Improved Oral Pharmacokinetics of Diclofenac Sodium from SNEDDS in Human Volunteers

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Abstract: The pharmacokinetics of diclofenac sodium in SNEDDS formulation and tablet were compared in healthy human volunteers. In this, randomized study with a cross over design, diclofenac sodium was administered as a single dose to subjects before food. Blood samples were obtained before dosing as a control and at 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hours after dosing. The serum concentrations were determined by high performance liquid chromatography. Possible adverse events were monitored during the entire study. After log-transformation of the comparable variables, statistically significant differences were found between the two formulations with respect to the time between dosing and the appearance of the drug in serum, time to reach maximum concentration, elimination half-life, absorption rate constant and mean residence time. The extent of absorption was assessed by estimating the area under the serum concentration-time curve (AUC). $AUC_{0\text{-}8hr}$ and $AUMC_{0\text{-}24hr}$ was statistically significantly higher for diclofenac sodium (DFS) self nanoemulsifying drug delivery systems (SNEDDS) (6.428mcg.hr/ml, 218.83mcg.hr/ml) than for voveran tablet (5.869mcg.hr/ml, 52.19mcg.hr/ml). No significant differences were found in $AUC_{0\text{-}24hr.}$ SNEDDS of diclofenac sodium showed a statistically significant higher maximum serum concentration than voveran tablet (2.289mcg/ml and 1.375mcg/ml for SNEDDS and tablet, respectively). The results of the present study suggest that SNEDDS of diclofenac sodium could be a clinically useful rapid release formulation for immediate relief without causing gastric ulcers.

Keywords: SNEDDS, tablet, diclofenac sodium, pharmacokinetics, absorption.

1. INTRODUCTION

Diclofenac sodium (DFS) being an NSAID is used to relieve pain [1, 2] induced by inflammation [3, 4]. It is also used in dental pain [5, 6], renal cholic [7] and post operative pain [8, 9]. It's anti inflammatory effect is mediated by prevention of prostaglandin systhesis inhibition [10, 11]. The bioavailability of diclofenac sodium from tablets is only 54% reaching peak concentration in 2-3 hrs having $T_{1/2}$ of 1-2 hrs [12-14]. The common side effects of DFS are gastric and duodenal ulcers due to direct interaction with gastric mucosa and prostaglandin synthesis inhibition [15]. Owing to its rapid clearance [16, 17], frequent administration is required and has lead to the development of sustained release formulations of DFS [18, 19]. But both immediate release and sustained release formulations are reported to cause gastric and duodenal ulcers [20, 21]. From the above reports, it is evident that the bioavailability enhancement and minimization of gastric and duodenal ulcers can be achieved by developing a novel drug delivery system. Self Nano emulsifying Drug Delivery System (SNEDDS) readily disperse in the stomach to form a fine nanoemulsion where the gastrointestinal motility can provide the agitating effect necessary for emulsification [22]. For drugs having characteristics of dissolution rate limited and diffusion rate limited absorption, these could enhance the rate and extent of absorption, as well as improve the reproducibility of the plasma blood level time profiles thus effectively minimizing the gastro intestinal side effects [23]. There are several studies on SEDDS developed with NSAIDS reporting excellent bioavailability [24]. The objective of the present investigation is to develop a stable SNEDDS of DFS and to conduct a two way cross over design to evaluate bioavailability of DFS in healthy human volunteers with DFS SNEDDS preparation and tablets (marketed preparation) following oral administration of these formulations.

2. MATERIALS AND METHODS

Oil phase containing DFS was emulsified using phosphate buffer by modification of the reported method by Yu *et al*., 1993 [25]. The resulting SNEDDS preparation of DFS was subjected to size analysis by photon correlation spectroscopy using Zetasizer 3000HSA/Zetasizer ZS-90 [26] (Malvern Instruments, Malvern, UK). Each sample was diluted to a suitable concentration. Analysis was performed at 25°C with an angle of detection at 90° [27]. The mean zetapotential was also obtained directly from Zetasizer 3000HSA/Zetasizer ZS-90 (Malvern Instruments, Malvern, UK).

