The Influence of Particle Size and Dissolution Rate on Bioavailability of Two Indomethacin Capsules.


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Abstract

Indomethacin is a drug of very low aqueous solubility and poor wetability, all characteristics which make it a drug with a potential bioavailability problem. Thus, the present study was undertaken to estimate the bioavailability of indomethacin capsules, having different particle sizes and dissolution rates. The particle size, dissolution rates and the bioavailabilities of two indomethacin capsules, indomethacin generic capsules DP (Darou Pakhsh Co.) and indocid (Merk sharp & Dohme) were studied. The median indomethacin particle size of indocid MSD and indomethacin capsules DP were found to be 5.23 mm and 8.61 mm respectively. It also has been found that the dissolution rates and rates of absorption (measured as $K_a$ and peak plasma time) are dependent upon the particle size of indomethacin preparations (i.e. the higher particle size, the slower dissolution and absorption). But the total amount of drug absorbed (measured as $AUC_{\text{inf}}$) is not affected by the particle size. While the plasma concentration time curve after the administration of indocid capsules...
shows a distinct distribution and elimination phases, this was less apparent following the administration of indomethacin generic capsules. Therefore, it is concluded that the particle size and rate of dissolution not only affect the peak time and level, but it may also affect the apparent pattern of indomethacin pharmacokinetics.

Introduction

Indomethacin is a anti-steroidal anti-inflammatory analgesic drug which has been widely used in the treatment of a variety of arthritic disorders since its introduction in 1964 [Rothermich, 1963]. It has a relatively narrow therapeutic range. Furthermore, it is a weak organic acid of very low aqueous solubility and poor wetability, all characteristics which make it a drug with a potential bioavailability problem [Rowland & Tozer, 1980.] thus, the present study was undertaken to estimate the bioavailability of indomethacin capsules, having different particle sizes and dissolution rates.

Methods and Materials

Formulation: Indomethacin capsule formulated in Iran by DP (Darou Paksh Co., lot No 057464) and indocid capsule formulated by MSD(Merck Sharp & Dohme, lot No 71096) were used in this study. Both preparations have lactose as the main filling agent.

Particle size : the particle size and particle size distribution of the two brands of indomethacin capsules, were determined using laser particle size distribution "Analysere 22" Fritsch Gmbh. The content of 15 randomly selected capsules of each brand was suspended in 20 ml of particle and bubble free distilled water and was placed in the measuring cell of the laser sizer. It must be mentioned that the main excipient of both capsules is lactose which is a water soluble agent and do not interfere with the measurement. To obtain a homogenous dispersion, an ultrasonic stirrer was used. After the particles
dispersion was completed, the measurement performed and the particle size
distribution of each sample were obtained.

Dissolution rate: The dissolution rates of the drug from the capsules
were determined at 37°C according to basket method specified by USP XXII
for the indomethacin capsules [USP, 1990]. The amount of the drug dissolved
was monitored at 318 nm of filtered portions of the solution under test, and
was expressed as a percent of the labeled amount. The average dissolution
rate was obtained after six different experiments.

Bioavailability: Ten healthy male and female volunteers participated in a
randomized cross-over study. Their ages ranged from 20 to 33 years and the
body weights of volunteers were in the normal range with respect to their
heights. No other drugs or alcoholic beverage were allowed prior to or during
the trial period. Each volunteer participated in two successive experiments,
separated by one week as a washout period. Each subject having fasted
overnight took 225 mg of test indomethacin capsules with 200 ml of water. The
volunteers were given a light breakfast 4 hours and a standard lunch 6 hours
after drug administration. They remained in the supine condition for first 4
hours. Several blood samples (5 ml) were taken after drug administration in
heparinized tubes. Plasma concentrations of indomethacin were determined
by the spectrofluorometric method of Lindquist et al. [1976]. The plasma was
separated and samples were frozen at -10°C until assayed.

Pharmacokinetic parameters were calculated from the plasma
concentration of indomethacin at various times, using a computer program
which was developed by one of the authors (M.M.). This program fits a two
compartmental model to experimental data using an iterative curve stripping
technique. $C_{\text{max}}$ and $T_{\text{max}}$ were calculated from fitted model by numerical
analysis. AUC 0-8 was calculated according to the trapezoidal rule. The $\text{AUC}_{\text{inf}}$
was calculated according to following equation:

$$\text{AUC}_{\text{inf}} = \text{AUC}_{0\rightarrow 8} + C_{8}/K_e \text{ terminal}$$
Results and Discussion

Particle size: A new method for determination of particle size and size distribution based on laser diffraction pattern was used in this study. The work is based on the Fraunhofer diffraction theory [Analysat instruction manual, 1991]. The size limitation for this equipment is in a range from one micrometer to one thousand micrometer diameter [Stanley-Wood et al., 1988]. This method is well applicable to our size range. The cumulative and frequency size distribution patterns of the two brand of capsules are presented in Figure 1. The median (50%) particle size of indocid MSD and indomethacin capsule DP was found to be 5.23 mm and 8.61 mm respectively with a significant difference between their distribution (Table 1).

