PHARMACEUTICAL COMPOSITIONS BASED ON DICLOFENAC

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Related U.S. Application Data

Continuation of application No. 11/030,537, filed on Jan. 5, 2005, now abandoned, which is a continuation of application No. 09/524,747, filed on Mar. 14, 2000, now Pat. No. 6,974,595, which is a continuation-in-part of application No. 09/192,493, filed on Nov. 17, 1998, now abandoned.

Abstract

New pharmaceutical compositions for oral use containing Diclofenac together with alkali metal bicarbonates in amounts of from 20 to 80 by weight with respect to Diclofenac are described. These compositions are entirely palatable and free from any unpleasant taste or other side effects; in particular, these formulations permit to obtain in human patients higher C_{max}, of the active principle and shorter T_{max}, together with a lower coefficient of variation.
POTASSIUM DICLOFENAC
FORMULATION C - AVERAGE VALUE OF THE 6 VOLUNTEERS

FIG 3
MEAN, OVERLAIID PLASMA CONCENTRATION-TIME CURVES MEASURED IN ALL VOLUNTEERS AFTER ADMINISTRATION OF DICLOFENAC TEST AND REFERENCE FORMULATIONS IN LINEAR AND LOG-SCALE DOSE ADMINISTERED = 50 mg.

**LINEAR**

![Graph of mean plasma concentration-time curves.](image)
MEAN, OVERLAID PLASMA CONCENTRATION-TIME PROFILES MEASURED IN ALL VOLUNTEERS AFTER ADMINISTRATION OF DICLOFENAC T₁, T₂, R₁ (CATAFLAM®) AND R₂ (VOLTAROL®) FORMULATIONS; LINEAR AND LOG-SCALES

FIG 6
MEAN PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF 7. FORMULATION. LINEAR SCALE.
MEAN PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF T² FORMULATION. LINEAR SCALE. VERTICAL BARS ARE SD.

FIG 8
MEAN PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF R (VOLTAREN® RAPIDE) FORMULATION. LINEAR SCALE. VERTICAL BARS ARE SD.

FIG 9
MEAN OVERLAPPED PLASMA CONCENTRATION-TIME PROFILE OF DICLOFENAC MEASURED IN ALL VOLUNTEERS AFTER ORAL ADMINISTRATION OF T1, T2, AND R (VOLARAGEN® RAPIDE) FORMULATION.

FIG 10
PHARMACEUTICAL COMPOSITIONS
BASED ON DICLOFENAC

[0001] The present application is a continuation of U.S. Ser. No. 09/524,747, filed Mar. 14, 2000 (pending), which is a continuation in part of U.S. Ser. No. 09/192,493, filed Nov. 17, 1998 (abandoned).

[0002] The present invention relates to new immediate release pharmaceutical compositions containing ([2,6-dichloro-anilino)-2-phenyl]-2-acetic acid (more commonly known as Diclofenac) in acid and/or salt form

[0003] Diclofenac is a non-steroidal drug which was invented at the end of the sixties by A. Sallmann and R. Pfister (NL-6,604,752 and U.S. Pat. No. 3,558,690 both to Ciba-Geigy) and whose structural formula is indicated below.

CH_{2}COOH

\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
\end{align*}

[0004] Diclofenac is widely dispensed and used owing to its well-known analgesic, anti-pyretic, anti-arthritis, anti-phlogistic and anti-rheumatic properties and it is generally taken orally in the form of normal tablets or tablets covered with coatings resistant to gastric juices, or rectally, or by injection, or topically.

[0005] The possibility of taking it in the form of sweets, tablets dissolving in the mouth, drages, chewing gum or other similar pharmaceutical forms or in formulations for the extemporary preparation of Diclofenac-based aqueous solutions and/or suspensions would represent a different mode of administration which is definitely more suitable, especially for children and elderly persons.

[0006] Owing to its poor solubility in water, Diclofenac is normally used in salt form; the salts of Diclofenac customarily used are those of sodium, potassium or other alkali and alkaline earth metals, together with salts of organic nature, such as the salts of basic amino acids, such as lysine, arginine and ornithine, or other pharmacologically acceptable organic bases which have the ability to render the resulting salt soluble in water.

