Pharmacokinetic Profiling and Bioavailability Assessment of Meloxicam Solid Dispersion Tablets

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ABSTRACT

The present investigation was focused on the comparative bioavailability assessments of meloxicam tablets prepared by solid dispersion using modified gum karaya and commercial meloxicam tablets. A non-blinded, open-label, cross-over study was performed in six healthy volunteers for the determination of bioavailability and pharmacokinetic parameters. Blood samples were collected for 12 hours at specified intervals of time after the administration of meloxicam formulations, then analyzed by high-performance liquid chromatography (HPLC). Pharmacokinetic parameters such as maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), elimination rate constant (K_{el}), biological half-life ($t_{1/2}$), absorption rate constant (K_a) and area under the curve (AUC_{0-12} and $AUC_{0-\infty}$) were determined. A significant difference in the bioavailability and pharmacokinetics of commercial meloxicam tablets and meloxicam solid dispersion tablets using modified gum karaya was found at $p < 0.05$, clearly indicating higher bioavailability with the meloxicam solid dispersion tablets.

Keywords: Cox-2, crossover design, gum karaya, kneading, plasma-drug concentration, solubility.

1. INTRODUCTION

Over the past few decades, the number of drug candidates with poor solubility has increased tremendously. For oral delivery of such drugs, circumventing the above problem is a challenging task for formulation scientists. Various methods have been employed so far to enhance the solubility of poorly water-soluble drugs, and in turn, their bioavailability, such as pH adjustment, cosolvency, particle size reduction, microemulsion, micellar solubilization, complexation, supercritical fluid processes, solid dispersion, and hydrotrophy.[1] Among the different techniques, solid dispersion is a promising one that enhances the bioavailability of such drugs. In solid dispersion, the poorly soluble drug is dispersed in a highly soluble, inert, solid, hydrophilic matrix.[2] Solid dispersions are prepared by melting, solvent evaporation, or melting-solvent processes.[3] A literature review reveals that drugs such as griseofulvin, chloramphenicol, prednisolone and digitoxin were benefited by this technique.[4]

Meloxicam (MEL), or 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, is an enolic acid derivative belonging to the drug class of nonsteroidal anti-

inflammatory drugs.[5] It is a selective cyclooxygenase-2 (COX-2) inhibitor which prevents the synthesis of prostaglandins and mediators of inflammation. It is widely used in the treatment of inflammation, pain, fever, rheumatoid arthritis and other joint disorders.[6] Meloxicam is practically insoluble in water (0.154 mg/mL). The low solubility of meloxicam in biofluids causes difficulty in the formulation of dosage forms, which results in variable dissolution rates.[7] Thus, enhancing the solubility and dissolution and, therefore, the bioavailability of meloxicam is of utmost importance for attaining better clinical and therapeutic efficacy.

The solid dispersion technique was chosen to enhance the bioavailability of meloxicam. Solid dispersion is a mixture of a hydrophilic polymer matrix amid a hydrophobic drug. The proposed mechanism for its ability to enhance dissolution of poorly water-soluble drugs is diminution in particle size and crystallinity, escalating wettability of the drug, either by hydrophilic polymer carriers and direct solubilization, or by a co-solvent effect of the carriers on the drug. Natural polymers as drug carriers lure the attention of investigators due to their biocompatibility, biodegradability and economical aspects.[8]

After an extensive literature survey, gum karaya, a gum exudate of *Sterculia urens* was selected as the carrier for this study. Its applicability in enhancing solubility was investigated due to its unique characteristics such as high swelling, high viscosity, high water retention capacity and anti-microbial properties.[9] However, its high viscosity restricts its ability to be utilized as a binder and disintegrant, so modified gum karaya (MGK), created by heating gum karaya, was used instead. MGK has comparable swelling and low viscosity properties to that of gum karaya since such characters are necessary in the preparation of optimal solid mixtures.[10]

