Adsorption of Meloxicam on Porous Calcium Silicate: Characterization and Tablet Formulation

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ABSTRACT

The purpose of the present study was characterization of microparticles obtained by adsorption of poorly water soluble drug, meloxicam, on a porous silicate carrier Florite RE (FLR) and development of a tablet formulation using these microparticles, with improved drug dissolution properties. The study also reveals the use of FLR as a pharmaceutical excipient. Meloxicam was adsorbed on the FLR in 2 proportions (1:1 and 1:3), by fast evaporation of solvent from drug solution containing dispersed FLR. Drug adsorbed FLR microparticles were evaluated for surface topography, thermal analysis, X-ray diffraction properties, infrared spectrum, residual solvent, micromeritic properties, drug content, solubility, and dissolution studies. Microparticles showed bulk density in the range of 0.10 to 0.12 g/cm^3. Dissolution of drug from microparticles containing 1:3, drug:FLR ratio was faster than microparticles containing 1:1, drug:FLR ratio. These microparticles were used for formulating directly compressible tablets. Prepared tablets were compared with a commercial tablet. All the prepared tablets showed acceptable mechanical properties. Disintegration time of prepared tablets was in the range of 18 to 38 seconds, and drug dissolution was much faster in both acidic and basic medium from prepared tablets as compared with commercial tablet. The results suggest that FLR provides a large surface area for drug adsorption and also that a reduction in crystallinity of drug occurs. Increase in surface area and reduction in drug crystallinity result in improved drug dissolution from microparticles.

KEYWORDS: Florite RE, meloxicam, adsorption, microparticles, dissolution.

INTRODUCTION

Most of the antiinflammatory drugs come under class II (drugs with low solubility and high permeability) according to the biopharmaceutical classification system.[1] For most orally administered poorly water soluble compounds, the bio-absorption is rate limited by dissolution.[2] The rate of drug dissolution of poorly water soluble drugs depends upon the effective surface area, crystal habit, and the energy state within the drug crystals. Although dissolution is directly proportional to the specific surface area of the hydrophobic drugs, other factors such as wettability, air adsorption, and agglomeration also play a vital role in dissolution phenomenon.[3] Various techniques such as spray drying, melt adsorption, and supercritical fluid processes and many polymeric carriers such as polyvinylpyridine (PVP), polyethylene glycol (PEG), and silica carriers have been attempted to load poorly soluble drugs in nano- or microcrystal and amorphous state to improve their dissolution and bioavailability.[3-7]

A relatively newer group of carriers include porous carriers, which are low-density solids with open or closed pore structure and that provide large exposed surface area for drug loading. Their hydrophobicity varies from completely hydrophilic carriers, which immediately disperse or dissolve in water, to completely hydrophobic ones, which float on water for hours. Owing to a wide range of useful properties, porous carriers have been used in pharmaceuticals for many purposes including development of novel drug delivery systems such as floating drug delivery systems and sustained drug delivery systems; improvement of solubility of poorly soluble drugs; and enzyme immobilization.[8-13] Examples of pharmaceutically exploited porous carriers include porous silicon dioxide (Sylysia), polypropylene foam powder (Accurel), porous calcium silicate (Florite), magnesium aluminometa silicate (Neusilin), and porous ceramic.

Florite RE (FLR) is a porous calcium silicate [$2CaO.3SiO_2.mSiO_2.nH_2O$ ($1<m<2$, $2<n<3$)] that possesses many interparticle and intraparticle pores, particularly of sizes 12 and 0.15 μm, respectively, on its surface.[9] FLR is easily dispersible in all aqueous fluids and has been used to adsorb oily and other drugs, as a compressive agent in pharmaceuticals, and to improve solubility.[14-16]

Meloxicam [4-hydroxy-2 methyl-N-(5-methyl-2-thiaolyl)-2H-1,2 benzothiazine-3-carboxamide 1,1-dioxide] is a nonsteroidal antiinflammatory drug (NSAID) used to treat rheumatoid arthritis, osteoarthritis, and other joint pains. It is a preferential COX-2 inhibitor and has a superior

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gastrointestinal tolerability.[17] Meloxicam has a very poor dissolution in aqueous fluids especially in acidic mediums. Many studies have been performed on improving dissolution and bioavailability of meloxicam.[18-20]

The present research work was attempted to improve dissolution rate of meloxicam using FLR as carrier. Meloxicam was adsorbed over FLR using solvent evaporation technique, and the resultant microparticles were evaluated by scanning electron microscopy (SEM), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), infrared spectroscopy (IR), micromeritic studies, and dissolution studies. Microparticles were formulated into a tablet, which was evaluated for physical properties and dissolution rate.

