Suppressing regrowth of microfluidic generated drug nanocrystals using ployelectrolyte coatings

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Materials and Methods:

Meloxicam,4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carbox-amide-1,1-dioxide was purchased from Dayang Chemical, Hangzhou, China, and was used as received. 0.01 M citric acid (pH 3.2) was used to precipitate the drug. Water with a resistivity greater than 18 MΩ.cm was acquired from a Millipure Milli-Q system and used for all experiments. To evaluate the redispersibility and to study the physiochemical properties of the nanoparticles, the resulting nanoparticles were freeze-dried (Labconco freeze dryer model 75035, Labconco Corporation, Kansas City, MO).

A range of conditions were studied in generating the meloxicam nanoparticles as listed in Table 1, with a concentration of the drug maintained throughout the experiments at 5.6 mM.

Table -1: Preparation of Meloxicam drug nanoparticles.

Sample No.	Flow rate (ml/sec) 5.6 mM Drug dissolved in alkaline solution	Flow rate (ml/sec) 0.01M citric acid solution	Rotation Speed	Mean particle size & polydispersity index (PDI)
1	0.3	0.3	1000	90(∂±32) 0.283±0.001
2	0.3	0.6	1000	100(∂±12) 0.034±0.001
3	0.3	0.9	1000	150(∂±45) 0.134±0.001

* All determinations were performed five times and values are expressed as mean ± SD, $n = 5$.

The formation of the unstable semicrystalline nanoparticles arises from the fast nucleation and growth associated with the intense mixing in the dynamic thin film in the RTP. While the

phase of the material is the same as bulk meloxicam, the XRD diffraction patterns show that they are semi crystalline. (Figure S1)

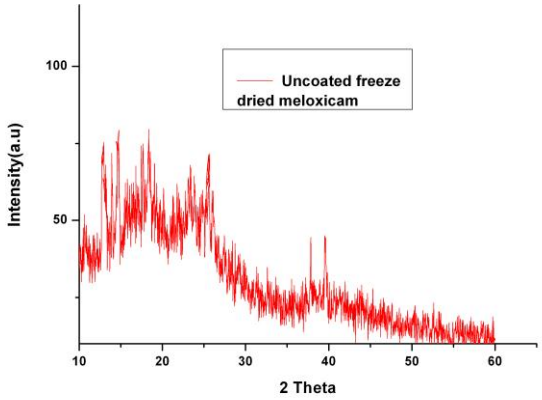

Figure S1 X-ray powder diffraction.

For comparison, precipitation experiments were also undertaken in a conventional flask, using the same concentration of reagents. Immediately after dissolution of the meloxicam in alkaline solution the aqueous citric acid was added forming aggregates of needle shaped crystals (Figure S2) which were similar to those from continuous flow RTP experiments after standing for ca 2 hours.

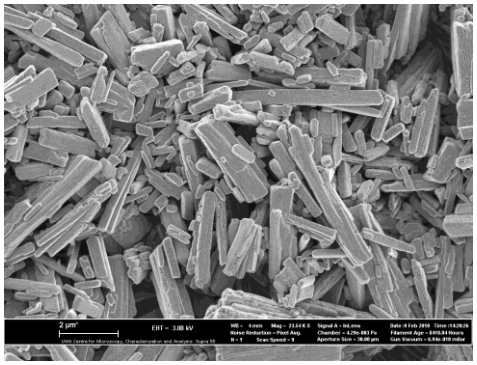

Figure S2 SEM of crystals formed after regrowth.

The size and morphology of the particles were examined using Transmission Electron Microscopy (TEM-2100) and Atomic Force Microscopy (AFM). For TEM studies the samples were fixed on copper grids before analysis. AFM measurements were made on an AFM D5000 instrument, with samples prepared by dispersing the meloxicam nanoparticles in

distilled water, followed by addition of 10 µL of the colloidal suspension onto freshly cleaved mica plates, and then dried over 24 h at 25^{o}C.

The dissolution of meloxicam nanoparticles, micron size particles and physical mixtures was determined using a Hanson Model SR2, USA instrument. The dissolution media consisted of 500 ml aqueous solution at pH 6.5. The paddles were rotated at 50(1) rpm and the temperature was maintained at 37.0(5)°C. The amount of each sample was equivalent to 10 mg of meloxicam dispersed in the medium. A 5 mL aliquot was withdrawn at appropriate time intervals, filtered, diluted with the medium and replaced with 5 mL of freshly prepared medium after each sampling to maintain a constant volume. The amount of meloxicam present was determined spectrophotometrically at 362 nm for uncoated meloxicam nanoparticles, polyelectrolyte coated meloxicam nanoparticles and commercial micron size meloxicam particles respectively. Meloxicam nanoparticles were stored at room temperature for two months. The stability of the material was then studied using DLS.