As a preliminary part to this study, meloxicam solid dispersions were prepared by different methods (the physical method, co-grinding method, kneading method, and solvent evaporation method) in various phase ratios of drug: polymer (i.e. 1:1, 1:5, 1:10 and 1:19).[11] After characterization and evaluation of the different methods and ratios of solid dispersion, the meloxicam solid dispersion at a1:1 ratio of meloxicam and modified gum karaya (MEL:MGK-1:1) prepared by the kneading technique (KT) showed highest drug release. In this study, 15 mg of meloxicam was compressed into each tablet. A pharmacokinetic investigation was carried out for a comparative bioavailability assessment of commercial meloxicam tablets (CMTs) and MEL:MGK-1:1-KT solid dispersion tablets (i.e. MSDTs).

MATERIALS AND METHODS

Materials

Meloxicam (MEL) was provided gratis from M/s. Unichem Laboratories Ltd., Mumbai, and gum karaya (GK) was purchased from M/s. Girijan Co-operative Corporation Ltd., Visakhapatnam. Acetonitrile and water of high-performance liquid chromatography (HPLC) grade, and ethyl acetate and methanol of analytical reagent grade were obtained from M/s. S.D. Fine Chem. Ltd., Mumbai.

Preparation of the solid dispersion

A solid dispersion of MEL with modified gum karaya (GK was modified by heating at 120°C) in the ratio of 1:1 was prepared using the kneading mixture method. Weighed quantities of drug and carrier were triturated in a mortar with a small volume of methanol. The thick slurry was kneaded for 45 minutes and then dried at 50°C until it reached uniform weight. The dried mass was pulverized and sifted through a sieve No. 100 and stored in a desiccator.[12]

Preparation of meloxicam solid dispersion tablets

Meloxicam solid dispersion tablets (MSDTs), each containing an equivalent of 15 mg of meloxicam and 85 mg of croscarmellose sodium were formulated by direct compression technique on a 16-station rotary tablet press (Type – CMD3 – 16. Cadmach Machinery Pvt. Ltd., Ahmadabad) using a 6-mm standard flat punch.[13] The MSDTs were examined for weight variation, hardness, friability, drug content and *in vitro* drug release as per Indian Pharmacopoeia protocols.

Methods

Subject selection

Six healthy male volunteers with a mean age of 25.8 ± 1.6 years (ranging from 22 to 28 years), a mean body weight of 72.5 ± 6.4 kg (ranging from 60 to 80 kg) and a mean height of 170.1 ± 6.2 cm (ranging from 162 to 178 cm) were involved in the study. They had provided written informed consent after being notified about the nature and implications of the investigation. The healthy volunteers were selected on the basis of their previous medical history and health condition based on laboratory findings. None of the subjects were on other medications for at least 2 weeks before and during the study. All subjects were accessible with complete investigation details, both verbally and in written form, prior to provision of written informed consent.[14] The study was approved by an independent ethics committee at Andhra University, Visakhapatnam (India).

Study design

The study followed a non-blinded, open-label and cross-over design. Subjects fasted for at least 10 hours prior to receiving a drug dose. For the first stage, all of the subjects received one of the two treatments (either one MSDT or one CMT) as a single dose in the assigned study period. In the second stage, the second treatment (different from the one the subject received in the first stage) was given (to reduce inter subject variability) after a washout period of 2 weeks (to avoid residual effects). The assigned tablet was taken with 200 mL of water. No fluid intake was allowed for at least 2 hours, and no food was allowed up to 4 hours following drug administration. A standard lunch was provided after 4 hours of drug treatment.[14]

Blood sampling

An indwelling cannula with heparin lock was applied in a suitable forearm vein, and blood samples were drawn at 0 (before drug administration), 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 hours following oral administration of the drug as per the designed protocol. Blood samples (5 mL), were collected into glass tubes, and plasma was separated by centrifugation at 3,000 rpm for 10 minutes. Then, plasma was transferred to a test tube labeled with the subject's identification number, the drug assignment number, treatment day and time of sampling, then stored at -20 °C until it was assayed.[15]