MATERIALS AND METHODS

Materials

Florite RE was a kind gift from Tokuyama Corporation (Yamaguchui, Japan). Meloxicam was supplied as a gift sample by Lupin Research Park (Pune, India). Primogel, magnesium stearate *Indian Pharmacopoeia* (*IP*), polyvinyl pyrrolidone (PVP K-30), and lactose *IP* were supplied by Get-Rid Pharma (Pune, India). All other chemicals were of analytical grade (Merck Ltd, Mumbai, India).

Methods

Preparation and Evaluation of Microparticles

Adsorption of Meloxicam over FLR

Calculated quantity of meloxicam was weighed accurately and put into a stoppered 500-mL round bottom flask (RBF). A quantity equal to 15.6 mL of chloroform per 100 mg of drug was used to dissolve drug, and weighed quantity of FLR was dispersed with shaking into drug solution. FLR was used in 3 different quantities to produce 1:0.5, 1:1, and 1:3 drug:FLR ratios on the weight basis, respectively, for Meloxicam Surface Dispersion (MSD) MSD0.5, MSD1, and MSD3 microparticles. Chloroform was allowed to evaporate under vacuum in rotary evaporator (IKA WERKE RV06ML, Stanfer, Germany) at a constant temperature of 60°C, and RBF was allowed to rotate at a constant speed of 40 rpm. Condensed chloroform was collected from outlet of condenser, and evaporation was terminated when dried powder started freely flowing along the surface of RBF. Collected microparticles were dried for 72 hours at a temperature of 80°C for complete removal of chloroform.

Yield and Drug Content

Microparticle samples were weighed and process yields were calculated. Microparticles (10 mg) were weighed accurately and extracted using 100 mL of phosphate buffer pH 7.6 by shaking for 12 hours on rotary shaker (Steelmet Industries, Pune, India). After filtration through membrane filter of pore size 0.45 μm and sufficient dilutions, samples were analyzed spectrophotometrically at 359.4 nm (Jasco-V500, Tokyo, Japan). Drug content was calculated from the standard curve of meloxicam in phosphate buffer pH 7.6.

Surface Topography

Meloxicam, FLR, and microparticles were coated with a thin gold-palladium layer by sputter coater unit (VG-Microtech, Uckfield, East Sussex, UK) and investigated with a Cambridge Stereoscan S120 SEM (Cambridge, UK).

Differential Scanning Calorimetry

Meloxicam, FLR, and microparticle samples were separately weighed and hermetically sealed in the aluminum pans. A Mettler Toledo DSC 821^e equipped with intracooler, a refrigerated cooling system, was used (Mettler-Toledo, Greifensee, Switzerland). Indium standard was used to calibrate the DSC temperature and enthalpy scale. The system was purged with nitrogen gas at a flow rate of 80 mL/min, and heating was performed from 25°C to 300°C at a rate of 5°C/min.

Powder X-ray Diffraction

PXRD patterns of meloxicam, physical mixture containing equal proportion of drug and FLR, and microparticle samples were obtained using a Philips PW 1729 X-ray diffractometer (Philips, Amsterdam, The Netherlands). Samples were irradiated with monochromatized Cu-K_α radiation (λ=1.542 Å) at 30 kV and 30 mA. The data were recorded over a range of 2° to 60° at a scanning rate of 5×10^3 cps using a chart speed of 10 mm/2θ.

Infrared Spectroscopy

IR spectra of drug, FLR, physical mixtures, and microparticle samples were obtained on Jasco V5300 Fourier transform infrared spectroscopy (FTIR) (Jasco, Tokyo, Japan). The pellets were prepared on KBr press (Spectra Lab, Mumbai, India) using mixture of sample and KBr in ~1:10 ratio. The spectra were recorded over the wave number range of 4000 to 400 cm^{-1}.

Micromeritic Properties

Particle size and particle size distribution of microparticles and FLR samples were determined using particle size analyzer (Mastersizer 2000, Version 2.0, Malvern Instruments Ltd, Malvern, UK). Microparticles were subjected to bulk density and tap density determination using tap density tester *United States Pharmacopeia (USP)* XXIV type II (Electrolab ETD-1020, Mumbai, India). Compressibility index (CI) was calculated for drug, FLR, and microparticles using Equation 1,

$$CI = (1-V/V_o) \times 100, \quad (1)$$

where, V is volume of sample after tapping and V_o is volume of sample before tapping.

