Liquisolid compacts of meloxicam: in-vitro and in-vivo evaluation

Remeth J. Dias, Shashi Ranjan, Kailas K. Mali, Vishwajeet S. Ghorpade, Vijay D. Havaldar

Department of Pharmaceutics, Faculty of Pharmacy, YSPM's Yashoda Technical Campus, Satara, India

Correspondence to Remeth J. Dias, MPharm, PhD, HOD, Department of Pharmacy, Government Polytechnic, National Highway No. 6, Jalgaon - 425 002;
Tel: +91 9850953955; fax: +91 257 2221719;
e-mail: rjdias75@gmail.com

Received 28 January 2017
Accepted 30 May 2017

Egyptian Pharmaceutical Journal
2017, 16:112–120

Background
Meloxicam (MXM) is a poorly soluble drug and its low aqueous solubility leads to poor dissolution and bioavailability.
Aim
The aim of this study was to investigate the potential of a liquisolid system to improve the dissolution rate and the bioavailability of MXM.
Materials and methods
The liquisolid compacts were prepared using Avicel PH102 as a carrier material, Aerosil 200 as a coating material, Polyethylene glycol 400 as a liquid vehicle, and sodium starch glycolate as a superdisintegrating agent. The 15 liquisolid compact formulations were prepared by varying drug concentrations in the liquid vehicle. Attenuated total reflectance Fourier transform infrared spectroscopy, differential scanning calorimetry, and powder X-ray diffraction were used to investigate the physicochemical interaction and crystallinity of the drug in the liquisolid compact. MXM compacts were evaluated for uniformity of drug content, tablet hardness, friability, disintegration, and dissolution. An in-vivo study was carried out in male albino rats. The data were presented as mean±SD and were compared using the one-way ANOVA. A *P*-value less than 0.05 were considered to be significant.
Results
The liquisolid system of MXM was formulated successfully using Avicel PH102, Aerosil 200, and Polyethylene glycol 200. The results of attenuated total reflectance Fourier transform infrared spectroscopy, differential scanning calorimetry, and X-ray diffraction study indicated the existence of hydrogen bonding between drug and excipients and the complete amorphization of MXM. In-vitro evaluation parameters for the liquisolid compact were found to be within the acceptable limits. It was found that optimized liquisolid tablet formulation showed higher dissolution than the marketed tablet, with more than 80% drug release within 10 min. The pharmacokinetic data showed a higher bioavailability of liquisolid compact of MXM compared with the marketed product.
Conclusion
The liquisolid compact can be a promising alternative for the formulation of water-insoluble drug MXM with improved dissolution and bioavailability.

Keywords:
dissolution enhancement, liquisolid compact, meloxicam, pharmacokinetic study

Egypt Pharmaceut J 16:112–120

1687-4315

Introduction

NSAIDs exert anti-inflammatory effects through inhibition of cyclooxygenase (COX) enzymes, namely, COX-1 and COX-2, respectively. The NSAIDs that inhibit the COX-1 isoenzyme are usually found to cause gastrointestinal (GI) adverse effects such as GI bleeding associated with intense pain, gastric perforation, etc. Therefore, drugs that inhibit the COX-2 isoenzyme are preferable over other NSAIDs [1]. Meloxicam (MXM), a selective COX-2 inhibitor, is a NSAID with a different pharmacokinetic profile than the classic NSAIDs. MXM belongs to the enolic acid class and has two p*K*a values (pKa_1=1.09 and pKa_2=4.18) [2]. It is effective against rheumatoid arthritis and osteoarthritis. Besides good gastric tolerability, it has also shown a higher therapeutic index compared with conventional NSAIDs [3]. Recently, the antifibrinolytic and antiproliferative activity of MXM has also been explored [4,5]. However, low solubility and a low dissolution rate are the major limiting factors for its poor absorption rate. The plasma concentration of MXM reaches the peak in 3–9 h after oral administration of an oral suspension and tablet [6]. Under acute pain conditions, this peak time tends to be much longer. To facilitate fast onset of analgesia and anti-inflammatory effects, there is a need to improve the dissolution of MXM. Various attempts

have been made to improve the dissolution and bioavailability of MXM, which include salt formation [7], micronization [8], cocrystals [9], cyclodextrin complexation [10], and solid dispersion [11]. However, the efficacy of the liquisolid system in improving the bioavailability of MXM has not been reported.

