PHYSICO-CHEMICAL CHARACTERIZATION AND IN VIVO PHARMACODYNAMIC EVALUATION OF LYOPHILIZED MELOXICAM: β-CYCLODEXTRIN INCLUSION COMPLEXES

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ABSTRACT

Objective: The objective of the present work was to enhance solubility, in vitro dissolution and in vivo pharmacodynamic activity of meloxicam (MLX) by preparation of lyophilized inclusion complexes with β-cyclodextrin.

Methods: Phase solubility studies were conducted to analyze the influence of βCD on solubility of MLX. Inclusion complexes (ICs) of MLX & βCD were prepared in 2:1, 1:1 and 1:2M ratio followed by in vitro dissolution studies. The amorphous nature of the optimized IC and interaction of MLX with βCD was studied by differential scanning calorimetry (DSC), X-ray diffraotmetry (XRD) and Fourier transform Infra-Red Spectroscopy (FTIR).

The in vivo anti-inflammatory ability of optimized IC was evaluated by carrageenan induced rat paw edema method while the analgesic study was conducted using acetic acid induced writhing test in mice.

Results: Solubility of pure MLX in water at 25 °C was found to be only 9.4 µg/mL. The A_1 type of phase solubility curve of MLX with β-CD confirmed the solubility enhancement capability of βCD. Based on the in vitro dissolution studies, 1:1M IC was found to be optimum for further studies. The in vivo anti-inflammatory ability of optimized IC was significantly higher and faster (edema inhibition 63.36 ± 6.43% at the end of two hours) as compared to plain MLX (39.75 ± 4.73% at the end of four hours). Analgesic studies revealed rapid onset of action from optimized IC (73.9% inhibition of writhes in 20 minutes) as compared to that of plain MLX (38.14% inhibition of writhes in 40 minutes).

Conclusion: These results prove that inclusion of MLX in βCD enhances not only the in vitro dissolution of the drug, but also improves its in vivo pharmacodynamic activity.

Keywords: Meloxicam, β-cyclodextrin, Lyophilisation, Dissolution, Analgesic and Anti-inflammatory activity.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are still one of the most widely prescribed medications worldwide. As a therapeutic class, they exhibit analgesic, anti-inflammatory, antipyretic and platelet inhibitory properties [1]. However, a vast majority of these drugs have serious side effects such as gastrointestinal (GI) toxicity, gastric mucosal ulcerations and hemorrhage due to inhibition of prostaglandin production [2,3]. The mechanism of action of NSAIDs has been attributed to their ability to inhibit the cyclooxygenase enzyme (Cox). Out of the 2 isomers of cyclooxygenase, cox-1 is responsible for mediating the production of prostaglandin while cox-2 is primarily associated with inflammation, pain and fever [4]. The traditional NSAIDs are nonselective Cox inhibitors and therefore Cox-2 selective NSAIDs like meloxicam (MLX) are ideal anti-inflammatory agents with minimum drug-related side effects, since they spare the cox-1 activity [5,6]. However, very poor aqueous solubility and wettability of MLX limits the in vivo absorption of the drug leading to variable oral bioavailability [7,8].

Complexation of such hydrophobic pharmaceutical compounds with hydrophilic carriers like cyclodextrin (CDs) leads to altered physicochemical properties of the guest molecule [9-11]. Inclusion complexes (ICs) of drugs with CDs, therefore, have been extensively studied and utilized to improve the solubility, dissolution rate, bioavailability and other desirable properties of poorly water-soluble drugs[12-15]. In the present study, β-cyclodextrin (βCD) was chosen to enhance the solubility of MLX because of its central cavity diameter (6-6.5 Å) which is appropriate to accommodate most aromatic rings, its efficiency in producing stable drug complexes, low toxicity and relatively low cost. Absorption of βCD in an intact form is limited because of its bulky nature and hence, it acts as a true carrier by keeping the hydrophobic drugs in solution and delivering them to the surface of the biological membrane, such as gastrointestinal mucosa, where they partition into the membrane [16-19]. The most commonly used methods for preparation of drug-CD complexes are co-precipitation, solvent evaporation, kneading, physical mixing, spray-drying and lyophilisation [20-24].