Thermogravimetric Analysis

Thermogravimetric analysis (TGA) (TGA-50, Shimadzu Corporation, Kyoto, Japan) was used to determine the quantity of residual solvent in microparticle samples. Air was used as a purge gas and heating was done from 30°C to 90°C at a rate of 5°C/min.

Solubility Studies

For the determination of saturation solubility, samples (pure drug and microparticles) containing known excess (~10mg) of meloxicam were added separately to 10 mL of distilled water and rotated at 20 rpm in a shaking water bath at 25°C ± 0.5°C for 48 hours. The saturated solutions were then filtered with a membrane filter having pore size of 0.45 μm. Filtered solutions were suitably diluted and analyzed by UV spectrophotometer (Jasco V-500) at 359.4 nm.

Dissolution Studies

The dissolution of pure drug (7.5 mg) and microparticle samples (equivalent to 7.5 mg drug) was performed using *USP* XXIV type II dissolution apparatus (Electrolab TDT-06P, Mumbai, India). The dissolution medium used was 900 mL of distilled water (pH 6.8 ± 0.2) maintained at 37° C ± 0.5°C. The paddle speed was 100 rpm. Samples (5 mL) were collected periodically and replaced with equal quantity of dissolution medium. After filtration through Whatman filter paper 41(Whatman, Middlesex, UK), samples were analyzed using UV spectrophotometer (Jasco V500) at 359.4 nm. Data were analyzed by PCP-Disso software (Poona College of Pharmacy, Pune, India).

Preparation and Characterization of Tablets

Microparticles equivalent to 7.5 mg of meloxicam, with primogel (5% wt/wt), PVP-K30 (6% wt/wt), and lactose *IP* (quantity sufficient) were geometrically mixed and lubricated with 2% wt/wt magnesium stearate *IP*. Formulations were passed through a no. 30 mesh sieve and were directly compressed using 10-punch station tablet machine (Rimek mini press, Mehsana, India), using 8-mm diameter, circular punches with flat faces. The machine setting was adjusted to produce tablets of 175 mg weight with hardness of ~2.5 ± 0.25 kg/cm^2.

Friability of tablets (n = 10) was determined by using a Roche friabilator (Electrolab EFL friabilator, Mumbai, India). Hardness tester (PharmaTest PTB, INCORP, Mumbai, India) was used to determine the hardness of tablet samples (n = 10). The disintegration time of tablets (n = 6) was determined using disintegration test apparatus (Electrolab, Mumbai, India) in distilled water maintained at 37°C ± 0.5°C.

Two sets of dissolution studies were performed for tablets in triplicate. In one set, dissolution was performed in 900 mL phosphate buffer (pH 7.4) using *USP* XXIV type II dissolution apparatus (Electrolab TDT-06P, Mumbai). The dissolution medium was stirred at 100 rpm and maintained at 37°C ± 0.5°C. In second set, dissolution studies were performed according to method A of *USP* XXIV for dissolution of enteric-coated (delayed release) tablets: 750 mL of 0.1N HCl for first 2 hours and then 1000 mL of pH 6.8 phosphate buffer for subsequent 3 hours. Drug release in acidic and basic medium was determined using UV spectrophotometer (Jasco V500) at 345 nm and 359.4 nm, respectively. For comparison a commercial tablet (M-Cam 7.5 mg, Unichem, Maharashtra, India) was also simultaneously studied. Data obtained from dissolution studies of formulated and commercial tablets was statistically analyzed by one-way analysis of variance (ANOVA) followed by Tukey posttest using Graphpad Instat Version 3.05 software (Graphpad Software Inc, San Diego, CA). A value of $P < 001$ was considered significant.

Results and Discussion

Process Design

Meloxicam has a very poor solubility even in polar organic solvents such as ethanol and methanol.[20] Ethanol basified with ammonium hydroxide to pH 8 ± 0.5 was first used as solvent in the present study, but its quantity required was ~10-fold more than chloroform. Therefore, chloroform was selected as a solvent in which meloxicam showed moderate solubility. Because of the porous nature of FLR, it possesses a low density and hence to limit bulk volume, the ratio of drug:FLR was restricted to a maximum of 1:3. Preliminary studies to obtain microparticles were performed by using 3 different drug:FLR ratios (1:0.5, 1:1, and 1:3), but MSD0.5 was not further evaluated and formulated because of its slower and extended drug dissolution. Drug content of MSD1 and MSD3 microparticles were 47.20% ± 2.852% and 23.12% ± 2.011%, respectively. The yield of the adsorption process was found in range of 80% to 90% wt/wt.