[0007] The pharmaceutical compositions of the Diclofenac salts for oral use are generally 25% accompanied by side effects of not inconceivable consequence; Diclofenac salts are in fact characterised by a particularly unpleasant and bitter taste and by the fact that they produce a sensation of strong astringency and cause an especially intense form of irritation in the buccal cavity, especially in the area of the larynx.

[0008] Although the first problem has been partly solved by using flavourings which are able in some manner to mask the taste, satisfactory solutions have still not been proposed for the two remaining problems.

[0009] Therefore, the pharmaceutical compositions containing Diclofenac salts still have a poor palatability which limits their adoption and possible fields of application, despite the excellent therapeutic effect with which they are associated.

[0100] A second problem connected to Diclofenac is that, when it is orally administered by means of immediate release formulations, the corresponding $T_{max}$ (the time to the maximum plasma concentration) is usually located at about 1 hour since administration, this being of course a not completely satisfactory result when a prompt and strong analgesic/anti-pyretic effect is sought for. Furthermore, the corresponding coefficient of variation is normally in the range of 70-90%, which means that the $T_{max}$ is strongly variable and dependent on the physical characteristics of the patient (Physicians’ Desk Reference, 52 edition, 1998, pag. 1831). Attempts are therefore still being made in order to enhance the rate of absorption of Diclofenac and to provide an earlier onset of the therapeutic effect (N. Davies, K. Anderson: Clinical Pharmacokinetic of Diclofenac, Clin. Pharmacokin., 1997, Sept. 33(3)).

[0111] The object of the present invention is therefore that of providing a fully palatable formulation of Diclofenac which is able to generate a more rapid, uniform and foreseeable release of the active principle if compared to the compositions known in the art and presently available on the market. For the purposes of the present invention $T_{max}$ means the time to the maximum plasma concentration whereas $C_{max}$ is the maximum plasma concentration of the active principle, namely Diclofenac. It has now been found that, by adding alkali metal bicarbonates or mixtures thereof to the Diclofenac in its acid and/or salt form, in amounts of from 20 to 80% by weight based on the acid form of Diclofenac, pharmaceutical compositions can be obtained which are substantially free from the side effects mentioned above. The first object of the present invention is therefore represented by a pharmaceutical formulation for oral use containing Diclofenac in acid and/or salt form together with alkali metal bicarbonates or mixtures thereof and customary excipients and adjuvants, wherein said alkali metal bicarbonates are present in amounts of from 20 to 80% by weight based on the weight of Diclofenac. It has in fact been surprisingly demonstrated that the use of alkali metal bicarbonates in the above-mentioned ratio permits to achieve constant, reproducible and foreseeable blood levels of the active ingredient, with the consequent indisputable advantages from the therapeutic point of view; furthermore, it has also been found that the combined use of Diclofenac together with alkali metal bicarbonates yields Diclofenac-based pharmaceutical compositions in which the active ingredient is released more rapidly compared with normal formulations, bringing about higher blood levels and therefore a more immediate therapeutic effect; finally the so-obtained immediate release formulations are substantially palatable and free from aftertaste.

[0112] According to the preferred embodiment of the present invention, the amount of alkali metal bicarbonates to be added is comprised between 40 and 80% by weight, based on the weight of the acid form Diclofenac, whereas the alkali metal bicarbonates are selected from sodium and/or potassium bicarbonates, Diclofenac being normally present in the form of its sodium and/or potassium salts.

[0113] It has also been found, and forms a second subject of the present invention, that the addition of flavouring substances selected from mint, aniseed, ammonium glycyrrhizinate and mixtures thereof to the compositions containing the Diclofenac salts and alkali metal bicarbonates produces, a synergistic effect which completely eliminates all the above-mentioned palatability/astringency effects, providing pharmaceutical compositions which are entirely palatable (and/or
drinkable in the case of those used for the preparation of solutions and/or suspensions) and free from aftertaste.

[0014] The flavouring substances may be used as such or supported on inert materials, for example maltodextrin, in order to obtain a better distribution of the granulates and to facilitate excellent dispersibility of the flavouring in solution. Preferably, they are absorbed on maltodextrin with a power of 1 to 2000 and 1 to 1000.