Liquisolid systems are powdered forms of liquid medication that have acceptable flowability and compressibility properties. The term 'liquid medication' refers to a solution or a suspension of a water-insoluble drug in a nonvolatile solvent. Liquisolid compacts are prepared by blending the liquid medication with a suitable carrier and coating materials. Various grades of cellulose, starch, lactose, etc., may be used as carriers, whereas fine silica powder may be used as a coating material [12]. The concept of 'liquisolid systems' as defined by Spireas *et al.* [13] may be used to convert a liquid into a free flowing, readily compressible, and apparently dry powder by simple physical blending with selected excipients, named the carrier and coating material. The liquisolid compact significantly increases the wetting properties and the surface area of drug available for dissolution. The liquisolid compacts of water-insoluble substances may be expected to show enhanced drug dissolution, which results in improved bioavailability [14]. The technique of liquisolid compact has been used successfully to improve the in-vitro release of poorly soluble drugs such as indomethacin [15], piroxicam [12], ezetimibe [16], repaglinide [17], prednisolone [18], progesterone [19], carbamazepine [20], etc.

The present investigation aims to improve the dissolution and bioavailability of MXM using the liquisolid technique. In this study, liquisolid tablets containing different concentrations of MXM with different excipient ratios were prepared and evaluated to obtain the optimized formulation. Finally, a pharmacokinetic study of the optimized formulation was carried out to compare the bioavailability of the optimized formulation and commercially available MXM tablets.

Materials and methods

Materials

MXM and Avicel PH102 (FMC Biopolymer, Mumbai, India) were obtained as gift samples from Dr Reddy's Laboratory Ltd (Hyderabad, India), and Cipla Ltd (Mumbai, India), respectively. Aerosil 200 (Akhil Healthcare, Vadodara, India), Explotab (Rettenmaier India Pvt Ltd, Thane, India), propylene glycol (PG), glycerin, Polyethylene glycol 400 (PEG 400), potassium metaphosphate [high-performance liquid chromatography (HPLC) grade], and acetonitrile were obtained from Loba Chemie (Mumbai, India). All other reagents and chemicals were of analytical grade. The marketed tablet of meloxicam (muvera, 15 mg) was purchased from the local market.

Solubility study

The best nonvolatile liquid that can dissolve MXM was selected by carrying out solubility studies in nonvolatile solvents. The saturation solubility studies were carried out in four different nonvolatile solvents, that is, PG, PEG 400, and glycerin to select the best nonvolatile solvent for the preparation of liquid medication. In brief, excess amount of MXM was mixed with four nonvolatile solvents separately in 50 ml vials. The mixtures were shaken on a shaker (Bio-Technics, Mumbai, India) for 48 h. Then solutions were filtered through a 0.45 µm membrane filter and diluted suitably and analyzed ultraviolet (UV) spectrophotometrically (UV 1700; Shimadzu Corp., Kyoto, Japan) at 362 nm for their drug content. Three determinations were carried out for each sample to calculate the solubility of MXM.

Determination of load factor and excipient ratio

In this study, PEG 400 was used as the liquid vehicle; Avicel PH102 was used as the carrier material, whereas Aerosil 200 was used as a coating material. The acceptable flowability and compressibility of liquid compacts can be ensured by calculating powder property called the flowable liquid retention potential (Φ value) of each liquid/powder admixture. This can be calculated using the following equation:

$$\Phi \text{ Value} = \frac{\text{Weight of liquid}}{\text{Weight of solid}}. \quad (1)$$

The flowable liquid retention potential values of Avicel PH102 (carrier, Φ) and Aerosil 200 (coating material, ϕ) were reported earlier by Spireas *et al.* [13,21] to be 0.005 and 3.26, respectively. These values were obtained directly to calculate the liquid load factor (L_f). The liquid load factor is calculated using the following formula:

$$L_f = \Phi + \frac{1}{R}, \quad (2)$$

where R is the excipient ratio.

The liquid load factor (L_f) is defined as the weight ratio of the liquid medication (W) and the carrier powder (Q) in the system.

$$L_f = \frac{W}{Q}. \quad (3)$$

The loading factor was calculated by adding PEG 400 (liquid medication without a drug) to 10 g Avicel PH102 (carrier material) and blending it for 1 min. This process was repeated until a powder with an acceptable flow rate was obtained.

The excipient ratio (R) of a powder is defined as the ratio between weights of the carrier (Q) and the coating material (q) present in the formulation. It can be calculated using the following formula:

$$R = \frac{Q}{q}. \quad (4)$$

Preparation of a liquisolid powder system

The desired quantities of the previously weighed solid drug and the liquid vehicle (PEG 400) were mixed to obtain different drug concentrations. The solution was then sonicated for 15 min until a homogeneous drug solution was obtained. The calculated amounts (W) of the resulting liquid medications (equivalent to 15 mg drug) were then incorporated into the calculated quantities of the carrier material (Q) and mixed thoroughly. The resulting wet mixture was blended with the calculated amount of the coating material (q) using a standard mixing process to form a simple admixture. The powder formulations of liquisolid compacts (F1–F15) were prepared by varying the concentrations of the drug in liquid vehicle from 20 to 40% w/w and varying the excipients ratio from 10 to 30 (different R values). Three liquid load factors (L_f=0.114, 0.168, and 0.331) were used. Finally, 5% w/w of sodium starch glycolate as the disintegrant was mixed with the above mixture for 10 min. Table 1 shows the amount of carrier, coating material, disintegrant, drug concentration, and L_f.

