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Trials of clear aceclofenac-loaded soft capsules with accelerated oral absorption in human subjects

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Abstract

To develop an effective oral drug delivery system with accelerated absorption in human subjects for a poorly water-soluble acelofenac, five aceclofenac-loaded soft capsule preparations containing various ratios of different solubilizers were prepared and their dissolution tests were carried out. Among five preparations tested, a preparation with ethanolamine was selected as a formula of aceclofenac soft capsule (Korea United Pharm. Co. Ltd., Clanza S^{TM}), since it was clear in appearance and showed the fastest dissolution rate due to the solubility-enhancing effect of aceclofenac. To evaluate and compare the pharmacokinetics of acelofenac-loaded soft capsules with the conventional aceclofenac tablets (Dae-Woong Pharm. Co. Ltd., Airtal^{TM}) in human subjects; 14 normal healthy male volunteers (age 20–25 years old) were divided into two groups and a randomized 2 × 2 cross-over study was performed. Following oral administration of one tablet or capsule, each containing 100 mg of aceclofenac, blood samples were collected at the predetermined time intervals and the concentration of aceclofenac in plasma was determined by HPLC method using UV detector. The AUC, C_{max}, MRT, $t_{1/2}$ and K_{el} of aceclofenac delivered from soft capsule were not significantly different from those from aceclofenac-loaded conventional tablet. However, soft capsule gave significantly higher initial concentration and significantly faster T_{max} of aceclofenac than did conventional tablet, suggesting that the soft capsule with ethanolamine showed the faster absorption of aceclofenac in human subjects. Thus, the clear aceclofenac-loaded soft capsule with ethanolamine was a more effective oral dosage form with fast absorption for poorly water-soluble aceclofenac.

Keywords: Aceclofenac; Ethanolamine; Soft capsule; Pharmacokinetics

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1. Introduction

Aceclofenac, 2-[[2-[2-[(2,6 dichlorophenyl)amino] phenyl]acetyl]oxy] acetic acid, is a non-steroidal anti-inflammatory drug (NSAID) of the phenyl acetic acid type, that is structurally related to diclofenac (Hinz et al., 2003; Martin-Mola et al., 1995). Like other NSAIDs, aceclofenac is a prostaglandin synthetase (cyclooxygenase) inhibitor, which inhibits lipoxygenase and decreases prostaglandin production, thereby inhibiting the inflammatory process. Aceclofenac has been shown to have potent anti-inflammatory, analgesic and antipyretic properties (Movilia, 1989)). Furthermore, aceclofenac is indicated for the acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and scapulohumeral periarthritis (Brogden et al., 1996; El Kousy, 1999). It is also indicated for pains of various etiologies, such as musculoskeletal pain, dental pain or post surgical pain.

The usual dose of aceclofenac is 100 mg twice a day (Najib et al., 2004; Kim et al., 2001). Aceclofenac is absorbed rapidly as an unchanged drug when taken orally, and its analgesic effects begin within 30 min of ingestion (Najib et al., 2004). Following oral administration, it reaches a peak plasma concentration within 1–3 h (Kim et al., 2001). Since it is indicated for various pains, its accelerated absorption after oral administration is needed (Kim et al., 1998).

In this study, to develop an effective novel oral drug delivery system with accelerated absorption in human subjects for a poorly water soluble drugs, the acelofenac, five soft capsule preparations with various ratios of different solubilizers were prepared using polyethyleneglycol 400 (PEG 400) as a base of soft capsule content (Amemiya et al., 1998, 1999; Hong et al., 1998) and their dissolution studies were performed. Diethanolamine, methylglucamine, L-arginine and Tween 80 were selected as solubilizing agents, since they were used as solubilizing agents for poorly water-soluble drugs (Cheong and Choi, 2002; Fang et al., 2003; Fini et al., 1999). Furthermore, the pharmacokinetics of conventional aceclofenac tablet (Dae-Woong Pharm. Co. Ltd., Airtal^{TM}) and aceclofenac-loaded clear soft capsule containing diethanolamine (Korea United Pharm. Co. Ltd., Clanza S^{TM}) were evaluated and compared in human subjects.

2. Materials and methods

2.1. Materials

Aceclofenac was of USP grade. Flufenamic acid, diethanolamine, methylglucamine, L-arginine, Tween 80, PEG 400 and aceclofenac soft capsule (Clanza S^{TM}) were supplied from Korea United Pharm. Co. Ltd. (Seoul, South Korea). Aceclofenac conventional tablet (Airtal^{TM}) was supplied from Daewoong Pharm. Co. Ltd. (Sungnam, South Korea). All other reagents were of analytical or chromatographic grade procured from Fisher Scientific (Fair Lawn, NJ, USA). Ultra pure water (18.2 MΩ) filtered through 0.45 μm membrane filter (Millipore, Miliford, MA, USA) was used in all the experiments.