[0015] The amount of flavouring substances in its pure form is also preferably from ½ to 3 times the weight of the acid-form Diclofenac.

[0016] These flavouring substances are used in the implementation of the present invention without altering their organoleptic properties and without depriving them of their intrinsic qualities of flavourings which are liposoluble and generally oily in the pure state.

DESCRIPTION OF THE FIGURES

[0017] FIG. 1 provides a graph of the average blood level value over time of potassium diclofenac from Formulation A (Ciba-Geigy Voltaren Rapid® tablet form) in the 6 volunteers.

[0018] FIG. 2 provides a graph of the average blood level value over time of potassium diclofenac from Formulation B (Ciba-Geigy second comparative formulation) in the 6 volunteers.

[0019] FIG. 3 provides a graph of the average blood level value over time of potassium diclofenac from Formulation C (composition of Example 1) in the 6 volunteers.

[0020] FIG. 4 provides a comparative graph of the average blood level value over time of potassium diclofenac from the respective Formulations A, B and C in the 6 volunteers.

[0021] FIG. 5 provides mean, overlaid plasma concentration-time curves measured in all volunteers after administration of diclofenac test and reference formulations.

[0022] FIG. 6 provides mean, overlaid plasma concentration-time profiles measured in all volunteers after administration of diclofenac T₁, T₂, R₁ (Catalam®) and R₂ (Voltarol®) formulations.

[0023] FIG. 7 provides a mean plasma concentration-time profile of diclofenac measured in all volunteers after oral administration of T₁ formulation.

[0024] FIG. 8 provides a mean plasma concentration-time profile of diclofenac measured in all volunteers after oral administration of T₂ formulation.

[0025] FIG. 9 provides a mean plasma concentration-time profile of diclofenac measured in all volunteers after oral administration of R (Voltarone Rapid®) formulation, in linear scale.

[0026] FIG. 10 provides mean, overlaid plasma concentration-time profiles measured in all volunteers after administration of diclofenac T₁, T₂, and R (Voltarone Rapid®) formulations.

[0027] As it will be clear from the examples, the immediate release formulations for oral use of the present invention containing from 10 to 60 mg of Diclofenac in acid and/or salt form together with alkali metal bicarbonates or mixtures thereof in amounts of from 20 to 80% by weight of the weight of Diclofenac permit to generate in human patients an average Cₘₚₑₚ of Diclofenac comprised between 400 and 2500 ng/ml independently on the age, sex or weight of the patients themselves.

[0028] Secondly, the formulations according to the present invention permit to obtain in humans an average Cₘₚₑₚ of Diclofenac after 5–30 minutes since administration, generally 13–27, independently on the amount of Diclofenac contained therein and also independently on the age, sex, weight of the patient.

[0029] Furthermore, the Tₘₚₑₚ of the formulations of the present invention show a coefficient of variation which is about 44–86% lower than the presently marketed formulations; this is evidently an extremely important result from the clinical point of view as it is now possible to have a therapeutic effect of Diclofenac which is foreseeable, reproducible and independent on the sex, weight and health conditions of the patient.

[0030] Thus, the presently claimed Diclofenac-based formulations permit to achieve a higher Cₘₚₑₚ in a shorter Tₘₚₑₚ and with a lower coefficient of variation if compared to the formulations available on the market, with therapeutic advantages which do not need to be commented.

[0031] According to the best mode for carrying out the present invention the pharmaceutical formulations will contain from 10 to 60 mg/dose of diclofenac in its potassium or sodium salt form together with 40 to 80% by weight of potassium or sodium bicarbonate based on the weight of Diclofenac in its acid form, together with the usual excipients and adjuvants; even more preferably they will packaged as:

[0032] a sachet or tablet formulation containing 50 mg of Diclofenac potassium salt and 22 mg of potassium bicarbonate or 50 mg of Diclofenac sodium salt and 19 mg of sodium bicarbonate;

[0033] a sachet or tablet formulation containing 12.5 mg of Diclofenac sodium salt and 5.5 mg of potassium bicarbonate or 25 mg of Diclofenac sodium salt and 11 mg potassium bicarbonate.