Precompression studies of liquisolid formulations

The flow properties of liquisolid powder formulations were determined by measuring the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was determined by the fixed cone method using the Eq. (5).

$$\mathrm{Tan}\,\theta = \frac{h}{r}, \quad (5)$$

where θ is the angle of repose, h is the height of the pile, and r is the base radius. Carr's index and Hausner's ratio were determined using Eqs (6) and (7).

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}}, \quad (6)$$

$$\text{Hausner' s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}. \quad (7)$$

Compression of powder formulations into tablets

The prepared liquisolid systems that were proven to have acceptable flowability and compressibility were compressed into cylindrical tablets of desired weight using a multistation tablet press machine (Rimek Minipress-II MT; Karnawati Eng. Ltd., Kadi, Gujrat, India). Each batch comprised of 100 tablets, containing 10 mg MXM per tablet. The prepared tablets were subjected to further evaluation.

Attenuated total reflectance Fourier transform infrared spectroscopy

Infrared spectra of MXM, Avicel PH102, a physical mixture of MXM and Avicel PH102 (1 : 1), and liquisolid formulation were determined using attenuated

Table 1 Composition of different liquisolid formulations

Formulation code	C_d (%)	R	L_f	Q (Q=W/L_f)	q (q=Q/R)	SSG	Total weight (mg)
F1	20	10	0.331	226.59	22.66	17.06	342
F2		20	0.168	446.43	22.32	28.61	573
F3		30	0.114	660.21	22.01	39.85	798
F4	25	10	0.331	181.27	18.13	13.65	274
F5		20	0.168	357.14	17.85	22.89	458
F6		30	0.114	528.17	17.60	31.88	638
F7	30	10	0.331	151.06	15.10	11.38	228
F8		20	0.168	297.62	14.88	19.08	382
F9		30	0.114	440.14	14.67	26.57	532
F10	35	10	0.331	129.49	12.94	9.75	196
F11		20	0.168	255.12	12.75	16.35	328
F12		30	0.114	377.29	12.57	22.77	456
F13	40	10	0.331	113.30	11.33	8.53	171
F14		20	0.168	223.21	11.16	14.31	287
F15		30	0.114	330.10	11.00	19.93	399

C_d, concentration of drug in a nonvolatile solvent; L_f, liquid load factor; Q, weight of carrier; q, weight of coating material; R, excipient ratio; SSG, sodium starch glycolate; W, weight of liquid medication.

total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) (α-T; Bruker, Ettlingen, Germany) in the frequency range of 600–3800 cm^{-1} at 4 cm^{-1} resolution.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) analysis was carried out to assess the thermotropic properties and thermal behavior of the MXM and the liquisolid compacts using a Mettler-Toledo DSC 821e instrument equipped with an intracooler (Mettler-Toledo, Greifensee, Switzerland). About 5 mg of the sample was sealed in aluminum pans and heated at the rate of 10°C/min, covering a temperature range of 40–300°C under a nitrogen atmosphere at a flow rate of 100 ml/min.

Powder X-ray diffraction analysis

The crystallinity of liquisolid powder formulations was characterized using X-ray diffraction (XRD). XRD patterns for MXM and the liquisolid system prepared were determined using an XRD (PW 1729; Philips, Eindhoven, Netherlands) with a copper target at a voltage of 40 kV and a current of 20 mA. The rate of the scanning was 0.30°/min.

Evaluation of liquisolid compacts of meloxicam

The liquisolid tablets were evaluated for thickness, diameter, weight variation, uniformity of content, hardness, friability, disintegration, and dissolution as per the official compendium.

For the content uniformity test, 20 tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was weighed and dissolved in PBS (pH 7.2). Sufficient dilutions were prepared and the absorbance of the resulting solutions was measured at 362 nm using a UV-visible spectrophotometer. From the absorbance values, the amount of the drug present in the given tablet was calculated [22].

The disintegration test was performed as described in the procedure for uncoated tablets in Indian Pharmacopoeia (IP) 1996. The test was carried out on six tablets in PBS (pH 7.2) at 37±2°C using a disintegration apparatus.