2.2. Dissolution test

2.2.1. Preparation of aceclofenac-loaded soft capsule preparations

Aceclofenac and various ratios of solubilizers, such as diethanolamine, methylglucamine, L-arginine and Tween 80 were added in PEG 400, respectively, and thoroughly blended. These soft capsule contents were then put in the gelatin soft capsule shell. The detailed compositions of soft capsule contents are given in Table 1 (Hong et al., 1998; Zawilla et al., 2002).

2.2.2. Dissolution test

Each soft capsule preparation and a conventional tablet containing 100 mg aceclofenac was placed in a dissolution tester (DST-600, Fine Chemical, Korea), respectively. Dissolution test was performed at 36.5 °C using the paddle method at 50 rpm with 900 ml of distilled water as a dissolution medium (Choi et al.,

Table 1
Formulation of aceclofenac soft capsule contents with various ratios of solubilizers

Formulation	A	B	C	D	E
Aceclofenac	100.0	100.0	100.0	100.0	100.0
Diethanolamine	7.0	–	–	–	–
Methylglucamine	–	7.0	–	–	–
L-Arginine	–	–	7.0	–	–
Tween 80	7.0	7.0	7.0	14.0	7.0
PEG 400	246.0	246.0	246.0	246.0	253.0
Total weight (mg/cap.)	360.0	360.0	360.0	360.0	360.0

2000). At predetermined interval, 5 ml of aliquots of the medium were sampled and filtered. The filtrate was analyzed by UV–vis variable wavelength detector (Philips, Model PU8730) at 277 nm (El-Saharty et al., 2002; Hinz et al., 2003). The dissolution rates of drug from various preparations were compared for statistical significance by the one-way analysis of variance (ANOVA). The statistical significance of means among different formulations was then compared by multiple range method of least significant difference.

2.3. Pharmacokinetic study

2.3.1. Clinical test

A group of healthy volunteers was screened by performing physical examination, liver function tests, hemogram, HBV, routine urine analysis and chest X-ray at Yeungnam Hospital (Daegu, South Korea). After screening, 14 healthy subjects aged between 20 and 25 years and weighing more than 60 kg with no history of drugs or alcohol abuse, liver kidney or gastro-intestinal disorders were selected. The scope of the study was explained to them and each one signed an informed consent form before the onset of the study (Najib et al., 2004; Kim et al., 2001).

2.3.2. In vivo experiments

Male healthy volunteers aged 23.4 ± 1.5 years weighing 65.5 ± 4.9 g were fasted for 12 h prior to the experiments but allowed free access to water. Fourteen normal male volunteers (age 20–25 years old) were divided into two groups and a randomized 2×2 cross-over study was performed in a period of 2 weeks. Seven human subjects in each group were administered with soft capsule (Clanza S^{TM}) or conventional tablet ((Airtal^{TM}) containing 100 mg aceclofenac, respectively. After 2 weeks, the human subjects in each group were reversely administered (Kim et al., 1998).

2.3.3. Administration and blood-collecting

One soft capsule or conventional tablet containing 100 mg aceclofenac was orally administered with 70 ml water, respectively. Venous blood samples (3 ml) were collected into heparinized vacutainers using indwelling catheters at 0 h (during the implantation of catheter just before the administration of dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after the ingestion of the dose in each experimental session. The samples were immediately centrifuged at $3000 \times g$ for 10 min using a centrifuge 5415C (Eppendorf, USA) and stored at $-20\,^{\circ}C$ until analysis.

2.3.4. Blood sample analysis

Plasma (100 μl) was mixed with 400 μl of acetonitrile solution containing flufenamic acid (2 μg/ml) as an internal standard. It was then centrifuged at $12{,}000 \times g$ for 5 min to precipitate the proteins. The supernatant layer (0.4 ml) was evaporated under N_2 (g). The residue was reconstituted in 50 μl of mobile phase. Then, the resulting solution was analyzed by HPLC (Hitachi, Model L-7100) equipped with an Inertsil ODS-3 C_{18} column (GL science, 5 μm, 15 cm × 0.46 cm i.d.) and UV detector (Model L-7450). The mobile phase consisted of acetoniltrile, distilled water and o-phosphoric acid (40:60:0.1, volume ratio). The eluent was monitored at 277 nm with a flow rate of 1.0 ml/min (Lee et al., 2000; Choi et al., 1998).