HPLC method of analysis for meloxicam

Meloxicam concentrations in plasma samples were estimated according to the HPLC method as described by Bae et al.[16] The chromatographic system consisted of a Model SPD-M10A VP with class M10A version 1.61 software (Shimadzu, Japan). Samples were chromatographed on a reversed phase, Luna 5 μ C 18(2), with column size 250 x 4.6 mm. The mobile phase consisting of a 20-mM potassium monophosphate: acetonitrile mixture in the ratio of 60:40 v/v was adjusted to a pH of 3.5 with ortho-phosphoric acid, at a flow rate of 1.2 mL/min. The mobile phase was filtered through a 0.2-μm pore size membrane filter (Millipore) and degassed ultrasonically after mixing. Meloxicam was measured at 355 nm using a Shimadzu Photo Diode Array detector. The HPLC method was validated for linearity, specification, accuracy, precision and stability. Reasonable retention times were achieved for meloxicam. This allowed complete analysis of samples from each volunteer in addition to a calibration curve within one day.

Bioavailability and pharmacokinetic profiling

Bioavailability and pharmacokinetic parameters were determined by non-compartmental analysis using Microsoft Office Excel® (2007). Peak plasma concentration (C_{max}) and time to reach the peak concentration (T_{max}) were directly observed from the individual plasma concentration versus time curves. The elimination rate constant (K_e) and elimination half-life ($t_{1/2}$) were calculated by a "best-fit" linear regression line using the method of least squares of the terminal concentration decay phase. The elimination rate constant (K_{el}) was calculated from the slope of the linear line in the elimination phase of the semi-logarithmic graph of time versus plasma concentration. The corresponding elimination $t_{1/2}$ was calculated using the following equation, $t_{1/2} = {0.693}/{K_{el}}$. The percentage of drug absorbed at various times and the absorption rate constant (K_a) were

calculated from plasma concentration data by the method described by Wagner and Nelson.[17,18] The equation developed for the determination of the absorption rate of the drug from blood concentration data was $\frac{dA}{dt} = V_d \cdot \frac{dC_b}{dt} + K_{el} \cdot C_b$, where dA/dt is the absorption rate, V_d is the apparent volume of distribution, dC_b/dt is the rate of change of blood concentration (C_b) at time t and K_{el} is the elimination rate constant. The equation was integrated between the limits of t = 0 and t = T and divided by V_d to give = $C_T + K_{el} (AUC)_{t=0-T}$, where A_T is the amount of drug absorbed to time T, C_T is the blood concentration at t = T and the quantity under the integral sign is the area under the blood level versus time curve between the indicated limits. When the successive values of A_T/V_d were calculated, a maximum or asymptotic value $(A_T/V_d)_\alpha$ was obtained. The maximum or asymptotic value was divided into successive values of A_T/V_d to yield

percentage absorbed data, i.e., $\left[\dfrac{(A_T/V_d)}{(A_T/V_d)_\alpha} \times 100 \right]$

as a function of time. When a semilogarithmic plot of percent unabsorbed of meloxicam versus time was drawn, a straight line was obtained, and the slope of that was equal to $K_a/2.303$. The absorption rate constant (K_a) was calculated from the slope of this line. The area under the time versus plasma concentration curve from 0 to t hrs

(AUC$_{0-t}$) was measured by applying the trapezoidal rule. The area under the curve from 0 to ∞ hrs (AUC$_{0-\infty}$) was calculated from equations (1) and (2), as below.

$$AUC_{0\text{-}t} = \int_0^t C(t)dt \tag{1}$$

$$AUC_{0\text{-}\alpha} = AUC_{0\text{-}t} + C_t/K_{el} \tag{2},$$

where C_t is the plasma concentration of the drug at t hr.