The USP23 paddle apparatus II was used for in-vitro dissolution studies. 900 ml PBS (pH 7.2) was used as dissolution media at 50 rpm and 37±0.5°C. Appropriate aliquots were withdrawn at suitable time intervals (5, 10, 15, 20, 30, 40, 50, and 60 min), filtered through a 0.45 μm membrane filter, suitably diluted with buffer, and analyzed at 362 nm using a UV-visible spectrophotometer. Sink conditions were maintained throughout the study. The study was carried out in triplicate.

In-vivo evaluation of liquisolid compacts of meloxicam

Animal study

The study protocol (SCOP/IAEC/03/2009–2010) was prepared and approved by the Institutional Ethics Committee of Satara College of Pharmacy (reg. no.:1314/ac/09/ CPCSEA) (Satara, India). Male Wistar albino rats weighing 280–300 g were obtained for study. These rats had free access to a normal standard diet and tap water. Animals were kept in these facilities for 1 week before the experiment and fasted overnight before the experiments, but were allowed water *ad libitum*. The rats were divided into three groups of six rats per group. Groups 1–3 were administered pure MXM, triturated marketed MXM formulation, and optimized formulation of the liquisolid system, respectively, in suspension form. A dose equivalent to 10 mg/kg of MXM was administered orally to each of the animals [23]. The oral suspension was prepared with 5% PEG and the dosing volume was 1 ml for each animal. Blood samples were collected into anticoagulant-containing tubes from the right femoral artery at 0, 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 48 h following the administration of each drug. Plasma was separated after centrifugation of the blood sample at 3000 rpm for 15 min and stored at −20°C until analysis of MXM [7].

Sample extraction

MXM was extracted from the plasma sample by adding 50 μl of piroxicam (20 μg/ml) as the internal standard (IS), and 50 μl of 0.1 N HCl to 50 μl of plasma and 6 ml of diethyl ether was added to this mixture. Then, the mixture was vortex mixed for 4 min and centrifuged for 15 min. The organic layer was separated and transferred into a clear tube and evaporated under a gentle stream of air at 35°C. The residue was reconstituted in 500 μl mobile phase and a 20 μl aliquot was injected into the HPLC system [24].

Analysis by the high-performance liquid chromatography method

The plasma samples were analyzed using a HPLC system (PU-2080; Jasco Inc., Hachioji, Tokyo, Japan). Fifty microliters of piroxicam (20 μg/ml) was used as an IS. The UV detector (UV-2075) was set at 355 nm. An analytical column (Kromasil, AKzo Nobel India Ltd., Navi-Mumbai, Maharashtra, India; 100 C-18; 10 μ, 300×4.0 mm^2) was eluted with a mixture of a 20 mmol/l PBS (pH 3.4) and acetonitrile (60 : 40, v/v) at a flow rate of 1.2 ml/min at 30°C [24].

Pharmacokinetic analysis

The pharmacokinetic parameters of MXM were estimated using the noncompartment method. The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal method. Maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (t_{max}) were read directly from the plasma concentration–time data. The terminal elimination rate constant (k) was estimated from the slope of the terminal phase of the log plasma concentration–time points fitted by the method of least squares and then the terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/k$ [25].

Statistical analysis

The data were presented as their mean±SD and for the in-vivo data the one-way analysis of variance, followed by a posteriori testing using the Dunnett correction. A P-value less than 0.05 was considered to be significant.

Results and discussion

Solubility study

It was observed that MXM showed the lowest solubility in glycerin (0.421±0.19 μg/ml). The solubility was found to be increased when semipolar solvents such as PG (2.30±0.66 μg/ml) and PEG 400 (7.75 ±0.57 μg/ml) were used. The solubility of the drug depends strongly on the intermolecular attractive forces between the drug and the solvent. A marked increase in the solubility of MXM in PEG 400 may be because of dipole and hydrogen-bonding interaction between them. Therefore, PEG 400 was selected as a nonvolatile solvent in the preparation of liquisolid compacts.

Precompression studies

The effect of flowable liquid loading factor (L_f), which is a ratio of mass of liquid added (PEG) to the mass of Avicel PH102 (carrier), on flowability and compressibility of the final admixture of the powder is shown in Table 2. Increasing the L_f value in the range of 0.114–0.331, that is, increasing the volume of liquid vehicle resulted in a decrease in the flowability of the final admixtures. This is evident from the increase in the angle of repose. It also resulted in a decrease in the compressibility of the final admixture. As a general guide, it has been reported that an angle of repose up to 34° has passable flow properties [26]. On the basis of the angle of repose, Carr's index, and Hausner's ratio, only formulations F8, F9, F11, F12, F14, and F15 were subjected to compaction.