2.3.5. Calculation of pharmacokinetic parameters

All the pharamcokinetic parameters were determined by non-compartmental analysis. AUC was calculated by linear trapezoidal method. C_{max} (the highest drug level measured) and T_{max} (the time to reach the highest concentration) were directly read from the concentration time plots. Elimination rate constant (K_{el}) was estimated from the linear regression line of the elimination phase. Elimination half-life ($t_{1/2}$) was calculated as $0.693/K_{el}$.

3. Results and discussion

To evaluate whether the solubilzers affected the dissolution rates of aceclofenac from soft capsule, five preparations A–E with various ratios of solubilizers, such as diethanolamine, methylglucamine, L-arginine and Tween 80 were prepared and their dissolution tests were carried out (Table 1 and Fig. 1). In this experiment, PEG 400 was used as a base of soft capsule content (Amemiya et al., 1998, 1999; Hong et al., 1998).

Diethanolamine and methylglucamine improved the dissolution rates of aceclofenac from soft capsule (preparation A–B versus E). Preparation A and B had significant higher dissolution rates of aceclofenac than preparation E. However, L-arginine and tween 80 insignificantly improved the dissolution rates of ace-

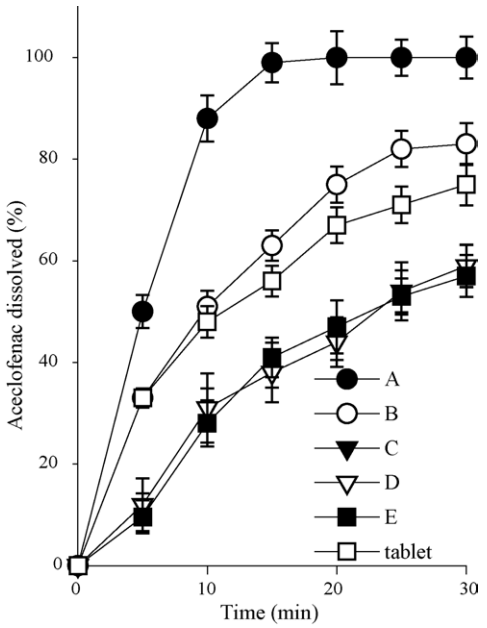

Fig. 1. Effect of solubilizer on the dissolution of aceclofenac from various soft capsules. Each value represents the mean ± S.E. ($n = 6$).

clofenac from soft capsule (preparation C–D versus E). Until 30 min, preparations A and B had significantly higher dissolution rates of aceclofenac than preparation E. Furthermore, until 15 min, the dissolution rates of aceclofenac in preparation A were significantly higher than from those in preparation B, even if, from 20 to 30 min, they were not significantly different (Choi et al., 2000). These results indicated that, among the solubilizer tested, diethanolamine was found to be best to improve the dissolution rates of aceclofenac from soft capsules. The reason for this improved dissolution of aceclofenac from soft capsules was dependent upon the aceclofenac solubility-improving effect of diethanolamine in the soft capsule content (Cheong and Choi, 2002). The content appearance in the aceclofenac-loaded soft capsule with diethanolamine was clear (Fang et al., 2003). Therefore, among five preparations tested, a preparation with ethanolamine was selected as a formula of aceclofenac soft capsule (Korea United Pharm. Co. Ltd., Clanza S^{TM}).

As shown Fig. 1, preparation A had significantly higher dissolution rates of aceclofenac than conventional tablet. A commercial product, Airtal^{TM} (Daewoong Pharm. Co. Ltd., South Korea) was used as a representative sample for conventional tablet. According to these results, it is expected that the acelofenac be better absorbed from a clear aceclofenac-loaded soft capsule containing diethanolamine than from aceclofenac-loaded conventional tablet (Choi et al., 1998, 2000).

The pharmacokinetic parameters of aceclofenac were determined after oral administration of a clear aceclofenac-loaded soft capsule with ethanolamine (Clanza S^{TM}) and conventional tablet (Airtal^{TM}), respectively. Fig. 2 shows the change of mean plasma concentration of aceclofenac after oral administration of preparations in human subjects (Najib et al., 2004; Kim et al., 2001).

The initial plasma concentrations of aceclofenac in soft capsule, until 1 h, were higher compared with those in conventional tablet. However, there were no significant differences between those initial plasma concentrations of aceclofenac. From 1 h 30 min after the dose, the plasma concentrations of aceclofenac in soft capsule, were not significantly different from those in conventional tablet. These results indicated that aceclofenac-loaded soft capsule with ethanolamine might improve the initial oral absorption of aceclofenac, which is very important in pain management, due to the solubility-improving effect of ethanolamine in soft capsule content (Fang et al., 2004; Fini et al., 1999).

