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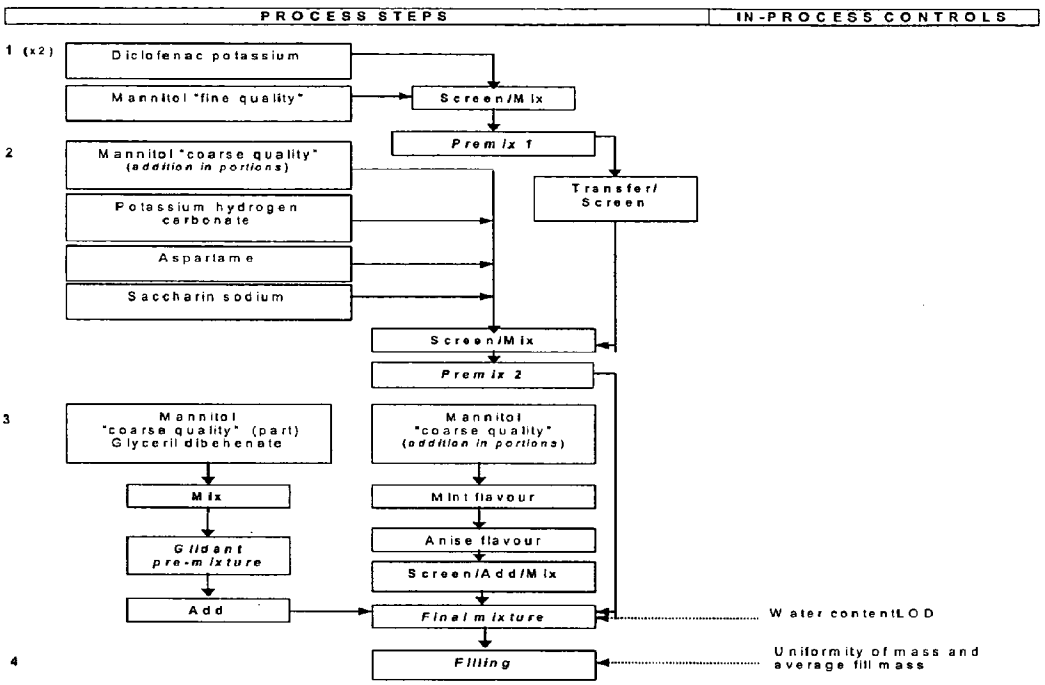
(54) **Title:** DICLOFENAC FORMULATIONS AND METHODS OF USE



(57) **Abstract:** Methods and formulations are provided for treating migraine and other acute pain episodes using diclofenac, and formulations of diclofenac that provide both rapid and sustained relief from acute pain. Methods and formulations are also provided for treating symptoms that often accompany migraine and acute pain such as photophobia, phonophobia, nausea and vomiting.

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DICLOFENAC FORMULATIONS AND METHODS OF USE

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) to United States Provisional Patent Application Nos. 60/692,024 (filed June 17, 2005), and 60/691,757 (filed June 17, 2005).

FIELD OF THE INVENTION

This invention concerns methods and formulations for treating migraine and other acute pain episodes using diclofenac, and formulations of diclofenac that provide both rapid and sustained relief from acute pain. The invention further concerns methods and formulations for treating symptoms that often accompany migraine and acute pain such as rebound headache, photophobia, phonophobia, nausea and vomiting.

BACKGROUND OF THE INVENTION

Diclofenac is a non-steroidal anti-inflammatory drug ("NSAID") known chemically as [(2,6-dichloro- anilino)-2-phenyl]-2-acetic acid. The drug was developed in the 1960s by scientists at Ciba-Geigy and is sold around the world by Novartis under various trade names, including Cataflam® and Voltaren® in the United States. A wet granulated formulation of diclofenac potassium was recently developed to provide an increased rate of absorption, and its pharmacokinetic properties tested against commercially available diclofenac potassium tablets. (Reiner et al., Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. Arzniem.-Forsch./ Drug Res. 2001; 51:885-890.) According to the authors, the granular formulation showed a higher C_{max} than the diclofenac potassium tablets, a shorter t_{max} (i.e. time to C_{max}) and a similar AUC when compared to the tablet form.

Owing to its excellent analgesic properties, diclofenac is widely used for treating various types of pain, including both chronic and acute painful episodes. The drug is administered for the treatment of musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; periarticular disorders such as bursitis and tendonitis; soft tissue disorders such as sprains and strains, and other painful conditions such as renal colic, acute gout, dysmenorrhoea, and following some surgical procedures.