Attenuated total reflectance Fourier transform infrared spectroscopy

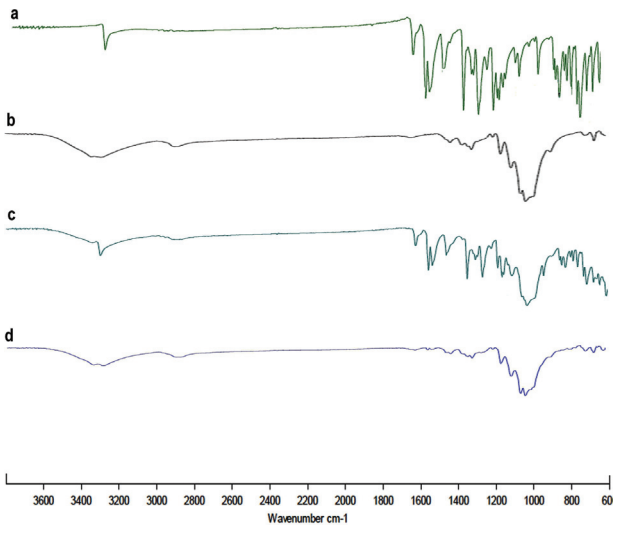
The ATR-FTIR spectra of a sample of pure MXM, Avicel PH102, physical mixture of drug and Avicel PH102 (1 : 1), and liquisolid powders are shown in Fig. 1. The ATR-FTIR spectrum of MXM showed a distinct peak at 3289 cm^{-1} (N–H stretching vibrations), 1619 cm^{-1} (C=N stretching vibrations), 1550 cm^{-1} (thizole ring), 1530 cm^{-1} (amide II band of the amide group), and 1152.6 cm^{-1} (S=O stretching vibrations). The spectrum of the physical mixture was equivalent to the drug, indicating that no unusual interaction occurred between the drug and Avicel. In the case of the liquisolid system of MXM, there is a reduction in the intensity of the characteristic

Table 2 Flowability parameters of the liquisolid system

Batch code	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
F1	36.43±1.11	26.09±1.5	1.35±0.012
F2	35.25±0.97	20.81±1.58	1.24±0.017
F3	34.13±0.93	17.85±1.31	1.23±0.021
F4	36.31±1.07	25.61±1.43	1.34±0.031
F5	34.95±0.95	22.57±1.21	1.28±0.015
F6	34.04±0.83	18.81±0.67	1.21±0.026
F7	35.53±1.07	25.10±1.62	1.33±0.015
F8	33.15±0.47	17.78±1.68	1.24±0.015
F9	31.18±0.85	14.29±1.15	1.18±0.026
F10	35.22±0.95	24.36±1.86	1.31±0.032
F11	32.24±1.01	17.80±1.66	1.19±0.010
F12	31.94±0.98	19.78±0.53	1.23±0.030
F13	31.92±1.06	25.82±1.10	1.35±0.026
F14	27.93±0.62	19.06±1.42	1.22±0.032
F15	28.88±0.88	14.96±2.24	1.16±0.030

Data expressed as mean±SD.

Figure 1



Attenuated total reflectance Fourier transform infrared spectroscopy spectra of (a) meloxicam, (b) Avicel PH102 (c), physical mixture, and (d) liquisolid system

absorption bands of drug that might be attributed to the hydrogen bonding interaction between the N–H, S=O, and C=N groups of MXM and the hydroxyl group of the liquid vehicles (PEG 400) [11,22]. Hydrogen bonding between the drug and the liquid vehicle may be one of the reasons for dissolution enhancement of MXM.

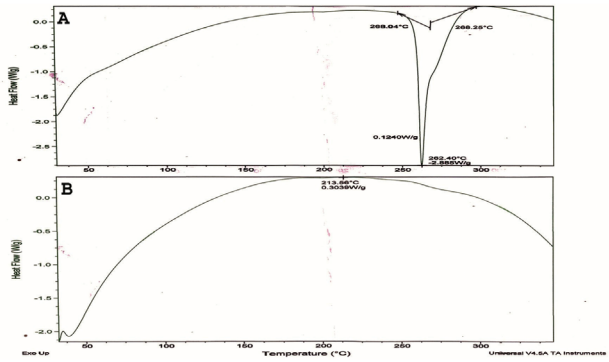
Differential scanning calorimetry

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation. Figure 2 shows DSC profiles of MXM and liquisolid compact. The DSC of pure MXM showed a sharp endothermic peak at 262.04°C because of drug melting [22]. This sharp endothermic peak signifies that the MXM used was in a pure crystalline state. However, the liquisolid system DSC showed complete disappearance of characteristic peaks of MXM. This may be because the formation of drug solution in the liquisolid powdered system, that is, the drug was molecularly dispersed within the liquisolid system.