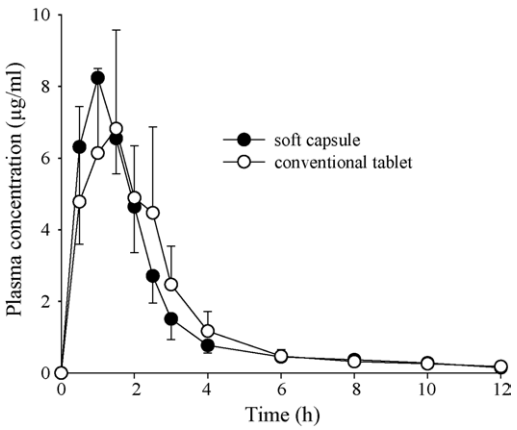

Fig. 2. Plasma concentration-time profiles of aceclofenac after oral administration of one soft capsule (Clanza S^{TM}) and conventional tablet (Airtal^{TM}) at the aceclofenac dose of 100 mg to human subjects. Each value represents the mean ± S.E. ($n = 14$).

Table 2
Pharmacokinetic parameters of aceclofenac delivered by conventional tablet and soft capsule

Parameters	Conventional tablet	Soft capsule
AUC (h μg/ml)	18.86 ± 4.26	19.44 ± 5.66
T_{max} (h)	1.00 ± 0.29	0.50 ± 0.19*
C_{max} (μg/ml)	6.82 ± 3.73	8.24 ± 3.10
MRT (h)	2.40 ± 0.52	2.60 ± 0.70
K_{el} (h^{-1})	0.16 ± 0.03	0.18 ± 0.03
$t_{1/2}$ (h)	4.49 ± 0.70	3.87 ± 0.67

Each value represents the mean ± S.E. ($n = 14$).
* $P < 0.05$ compared with conventional tablet.

The pharmacokinetic parameters are shown in Table 2. The AUC, C_{max}, MRT, $t_{1/2}$ and K_{el} of aceclofenac from soft capsule (19.44 ± 5.66 h μg/ml, 8.24 ± 3.10 μg/ml, 2.60 ± 0.70 h, 3.87 ± 0.67 h and 0.18 ± 0.03 h^{-1}, respectively) were not significantly different than those from conventional tablet (18.86 ± 4.26 h μg/ml, 6.82 ± 3.73 μg/ml, 2.40 ± 0.52 h, 4.49 ± 0.70 h and 0.16 ± 0.03 h^{-1}, respectively). Thus, this clear aceclofenac-loaded soft capsule with ethanolamine could not improve the oral bioavailability of aceclofenac in human subjects. However, the T_{max} of aceclofenac (0.50 ± 0.19 h) in this clear soft capsule was significantly lower than that of conventional tablet (1.00 ± 0.29 h), indicating that the aceclofenac from soft capsule could be absorbed faster than that from conventional tablet initially in human subjects. Our results suggested that the aceclofenac-loaded soft capsule with ethanolamine was a more effective oral dosage form with fast absorption and similar bioavailability for poorly water-soluble aceclofenac. The reason for this difference might be dependent upon the aceclofenac solubility-improving effect of diethanolamine in the soft capsule content (Cheong and Choi, 2002; Fang et al., 2003). Conventional tablet contained aceclofenac was in less soluble solid-state and dissolved slowly. In contrast, soft capsule was dissolved faster, since it was in liquid state in clear soft capsule containing diethanolamine, which also enhanced the solubility of aceclofenac in soft capsule content. Our results indicated that the aceclofenac from soft capsule could initially be faster absorbed than that from conventional tablet in human subjects (Hong et al., 1998).

Zuniga et al. (2004) reported that the pharmacokinetic parameters of diclofenac sodium in soft gel, a steroidal anti-inflammatory drug, were compared with those in conventional tablet in human subjects. The AUC of diclofenac sodium from soft gel was not significantly different than that from conventional tablet. However, the C_{max} and T_{max} of diclofenac sodium from soft gel were significantly higher and lower than that of conventional tablet, respectively. Compared with this diclofenac sodim-loaded soft gel, even if its compostion is not known, an aceclofenac delivered from this soft capsule could initially be faster absorbed in human subjects without relatively high maxium plasma concentration. Thus, the clear aceclofenac-loaded soft capsule with ethanolamine was expected to reduce the time of onset of inflammatory pain without side effects.

4. Conclusion

It is concluded that the clear aceclofenac-loaded soft capsule with ethanolamine gave significantly higher initial plasma concentrations and T_{max} of aceclofenac than did conventional tablet, indicating that the drug from soft capsule could be faster absorbed in human subjects. Therefore, the clear aceclofenac-loaded soft capsule with ethanolamine was a more effective oral dosage form with fast absorption and similar bioavailability for poorly water-soluble aceclofenac.

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