ABSTRACT

Background: This study was undertaken to develop and formulate aceclofenac matrix sustained release tablets using a natural gum and to conduct its pharmacokinetic and pharmacodynamic evaluation. Methods: Sustained release matrix tablets of aceclofenac were prepared by using a direct compression technique, using Salmalia malabarica gum as matrix forming material while microcrystalline cellulose was as filler. All the ingredients were passed through a # 20 sieve, weighed, and blended. These formulations were compressed with a single station tablet compression machine using 9 mm flat faced punches. Results and discussion: The drug–polymer interactions were studied using FT-IR spectroscopy which indicated the absence of interactions. Scanning electron microscopy was used to visualize the surface morphology of the tablets and confirm drug release mechanisms. The stability studies were performed using ICH guidelines for a period of six months and found that the developed formulation was stable. In-vivo studies for anti-inflammatory activity and pharmacokinetics were performed in wistar rats and young male rabbits respectively. The in-vivo results showed that the optimized tablet (F-5) exhibited significant difference in the drug release in comparison to that of pure drug and marketed formulation. Conclusion: It can be concluded that the developed formulation shows sustained release and is of cost effective for the formulation development of aceclofenac tablets.

KEYWORDS: Aceclofenac, salmalia malabarica gum (SMG), anti-inflammatory, pharmacokinetics, sustained release.

1. INTRODUCTION

Sustained release systems are the methods that can achieve therapeutically effective concentration of drug in the systemic circulation over an extended period of time with better patient compliance. The Non-steroidal anti-inflammatory drugs (NSAIDs) are used for relief from pain and inflammation in rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Aceclofenac is an oral NSAID and emerged as a new molecule for arthritis treatment. It is a novel derivative of diclofenac with minimal gastrointestinal complications. The effective treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. The aceclofenac has biological half-life of 4 h and is an ideal candidate for sustained release formulations.

In recent years, many plant derived natural polymeric materials such as ispaghula husk, Gleditsia triacanthos gum (honey locust gum), Sesbania gum, mucilage from the pods of Hibiscus esculenta, tamarind seed gum, gum copal and gum dammar, agar, glucomannan gum from Amorphophallus konjac have been successfully used in sustained-release tablets. Gums are interesting polymers for the preparation of pharmaceutical formulations because of their high water-swellability, non-toxicity, unique physicochemical properties and are used as matrices for sustained release of drugs. They are freely available, often, at costs below that of their synthetic polymers analogues.

SMG is a naturally occurring plant polysaccharide gum obtained from the plant Bombax ceiba, a native tree of India. SMG is a negatively charged colloid and a high molecular weight complex polysaccharide. The complete hydrolysis of gum has revealed that it contains a mixture of various sugars, such D-galacturonic acid, 2,3,4,6-tetra-O-methyl-
thyl-D-galactose, 2,6-di-O-methyl-D-galactose, 2,4-di-O-methyl-D-
galactose, 2,3,5-tri-O-methyl-L-arabinose, 2,5-di-O-methyl-L-arabinose
and α-norneolignan.6-7 It is easily available, cost effective, non-toxic,
eco-friendly, biodegradable, and renewable polysaccharide material.
This gum is generally used in traditional ayurvedic and unani medical
preparations for treatment of anti-inflammatory, antimicrobial, anal-
gesic, hepatoprotective, hypotensive, anticancer, antioxidant and
hypoglycemic activity.8-11 The SMG obtained from this plant is used
as a drug retaining polymer for preparation of matrix systems. Owing
to its advantageous and ideal physical and chemical properties, SMG
could become a prospective candidate for the sustained release tab-
lets of aceclofenac.