Statistical Analysis

The pharmacokinetic parameters were expressed as the mean ± standard deviation of the test product (MSDT) and reference product (CMT), which were statistically evaluated using analysis of variance (ANOVA). In the case of normally distributed results, an equal variance test was used, while the Kruskal-Wallis H test was used for non-normally distributed data. Differences in values were considered statistically significant at $p < 0.05$ to evaluate results.

Results and Discussion

Meloxicam solid dispersion tablets (MSDTs) were examined for weight variation, hardness, friability, drug content and dissolution. As shown in Table 1, values were within the Indian pharmacopoeia limits.

Table 1. Tableting characteristics of prepared tablets

Formulation	Weight[a] (mg)	Drug content[b] (%)	Hardness[c] (kg/cm²)	Friability[b] (%)	% drug release at the end of 2 hr[d] (%)
MSDT	125.36 ± 1.31	99.64 ± 0.16	4.27 ± 0.36	0.65	94.89 ± 0.25
CMT	124.55 ± 1.96	99.96 ± 0.87	4.67 ± 0.49	0.41	91.85 ± 1.69

[a] Mean ± SD, n = 20 tablets
[b] Mean ± SD, n = 10 tablets
[c] Mean ± SD, n = 5 tablets
[d] Mean ± SD, n = 5 tablets

MSDT: meloxicam solid dispersion tablet
CMT: commercial meloxicam tablet
SD: standard deviation

Both formulations were well tolerated in all 6 subjects. There were no drop outs, premature withdrawals, replacements or deaths during the study that might have otherwise influenced the outcome of study. No adverse effects were reported. All subjects were discharged in good health after the study as per study protocol. The study was conducted in an unfed condition as meloxicam is well absorbed after oral administration.[19]

Meloxicam products were administered to human subjects, and their plasma concentrations were determined by the HPLC method (Figure 1). When the MSDT was administered orally, higher plasma concentrations of meloxicam were found compared to CMT. Application of the Wagner-Nelson method to the plasma concentration data of both commercial and experimental formulations indicated significantly higher absorption rate (K_a) with the experimental formulation ($p < 0.05$).
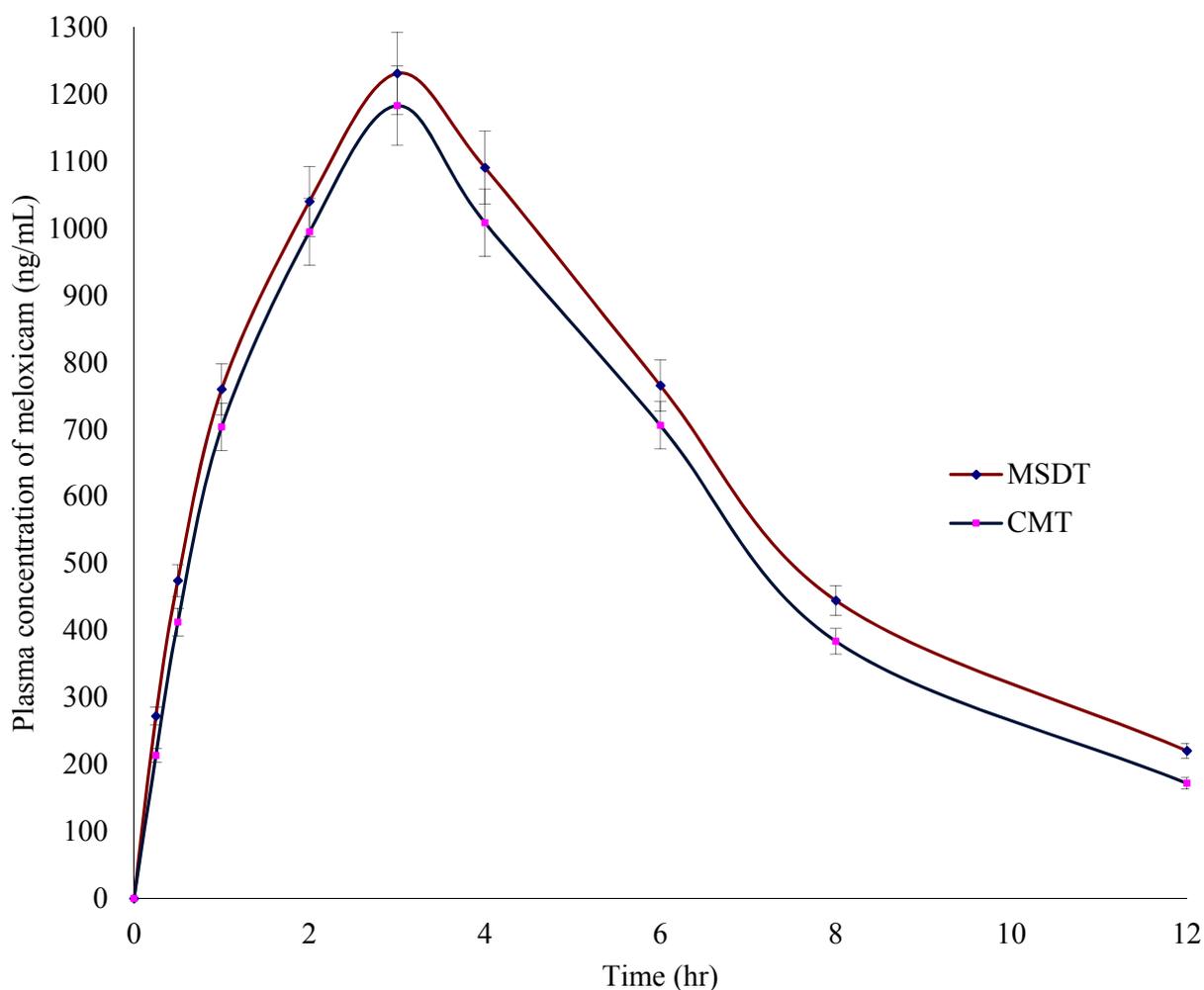
Figure 1: Plasma concentrations of meloxicam following the oral administration of MSDT and CMT to healthy human volunteers