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2.1. Subjects

The pharmacokinetic study was performed in eight healthy male volunteers for two way crossover design and was selected after passing a clinical screening procedure that included medical history, physical examination and standard laboratory tests (blood cell count, biochemical profile and urinalysis). The volunteers were to receive two different treatments of DFS separated by 2-week washout intervals. The demographic data of these volunteers were: weight between 45 to 65 kg with 150 to 175cm [28]. The subjects ranged in age from 20 to 30 years. The inclusion criteria were as follows: Healthy as per physical examination, non allergic to the drug being administered, without other medication, written informed consent [29]. This study was performed according to the revised biomedical research protocol involving human subjects and the rules of Good Clinical Practice [30]. The protocol of the bioavailability studies was approved by the Institutional Human ethical committee of kakatiya university with letter No:UCPSC/BA/2008-02. After an overnight fast, a catheter was introduced into a forearm vein, and a pre-dosing blood sample was collected. The subjects received a single oral dose (100mg) of all the formulations with 100ml of water in the fasted state followed by breakfast after 30 min after administration. Standardized food consisted of two idlis. The total caloric value of the breakfast was 350 kcal and was based on FDA recommendations. The breakfast had to be consumed in less than 20 min. Standardized meals were served 4h and 8h post-dose. Venous blood samples (3ml) were withdrawn from the forearm vein at the designated time intervals to determine DFS in serum following the oral treatments. After centrifugation at 2000×g for 15 min, serum samples were stored at −20°C prior to analysis [31].

2.2. Study Protocol

The aim of the experimental design was to minimize experimental variables and to avoid bias. Therefore random administration and crossover design [32] is preferred. The crossover design minimizes the effect of inter subject variability in the study by using each subject as his own control. The study protocol was approved by institutional human ethical committee.

2.3. Study Design

The study was a two way cross over design. It comprised eight volunteers distributed into two groups. The bioavailability of two formulations i.e. tablet and DFS SNEDDS were selected for the study. During the first part of the study period, subjects 1 to 4 received tablet and subjects 5 to 8 received DFS SNEDDS formulation. A second study period was initiated after the washout period of two weeks during which complete elimination of the drug and its major metabolites took place. In the second part of the study period, subjects 1 to 4 received DFS SNEDDS formulation and subjects 5 to 8 received tablet. Therefore each subject acted as his own control.

2.4. Blood Sample Collection

The selected subjects were maintained on a uniform diet and it was ensured that none of them had taken any drug at least one week prior to the study [33]. After overnight fasting, a 2ml blood sample was withdrawn from all the subjects to serve as blank at the time of analysis and then the subjects were administered the formulations orally (containing 100mg DFS) with 100ml of water. Blood samples were collected by catheterized vein puncture on forearm at predetermined time points (0.5, 1, 1.5, 2, 4, 8, 12 and 24 hours) into eppendroff tubes. The blood was allowed to clot, serum separated by centrifugation at 2000g for 10 min and then stored at -20ºC till analysis.

2.5. Pharmacokinetics and Statistical Analysis

A sensitive reverse phase high performance liquid chromatographic (HPLC) method was used to determine the amount of DFS in human serum [34]. The experimental procedure consisted of extraction of the drug with dichloromethane from the acidic serum sample. The organic layer was separated, evaporated to dryness and the residue dissolved in mobile phase and analyzed by HPLC. Carbamazepine was used as an internal standard. The linearity of the method for carbamazepine was evaluated in the range of concentration between 0.1mcg/ml and 16mcg/ml. The pharmacokinetic parameters of DFS were calculated by the analytical bioavailability program, Winonlin 3.3 Pharsight, Mountain View, CA. The area under the serum concentration − time curve from 0h to 24h (AUC_{0-24}) was calculated using the linear trapezoidal rule. The maximal serum concentration of DFS (C_{max}), the time to C_{max} (T_{max}), and the half-life ($T_{1/2}$) were also calculated. Inter-individual variability for the considered parameters was evaluated by coefficient of variation (CV%). The differences between treatment means for each pharmacokinetic parameters were examined by one way analysis of variance. Where significant differences were found, a paired *t*-test was applied with significance level of 0.05. The pharmacokinetic