Powder X-ray diffraction analysis

The XRD results were in good agreement with the thermal analysis data. The crystalline nature of the drug was determined by the characteristic XRD pattern, with peaks appearing at (2θ) angles of 19.35, 27.67, 38.63, 22.1, and 24.7 (Fig. 3a). However, the XRD pattern of liquisolid powder (Fig. 3b) showed only one sharp diffraction peak at 2θ angle of 22.5 belonging to Avicel PH102, indicating that only Avicel PH102 maintained its crystalline state. This absence of MXM constructive reflections (specific peaks) in the liquisolid XRD indicates that the drug has almost entirely converted from crystalline into an amorphous or a solubilized form [27]; this lack of crystallinity in the liquisolid system was understood to be a result of MXM solubilization in the liquid vehicle.

Figure 2

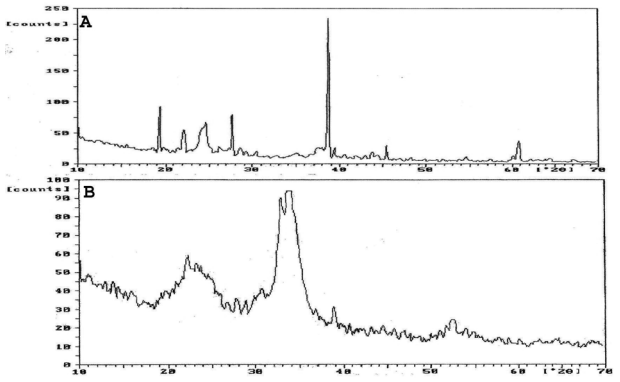


Differential scanning calorimetry of (A) pure drug (B) liquisolid system

In-vitro evaluation of liquisolid compacts of meloxicam

Table 3 shows the results obtained for the quality control tests of liquisolid tablets of MXM. The thickness of the tablets was found to be between 4.1 ±0.11 and 6.1±0.10 mm and the diameter was found to be in the range of 9.5–11 mm. The weight variation test showed that the liquisolid tablets were within the specified range as stated in IP 1996. The hardness of the liquisolid tablets was found to be in the range of 2.3±0.50–4.7±0.28 kg/cm^2. Formulation F14 showed minimum hardness. This may be attributed to the addition of fewer amounts of highly compressible Avicel PH102 and poorly compressible Aerosil. The high compressibility and compactness of Avicel PH102 can be explained by the formation of hydrogen bonds during compaction. When microcrystalline cellulose is compressed, the particles become deformed plastically and a strong compact is formed because of the extremely large numbers of surfaces brought in contact during the plastic deformation

Figure 3



X-ray diffraction of (A) pure drug (B) liquisolid system

Table 3 Evaluation of liquisolid compacts of meloxicam

Batch code	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (min)	%Drug content
F1	4.0±0.57	0.86	18.2±0.15	95.42
F2	4.0±0.76	0.81	11.1±0.21	97.64
F3	4.0±0.50	0.74	3.45±0.06	98.53
F4	1.7±0.28	0.98	11.5±0.18	96.75
F5	4.5±0.86	0.26	10.3±0.22	98.95
F6	4.6±0.57	0.30	5.2±0.19	96.84
F7	1.5±0.86	0.92	10.5±0.15	101.24
F8	3.6±0.76	0.47	2.3±0.11	101.66
F9	4.7±0.28	0.24	0.5±0.07	102.07
F10	1.4±0.50	0.96	11.2±0.22	95.66
F11	4.6±0.76	0.54	10.4±0.31	95.99
F12	4.1±0.57	0.44	3.2±0.12	97.46
F13	1.3±0.50	0.92	10.5±0.43	100.81
F14	4.1±0.55	0.66	7.5±0.27	96.08
F15	4.0±0.72	0.55	2.3±0.12	98.17

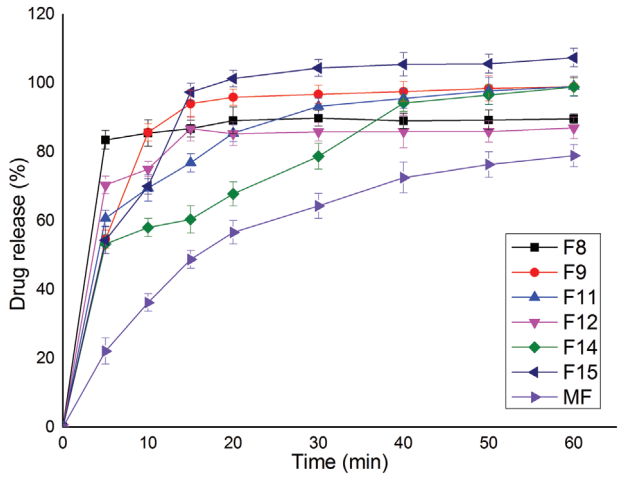
Data expressed as mean±SD.

and the strength of the hydrogen bonds formed [28]. All the liquisolid tablets showed acceptable friability as none of the tested formulae had percentage loss in the tablets weight that exceeded 1%. The drug content of all the liquisolid formulations was found to be uniform as per the IP 1996 specifications (within the range of 90–110%).