The primary pharmacokinetic parameters are shown in Table 2. The elimination rate constant K_{el} for MSDT was found to be 0.1997 hr^{-1}, and 0.1899 hr^{-1} for CMT. The

difference in K_{el} between the two formulations was not statistically significant.

Table 2. Pharmacokinetic parameters (Mean ± SEM) of meloxicam following oral administration of MSDT and CMT in human volunteers

Pharmacokinetics	MSDT	CMT	Test of significance
C_{max} (ng/mL)	1231.33±7.17	1183±9.87	S
T_{max} (hr)	3± 4.98	3± 5.76	NS
$t_{1/2}$ (hr)	3.47± 6.91	3.64± 6.35	NS
K_{el} (hr^{-1})	0.1997± 8.54	0.1899± 2.87	NS
K_a (hr^{-1})	0.9833± 3.86	0.9971± 4.21	S
AUC_{0-12} (ng hr mL^{-1})	8029.37± 5.27	7333.92± 7.89	S
$AUC_{0-\infty}$ (ng hr mL^{-1})	9133.52± 6.36	8239.65± 8.43	S

Statistical significance at $p<0.05$
S: Significant
NS: Not significant

C_{max}: maximum concentration of drug in plasma
T_{max}: time to reach maximum concentration of drug in plasma
SEM: standard error mean

The biological half-life ($t_{1/2}$) of MSDT was found to be 3.47 hrs with a T_{max} of 3 hrs, and the $t_{1/2}$ of CMT was 3.64 hrs with a T_{max} of 3 hrs. The differences in T_{max} and $t_{1/2}$ between the two formulations were not statistically significant.