The purpose of the present study was to increase the in vitro solubility and dissolution rate, as well as in vivo analgesic and anti-inflammatory activity of MLX, as these activities were never analyzed and reported before [25-28]. To achieve this objective, amorphous ICs of MLX with βCD were prepared in different ratios using the lyophilisation technique, followed by evaluation of in vitro dissolution rate [29-32]. Possible physical interaction between the two components were investigated by performing Fourier transform infrared (FTIR) spectroscopy, Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD) [33,34]. Optimized IC with maximum in vitro release was subjected to in vivo pharmacodynamic studies in animal models.

MATERIALS AND METHODS

Materials

MLX was received as a gift sample by Unichem Lab. Ltd., Mumbai, India. βCD was generously donated by Carestar, USA. Ultrapure water (Millipore) and analytical grade reagents/ chemicals were used throughout the study.

Phase Solubility Studies

Phase solubility studies were carried out according to the method reported by Higuchi and Connors in order to understand the influence of βCD on solubility of MLX [35,36]. Excess amount of MLX (125 mg) was added in screw-capped conical flasks containing 50 mL of aqueous solution each of different concentrations (0, 0.125, 0.250, 0.375, 0.50, 0.625, 0.75 and 0.875g) of βCD in ultra-pure water. The suspensions were continuously stirred on mechanical shaker (Siena equipment, India) at ambient temperature and 200 rpm for 48 hours (this duration was previously tested to be sufficient to reach equilibrium). The suspensions were filtered through 0.45μm Millipore membrane filter (Agilent, USA). The filtrates were suitably diluted with water and analyzed, spectrophotometrically (Cecil 2000, UV/Vis spectrophotometer, England), for the dissolved drug at 362 nm. Blank samples of βCD at different concentrations used in the study were analyzed to rule out
interference. All assays were performed in triplicate. The standard curve of MLX in water over a concentration range of 2 to 16 μg/mL at 362 nm was plotted. The mean calibration curve (regression equation: \( y = 0.0533x + 0.0036 \)) was found to be linear \((n=6)\) with a correlation coefficient of \( r^2 = 0.9997 \).

The data was treated statistically using linear least square regression and the apparent 1:1 ratio stability constant \((K)\) and the Gibbs free energy \((\Delta F)\) were calculated from the phase-solvability diagram using equations (1) and (2) respectively.

\[
K = \frac{\text{slope}}{\text{y intercept} - 1} \quad \text{.........................(1)}
\]

Where, the \( y\)-intercept corresponds to the intrinsic solubility of MLX in the absence of β-CD at 25 ± 1°C.

\[
\Delta F = -RT \ln K \quad \text{......................... (2)}
\]

Where, \( R\) is the ideal gas constant and \( K\) is the absolute temperature.

**Preparation of ICs**

The lyophilisation (freeze drying) technique (LABCONCO, Freeze Dry System, Freezone 4.5) was used to prepare ICs of MLX and βCD in 2:1, 1:1 and 1:2 molar ratios. Physical mixture \((PM)\) of MLX and βCD was also prepared in 1:1M ratio by mixing in geometric proportions. The prepared samples were sieved through 60 mesh and stored in air tight containers till further analysis.

**Drug content**

Content analysis of the samples was performed using UV spectrophotometry. The mean calibration curve of MLX (regression equation: \( y = 0.0556x - 0.0036 \)) in 0.1 N sodium hydroxide \((\text{NaOH})\) over a concentration range of 2 to 16 μg/mL at 365 nm was found to be linear \((n=6)\) with a correlation coefficient of \( r^2 = 0.9999 \) and hence it could be employed for routine assay. ICs and PM, containing an equivalent of 15 mg of MLX were discharged in a suitable quantity of 0.1 N NaOH and sonicated \((\text{Elma Transonic, 460/H, Germany})\) for 15 minutes. The filtered samples were suitably diluted with 0.1N NaOH and measured for drug content.