Dissolution rate: Table 2 and Figure 2 show the dissolution rate (expressed as T 50, T 90; the time required for 50% and 90% dissolution and dmax; the percent of maximum drug dissolved) of the indomethacin capsules. There is a time lag of 2.0 min. before the dissolution process begins in both cases. This is probably due to the time required for disintegration of the gelatine shells (Fig.2). It was shown that dmax, the maximum amount of drug dissolved from two brand of indomethacin capsules are approximately similar. However in agreement with data of particle size analysis, the rate of dissolution for generic capsule (median particle size = 8.61 mm) is slower than indocid MSD capsule (median particle size = 5.23 mm). The distribution of particle size may largely affect the dissolution rate, therefore, a narrow particle size distribution is desired [Goldberg et al., 1966]. In this study, it was found that 99% of the indomethacin particles of MSD sample is less than 17.96 mm. However, only 75% of DP sample is less than 16.16 mm. and the remain (27%) contained particles from 16.16 to 49.23 mm.
Figure 1. Comparison between frequency size distributions of indomethacin particle size of DP indomethacin (B) and MSD indocid (A) capsules.
Table 1. Indomethacin particle size distribution of either indomethacin capsule (DP) or indocid capsule (MDS).

<table>
<thead>
<tr>
<th>Fixed Percentage Volumes</th>
<th>Indocid MSD micron</th>
<th>Indomethacin DP micron</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>&lt;0.38</td>
<td>&lt;0.59</td>
</tr>
<tr>
<td>25%</td>
<td>&lt;2.45</td>
<td>&lt;4.06</td>
</tr>
<tr>
<td>50%</td>
<td>&lt;5.23</td>
<td>&lt;8.61</td>
</tr>
<tr>
<td>75%</td>
<td>&lt;7.64</td>
<td>&lt;16.16</td>
</tr>
<tr>
<td>99%</td>
<td>&lt;17.96</td>
<td>&lt;49.23</td>
</tr>
</tbody>
</table>

Table 2. Dissolution rate parameters. $T_{50}, T_{90}$ (times required for 50% and 90% of the drug to be dissolved) and $d_{max}$ (maximum percent of drug dissolved) of indomethacin capsule (DP) and indocid capsule (MDS).

<table>
<thead>
<tr>
<th>Sample</th>
<th>$d_{max}$+S.E (% of label)</th>
<th>$T_{50}$+50+S.E(min)</th>
<th>$T_{90}$+S.E(min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indocid MSD</td>
<td>97.16 (+1.49)</td>
<td>2.8 (+0.2)</td>
<td>12.4 (+1.3)</td>
</tr>
<tr>
<td>Indomethacin DP</td>
<td>94.34 (+3.7)</td>
<td>3.7 (+1.6)</td>
<td>38.2 (+1.2)</td>
</tr>
<tr>
<td>t-test</td>
<td>NS</td>
<td>P&lt;0.1</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

* S.E. = standard error
Figure 2. Mean dissolution-time curves of indomethacin from either indomethacin capsule 25 mg DP (O) or indocid capsule 25 mg MSD (●). The vertical lines show S.E.

Regarding the dissolution rate profile; the time interval elapsed for 50% to 90% dissolution is 9.6 min. for MSD brand and 34.5 min. for DP brand. This shows a clear cut difference between dissolution rates, because of the larger population of bigger size particles in the generic preparation. Bioavailability: The method used for the determination of plasma concentration of indomethacin was sensitive and precise one. The standard curve was linear in the range of 0.25-8 mg/ml (r = 0.9983) and minimum detectable concentration in plasma was 0.1 mg/ml. The mean precision and accuracy of the assay was found to be 1.58% & 1.19% respectively Figure 3 shows the mean plasma-concentration of indomethacine following oral administration of two test capsules and Table 3 summarizes the mean values of calculated
pharmacokinetic parameters. As it can be seen from Table 3 and Figure 3, indomethacin will be absorbed faster from indocid capsules, and its peak plasma level is achieved 20 min. earlier compared to the generic capsules. The peak level is also 20% higher in the case of indocid capsules. However, the $\text{AUC}_{\text{inf}}$ values are similar in both cases. This shows that the total amount of absorption in these formulation are similar. The slower rate of absorption in the case of the generic preparation (DP) has resulted in the overlap of the distribution and elimination phases. While in the case of indocid capsules the $t_{1/2}$ of distribution phase is 1/6 of the $t_{1/2}$ of elimination, these two phases are not separated in the case of generic preparation. In agreement with Aoyagi et al. [1985] these results clearly show that the particle size and size distribution of indomethacin will affect its rates of dissolution and absorption. However in the range of particle size studied, the maximum amount of drug dissolved and the total amount of drug absorbed (measured as $\text{AUC}_{\text{inf}}$) is not affected by this factor.