parameters K_a, AUC, C_{max}, T_{max}, CL and K_e were calculated. Results are expressed as mean values ±SD. Maximal serum concentrations (C_{max}) and time to C_{max} (T_{max}) were obtained directly from the raw data. The terminal half life $T_{1/2}$ was calculated from the terminal slope. The data of all the formulations were subjected to one way analysis of variance (ANOVA) to get the statistical significance [35].

3. RESULTS AND DISCUSSION

The SNEDDS preparation of DFS with a size of 137 nm and zeta potential of -11.6 mv was subjected to pharmacokinetic studies in human volunteers.

3.1. Clinical Safety Measurements

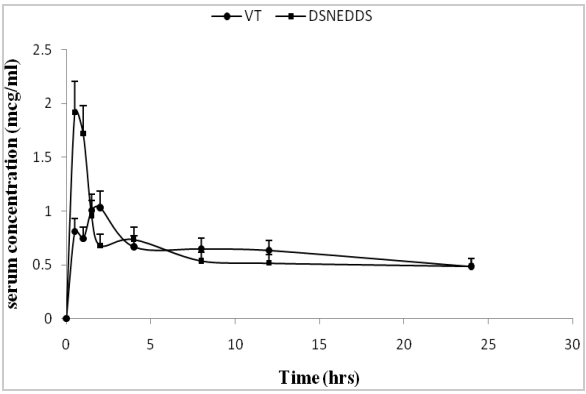
Vital signs of oral temperature, sitting blood pressure and radial pulse were found to be normal for all the subjects during the course of the study in all periods of the study. The clinical examination results of all the study subjects were found to be normal.

3.2. Adverse Events and Dropouts

The study treatments were well tolerated by the study subjects. All the subjects completed the study without experiencing any adverse events during study period.

3.3. Serum Analysis

The mean serum concentrations of diclofenac sodium vs time plots following oral administration of tablet and SNEDDS formulation in human volunteers at a dose of 100mg over a period of 24 hours was observed. The tablet showed a gradual increase in serum drug concentration up to 2 hours and thereafter a gradual fall in drug levels were seen upto 4 hours after which drug levels remained low and fairly constant. With the SNEDDS formulation, the C_{max} was obtained rapidly within 30 minutes and thereafter there was a gradual fall till 8 hours and fairly constant and low levels of the drug were maintained upto 24 hours. The C_{max} obtained with SNEDDS was significantly higher ($p<0.05$) than that of tablet. The drug levels at 4 and 8 hours were significantly higher ($p<0.01$) with SNEDDS compared to tablet as shown in Figure **1**. This is a significant sign of improvement in the performance of DFS SNEDDS formulation since several research studies report that the immediate release and sustained release formulations are observed to cause both gastric and duodenal ulcers with chronic use leading to mucosal injury after prolonged usage and also how multiple peak patterns after administration. Other NSAIDS also show similar adverse effects [36-45]. The C_{max} obtained due to oral ingestion of SNEDDS formulation was significantly higher than tablet. Also, the T_{max} value was lower for SNEDDS than tablet indicating a rapid rate of absorption of DFS due to oral ingestion of SNEDDS formulation (Table **1**). This is also conspicuous from the value of absorption rate constant which is higher for SNEDDS formulation than tablet. The C_{max} and AUC_{0-8h} and C_{max} and $AUC_{0-24hrs}$ (Figure **1.1** and Figure **1.2**) of DFS from SNEDDS formulation was enhanced when