[0034] It will be by the way evident to any skilled in this art that the present formulations can also be used as immediate release layers of multilayered release pharmaceutical formulations containing Diclofenac as one of the active ingredients; said formulations are therefore a further object of the present invention.

[0035] The following Examples are given purely by way of non-limiting illustration.

EXAMPLE 1

Composition Dissolving Instantly in Water

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Diclofenac potassium salt*</td>
<td>50 mg</td>
</tr>
<tr>
<td>2) Potassium bicarbonate</td>
<td>22 mg</td>
</tr>
<tr>
<td>3) Mint flavouring on maltodextrin (1:2000)**</td>
<td>60 mg</td>
</tr>
<tr>
<td>4) Aniseed flavouring on maltodextrin (1:1000)**</td>
<td>104 mg</td>
</tr>
<tr>
<td>Excipients and adjuvants</td>
<td></td>
</tr>
<tr>
<td>5) Saccharin</td>
<td>4 mg</td>
</tr>
<tr>
<td>6) Aspartame</td>
<td>10 mg</td>
</tr>
</tbody>
</table>
EXAMPLE 2
Tablet for Dissolving in the Mouth

[0041] Active ingredients

1) Diclofenac potassium salt*: 50 mg
2) Potassium bicarbonate: 35 mg
3) Mint flavouring on maltodextrin**: 50 mg
4) Aniseed flavouring (1:000) on maltodextrin*** + silicon dioxide (E 551): 120 mg
5) Excipients and adjuvants

Example 3
Gum Tablet

[0042] Active ingredients

1) Diclofenac potassium salt*: 50 mg
2) Potassium bicarbonate: 35 mg
3) Mint flavouring on maltodextrin**: 30 mg
4) Aniseed flavouring on maltodextrin***: 80 mg
5) Excipients and adjuvants

Comparison:

The packaged composition containing 50 mg of Diclofenac potassium of Example 1 (formulation C) was subjected to a pharmacokinetic test for comparison with a similar composition not containing alkali metal carbonates and bicarbonates (formulation B), and with a second composition in tablet form (formulation A) produced by Ciba-Geigy (Voltaren Rapid®), also in this case not containing alkali metal carbonates and bicarbonates, both formulations A and B containing 50 mg of Diclofenac potassium.

This comparative evaluation was carried out on the same 6 healthy volunteers in accordance with the experimental plan described hereinafter.

Experimental scheme: Single-dose study using three methods in randomised cross-over with a wash-out of three days.

Sampling times: 0 h (before administration), 5 min, 10 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, after each administration.

Blood sample treatment: 8 ml in heparinised test tubes, centrifugation for 15 min at 1500 rev/min, subdivided into two fractions and subsequently frozen at -20°C.

Times: wash-out of two days between treatments.

Determination method: HPLC, with internal standard, sensitivity 10 mg/ml.

Analysis Method

Column: Nova Pak C18, 3.9×150 mm, 4 μm Waters S.p.A.—Vimodrone, Italy.
Eluant: NaH2PO4 0.01 M +0.1% TEA, pH 3.0 (1504)/acetonitrile, 60/40.
Flow: 1.2 ml/min
Detection: UV 275 nm
Temperature: 30°C.
Injection: 50 μl
Analysis time: 16 min.

Sample Preparation

10 ml of the internal standard methanolic solution, and flufenamic acid (corresponding to 1320 mg) are added to 1 ml of defrosted plasma in 10 ml glass test tubes. The tubes are agitated in a Vortex mixer for 1 minute. 0.5 ml of a 0.5N HCl/IN NaCl solution is added. The whole is agitated in a Vortex mixer for 1 minute. 6 ml of a 95/5 n-hexane/isopropanol solution are added.

The mixture is then agitated in the Vortex mixer for a further 15 minutes. Centrifugation is carried out at 3000 rev/min for 15 minutes and the organic phase is transferred to fresh 10 ml glass test tubes and evaporated to dryness in a centrifugal evaporator under vacuum at ambient temperature. The whole is taken up in 200 ml of a 70/30 acetonitrile/water solution, and the precipitate is dissolved under ultrasound for 2 minutes.