2. MATERIALS AND METHODS

2.1. Materials
Aceclofenac was a gift sample from Aarti Drugs Ltd., Mumbai, India
and SMG grade 1 was purchased from Girijan Co-operative Corpora-
tion, Andhra Pradesh, India. Microcrystalline Sodium carboxymethyl
cellulose (SCMC), Sodium starch glycolate and Magnesium stearate
are of AR grade, and were purchased from S.D. Fine-Chem Limited,
Mumbai, India. All other reagents are of analytical grade and were
supplied by Merck Specialties Pvt. Ltd., Mumbai, India.

2.2. Preparation of gum from Salmalia malabarica
The SMG was soaked in water for 8-9 h and later boiled for 30 min and
left to stand for 1 h to allow complete extraction of the gum. The
above solution was filtered using a multi-layer muslin cloth bag to
remove the dirt and foreign matter from the solution. Acetone (three
times the volume of filtrate) was added to precipitate the gum. The
gum was separated, dried in an oven at 35°C for 30 min, The gum was
collected and passed through high speed mechanical blender (Philips
India Ltd., Kolkata, India), and sieved by using #80 mesh and finally
was stored in a desiccator.

2.3. Preparation of SMG based aceclofenac matrix tablets
Sustained release matrix tablets of aceclofenac were prepared by us-
ing different ratios of drug: gum viz. 1:0.4, 1:0.5, 1:0.6, 1:0.7 and 1:0.8
for F1, F2, F3, F4 and F5 formulations respectively (Table 1). SMG
was used as matrix forming material, while microcrystalline cellulose
was used as filler. All the ingredients were passed through a #20
sieve, weighed, and blended. These formulations were compressed
by using a direct compression technique, with single station tablet
compression machine, (Cadmach, Ahmedabad, India) using 9 mm flat
faced punches.

Table1. Composition of Formulations of aceclofenac matrix tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>F1</td>
</tr>
<tr>
<td>F2</td>
<td>F3</td>
</tr>
<tr>
<td>F4</td>
<td>F5</td>
</tr>
<tr>
<td>Salmalia malabarica gum</td>
<td>100 mg</td>
</tr>
<tr>
<td>Microcrystalline SCMC</td>
<td>56 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>2 mg</td>
</tr>
<tr>
<td>Gum</td>
<td>40 mg</td>
</tr>
<tr>
<td>150 mg</td>
<td>46 mg</td>
</tr>
<tr>
<td>26 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>70 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>80 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

2.4. Evaluation of matrix tablets
The matrix tablets were evaluated for thickness, hardness and friabil-
ity by using digital micrometer (Mitutoyo, Japan), Monsanto hard-
ness tester and Roche Friabilator respectively. At the end of the tests,
the tablets were reweighed; loss in the weight of tablets is the mea-
sure of friability and is expressed in percentage as

% Friability = [(W₁ - W₂) / W₁] × 100

where, W₁ = Initial weight of 20 tablets, W₂ = Weight of the 20 tablets
after testing. For weight variation, “USP 2004 procedure for uniform-
ity of weight” was followed. Twenty tablets were taken and their
weight was determined individually and collectively on a digital weigh-
ing balance.

2.4.1. Drug content
Three tablets were collected from each batch and triturated individu-
ally. 100 mg of powder was dissolved in 100 mL of pH 7.4 phosphate
buffer and then passed through a Whatman filter (No.1) and analyzed
spectrophotometrically at 275 nm, after sufficient dilution with phos-
phate buffer (pH 7.4)12.

2.4.2. Stability study
The tablets were charged for the accelerated stability studies accord-
ing to ICH guidelines for a period of 6 months in stability chambers
(Thermo lab, Vasai (West), Dist. Thane, India). The samples were
removed at 15, 30, 60, 90 and 180 days and were evaluated for drug
content and physical parameters.