The disintegration test showed that an increase in the hardness of the tablets increased the disintegration time. Tablets with increased hardness usually have smaller pores that provide resistance to the penetration of water into the tablet. This results in a prolonged disintegration time. The formulation F14 showed the minimum disintegration time (0.5± 0.07 min) despite the lower quantity of sodium starch glycolate, whereas formulation F9 showed a longer disintegration time (3.5±0.11 min), although it contained a large amount of sodium starch glycolate. This may be attributed to the minimum hardness of formulation F14 and the maximum hardness of formulation F9.

Figure 4 shows the in-vitro drug release profile of the liquisolid formulations and marketed formulation of MXM. It was found that liquisolid tablets of MXM showed higher dissolution than the marketed formulation at the end of 15 min. This may be attributed to the molecular dispersion of MXM in PEG 400 and hydrophilicity of the carrier. PEG 400 and Avicel help to accelerate the dissolution of MXM by increasing its wettability and surface availability to the dissolution medium [29,30]. PEG mainly facilitates wetting of drug particles by decreasing interfacial tension between the dissolution medium and the tablet surface. An increase in the drug concentration in PEG 400 caused a decrease in dissolution. This may be because of the differences in the amount of soluble form of the drug or molecular dispersion states of the drug in the formulation [18,31]. It was observed that an increase in the excipient ratio increased drug dissolution. This can be ascribed to the faster diffusion of the liquid medication through the numerous porous carrier powder particles [13].

Figure 4



In-vitro dissolution of liquisolid meloxicam compacts and marketed formulation (MF)

A significant difference ($P<0.05$) was found between the release profile of liquisolid tablets and the marketed formulation. Further, to select a better formulation, the model independent parameters such as dissolution efficiency (DE) and mean dissolution time (MDT) were determined [32]. The DE of the liquisolid compacts was found to be in the range of 75.89–92.63%, whereas MDT was observed to be in the range of 4.65–13.93 min. Formulation F9 showed higher dissolution than other formulations at the end of 10 min, with 85.62% of DE and 6.31 min MDT (Table 4).

In-vivo evaluation of liquisolid compacts of meloxicam

Analysis by the high-performance liquid chromatography method

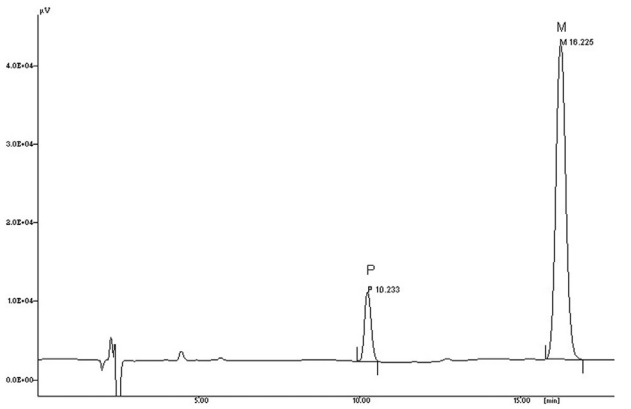
Both piroxicam (IS) and MXM peaks were well resolved, with no interference from endogenous peaks. The retention times of piroxicam and MXM were found to be 10.23 and 16.22 min, respectively (Fig. 5). The calibration curve from the standard samples was linear over the concentration range of 10–120 µg/ml. The squared correlation coefficient (r^2) was over 0.9998. The average coefficient of variation (CV) for intraday and interday precision was found to be 4.57 and 9.23, respectively. According to ICH guidelines, the CV for the analytical method should be less than 20%. Hence, the HPLC method set for the estimation of MXM is reliable.