**In-vitro dissolution studies**

Pure MLX, PM and ICs \((\text{equivalent to 15 mg of MLX})\) were all subjected to dissolution studies \((n = 6)\). Dissolution medium was 900 ml distilled water \((\text{containing 0.02% tween 80 as wetting agent})\). The test was performed in a USP XXV Type II dissolution apparatus \((\text{Erweka DT 80, GmbH, Germany})\). The stirring speed employed was 100 rpm and the temperature was maintained at 37°C ± 0.5°C. 5 ml aliquots were withdrawn at different time intervals, filtered and measured at 366 nm spectrophotometrically, after suitable dilution with the dissolution medium if needed, to determine the amount of drug released. The mean calibration curve of MLX \((\text{regression equation: } y = 0.0536x - 0.0036)\) in the dissolution medium was found to be linear \((n=6)\) over a concentration range of 2 to 16 μg/mL with a correlation coefficient of \( r^2 = 0.9995 \).

**DSC studies**

The thermal behavior of MLX, βCD, PM and optimized IC was studied using Perkin Elmer DSC 7 model in aluminum pans under a nitrogen flow of 40 mL/min and heating rate of 10°C/min in a 20 to 250°C temperature range.

**XRD studies**

The XRD patterns of MLX, βCD, PM and optimized IC were recorded using Philips X-ray generator \((\text{PW 1729})\) and automatic X-ray diffractometer model PW 1710 unit. The radiation used was Nickel filtered Cu Kα radiation having a wavelength of 1.542 Å, operating at 35 K watts and 20 m-amps in the range \((2θ)\) of 5° to 60° at a scanning rate of 1°/min.

**FTIR studies**

FTIR spectroscopic studies of MLX, βCD, PM and optimized IC were conducted by KBr disc method using JASCO FT/IR-5300 Spectrophotometer. The samples were scanned from 4000 to 400 cm\(^{-1}\) at room temperature.

**In vivo Pharmacodynamic studies** \([37 - 39]\

**Anti-inflammatory activity**

The anti-inflammatory study was performed on male albino rats \((\text{weight range: } 180-250 \text{ g})\). The animals were housed into three groups \((n = 6)\) and maintained on a standard pellet diet. They were fasted overnight prior to the study with water ad libitum.

Optimized IC or pure drug suspension was prepared in a mortar and pestle using sodium carboxy methyl cellulose \((\text{Na CMC})\) equivalent to 0.25% w/v of the drug as the suspending agent. 2 ml dose equivalent to 4mg/kg was administered orally via syringe to each animal in group two \((\text{suspension of pure drug})\) and group three \((\text{suspension of IC})\). An aqueous solution of 0.25% Na CMC was administered to the control group \((\text{group one})\). Each dose was followed by 1 ml of distilled water to wash off any drug remaining in the upper alimentary tract.

Edema was induced by injecting 0.1 ml of carrageenan \((1\% \text{ w/v prepared in } 0.9\% \text{ w/v saline})\) into sub plantar tissue of right hind paw of each rat. The paw of each animal was marked at the same level over the lateral malleolus. The volume of the treated paw was measured at hourly intervals from 0 to 5 hours plethysmometrically by submersion in a mercury bulb. The percent swelling of the carrageenan injected paw was calculated using the formula given below:

\[
\% \text{Inhibition of Swelling} = \left( \frac{V_{\text{untreated}} - V_{\text{treated}}}{V_{\text{untreated}}} \right) \times 100
\]

The percent inhibition of swelling was determined in each case using the formula:

\[
\% \text{Inhibition of Swelling} = \left( \frac{V_{\text{untreated}} - V_{\text{treated}}}{V_{\text{untreated}}} \right) \times 100
\]

The % inhibition of swelling values were plotted against time in hours to get a comparative anti-inflammatory profile of the samples under investigation.

**Analgesic activity**

The abdominal writhing test in mice was carried out to compare the analgesic activity of MLX and optimized IC. The study was performed on albino mice \((\text{weight range: } 25 - 30 \text{ g})\). The animals were housed into three groups \((n = 6)\) and maintained on a standard pellet diet. They were fasted overnight prior to the study with water ad libitum. IC or pure drug suspension was prepared in a mortar and pestle using sodium carboxy methyl cellulose \((\text{Na CMC})\) equivalent to 0.25% w/v of the drug as the suspending agent. 0.5 ml dose \((\text{equivalent to 4mg MLX/kg})\) was administered orally via syringe to each animal in group two \((\text{suspension of pure drug})\) and group three \((\text{suspension of IC})\). An aqueous solution of 0.25% Na CMC was administered to the control group \((\text{group one})\). Each dose was followed by 0.5 ml of distilled water to wash off any drug remaining in the upper alimentary tract.