2.4.3. FTIR & DSC Studies
Infra-red (IR) spectra were recorded by using Bruker–TENSOR 27
Spectrophotometer (Bruker Optik GmbH, Ettlingen, Germany) at
wavenumber region of 4,000 to 400 cm⁻¹. The sample was dispersed
(drug alone or mixture of drug and gum along with excipients) in KBr
and compressed into disc by applying a pressure of 5 tons for 5 min
in a hydraulic press. The pellet was placed in the light path and the
spectrum was obtained. Differential scanning calorimetry (DSC) was
performed by using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal effects. The thermographs were obtained at a scanning rate of 10 °C/min conducted over a temperature range of 20-200 °C under nitrogen atmosphere (gas flow rate 80 mL min⁻¹). Onset of melting point, glass transition temperature and enthalpy of fusion values were obtained from the thermograms.

2.4.4. Swelling Studies
The water uptake into matrix tablets was performed by equilibrium weight method¹³. The tablets were placed in the baskets of dissolution apparatus. The baskets were immersed in acidic solution at 1.2 and 7.4 pH of phosphate buffer. At regular intervals, the baskets were taken out from buffer media and weighed immediately after drying the surface of basket with blotting paper.

\[
\text{Final weight} - \text{Initial weight} \times 100 \text{/Initial weight}
\]

2.5. In-vitro drug release studies
Drug release studies were carried out using USP dissolution test apparatus, Type II (Tablet Dissolution Apparatus, DS 8000, Lab India Analytical, Thane, India). A volume of 900 mL of dissolution medium at 37 °C and the stirrer speed of 75 rpm was used. All the formulations were tested for drug release in phosphate buffer medium at two different pH levels 1.2 and 7.4 for 2 h and 24 h respectively. At predetermined time intervals, 3 mL samples were withdrawn and estimated for release rate of drug using double beam UV/Vis-spectrophotometer (Shimadzu, Japan) at 275 nm. Release studies were conducted in triplicate.

The release data were kinetically analyzed by using Microsoft Office Excel 2007 (Microsoft Corporation, USA) to determine the mechanism and the order of drug release from different formulations. Generally, zero order, first order, Higuchi and Korsmeyer-Peppas models were used for the analysis of the release kinetics.

2.5.1. Scanning electron microscopy (SEM)
The surface morphology of F5 formulation tablets at 0, 2 and 24 h of dissolution was analyzed by SEM (Hitachi S-3400N, Hitachi High-Tech, Tokyo, Japan). Prior to analysis, the tablets were mounted onto double-sided adhesive tape that had previously been secured on copper stubs and coated with gold.

2.6. In vivo Studies
The anti-inflammatory activity and pharmacokinetic studies were performed on wistar rats and New Zealand rabbits respectively. Male wistar rats (weighing 180-200 g) and rabbits (weighing 2-3 kg) were obtained from the central animal house, National Institute of Nutrition (NIN), Hyderabad, India. They were housed in elevated polypropylene cages, one animal per cage, with free access to food and water ad libitum. The in vivo study protocol was approved by the institutional animal ethical committee of School of Pharmacy, Anurag Group of Institutions, Hyderabad. (Approval No: SOP/PS/IAEC/007).

2.6.1 Anti-inflammatory activity
Carrageenan-induced rat paw edema model was used to assess the anti-inflammatory effect of the plain drug, optimized tablet composition (F-5) and market tablet composition¹⁴. Wistar rats weighing between 180-200 g were fasted overnight, divided into 3 groups (n=6) and treated as follows:

Group I: (Control): 2.5 mL of 0.5% SCMC
Group II: Pure aceclofenac (10 mg/kg body weight) in 0.5% SCMC
Group III: Composition of optimized tablet (F5) (10 mg/kg body weight) in 0.5% CMC.

After 60 min of drug administration, rats of all groups were challenged by a subcutaneous injection of 0.05 mL of 1% solution of carrageenan in saline into the plantar site of the left hind paw. The paw volumes were measured with a plethysmometer, prior to administration of carrageenan and after 1-5 h of administration. The percent inhibition of edema for intervals was then calculated.

2.6.2. Pharmacokinetic study in rabbits
The pharmacokinetic studies were performed using male New Zealand rabbits. They were divided into 4 groups (n=3) and treated orally.