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(Martindale (2000) Diclofenac. In: Reynolds, The Extra Pharmacopoeia. London: The Pharmaceutical Press; p. 31-33.) Diclofenac has also been studied for the treatment of headache pain from migraine attacks, using various doses and dosage forms, including 75 mg. intramuscular injections (Del Bene et al., Intramuscular treatment of migraine attacks using diclofenac sodium: a cross-over trial. J. Int. Med. Res. 1987; 1544-8), 100 mg. suppositories (Del Bene et al., Migraine attack treatment with diclofenac sodium. Cephalalgia 1985; 5:144-5), and 50 mg. enteric coated tablets. (Massiou et al., Effectiveness of oral diclofenac in the acute treatment of common migraine attacks: a double blind study versus placebo. Cephalalgia 1991; 1:59-63.)

Migraine attacks manifest a diverse array of symptoms that must be resolved in order for a treatment to be deemed truly effective against migraine (instead of just treating the symptoms). In particular, the treatment must be effective against the pain, photophobia, phonophobia and nausea that are caused by migraine, and it must be effective within the first two hours of treatment, in order to be considered a true treatment for migraine. None of the studies reported to date suggests that a 50 mg. diclofenac product could treat all of these symptoms within two hours of treatment.

In 1993, investigators studied 100 mg. and 50 mg. diclofenac tablets, in comparison to placebo, and determined that both strengths were effective against migraine pain within two hours of treatment, but that only the 100 mg. strength was effective against phonophobia and photophobia within two hours. (Dahlöf et al., Diclofenac-K (50 and 100 mg.) and placebo in the acute treatment of migraine. Cephalalgia 1993; 13:117-123). In 1999, a separate group of investigators tested 50 mg. and 100 mg. sugar coated tablets of diclofenac potassium to treat migraine, and once again confirmed the ability of both doses to relieve migraine pain within two hours of treatment. (The Diclofenac-K/Sumatriptan Migraine Study Group, Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac potassium, in comparison to oral sumatriptan and placebo. Cephalalgia 1999; 19:232-40.) The investigators concluded that neither dose was effective against photophobia two hours after treatment, that both doses were effective against photophobia eight hours after treatment, that only the 100 mg dose was effective against phonophobia two hours after treatment, and that the 50 mg dose was effective against photophobia eight hours after treatment.

The 1999 investigators also studied the effectiveness of 100 mg and 50 mg. diclofenac-K immediate release tablets at preventing recurrence of headaches within 48 hours of treatment. The investigators concluded that patients treated with the 50 mg and the 100

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mg diclofenac-K tablets actually had a higher incidence of headache recurrence than patients treated with placebo (i.e. that the diclofenac-K performed worse than placebo), although the statistical significance of these findings is not reported.

This latter finding is consistent with other recent literature which recommends the use of a "long acting NSAID" to reduce the frequency of rebound headaches. For example, Plachetka recommends in U.S. Patent No. 6,586,458 that triptan therapy be augmented with a "long acting NSAID" to provide "a substantial reduction in the frequency [of] relapse of headaches." Diclofenac potassium is not considered a long acting NSAID because it displays an average C_{max} within only about one hour and a terminal half life of only about 1.9 hours when administered in commercially available sugar coated tablets.

Diclofenac 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. Recently, however, in WO 97/44023, Reiner et al. proposed to administer diclofenac in a number of less conventional dosage forms – including as a powder sachet for oral administration after dissolving in water -- for quicker onset of analgesic relief. One of the primary obstacles in the manufacture of powder sachets is the distribution of the drug in the powder, and the uniformity of content in the finished product. These hurdles are magnified in the production of diclofenac sachets due to the poor aftertaste of diclofenac, and the need to incorporate additional ingredients to compensate for this poor taste.

To ensure an adequately homogenous distribution of drug product in the bulk powder, Reiner et al. disclose a wet granulation process for manufacturing the powder sachets. In the first step of the process, a wet granulate is prepared from diclofenac potassium, potassium bicarbonate, saccharin, aspartame and mannitol, using 95% ethanol as the wetting agent. The granulate is then mixed with over one gram of sugar (saccharose) and various flavoring agents to improve the taste of the composition.

The method described by Reiner et al. produces an excellent pharmaceutical dosage form but suffers from a number of disadvantages including the size of the sachet (2g) which makes the sachet more difficult to dissolve, and the presence of sugar in the formulation, which should be avoided in the diabetic population. In addition, the process requires precise controls on the granulometric process to assure uniform distribution of drug in the granulate and consistent amounts of drug in the finished product. What is needed is an alternative method for producing sugar-free powder diclofenac sachets and other fast acting dosage forms of diclofenac.

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