Acetic acid \((0.7\% \text{ v/v; } 10 \text{ ml/kg})\) was injected intraperitoneally at various time intervals viz. 10, 20, 30 or 40 minutes after oral administration. The mice were immediately placed individually in upturned transparent acrylic chambers and the number of writhes those made from 5 minutes following the acetic acid injection was counted until 20 minutes. A writh is defined as an assumption of the posture of flattened abdomen, stretching of hind limbs and depression of back. One writh is considered to be the adoption of this posture and is terminated upon attainment of normal posture. The anti-nociceptive efficacy of the samples was evaluated as percent protection using the formula given below:

\[
\% \text{Protection} = 100 - \frac{\text{Writhes of experimental group} \times 100}{\text{Writhes of control group}}
\]
RESULTS AND DISCUSSION

Phase Solubility Studies

The plot of drug solubility against increasing βCD concentrations investigated at 25±1°C is represented in figure 1. The solubility curve was classified as A₁ type according to Higuchi and Connors. Solubility of pure MLX in water at 25°C was found to be only 9.4 µg/mL. The extent of interaction between the drug and the carrier in aqueous media characterized by the apparent stability constant K₁:₁, calculated according to the equation given by Higuchi and Connors, was found to be 22.056 M⁻¹ whereas the Gibbs free energy (ΔF°) was − 7.665 KJ/mole. The results confirmed the solubility enhancement capability of βCD, as the solubility of MLX increased linearly with increasing carrier concentration. The negative nature of the Gibbs free energy is indicative of the spontaneous process of solid solution formation process.

Drug content Analysis

Content analysis of all the samples confirmed that MLX could be found to a level of 99.18 to 101.32% (RSD < 2%) of the theoretically added amount in various drug – carrier combinations.

In vitro dissolution studies

The dissolution profiles of MLX, PMs and ICs are depicted in figure 2. Tween 80 (0.02%w/v) was found to be optimum as a wetting and suspending agent. The initial dissolution rate of pure MLX was extremely slow and erratic with only 6.48 (± 2.36) % of the drug dissolved in 10 minutes and 17.91 (± 1.18) % dissolution at the end of one hour. This could be due to its highly hydrophobic nature and poor wettability. Rapid dissolution is a characteristic behavior observed for various βCD inclusion complexes. It was noted that the ICs showed a faster release as compared with the pure drug and PM. The dissolution parameters of all the samples under study are listed in table 1. The release pattern of PM was better than pure MLX, due to the presence of βCD, however significantly less than that of ICs. The rate of dissolution from ICs was enhanced as the ratio was increased from 2:1 to 1:1M, however further increase in ratio to 1:2M did not show any significant effect on drug release. 1:1 M IC showed 95 (± 2.351) % release at the end of 20 minutes and thus was considered to be optimum for further studies. The improvement in the dissolution rate of the lyophilized system may be attributed to complexation and amorphisation of the drug with βCD, caused by lyophilisation and also due to the hydrophilic property of the carrier which together leads to the increase in wettability and solubility of MLX.

Fig. 1: Phase solubility diagram of MLX with βCD (n=6)

Fig. 2: Dissolution profiles of various MLX-βCD samples (n=6)
Table 1: Dissolution parameters of various MLX-βCD samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time (min.)</th>
<th>First order rate constant</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T25</td>
<td>T50</td>
<td>T75</td>
</tr>
<tr>
<td>MLX</td>
<td>70.61</td>
<td>182.96</td>
<td>374.45</td>
</tr>
<tr>
<td>MLX-β-CD 1:1M PM</td>
<td>67.93</td>
<td>179.93</td>
<td>371.27</td>
</tr>
<tr>
<td>MLX-β-CD 2:1M IC</td>
<td>10.18</td>
<td>32.71</td>
<td>85.78</td>
</tr>
<tr>
<td>MLX-β-CD 1:1M IC</td>
<td>3.76</td>
<td>9.08</td>
<td>15.92</td>
</tr>
<tr>
<td>MLX-β-CD 1:2M IC</td>
<td>2.35</td>
<td>8.59</td>
<td>15.28</td>
</tr>
</tbody>
</table>