Microparticles Characteristics

SEM showed microsized drug crystals as well as agglomerates of pure meloxicam and irregular FLR particles with numerous pores on surface (Figure 1). Drug adsorption over FLR particles can be seen in surface topography of microparticles. In case of MSD3, the recrystallized drug was distributed more evenly, covering larger FLR surface as compared with MSD1. No agglomeration of drug crystals was

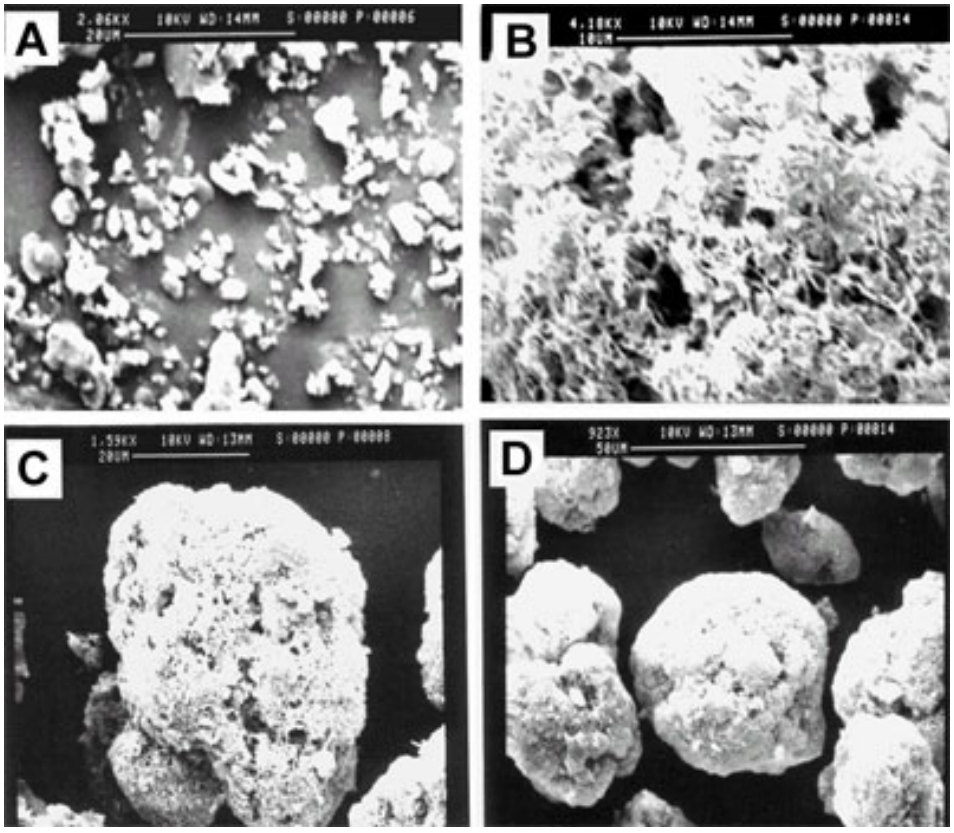

Figure 1. SEM photographs of (A) pure drug at 2060X, (B) FLR at 4100X, (C) MSD1 at 1590X, and (D) MSD3 at 923X.

seen in case of microparticles. This finding indicates that in spite of small crystal size, the drug possesses poor wettability due to agglomeration and air adsorption over surface.

Thermal properties of drug, FLR, physical mixtures, and microparticles were studied using DSC (Figure 2). Meloxicam showed sharp melting endotherm at 257.53°C. Exothermic peak just after melting peak may be part of decomposition peaks as also observed in case of tenoxicam reported by Cantera et al.[21] Thin layer chromatography of meloxicam melt obtained by melting it at 265°C on oil bath also showed 2 different bands, which indicate decomposition