Table 4 Drug-release profile of liquisolid compacts and marketed formulation

Formulation code	Q_{10} (%)	%Drug released in 1 h	DE (%)	MDT (min)
F8	85.44±2.1	89.60±1.37	84.56	3.37
F9	85.62±2.89	98.92±2.67	88.51	6.31
F11	69.49±1.53	99.02±2.91	83.91	9.15
F12	75.00±2.87	86.91±3.14	80.16	4.65
F14	58.02±1.84	98.86±2.59	75.89	13.93
F15	69.98±1.98	107.36±2.56	92.63	8.23
MF	36.19±2.38	78.88±3.21	58.08	15.81

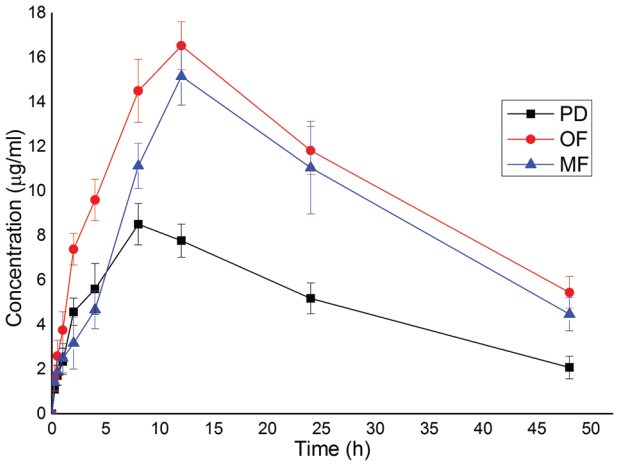
Q_{10}, drug release at the end of 10 min. DE, dissolution efficiency; MDT, mean dissolution time; MF, marketed formulation.

Figure 5



Sample chromatogram of the internal standard (P) and meloxicam (M) spiked in rat plasma

Figure 6



Pharmacokinetic profile of meloxicam following a single administration of pure drug (PD), marketed formulation (MF), and optimized formulation (OF)

Pharmacokinetic analysis

The liquisolid tablets of MXM were evaluated for their in-vivo performance by comparing its pharmacokinetic parameters with the marketed product (immediate-release MXM tablet). The mean plasma concentration–time curves following the oral administration of the marketed product, optimized liquisolid formulation (F12), and pure drug of MXM are shown in Fig. 6 and the pharmacokinetic parameters obtained are shown in Table 5. It is clear from the results of the pharmacokinetic study that the mean peak plasma concentration (C_{max}) and the mean $AUC_{0-\infty}$ for an optimized liquisolid formulation were significantly higher ($P<0.05$) than those for the marketed formulation and pure drug. A 1.2-fold and 1.09-fold increase was found in $AUC_{0-\infty}$ and C_{max} values of MXM from liquisolid compacts than the corresponding values of the marketed formulation.

Table 5 Pharmacokinetic parameters of meloxicam in rats

Pharmacokinetic parameters	Marketed formulation (mean±SD)	Optimized formulation (mean±SD)	Pure drug (mean±SD)
C_{max} (μg/ml)	15.22±1.29	16.62±1.08*	8.59±0.90
t_{max} (h)	12±0.76	11.17±0.20*	8.65±0.42
$t_{1/2}$ (h)	20.099±2.97	22.33±3.23	19.43±2.48
Ke (h^{-1})	0.034±0.004	0.031±0.004	0.036±0.004
$AUC_{0-\infty}$ (μg h/ml)	572.85±63.75	692.52±64.06*	298.59±51.48
Ka	0.16±0.02	0.15±0.04	0.329±0.08
Relative bioavailability (*F*)	–	1.21	0.52

Data expressed as mean±SD. AUC, area under cure; C_{max}, maximum peak concentration; *Ka*, absorption rate constant; *Ke*, elimination rate constant; $t_{1/2}$, elimination half life; t_{max}, time to reach peak concentration. *Significantly different ($P<0.05$) from the marketed formulation and pure drug.

The mean time to obtain the peak plasma concentration (t_{max}) for the optimized formulation is lower than the marketed formulation and higher than the pure drug. On the basis of these results, it can be concluded that the greater bioavailability can be obtained from optimized liquisolid formulation, with higher C_{max} and t_{max}, which can be attributed to rapid and efficient absorption of MXM. The results obtained are in agreement with the earlier studies carried out by Etman *et al.* [33] and Eroglu *et al.* [34].

Conclusion

The liquisolid compacts of MXM were formulated and evaluated to check the utility of the liquisolid technique to improve the dissolution properties of a water-insoluble drug. Compared with the conventional direct compressed tablet, liquisolid compacts of MXM showed enhanced in-vitro drug-release properties. The results showed that dissolution properties were affected by the excipient ratio and the concentration of the drug. In-vivo study indicated that the liquisolid formulation showed higher bioavailability than marketed formulation.

Therefore, liquisolid formulations can be a promising alternative for the formulation of water-insoluble drug MXM and it has the potential to be manufactured on a large scale.

Acknowledgements

The authors are grateful to Dr Reddy's Laboratory Ltd, Hyderabad, for providing the gift sample of meloxicam. Also, the authors are grateful to Yashoda Technical Campus, Satara, and Shivaji University, Kolhapur, for providing research facilities.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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