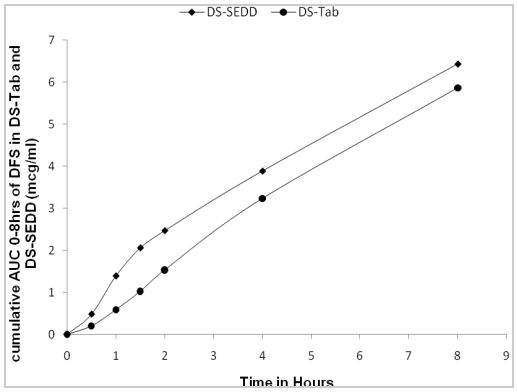
Each point represents mean ± S.D. VT – voveran tablet, DSNEDDS – diclofenac sodium self nanoemulsifying drug delivery system

Figure 1: Mean serum drug concentrations vs time of tablet and SNEDDS following oral administration in human subjects at a dose 100mg (n=8).

Table 1: Pharmacokinetic Parameters (Mean ± SD; n=8) of Diclofenac Sodium Following Oral Administration of Tablet and SNEDDS Formulations in Human Volunteers at a Dose of 100 mg (n=8)

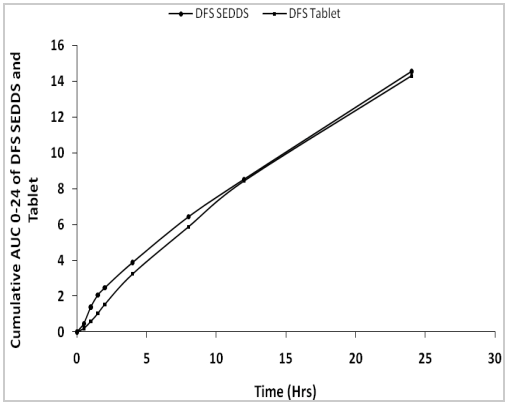
Parameters	DFS-SNEDDS	DFS-Tablet
C_{max}	2.289 ± 0.12	1.375 ± 0.61
T_{max}	0.5	2.5
K	0.029 ± 0.001	0.065 ± 0.005
Ka	0.218 ± 0.002	0.174 ± 0.0001
T1/2	7.21 ± 2.3	5.39 ± 1.9
CL	3.108 ± 1.09	28.082 ± 2.7
Vss	137.56 ± 6.9	92.081 ± 11.3
AUC(0-8hr)	6.428 [c]	5.869 [a]
AUC(0-24hr)	14.552 ± 4.7	14.3 ± 5.1
AUMC(0-24hr)	218.83 ± 13.8	52.19 ± 12.9
MRT(0-24hr)	127.46 ± 11.8	53.64 ± 9.3

Each point represents mean ± S.D a, c, d represent $p<0.05$, 0.01, 0.001. C_{max} in µg/mL; T_{max} in hours; Cl in mL/hr;AUC_{0-24h} in µg.h/mL;MRT in hours;Vss in mL;K in $h\ r^{-1}$.



DS Tab – voveran tablet, DS SEDD – diclofenac sodium self nanoemulsifying drug delivery system.

Figure 1.1: Time versus Cumulative $AUC_{(0-8)}$ plots of DFS following oral administration of tablet and DFS SNEDDS at a dose of 100mg (n=8).



DFS Tablet – voveran tablet, DFS SEDDS – diclofenac sodium self nanoemulsifying drug delivery system.

Figure 1.2: Time versus Cumulative $AUC_{(0-24)}$ plots of DFS following oral administration of tablet and DFS SNEDDS at a dose of 100mg (n=8).