The absorption rate constant (K_a) was found to be 0.9833 h^{-1} for MSDT and 0.9971 h^{-1} for CMT. There was a significantly higher absorption rate with MSDT compared to CMT ($p < 0.05$).

Peak plasma concentrations (C_{max}) of 1231.33±7.17 ng/mL and 1183±9.87 ng/mL were observed for MSDT and CMT respectively. When compared to CMT, the C_{max} of MSDT was1.04 times higher, which was statistically significant ($p < 0.05$), indicated the superiority of MSDT.

The AUC_{0-12} for MSDT was 8029.37 ng hr mL^{-1} and that for CMT was 7333.92 ng hr mL^{-1}, meaning AUC_{0-12} for MSDT was 1.09-fold more to that of CMT. The $AUC_{0-\infty}$ for MSDT was 9133.52 ng hr mL^{-1} and that for CMT was 8239.65 ng hr mL^{-1}, meaning $AUC_{0-\infty}$ for MSDT was 1.13-fold higher than that of CMT. The differences in these AUC values were statistically significant, indicating the

enhanced bioavailability of the drug in the MSDT.

Modified gum karaya, a colloidal polymer which possesses high swelling index and high hydrophilicity, was able to increase the solubility and dissolution of MEL. Therefore, the bioavailability of meloxicam was increased linearly as resulted with increased AUC of MSDT. Apart from the increased bioavailability result, maximum concentration of MEL in plasma was reached within 3 hrs upon oral administration of MSDT, which was an important outcome of application MGK as carrier.

Conclusion

Solid dispersions of meloxicam using the water swellable polymer modified gum karaya were successfully compressed into tablets. A non-blinded, open-label and cross-over design was used in this *in vivo* evaluation. Healthy human volunteers were administered meloxicam solid dispersion tablets (MSDTs) and commercial meloxicam tablets (CMTs). Plasma concentrations of meloxicam were assessed using HPLC. Pharmacokinetic (K_{el} and $t_{1/2}$) and bioavailability (AUC, C_{max} and T_{max})

parameters of the MSDTs were found to be significantly higher than that of the CMTs. Hence, modified gum karaya maybe used as a potential carrier to improve the solubility, dissolution rate and bioavailability of meloxicam and potentially other, similar agents.

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تقييم النمط الحركي الدوائي والتوافر الحيوي لأقراص الميلوكسيكام من نوع التشتت الصلب

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ملخص

ركزت هذه الدراسة على تقييم التوافر الحيوي المقارن لأقراص الميلوكسيكام المحضرة بواسطة التشتت الصلب باستخدام صمغ الكارايا المعدل مقارنة بأقراص الميلوكسيكام التجارية. حيث تم إجراء دراسة غير معمّاة، مفتوحة التسمية، ومتعاكسة على ستة متطوعين أصحاء وذلك لتحديد العوامل الدوائية−الحركية. حيث تم جمع عينات الدم لمدة 12 ساعة على فترات زمنية محددة بعد إعطاء تركيبات الميلوكسيكام للمتطوعين، ثم تحليلها بواسطة التفريق اللوني السائل عالي الأداء (HPLC). هذا وتم قياس قيم العوامل الحركية الدوائية مثل: التركيز الأعلى للمادة في البلازما (Cmax) والوقت للوصول إلى Cmax (tmax) وثابت معدل الازالة (Kel) والعمر النصفي الحيوي (t1/2) وثابت معدل الامتصاص (Ka) وكذلك المساحة تحت المنحنى (AUC0-12 وAUC0-∞). حيث أظهرت الدراسة وجود اختلاف واضح في التوافر الحيوي ما بين أقراص ميلوكسيكام التجارية وأقراص ميلوكسيكام من نوع التشتت الصلبة المحضرة باستخدام صمغ الكارايا المعدل، مؤشرة بوضوح على توافر حيوي أعلى لأقراص التشتت الصلب.

الكلمات الدالة: النمط الحركي الدوائي، أقراص الميلوكسيام، التشتت الصلب.