Group I: normal control
Group II: treated with pure drug 10 mg/kg body weight in SCMC as a dispersion
Group III: treated with dose equivalent proportion of tablet
Group IV: treated with Market formulation

Animals were fasted for 12 h before dosing. On the day of experiment, animals were dosed at 10 mg/kg body weight of aceclofenac pure drug orally⁵. No other food was allowed until 36 h after dose administration while water intake was free. The blood samples were collected from retro-orbital plexus periodically at 0, 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 36 h into sterile, heparin added 2 mL sample tubes. Plasma samples were obtained following centrifugation of blood at 3000 rpm for 10 min at 4 °C and kept frozen at -70 °C until analysis.

2.6.2.1. Analysis of drug in plasma
A sensitive high performance liquid chromatographic (HPLC) method...
was used to analyze the aceclofenac in plasma\textsuperscript{16}. The HPLC system (Shimadzu Class VP series having Class VP 1.25 version software) with two pumps (LC-20AD VP), a variable wavelength programmable UV/Vis detector (SPD-M20A VP), fixed wavelength UV–Vis detector, (CBM-20A VP), a system controller (SCL-10A VP) and a Column, Luna C18(2) 5µ 100 Å, size: 250mm×4.6 mm (Phenomenex\textsuperscript{8}, USA) were used.

### 2.6.2.2. Preparation of the calibration standards in plasma curve

The stock solution of aceclofenac was prepared in dilution fluid (methanol: Milli-Q water 20:80, v/v) at a concentration of 1.0 mg/mL. The stock solution was used for the preparation of the spiking stock solutions for construction of five-point calibration curve (40-1250 µg/mL) and all the stock solutions were refrigerated (2–8 °C) when not in use (data not shown). Calibration standards were prepared in bulk by spiking 0.3 mL of respective spiking stock solutions to 0.1 mL of control rabbit plasma.

### 2.6.2.3. Sample preparation for analysis

0.2 mL of 1:1 acetonitrile: Milli-Q water mixture was added for precipitation of protein in plasma mixed thoroughly using a vortex mixer for 1 min followed by addition of 1 mL benzene, mixed once again using vortex mixer for 1 min and centrifuged at 3500 rpm for 10 min. The cloudy bottom layer was removed carefully with the help of 1 mL pipette and the remaining clear supernatant was evaporated under a stream of nitrogen in a turbo-VAP evaporator (Zymark, Hopkinton, MA, USA) at 40°C. After evaporation, the remaining residue was reconstituted with 0.3mL of reconstitution solution (methanol: Milli-Q water 20:80, v/v). 20.0µL of the reconstituted samples was injected using Hamilton syringe to the HPLC system for analysis. All the procedures were performed at room temperature.

### 2.6.2.4. Chromatographic conditions

The mobile phase used for the chromatographic method was methanol and water (80:20) with a flow rate of 10mL/min and the injection volume of the sample was 20.0 µL. A UV-Visible detector was used and the wavelength was set to 275 nm.

### 2.6.2.4.1 Method

The standard and sample solutions were injected with the above chromatographic conditions and the chromatograms were recorded. The response factor of the standard solution and the sample were calculated and the concentration of the aceclofenac present in the plasma samples was calculated from the calibration curve.

The blank plasma samples were analyzed prior to the analysis of aceclofenac standard preparations. No interference from the blank plasma was observed for the drugs analyzed. The peaks were well resolved and the retention time of aceclofenac was found to be 10.20 min.

### 2.6.2.4.2 Data analysis

Student’s t-test was employed to analyze the results (Graph Pad Instat Software-1.13 version). Difference below the probability level 0.05 was considered statistically significant. The pharmacokinetic parameters were calculated by using PK Solutions 2.0™ Non-compartmental pharmacokinetic data analysis software.