compared to that of tablet. These results correlate with a research report in which after an oral administration of the self emulsifying system containing indomethacin to rats, the plasma concentrations and peak plasma concentration of were significantly higher than suspension. The significantly higher plasma concentrations of indomethacin, resulted in a significantly greater $AUC_{0\text{-}12\ h}$. The absorption of indomethacin from self emulsifying system increased significantly (57% increase based on $AUC_{0\text{-}12\ h}$) [46]. In another study the C_{max} and $AUC_{0\text{-}t}$ of oridonin from SMEDDS were significantly higher showing greater extent of absorption than those of the suspension. The relative bioavailability was approximately 2.2 fold with bioavailability of the SMEDDS to suspension was 220.21% [47]. After oral dosing of SNEDDS, an early serum levels were observed, which was higher than that obtained with the tablet. We have interpreted this as probably due to particulate absorption and release of the drug from SNEDDS formulation in molecular form but in the market preparation it has to undergo dissolution which is rate limited and also it exists in its acidic form in gastric medium which is practically insoluble in water (3.6 mcg/ml) but soluble in intestinal fluid (26 mcg/ml) [48]. The observed difference in the serum levels of the two formulations could be due to their different release behaviour in the GIT. The tablet might have taken time to disintegrate, dissolve and undergo absorption into the systemic circulation. This would have caused a delay in achieving C_{max}, whereas DFS SNEDDS might have straight away led to systemic absorption. This accounts for the difference observed in the T_{max} values and the difference in the AUC in the initial time points. In the later time points, the serum drug vs time curve of DFS tablet takes a higher position to that of DFS SEDDS which could mean that the SEDDS formulation was taken up into extravascular clearance. After oral dosing of SNEDDS, an early serum levels were observed, which was higher than that obtained with the tablet. We have interpreted this as probably due to particulate absorption [49] and release of the drug from SNEDDS formulation in molecular form but in the market preparation it has to undergo dissolution which is rate limited. The half-life of DFS in SNEDDS tablet was 7.21 hrs and 5.39 hrs respectively. The early peak levels observed in SNEDDS indicates extremely fast absorption of the drug and it is rather a typical of absorption from the human intestine [50]. Since it has been postulated that diclofenac sodium has some action on the structure of the jejenum membrane responsible for gastric ulcers [51], drug retention and effecting permeability, such behavior was not seen due to enhancement in the rate and extent of absorption. Our findings of improved absorption of diclofenac sodium, correlate with a study in which when diclofenac sodium is incorporated in lecithin based nanoemulsion, the rate of absorption were improved enhancing the permeability of diclofenac sodium through caco-2 monolayer cells [52]. For SNEDDS formulation treatment, the higher C_{max}, lower T_{max} consequently higher rate of absorption ($K_{\mathbf{a}}$), higher $T_{1/2}$ and lower clearance did not enhance the overall bioavailability although the higher rate of absorption and lower rate of elimination should have resulted in the higher oral bioavailability. This indicates that SNEDDS formulation only significantly altered rate of absorption but not the overall bioavailability which means both the formulations are capable of rendering complete absorption of DFS, only with a difference that the SNEDDS formulation is capable of enhancing the rate of absorption. However the $T_{1/2}$ of DFS being 1-2

hrs as per pharmacokinetic study norms, one should consider AUC assessment (oral bioavailability) only up to 4-6 half lives to arrive at measuring bioavailability data for comparison. When we did this, the SNEDDS formulation resulted in higher bioavailability of DFS compared to voveran tablet (Figure **1**). The elimination rate constant (K) for SNEDDS was seen to be lower ($p<0.001$) with a value of 0.029 hr^{-1} compared to 0.065hr^{-1} with that of voveran tablet. The half life for tablet was 5.39 hours which was significantly lower ($p<0.01$) than that of SNEDDS of 7.21 hours which is a direct consequence of low value of elimination rate constant. There was a faster systemic clearance with voveran tablet ($p<0.001$) 28.08/hr, compared to SNEDDS i.e. 3.11/hr respectively. The volume of distribution at steady state level was found to be significantly lower ($p<0.05$) with that of voveran tablet compared to SNEDDS (Table **1**). So, there is a slight improvement in the AUC of SNEDDS formulation.

4. CONCLUSION

An attempt was made to develop a novel carrier (SNEDDS) of diclofenac sodium to enhance the absorption characteristics i.e. oral bioavailability. From the studies conducted, we could get positive results as per the hypothesis made. But, further the study has to be conducted in a larger group of population for a better clinical assessment of the novel formulation.

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