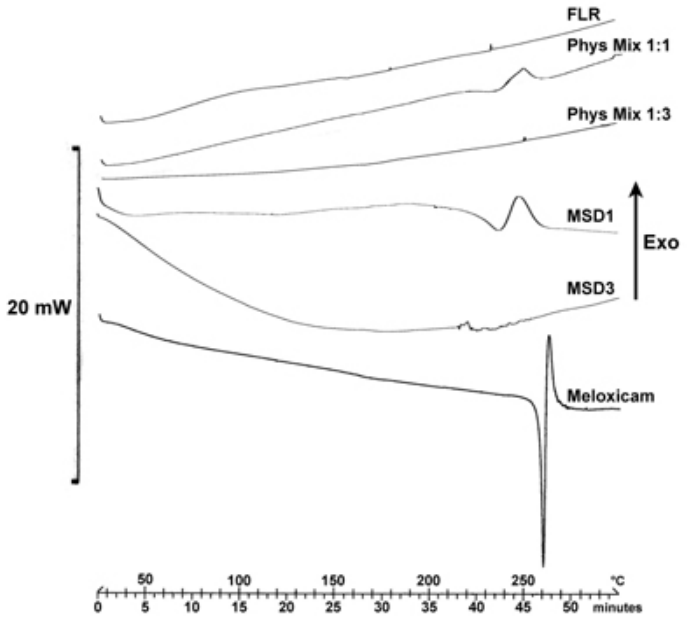

Figure 2. DSC of FLR, physical mixtures (1:1 and 1:3), MSD1, MSD3, and meloxicam.

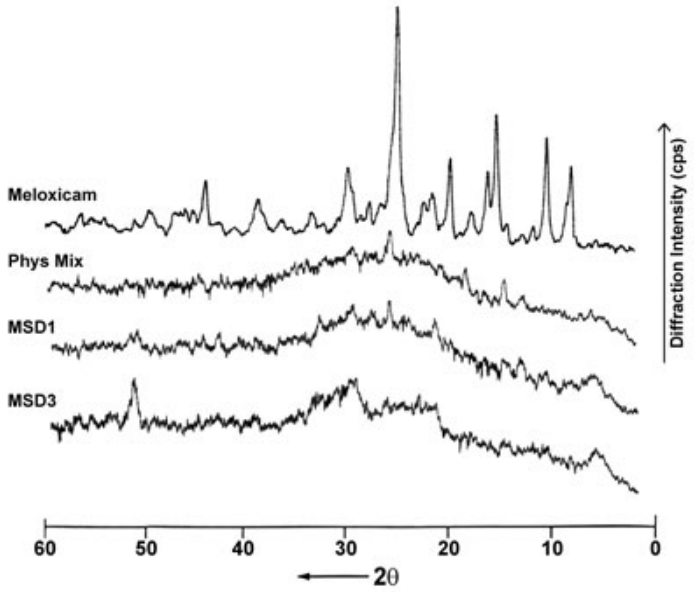

Figure 3. PXRD of meloxicam, physical mixture (1:1), MSD1, and MSD3.

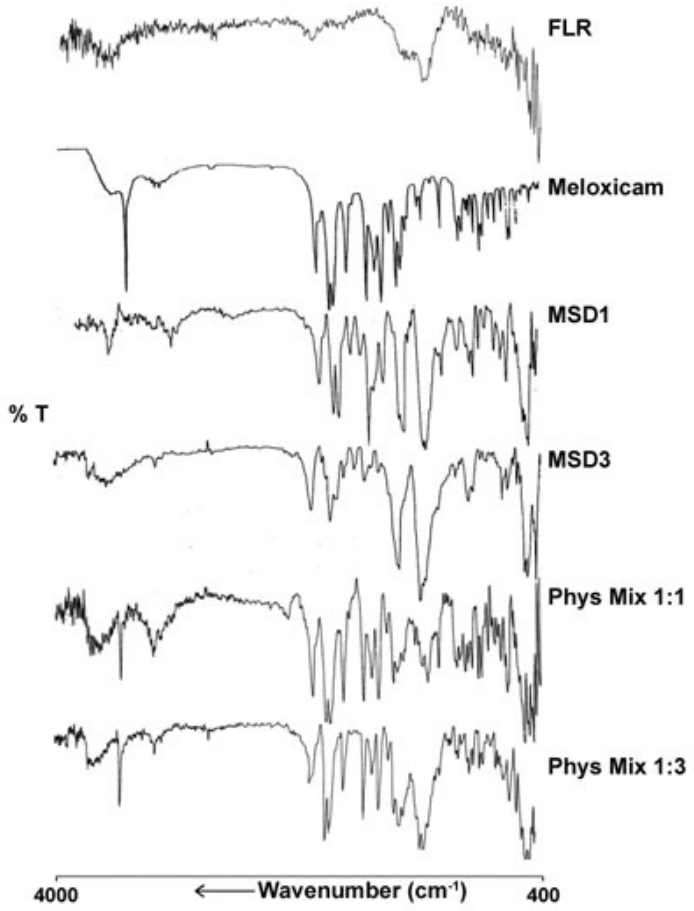

Figure 4. IR of FLR, meloxicam, MSD1, MSD3, and physical mixtures (1:1 and 1:3).