FIGS. 1, 2 and 3 show the concentrations of Diclofenac in the blood of the six volunteers as regards for-
mulations A, B (Ciba-Geigy comparative formulations) and C (formulation corresponding to the composition of Example 1), respectively. As will be appreciated, the blood concentration of the formulation of the present invention has, compared with the comparative formulations, a more constant and uniform pattern. This characteristic is also found in FIGS. 4, 5 and 6 which show the average values corresponding to the blood levels of the six volunteers together with the corresponding standard deviation.

[0062] The result is clear and surprising: compared with the sample compositions, the compositions of the present invention permit constant, reproducible and foreseeable blood levels of the active ingredient, irrespective of the characteristics of the volunteer (weight, age, etc.), with the consequent indisputable advantages from the therapeutic point of view.

[0063] Finally, FIG. 7 shows, by comparison, the graphs relating to the average values of the six volunteers (that is to say, the preceding FIGS. 4, 5 and 6); as will be noted, the formulation of the present invention permits, in addition to the advantages already mentioned, the attainment of a blood peak higher than that of the other formulations.

EXAMPLE 5

Two Layered Tablet (Fast and Slow Release)

[0064]

Fast release layer

1) Diclofenac potassium salt: 15 mg
2) Potassium bicarbonate: 30 mg
3) Lactose: 13.2 mg
4) Maize starch (intragranular): 6 mg
5) Methyl cellulose: 0.12 mg
6) Sodium laurylsulfate: 0.06 mg
7) Maize starch (extragranular): 9 mg
8) Crospovidone: 0.6 mg
9) Sodium carboxymethylstarch: 1.5 mg
10) Magnesium stearate: 2.7 mg
11) Colloidal silicon dioxide: 0.6 mg

Slow release layer

1) Diclofenac potassium salt: 70 mg
2) Potassium bicarbonate: 30.8 mg
3) Lactose: 32.2 mg
4) Polyvinylpyrrolidone: 1.16 mg
5) Hydroxypropylmethylcellulose: 70 mg
6) Magnesium stearate: 0.84 mg
7) Colloidal silicon dioxide: 0.21 mg
8) Talc: 3.62 mg
9) Polyethylene glycol: 0.56 mg

EXAMPLE 6

Drops

[0065]

1) Diclofenac potassium salt: 75 g
2) Methyl p-oxybenzoate: 2.7 g
3) Propyl p-oxybenzoate: 0.3 g
4) Aspartame: 37.5 g
5) Potassium bicarbonate: 37.5 g
6) Glycerol: 300 g
7) Ethyl alcohol: 450 g
8) Water q.s.: 1500 g

Possible modifications:
- Addition of sodium metabisulfite (0.06%)
- Addition of sodium metabisulfite (0.05%)
- Mint flavouring (1.25%)
- Strawberry flavouring (0.75%)

EXAMPLE 7

Drops

1) Diclofenac potassium salt: 37.5 g
2) Methyl p-oxybenzoate: 2.7 g
3) Propyl p-oxybenzoate: 0.3 g
4) Aspartame: 37.5 g
5) Potassium bicarbonate: 18.75 g
6) Saccharin: 6.0 g
7) Glycerol: 300 g
8) Ethyl alcohol: 450 g
9) Water q.s.: 1500 g

Possible modifications:
- Addition of sodium metabisulfite (0.05%)
- Addition of sodium metabisulfite (0.05%)
- Mint flavouring (1.25%)
- Strawberry flavouring (0.75%)

EXAMPLE 8

Mouthwash

[0067]

1) Diclofenac potassium salt: 0.75 g
2) Glycerol: 50 g
3) Sorbitol: 12 g
4) Saccharin: 0.5 g
5) Aspartame: 1.0 g
6) Methyl p-oxybenzoate: 0.5 g
7) Propyl p-oxybenzoate: 0.1 g
8) Mint flavouring: 1.0 g
9) Ethyl alcohol: 100 g
10) Potassium bicarbonate: 0.33 g
11) Water q.s.: 500 ml

EXAMPLE 9

Gum-Paste

[0068]

1) Diclofenac potassium salt: 5.0 g
2) Glycerol: 630 g
3) Sodium benzoate: 5.0 g
4) Silica (Wessonin 98 - Degussa): 120 g
5) Silica (Siddent 98 - Degussa): 80 g
6) Cellulose gum: 3.0 g
7) Polyethylenglycol 600: 30 g
8) Sodium lauryl sarcosinate (or sodium lauryl sulfate): 60 g
EXAMPLE 10
Tooth-Paste