### 3. RESULTS AND DISCUSSION

#### 3.1. Evaluation of tablets

The thickness of different tablet formulations ranging from 2.10±0.08 to 2.60±0.04 mm was prepared. The diameter was 9 mm and the hardness was from 5.0± 0.25 to 5.4±0.64 kg/cm\textsuperscript{2}. The friability of the tablets was observed from 0.34±0.05 to 0.17±0.09% and the weight variation (% deviation) was found to be from ±2.10 to ±4.02%. The drug content was found to be > 97% and the results were shown in **Table 2**.

#### 3.2. Stability studies

The accelerated stability studies were carried out according to ICH guidelines which indicated that the tablets did not show any physical changes (colour change, friability and hardness) during the study period and the drug content (n=3; Mean ± SD) was found to be above 95% at the end of 180 days (0 day: 98.92 ± 0.76%; 15 days: 98.05 ± 0.30%; 30 days: 96.85 ± 0.63%; 60 days: 96.54 ± 0.12%; 90 days: 95.25 ± 0.58%; 180 days: 95.05 ± 0.88%). This indicates that F 5 tablet is fairly stable at accelerated storage condition.

#### 3.3. Drug excipient compatibility studies

Drug excipient compatibility studies were carried out by FT-IR spectroscopy and DSC. Pure aceclofenac showed major peaks at the wave numbers 3318, 2937, 1715, 1589, 1506, 1480, 1344, 1280, 1254 and 665 cm\textsuperscript{-1} (**Figure 1**). There were no considerable changes in the FT-IR peaks of aceclofenac, when mixed with excipients, indicating the absence of its interaction with excipients used. The results of DSC studies are shown in **Figure 2**. Pure aceclofenac exhibited an endot-
hermic peak at 151.68°C, corresponding to its melting point. There was no considerable change in the endotherm values of aceclofenac when it was mixed with other excipients compared to that of pure aceclofenac. This observation further supports the absence of the interaction between drug and excipients by FT-IR spectra results. Hence the excipients selected in this study are of inert in nature with aceclofenac and are suitable for the formulation development.

3.5 In-vitro drug release
The in-vitro studies were carried out by using USP II Apparatus for formulations F1, F2, F3, F4 & F5 in phosphate buffer pH 7.4 for determining the percent drug release. At 120th min the percent release rate was found to be 2.6, 1.03, 2.28, 1.33 and 4.64 for F1, F2, F3, F4 and F5 respectively. It has been understood that F1 & F2 tablets which contained drug and gum in 1:0.4 and 1:0.5 ratio did not protect the drug release in the gastric media. Up to 96.14% and 96.633 % of drug has been released from the F1 and F2 formulations at the end of the 8th and 9th hours studies whereas F3 (96.535), F4 (96.22) and F5 (96.56) formulations were found to increase release rate at the end of 12th, 16th and 24th hrs respectively (Figure 4). From the in-vitro studies, it was found that the decrease in the drug release with increase in the SMG concentration. Initially there was no drug release up to 30 min and drug release started increasing after 30 min in a controlled manner at pH 1.2. This is due to the time lag for swelling of the tablets. All formulation showed very low drug release in pH 1.2 buffer when compared to pH 7.4 buffer. This may be due to the less solubility of the drug aceclofenac in pH 1.2 buffer. These results were in accordance with Santanu Chakraborty et al experiments of matrix tablets using HPMC. The kinetic data of formulation F3 showed good fit in
the Korsmeyer-Peppas Model ($r^2 = 0.9909-0.999$) and obeys zero order non-Fickian diffusion, whereas formulations F1, F2, F4 and F5 showed high linearity with zero order equation ($r^2 = 0.959-0.990$). The kinetic results were tabulated in Table 3.