DSC studies

DSC enables quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). To characterize possible interactions between the drug and βCD in the solid state, DSC thermogram of MLX, βCD, MLX-βCD PM and MLX-βCD IC (1:1M) were recorded (figure 3). The DSC graph of pure MLX showed a sharp endothermic peak at 268.5˚C, which is indicative of its melting temperature. The thermogram of βCD depicts a melting endotherm at 67.9˚C, whereas that of PM, shows an addendum of peaks of both the pure compounds. The thermogram of IC exhibited complete disappearance of the endothermic peak characteristic of the drug; which can be attributed to its amorphous character in the complex state; strongly indicating that the drug is well dispersed in βCD matrix and its re-crystallization is restrained. The results of thermal analysis are thus suggestive of maximal complex formation of the drug and the carrier.

XRD studies

The XRD pattern of MLX and βCD (figure 4) showed peaks that were intense and sharp; indicating their crystalline nature while that of the PM was found to be a combination of the drug and βCD, with little decrease in the peak intensity. However, the XRD pattern of the MLX-βCD IC was found to be diffused. Crystalinity was determined by comparing prominent representative peak heights in the diffraction patterns of the IC with those of MLX and PM. The characteristic peaks at 15.5°, 17.5°, 22°, 23°, 24.5° and 28° (28°) observed in figure 4A for MLX are significantly diminished in the complex (figure 4D) thus confirming the formation of a new amorphous solid phase in the inclusion complex.

Fig. 3: DSC thermogram of [A] βCD; [B] MLX; [C] MLX-βCD 1:1M PM and [D] MLX-βCD 1:1M IC

Fig. 4: X ray diffractogram of [A] βCD; [B] MLX; [C] MLX-βCD 1:1M PM and [D] MLX-βCD 1:1M IC
FTIR studies

FTIR spectral studies were employed to confirm complexation of MLX with βCD. The spectra of the IC was compared with that of MLX, βCD and PM (figure 5). The intense peaks appearing in the spectra of MLX and βCD are due to the asymmetric stretching vibrations of their functional groups. The IR spectrum of βCD (figure 5A) shows prominent peaks at 3389.64 cm⁻¹ (O–H), 2924.86 cm⁻¹ (C–H), 1649.90 cm⁻¹ (H–O–H bending), 1157.71 cm⁻¹ (C–O) and 1028.51 cm⁻¹ (C–O–C). The IR spectrum of pure MLX (figure 5B) showed characteristic principle peaks at 1529.10 cm⁻¹ (aromatic–C–C–), 3085.49 cm⁻¹ (aromatic–C–H–), 2930.11 cm⁻¹ (C–H aliphatic), as well as at 1346.43 cm⁻¹ (–S=O), 3292.79 cm⁻¹ (–S–N–) and 1620.35 cm⁻¹ (–N–H–). The spectrum of the PM (figure 5C) showed a summation effect i.e. simple superposition of the peaks due to the functional groups of the two compounds, indicating the presence of MLX in crystalline state. In the spectrum of MLX–βCD IC (figure 5D), the presence and absence of characteristic peaks associated with specific structural characteristics of the drug molecule were noted; however, there were no new peaks, indicating any new chemical bond formation between the two in solid state. The spectrum of the complex showed appearance of an intense broad peak at 3431.2 cm⁻¹. This peak broadening indicates possible hydrogen bonding between MLX and βCD. Shifts are seen in the peak of the aromatic –C–H (2927.1 cm⁻¹) and aromatic –C–C (1568.4 cm⁻¹) stretching of the benzene ring, suggesting that these groups are taking part in hydrogen bonding leading to entrapment of the aromatic ring of the guest molecule in the hydrophobic cavity of the host, whereas the sulfide (1353.6 cm⁻¹) and amide group (1626.4 cm⁻¹) peaks do not exhibit any significant contribution in the hydrogen bonding process. These chemical shifts could be attributed to the physical interaction of the drug with βCD which in turn enhance wettability, aqueous solubility and dissolution of the drug.