1) Diclofenac potassium salt: 5.0 g  
2) Glycerol: 630 g  
3) Sodium benzoate: 5.0 g  
4) Silica (Wessulan 8® - Degussa): 20 g  
5) Silica (Sidident 9® - Degussa): 80 g  
6) Cellulose gum: 3.0 g  
7) Polyethylene glycol 600: 90 g  
8) Sodium lauryl sarcosinate (or sodium lauryl sulfate): 60 g  
9) Mint flavouring: 10 g  
10) Sodium saccharin: 1.0 g  
11) Aspartame: 3.0 g  
12) NaF: 1.0 g  
13) Na-FPO: 4.0 g  
14) Potassium bicarbonate: 2.2 g  
15) Water q.s.: 1 kg

EXAMPLE 11
Tablet

1) Diclofenac potassium salt: 50 mg  
2) Mannitol: 50 mg  
3) Potassium bicarbonate: 22 mg  
4) Maize starch (intrgranular): 10 mg  
5) Methyl cellulose: 0.2 mg  
6) Sodium lauryl sulfate: 0.1 mg  
7) Maize starch (extragranular): 15 mg  
8) Crystavodone: 1.0 mg  
9) Sodium carboxymethylcellulose: 2.5 mg  
10) Magnesium stearate: 4.5 mg  
11) Colloidal silicon dioxide: 10 mg

EXAMPLE 12
Comparative Test

In the present experiment a sachet formulation containing 50 mg of Diclofenac potassium was compared to a bioequivalent sugar coated fast release tablet also containing 50 mg of Diclofenac potassium, produced and marketed in Italy by Novartis as Cataflam®.

The sachet formulation according to the present invention had the following composition:

1) Diclofenac potassium salt: 50 mg  
2) Potassium bicarbonate: 22 mg  
3) Mint flavour: 50 mg
EXAMPLE 14

Comparative Test

A further comparative test was carried out on immediate release formulations according to the present invention, containing 50 mg of Diclofenac potassium and 22 mg of potassium bicarbonate, manufactured with different that is, respectively: T1=wet granulation using alcohol, T2=dry granulation by direct compression. The composition in mg of the two formulations is herebelow reported:

<table>
<thead>
<tr>
<th>Component</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac potassium</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Potassium bicarbonate</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Mannitol/poartitol 400 DC</td>
<td>119</td>
<td>9</td>
</tr>
<tr>
<td>Mannitol EP of</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Maize starch</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Methocel A4C</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

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- Comparative bioavailability study was carried out on 6 healthy volunteers of both sexes in order to evaluate the in vivo results of the pharmacokinetic profiles of the present formulations if compared to those of a bioequivalent fast release formulation such Voltaren Rapid® (50 mg of Diclofenac potassium), both by Novartis. The results, which are reported in FIGS. 7-10 are also in this case excellent the T_max is in fact prompter with the present formulations (T1=18.6 min, T2=16.8 min vs R1=40.8 min) and the Cmax is higher (T1=1878.3 ng/ml and T2=1744.8 ng/ml vs R1=1307 ng/ml); furthermore, also in this case the T_max of both present formulations shows a coefficient of variation lower than reference formulation (T1=12.9% and T2=25% vs R1=95.6%).

**TABLE 1**

Pharmacokinetic parameters for two different Diclofenac formulations: test (Diclofenac potassium salt sachets) and reference (Diclofenac potassium salt sugar coated tablets)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>T_max (h)</td>
<td></td>
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<tr>
<td>C_max (ng/ml)</td>
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<tr>
<td>t_1/2 (h)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>AUC/Co (ng - ml^-1 - h)</td>
<td></td>
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</tbody>
</table>

-continued


1) A fast-release diclofenac composition, in the form of a unit dose packet of powder for dissolving or suspending in water, or in the form of a fast release layer in a two layered diclofenac tablet that comprises a fast layer and a slow layer, wherein said composition comprises diclofenac in acid and/or salt form.