### 3.6. Anti-inflammatory activity

The anti-inflammatory activity of the optimized tablet (F5) in comparison with pure drug was evaluated on the basis of its capability to inhibit the edema produced in paw of rats after administering carrageenan, an inflammation producing drug. The increase in paw volume in different groups is compared to evaluate possible improvement in activity of drug. The difference in paw volume values before and after drug administration was calculated and % inhibitions of edema at each time point were calculated and were shown in Table 4. The % inhibition values of pure drug were higher than those of F5 (test sample) in the beginning upto 5 h. The anti-inflammatory activity with the F5 formulation was slowly attained; but at the end of the experiment, F5 exhibited highest activity. This could be due to slow absorption of drug in gastrointestinal tract because of increased viscosity contributed by swellable hydrophilic natural gum. The results indicated that the tablet produces sustained action of aceclofenac.

![Fig.5. SEM photomicrographs of matrix tablets showing surface morphology at different time intervals in dissolution study. F5 tablet at 0 h; 4 h; 24 h, Magnification 1000x](image)

### Table 3. Kinetic parameters of the release studies of prepared aceclofenac matrix tablets

<table>
<thead>
<tr>
<th>Code</th>
<th>Drug release Zero order</th>
<th>First order</th>
<th>Kinetics (R²)</th>
<th>Korsmeyer -Peppas Exponent (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.981</td>
<td>0.900</td>
<td>0.974</td>
<td>0.980</td>
</tr>
<tr>
<td>F2</td>
<td>0.977</td>
<td>0.855</td>
<td>0.956</td>
<td>0.996</td>
</tr>
<tr>
<td>F3</td>
<td>0.996</td>
<td>0.948</td>
<td>0.985</td>
<td>0.962</td>
</tr>
<tr>
<td>F4</td>
<td>0.985</td>
<td>0.972</td>
<td>0.994</td>
<td>0.991</td>
</tr>
<tr>
<td>F5</td>
<td>0.949</td>
<td>0.993</td>
<td>0.979</td>
<td>0.991</td>
</tr>
</tbody>
</table>

### 3.5.1 SEM studies

SEM studies of the optimized formulation were carried out for determining the surface morphology and to confirm the mechanism of drug release. SEM photomicrographs of tablet at 0 h, 4 h and 24 h of dissolution studies are shown in Figure 5. The surface of the fresh tablets did not show any pores and cracks at 1,000X magnification; but the surface showed pores and cracks at 4 h and 24 h of dissolution. At the end of 24 h, a very small amount of matrix was present and pores were formed throughout the matrix. It also showed the formation of gelling structure, especially at the end of 24 h. The formation of pores and gelling structure on surface of the tablet and also decrease in total mass of tablet with time indicates the involvement of both erosion and diffusion mechanisms behind the drug release from the prepared matrix tablets. The results so obtained were similar to that of Srinivas Mutalik et al work.²

### Table 4. Effect of aceclofenac matrix formulation on the paw edema induced by carrageen in wistar rats. All values are expressed as Mean ± SD, n=6; A=Pure aceclofenac: F5=Composition of F5 tablet

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Control Paw volume (mL)</th>
<th>F5 Paw volume (mL)</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.18 ± 0.02</td>
<td>0.15 ± 0.01</td>
<td>16.67</td>
</tr>
<tr>
<td>2</td>
<td>0.25 ± 0.03</td>
<td>0.16 ± 0.05</td>
<td>15.04</td>
</tr>
<tr>
<td>3</td>
<td>0.37 ± 0.021</td>
<td>0.14 ± 0.04</td>
<td>10.03</td>
</tr>
<tr>
<td>4</td>
<td>0.52 ± 0.01</td>
<td>0.13 ± 0.02</td>
<td>12.03</td>
</tr>
<tr>
<td>5</td>
<td>0.62 ± 0.04</td>
<td>0.11 ± 0.01</td>
<td>14.00</td>
</tr>
</tbody>
</table>

### 3.7. Pharmacokinetic study in rabbits

The plasma concentrations vs time profiles of aceclofenac after a single oral dose of 10 mg/kg body weight in rabbits are shown in Figure 6. The $C_{\text{max}}$ and $T_{\text{max}}$ values were obtained from plasma concentration vs time curves with interpolation. The area under the plasma concentration vs time curve (AUC$_{0-36h}$) and absorption rate constant ($k_a$) were estimated by using PK solutions 2.0™ Pharmacokinetics...
data analysis software. The pharmacokinetic parameters in rabbits were estimated based on the mean concentration vs time curve. Data from pharmacokinetic analysis were summarized in Table 5.

