showed that the mechanical physical mixing of raw MLX and stabilizers had little effect on the dissolution of raw MLX. The \textit{in vitro} dissolution of nano-sized MLX was excellent in comparison with that of raw MLX (Figure 6).

According to Noyes-Whitney equation, the solid dissolution rate is directly proportional to its surface area exposed to the dissolution medium. The increased dissolution rate of SHD could be attributed to the combination of effects like amorphization and particle size which was reduced to nano scale, greatly increasing the specific surface area and decreasing diffusion layer thickness.

### 3.9. Stability Study

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. During stability study, optimized formulation was placed in glass vial fitted with aluminum foil and make pinhole in it. The formulation was subjected to stability studies as per ICH (The International Conference of Harmonization) guidelines for a period of 3 months at room temperature and refrigeration temperature (0-4°C). The samples subjected to stability studies were then analyzed at 1 month and 3 months. Dry nanosuspension was evaluated by comparisons of % Drug content and $Q_{5\text{min}}$. Stability study data are shown in Table 3. As observed there were only minor changes in both the data of drug content and $Q_{5\text{min}}$ for a period of 3 months study. This study ensures the formation of stable nanosuspension of meloxicam.

### Table 3. Stability Study for 3 Months

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial</th>
<th>After 1 Month</th>
<th>After 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At Room Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>97.68</td>
<td>97.62</td>
<td>97.58</td>
</tr>
<tr>
<td>$Q_{5\text{min}}$ (%)</td>
<td>82.59</td>
<td>81.16</td>
<td>81.12</td>
</tr>
<tr>
<td><strong>At 4 Degrees</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>97.68</td>
<td>97.32</td>
<td>97.30</td>
</tr>
<tr>
<td>$Q_{5\text{min}}$ (%)</td>
<td>82.59</td>
<td>80.42</td>
<td>78.83</td>
</tr>
</tbody>
</table>

### 4. Conclusion

The solubility and hence the dissolution of BCS class II drug, meloxicam was enhanced by formulating Meloxicam nanosuspension by Bottom up technique (Precipitation method) followed by high pressure homogenization. Spray drying process produced dry nanosuspension with high stability compared to liquid formulation. In the preliminary trials, we found HPMC E5 and SDS provided good stability criteria. Optimization of the process and the formulation was carried out. Batches were analyzed for particle size and % drug content. Stable meloxicam dry nanosuspension batch was evaluated by SEM, XRD, DSC, FTIR, solubility, \textit{in-vitro} dissolution, and stability study. The amorphous MLX nanoparticles showed dramatic improvement in rate as well as extent of \textit{in-vitro} drug dissolution. The improvement can be attributed to amorphization and surface area, reduced particle size and decreased diffusion layer thickness.

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### References