**Table 3.** Mean values of pharmacokinetic parameters following oral administration of 2 x 25 mg indomethacin capsule (DP) or 2 x 25mg indomethacin capsule (DP) or 2x25mg indocid capsule (MSD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A: Indocid MSD</th>
<th>B: Indomethacin DP</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_e$ (h.)</td>
<td>0.21 (+0.03)</td>
<td>0.43 (+0.01)</td>
<td>$P&lt;0.05$</td>
</tr>
<tr>
<td>$K_d$ (h.)</td>
<td>1.53 (+0.01)</td>
<td>0.46 (+0.04)</td>
<td>NS</td>
</tr>
<tr>
<td>$K_a$ (h.)</td>
<td>1.99 (+0.01)</td>
<td>2.24 (+0.10)</td>
<td>$P&lt;0.05$</td>
</tr>
<tr>
<td>$t_{1/2}$ elim. (h.)</td>
<td>3.25 (+0.48)</td>
<td>1.61 (+0.23)</td>
<td>$P&lt;0.05$</td>
</tr>
<tr>
<td>$t_{1/2}$ dis. (h.)</td>
<td>0.45 (+0.04)</td>
<td>1.48 (+0.25)</td>
<td>NS</td>
</tr>
<tr>
<td>Lag time (h.)</td>
<td>0.41 (+0.03)</td>
<td>0.46 (+0.04)</td>
<td>NS</td>
</tr>
<tr>
<td>$T_{max}$ (h.)</td>
<td>1.04 (+0.08)</td>
<td>1.36 (+0.18)</td>
<td>$P&lt;0.05$</td>
</tr>
<tr>
<td>CP max (mg/L)</td>
<td>2.76 (+0.46)</td>
<td>3.02 (+0.50)</td>
<td>NS</td>
</tr>
<tr>
<td>AUC 8 (mg.h/L)</td>
<td>8.51 (+0.99)</td>
<td>9.40 (+0.86)</td>
<td>NS</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{inf}}$ (mg.h/L)</td>
<td>9.69 (+1.32)</td>
<td>9.89 (+1.18)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* *SE = Standard error.
** AUC 8 = Area under concentration-time curve to 8 hours.
*** AUC_{inf} = Area under concentration-time curve to infinity.
**** NS = Not significant.
Figure 3. Mean plasma levels of indomethacin after oral administration of 2x25mg of either indomethacin generic capsules DP (O) or indocid capsule MSD (●) to human volunteers (n=10). The vertical lines show S.E.

While, Alvan et al. [1975] have reported that the indomethacin pharmacokinetics obeys a two compartment model, others [Duggan et al., 1972, Hucker et al., 1966 & Holt & Hawkins, 1965] could not identify a distribution phase. Our results show that in the case of indocid capsules we have observed a clear distinction between distribution and elimination phases. However, when the drug is more slowly absorbed (i.e., in the case of the generic form), the distribution becomes less pronounced and half life values of distribution and elimination reach a mean value of 1.5 hours. Therefore, the discrepancies reported for the model of indomethacin pharmacokinetics may be a reflection of its rate of absorption. When the drug is slowly absorbed, the distribution and elimination phases overlap and the plasma concentration-time curve follows a pseudo one compartment model and when the absorption is
rapid, there is enough times for the absorbed drug to be distributed, its plasma concentration-time curve follows a two compartment model. These differences in the absorption of indomethacin may affect its clinical performance. It have been reported that fast dissolving formulation is less desirable than a slow dissolving formulation, since an increased frequency of side effect occurrence and a decreased interval of therapeutic effectiveness may result from the steep rise and fall in blood drug levels [Rothermich, 1966 & Rane et al., 1978]. However, other work on the effect of particle size on the indomethacin gastro-toxicity in rats shows that the administration of formulation with larger particles results in a greater number of stomach lesion [Ford & Elliot, 1985]. This might be due to the higher local irritancy of larger particles.

References