**Table 5. Pharmacokinetic parameters from the plasma concentration-time curves after oral administration of optimized formulation F5, pure drug and market formulation to albino rabbits**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Parameter</th>
<th>SCMC Suspension</th>
<th>Tablet (F5) (test)</th>
<th>Market Tablet (reference) (DOLOKIND® SR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K (h⁻¹)</td>
<td>0.03</td>
<td>0.034</td>
<td>0.181</td>
</tr>
<tr>
<td>2</td>
<td>Kₐ (h⁻¹)</td>
<td>2.23</td>
<td>0.121</td>
<td>0.276</td>
</tr>
<tr>
<td>3</td>
<td>AUC₀-36ₜ (µg/mL)</td>
<td>34.1</td>
<td>35.80</td>
<td>33.91</td>
</tr>
<tr>
<td>4</td>
<td>Vₐ(L)</td>
<td>3.66</td>
<td>4.143</td>
<td>5.51</td>
</tr>
<tr>
<td>5</td>
<td>Cₘₙ₉(µg/mL)</td>
<td>4.89</td>
<td>3.66</td>
<td>3.12</td>
</tr>
<tr>
<td>6</td>
<td>Tₘₙ₉ (h)</td>
<td>0.99</td>
<td>16.00</td>
<td>4.435</td>
</tr>
</tbody>
</table>

The pharmacokinetic data showed that market formulation exhibited immediate effect whereas the developed formulation has shown the prolonged effect. There was no significant difference between pure drug and formulations which was evident from their rate constants (K) 0.03 and 0.034 respectively. The absorption rate constant (Kₐ) of the market formulation (DOLOKIND® SR) was significantly more which shows the immediate release effect of the drug aceclofenac. The low value AUC observed with pure drug (33.91) may be due to its rapid absorption and elimination from the body; on the contrary, the observed AUC value for developed formulation slightly increased (35.80 µg-h/mL) as compared to that of market formulation (33.91 µg-h/mL) indicating increased bioavailability of drug. The Volume of Distribution (Vₐ) of F5 formulation (4.143) was found to be less as compared to that of the market product (5.51). The Tₘₙ₉ is found to be less in market product (4.435 h) as compared to that of the developed formulation (16 h), showing the immediate release of drug from the formulation in market product. This delayed absorption may be due to the extended release effect of the swellable hydrophilic polymer present in the F5 which might have increased the viscosity and hence reduced the absorption rate. By observing the values of Tₘₙ₉ of the formulation, it can be concluded that the developed formulation has shown the sustained release effect. The present pharmacokinetic study results are better corroborated than that of the previous study of Srinivas Mutalik et al.18, 20 and hence, demonstrated the successful preparation of the sustained release tablets of aceclofenac.

**4. CONCLUSION**

The sustained release formulations of aceclofenac matrix tablets were prepared by using SMG. The overall sustained release was observed for 24 h at different pH conditions. The results from the IR spectroscopy and differential scanning calorimetry showed the absence of drug–excipient interactions. Scanning electron microscopy was used to visualize the surface morphology of the tablets and to confirm drug release mechanisms. The results of dissolution studies indicated that the formulation F5 could extend the drug release up to 24 h. A decrease in release rate of the drug was observed when the gum concentration was increased. The In vivo results of anti-inflammatory and pharmacokinetic studies in wistar rats and young male rabbits showed that the optimized tablet (F5) exhibited significant difference in the in vivo drug release in comparison to pure drug and market formulation. Therefore it can be concluded that the developed formulation shows sustained release and is of cost effective for the formulation development of aceclofenac tablets.

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