2) The composition of claim 1 wherein said diclofenac is present as diclofenac potassium.

3) The composition of claim 1 wherein said diclofenac is present in an amount ranging from about 10 to about 60 mg.

4) The composition of claim 1 in the form of a unit dose packet of powder wherein said diclofenac is present in an amount of about 50 mg.

5) The composition of claim 1 in the form of a unit dose packet of powder wherein said diclofenac is present as diclofenac potassium in an amount of about 50 mg.

6) The composition of claim 1 in the form of a unit dose packet of powder, wherein said composition is capable of yielding an average $T_{max}$ of diclofenac in a human patient between 5 and 30 minutes after administration of said diclofenac to said patient, said average $T_{max}$ having a coefficient of variation (CV %) less than about 70%.

7) The composition of claim 1 in the form of a unit dose powder, wherein said composition is capable of yielding an average $T_{max}$ of diclofenac in a human patient between 13 and 27 minutes after administration of said diclofenac to said patient, said average $T_{max}$ having a coefficient of variation (CV %) less than about 70%.

8) The composition of claim 1 in the form of a fast release layer in a two layered diclofenac tablet.

9) The composition of claim 1 in the form of a fast release layer, wherein said composition comprises about 15 mg of diclofenac potassium salt, and said slow release layer comprises about 70 mg of diclofenac potassium salt.

10) The composition of claim 1, further comprising means for potentiating the bioavailability of said diclofenac.

11) The composition of claim 10 wherein said means decreases the T$\max$ of said diclofenac.

12) The composition of claim 10 wherein said means increases the C$\max$ of said diclofenac.

13) The composition of claim 10 wherein said means decreases the coefficient of variation of the C$\max$ of said diclofenac.

14) The composition of claim 10 in the form of a unit dose packet of powder wherein said diclofenac is present in an amount of from about 10 to about 60 mg.

15) The composition of claim 10 in the form of a unit dose packet of powder wherein said diclofenac is present in an amount of about 50 mg.

16) The composition of claim 10 wherein said means comprises one or more alkali metal carbonates or bicarbonates.

17) The composition of claim 10 wherein said means comprises one or more alkali metal carbonates or bicarbonates in an amount greater than about 20 wt. % based on the weight of said diclofenac.

18) The composition of claim 10 in the form of a unit dose packet of powder wherein said diclofenac is present in an amount of about 50 mg, and said means comprises one or more alkali metal carbonates or bicarbonates in an amount greater than about 20% based on the weight of said diclofenac.

19) The composition of claim 10 in the form of a unit dose packet of powder wherein said diclofenac is present as diclofenac potassium in an amount of about 50 mg, and said...
means comprises potassium bicarbonate in an amount greater than about 20% based on the weight of said diclofenac.

20) The composition of claim 10 in the form of a unit dose packet of powder wherein said diclofenac is present as diclofenac potassium in an amount of about 50 mg, and said means comprises potassium bicarbonate in an amount of from about 40 wt. % to about 80 wt. % based on the weight of said diclofenac.

21) A fast-release diclofenac composition, in the form of a unit dose packet of powder for dissolving or suspending in water, or in the form of a fast release layer in a two layered diclofenac tablet comprising a fast layer and a slow layer, wherein the composition comprises diclofenac in acid and/or salt form and means for potentiating the bioavailability of said diclofenac.

22) The composition of claim 21 wherein said means comprises greater than about 20 wt. % of one or more alkali metal carbonates or bicarbonates based on the weight of said diclofenac.

23) A fast-releasing diclofenac composition, in the form of a unit dose packet of powder for dissolving or suspending in water, comprising about 50 mg, of diclofenac in acid and/or salt form.

24) The composition of claim 23 wherein said diclofenac is present as diclofenac potassium.

25) The composition of claim 23 wherein said diclofenac is present as diclofenac potassium, further comprising from about 40 to about 80 wt. % of potassium bicarbonate.

26) A fast-release diclofenac composition, in the form of a fast release layer in a two layered diclofenac tablet comprising a fast layer and a slow layer, comprising from about 10 to about 60 mg, of diclofenac in acid and/or salt form.

27) The composition of claim 26 wherein said diclofenac is present as diclofenac potassium.

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