Pharmacodynamic studies

Anti-inflammatory activity

IC, at dose equivalent to 4 mg/kg of MLX, showed greater inhibition in carrageenan-induced hind paw edema as compared to MLX alone (figure 6). The inhibitions of edema were analyzed statistically by one-way ANOVA (SPSS Inc. Statistics 17.0). The % inhibition was significantly high in IC compared to the inhibition of plain MLX (P < 0.05) as shown in table 2. Also IC showed maximum % inhibition of edema at the end of 2 hours (64.48% ± 3.92) whereas plain MLX showed maximum % inhibition of edema at the end of 4 hours (39.75% ± 4.73), which was significantly less than that shown by IC. These results strongly suggest a faster onset of action and a better therapeutic response from IC compared to MLX alone.
Table 2: Effects of plain MLX and its 1:1 M inclusion complex with β-CD on carrageenan-induced hind paw edema in rats.

<table>
<thead>
<tr>
<th>Time interval (hr.)</th>
<th>% edema inhibition</th>
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<tbody>
<tr>
<td></td>
<td>MLX</td>
</tr>
<tr>
<td>1</td>
<td>8.62 ± 2.94</td>
</tr>
<tr>
<td>2</td>
<td>11.86 ± 3.74</td>
</tr>
<tr>
<td>3</td>
<td>28.39 ± 5.38</td>
</tr>
<tr>
<td>4</td>
<td>39.75 ± 4.73</td>
</tr>
<tr>
<td>5</td>
<td>38.52 ± 4.39</td>
</tr>
</tbody>
</table>

Analgesic activity

The IC, at dose equivalent to 4 mg/kg of MLX showed greater inhibition in acetic acid induced writhing as compared to MLX alone (figure 7). The reduction in writhing’s were analyzed statistically by one-way ANOVA (SPSS Inc. Statistics 17.0). The analgesic activity, calculated in terms of % protection was significantly high in IC compared to that of plain MLX (P < 0.05). In case of plain MLX there was a gradual increase in anti-nociceptive efficacy with increase in time, reaching a maximum (38.14%) at 40 minutes. Whereas, IC showed maximum efficacy (75.18%) in 20 minutes. The data (Table 3) revealed the fact that extent of protection offered by IC was much higher compared to that of plain MLX, suggesting faster absorption of the drug from the complex compared to the pure drug.

Fig. 7: Effects of plain MLX and MLX-βCD 1:1 M IC on acetic acid-induced writhes in mice (n=6).

Table 3: Effects of plain MLX and its 1:1 M inclusion complex with β-CD on acetic acid induced writhing in mice.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time (min.)</th>
<th>Abdominal constriction % inhibition of writhes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>42.91 ± 4.33</td>
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<td>20</td>
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<td>37.8 ± 3.94</td>
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<td>30</td>
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<td>30.6 ± 3.08</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>33.9 ± 4.53</td>
</tr>
<tr>
<td>MLX-β-CD 1:1 M IC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>20.7 ± 3.76</td>
</tr>
<tr>
<td>20</td>
<td></td>
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<tr>
<td>30</td>
<td></td>
<td>33.9 ± 4.53</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>30.6 ± 4.65</td>
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</table>

CONCLUSION

The cyclodextrin complexation technology serves as an important tool in the current armamentarium of agents for relief of pain and inflammation. It is evident from the in vitro physicochemical characterization and in vivo pharmacodynamic studies performed, that the complexation process not only enhances the aqueous solubility and dissolution of MLX, but also offers the triple advantage of improved gastrointestinal tolerability, significantly faster onset of action and better efficacy as compared to the pure drug. Thus, the inclusion phenomenon should be further explored for production of more efficacious and safer cyclodextrin based commercial formulations and better patient care in future.

REFERENCES

Bandarkar et al.