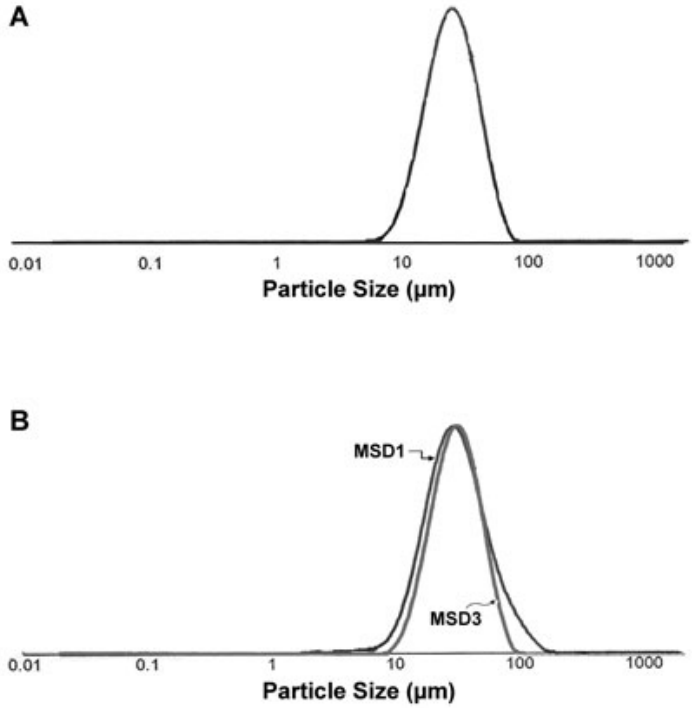

Figure 5. Particle size distribution of (A) pure FLR and (B) microparticles.

of drug in melt form. Color of drug after melting at 265°C also changed from yellow to reddish brown. Even slow controlled heating of drug in DSC did not give 2 separate peaks for melting and decomposition. DSC of pure FLR shows no endothermic peak up to 300°C. Thermogram of physical mixture containing equal proportions of drug and FLR showed small melting endotherm at 233.9°C followed by a small exotherm indicating decomposition of drug. Thermogram of MSD1 showed a broad endotherm ranging from 215°C to 245°C with a peak at 236.34°C. Normalized enthalpy of MSD1 (−106.18 J/g) also showed a decrease as compared with that of pure drug (−221.57 J/g). The shift and broadness in endothermic peak is probably due to partial reduction in crystallinity. Kinoshita et al[4] correlated this phenomenon to hydrogen bonding between C=O groups of drug and the sylanol group of FLR. Sharp absorption of energy just after melting endotherm is probably due to decomposition of drug. In case of MSD3 all the peaks were suppressed, probably due to the dilution effect of FLR. This hypothesis is supported by suppression of all peaks in DSC of physical mixture having composition similar to MSD3.

PXRD of meloxicam showed characteristic peaks at ~13°, 14.5°, 18.5°, and 25.7° (2θ). Peak at 25.7° (2θ) was used to compare PXRD pattern of drug with microparticles (Figure 3). Significant reduction in peak intensities was observed in PXRD pattern of microparticles when compared with pure drug, but this reduction was not significantly different from reduction obtained in case of physical

Table 1. Characteristic Properties of Meloxicam, FLR, and Microparticles*

Sample → Parameters ↓	Pure Meloxicam	MSD1	MSD3	FLR
Bulk density (g/cm^3)	0.31 ± 0.014	0.12 ± 0.007	0.10 ± 0.006	0.07 ± 0.004
Tap density (g/cm^3)	0.44 ± 0.031	0.17 ± 0.012	0.15 ± 0.009	0.11 ± 0.008
Compressibility index (%)	28.57 ± 1.120	28.61 ± 0.103	30.14 ± 0.081	40.91 ± 0.071
VW mean diameter (μm)	-	36.15	32.14	29.57
Solubility (μg/mL)	15.45 ± 0.009	16.22 ± 0.001	16.20 ± 0.002	-
$t_{80\%}$† (minutes)	1349.00 ± 17.620	43.80 ± 2.035	3.90 ± 0.404	-

*FLR indicates Florite RE; Meloxicam Surface Dispersion (MSD); and VW, volume weighted. All values are expressed as mean ± SD (n = 3).
†Time for 80% wt/wt drug dissolution in distilled water.

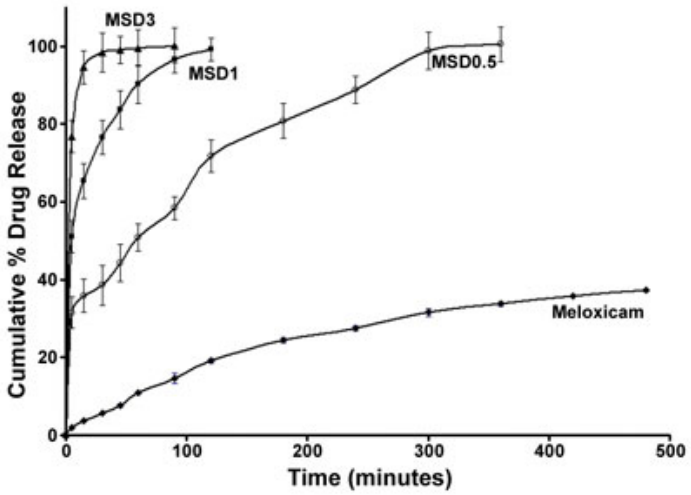

Figure 6. Graph of dissolution studies of meloxicam, MSD 0.5, MSD1, and MSD3 in distilled water.

mixture (1:1). It may be attributed to dilution effect of FLR, as also indicated in DSC studies.

IR studies were performed to determine interactions and structural changes in drug and excipient. IR spectrum of pure meloxicam showed characteristic peaks at 1620 cm^{-1} (C=O stretching), 3292 cm^{-1} (secondary -NH or –OH) and some prominent bands such as 846 to 567 cm^{-1} (-CH aromatic ring bending and heteroaromatics) and 1346 to 1163 cm^{-1} (S=O stretching) as shown in Figure 4. Characteristic peaks of drug were also present in IR spectrum of microparticles with some broadening and reduction in intensity, except that the peak at 3292 cm^{-1} was significantly suppressed in case of microparticles compared with physical mixture and pure meloxicam. This result indicates presence of hydrogen bonding between meloxicam and FLR.

Quantity of residual solvent was determined by calculating percentage weight loss in sample near boiling point of solvent using TGA as instrument. Quantity of chloroform present in MSD1 and MSD3 was 54 ± 0.85 ppm and 53 ± 0.88 ppm, respectively; it was within the permissible limit as per International Conference on Harmonization (ICH) guidelines.[22] Micromeritic properties of drug, FLR, and microparticles are listed in Table 1. Particle size analysis of FLR and microparticles (Figure 5) showed that particle size increases and distribution becomes wider with increase in drug loading on FLR.

Dissolution and saturation solubility of pure drug and from microparticles was determined in distilled water (pH 6.8 ± 0.4), so that results can be interpreted on the pH independent basis. Saturation solubility of drug deposited on FLR was not significantly different from saturation solubility of pure drug (Table 1). This result can be attributed to crystalline form of drug in both pure and adsorbed cases as supported by DSC and PXRD studies. On the other hand, dissolution rate of drug from microparticles was significantly rapid compared with pure drug, and the dissolution rate increases with increase in proportion of FLR (Figure 6). MSD0.5 microparticles showed extended drug dissolution may be due to insufficiency of FLR quantity for drug adsorption. Time required for 80% wt/wt drug dissolution (Table 1) was calculated for pure drug and microparticles using Korsmeyer-Peppas equation[23] (Equation 2):

$$Q = kt^n, \tag{2}$$

where, Q is cumulative percentage release, t is time required for Q release, and k and n are constants (Figure 6).

Increase in dissolution rate is probably owing to increase in effective surface area due to reduction in crystal size and large surface area provided by porous surface of FLR for adsorption. Large surface area of FLR for adsorption has reduced the chances of agglomeration of drug particles and, since FLR is easily dispersible in aqueous fluids, the wettability of drug might be improved in aqueous fluids.[6,24]

Tablet Characteristics

Tablets of microparticles were prepared by direct compression using commonly used excipients, lactose *IP*, primogel, PVP-K30, and magnesium stearate *IP*. The tablets were evaluated for thickness, hardness, friability, disintegration

Table 2. Physical and Dissolution Properties of Formulated and Commercial Tablets*

Sample → Parameters ↓	MSD1 Tablets	MSD3 Tablets	Commercial Tablets
Disintegration time (seconds)	18.67 ± 0.580	38.67 ± 1.150	17.67 ± 1.150
% Friability	0.24 ± 0.003	0.22 ± 0.010	0.24 ± 0.008
Thickness (mm)	2.73 ± 0.033	2.85 ± 0.024	3.61 ± 0.114
Hardness (kg/cm^2)	2.53 ± 0.170	2.35 ± 0.130	2.64 ± 0.200
Q_{10min}†	97.15 ± 1.530	97.52 ± 0.680	79.09 ± 0.510
Q_{2hr}‡	31.04 ± 0.450	46.29 ± 1.180	12.47 ± 1.320

*MSD indicates Meloxicam Surface Dispersion. All values are expressed as mean ± SD.

†Cumulative percentage drug release at 10 minutes in phosphate buffer pH 7.4 from tablet samples.

‡Cumulative percentage drug release at 2 hours in 0.1N HCl from tablet samples.

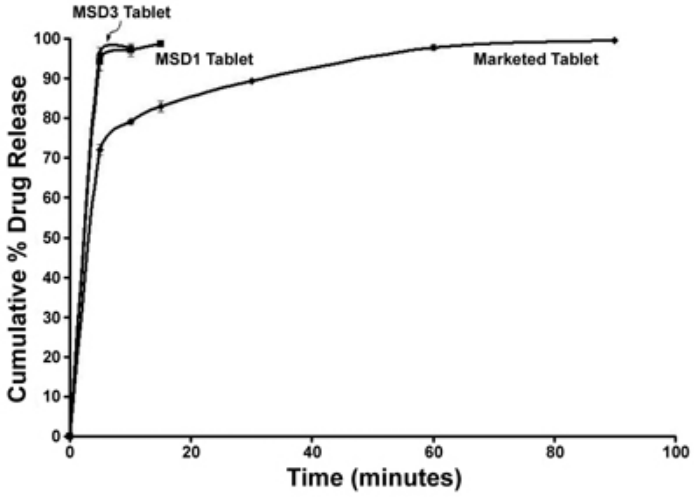

Figure 7. Graph of dissolution studies of MSD1 tablets, MSD3 tablets, and commercial tablets in phosphate buffer pH 7.4.

time, and dissolution (Table 2). Tablets prepared from MSD3 microparticles showed delayed disintegration as compared with tablets prepared from MSD1 microparticles and commercial tablets. This result may be attributed to the binding properties of FLR and decrease in lactose quantity. The low friability of tablets indicated good mechanical properties built in by FLR. This is in accordance with findings of Yuasa et al,[15] who reported the brittle fracture and plastic deformation of the petal structure of the FLR, adding a high formability and mechanical strength to the tablets.

Dissolution studies of tablets performed in phosphate buffer pH 7.4 showed rapid drug dissolution from tablets prepared by using microparticles (Figure 7). Dissolution was also performed in 750 mL of 0.1N HCl (for first 2 hours) and then in 1000 mL of pH 6.8 phosphate buffer for subsequent 3 hours (Figure 8). Cumulative drug release at 10 minutes in phosphate buffer pH 7.4 from formulated tablets (MSD1 and MSD3 tablets) was significantly higher from that of commercial tablet but there was no statistically significant difference in drug release within formulated tablets at 10 minutes (Table 2). Since meloxicam showed a very poor solubility in acidic medium, complete dissolution of drug did not take place in acidic medium in 2 hours even in presence of FLR but, cumulative drug release at 2 hours in 0.1N HCl was significantly higher from formulated tablets compared with commercial tablets (Table 2). Within formulated tablets, MSD3 tablets showed significantly higher drug release compared with MSD1 tablets. The medium-dependent difference in drug release from formulated tablets may be attributed to pH-dependent increase in solubility of meloxicam with increase in pH of medium.

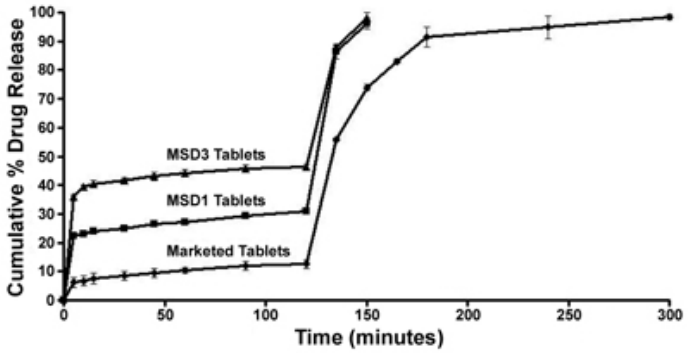

Figure 8. Graph of dissolution studies of MSD1 tablets, MSD3 tablets, and commercial tablets as per method A of *USP* XXIV for dissolution of enteric coated (delayed release) tablets.

CONCLUSION

The present study determined the utility of the porous excipients to enhance the dissolution rate of the insoluble drugs. The simple process adopted for drug absorption and improved tabletting properties of microparticles would be also applicable for hydrophobic and poorly compressible drugs. The results indicate that FLR can be used as a potential pharmaceutical excipient.

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