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COMPOSITION COMPRISING A TRAMADOL MATERIAL AND A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

I. CROSS REFERENCE

This case is related to attorney Docket Nos. MCN-499 AND MCN-500.

II. BACKGROUND OF THE INVENTION

United States Patent No. 3,652,589 discloses a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, commonly known as tramadol, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of tramadol are found in Arzneim. Forsch. (Drug Res.), 28(I), 114 (1978). Driessen et al., Arch. Pharmacol., 341, R104 (1990) disclose that tramadol produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VIth World Congress on Pain, April 1-6 (1990), disclose that tramadol hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that tramadol lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., Arzneim. Forsch. (Drug Res.), 28(I), 183 (1978)), constipation (I. Arend et al., Arzneim. Forsch. (Drug Res.), 28(I), 199 (1978)), tolerance (L. Flohe et al., Arzneim. Forsch. (Drug Res.), 28(I), 213 (1978)), and abuse liability (T. Yanagita, Arzneim. Forsch. (Drug Res.), 28(I), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, tramadol may produce certain side effects unique to tramadol including hot flushes and sweating. Despite these side effects, tramadol's combination of non-opioid and opioid activity makes tramadol a very unique drug. Tramadol is currently being marketed by Grunenthal GMBH as an analgesic.

Opioids have for many years been used as analgesics to treat severe pain. They, however, produce undesirable side effects and as a result cannot always be given repeatedly or at high doses. The side effect problems are well

documented in the literature. See, for example, J. Jaffe in "Goodman and Gilman's, The Pharmacological Basis of Therapeutics", 8th edition; Gilman et al.; Pergamon Press, New York, 1990; Chapter 22; pages 522-573 wherein it is disclosed that morphine and its congeners, e.g., codeine, hydrocodone and oxycodone, are opioid agonist analgesics that exhibit side effects such as respiratory depression, constipation, tolerance and abuse liability.

As alternatives to using opioids, non-opioids such as acetaminophen, aspirin and ibuprofen are used as analgesics. Ibuprofen, like aspirin, is not subject to the tolerance, addiction and toxicity of the opioid analgesics. However, ibuprofen, aspirin and other nonsteroidal antiinflammatory drugs (commonly referred to as NSAIDs) are only useful in relieving pain of moderate intensity, whereas the opioid analgesics are useful in relieving more intense pain; See Woodbury, D. and Fingl, E. in "The Pharmacological Basis of Therapeutics", 5th Ed.; Goodman, L. and Gilman, A., Chapter 15, (1975).

To reduce the side effect problems of opioids, opioids have been combined with other drugs including non-opioid analgesic agents, which lower the amount of opioid needed to produce an equivalent degree of analgesia. It has been claimed that some of these combination products also have the advantage of producing a synergistic analgesic effect. For example, A. Takemori, Annals New York Acad. Sci., 281, 262 (1976) discloses that compositions including combinations of opioid analgesics with drugs other than analgesics exhibit a variety of effects, i.e., subadditive (inhibitory), additive or superadditive. R. Taber et al., J. Pharm. Expt. Thera., 169(1), 29 (1969) disclose that the combination of morphine and methadone, another opioid analgesic, exhibits an additive effect. United States Patent No. 4,571,400 discloses that the combination of dihydrocodeine, an opioid analgesic, and ibuprofen, a non-opioid analgesic, provides superadditive effects when the components are within certain ratios. See also U.S. Patent Nos. 4,587,252 and 4,569,937 which disclose other ibuprofen opioid combinations. A. Pircio et al., Arch. Int. Pharmacodyn., 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and acetaminophen, a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant superadditive analgesia.

Combinations of non-opioid analgesics have also been prepared to avoid the side effects associated with opioids, and the combinations are noted to have

the benefit of requiring less of each ingredient and producing superadditive effects. G. Stacher et. al., Int. J. Clin. Pharmacol. Biopharmacy, 17, 250 (1979) report that the combination of non-opioid analgesics, i.e., tolmetin (another NSAID) and acetaminophen, allows for a marked reduction in the amount of tolmetin required to produce analgesia. In addition, United States Patent No. 4,260,629 discloses that an orally administered composition of acetaminophen and zomepirac, a non-opioid analgesic, in a particular weight ratio range produces a superadditive relief of pain in mammals. Furthermore, United States Patent No. 4,132,788 discloses that 5-aroyl-1-(lower)alkylpyrrole-2-acetic acid derivatives, non-opioid analgesics, when combined with acetaminophen or aspirin exhibit superadditive antiarthritic activity. However, there have been warnings against the daily consumption of non-opioid analgesic mixtures and of the consumption of a single non-opioid analgesic in large amounts or over long periods (see, D. Woodbury and E. Fingl at page 349). In addition, ibuprofen, aspirin and some other NSAIDs may cause gastrointestinal side effects especially if used repeatedly. See, for example, M.J.S.Langman, Am. J. Med. 84 (Suppl. 2A): 15-19, 1988; P.A. Insel in "The Pharmacological Basis of Therapeutics" 8th Ed.; Gilman, A.G. et al., Chapter 26, pp. 664-668, 1990.

The prior art , however, does not disclose that tramadol, an 'atypical' opioid analgesic, can or should be combined with another analgesic to lessen the side effects of each or to yield a composition comprising a tramadol material and another analgesic that exhibits superadditive analgesia.

III. SUMMARY OF THE INVENTION

It has now been found that a tramadol material which includes various forms of tramadol as defined hereinafter can be combined with nonsteroidal antiinflammatory drugs (hereinafter NSAIDs) to produce analgesia. The combination employs lesser amounts of both the tramadol material and the NSAID than would be necessary to produce the same amount of analgesia if either was used alone. By using lesser amounts of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising the tramadol material and one or more NSAIDs have been found to exhibit synergistic analgesic effects when combined in certain ratios. Particularly preferred compositions are those comprising a tramadol material and ibuprofen. The compositions according to this invention may also be useful in treating tussive conditions.

IV. BRIEF DESCRIPTION OF THE DRAWING

Figure I is an isobologram showing the analgesic effect of tramadol hydrochloride and ibuprofen composition on the acetylcholine-induced abdominal constriction in mice.

V. DETAILED DESCRIPTION OF THE INVENTION

The present invention is generally directed to compositions comprising a tramadol material and an NSAID. The tramadol material is any one of (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol (tramadol), its N-oxide derivative ("tramadol N-oxide"), and its O-desmethyl derivative ("O-desmethyl tramadol") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the tramadol material. Tramadol is commercially available from Grunenthal or may be made by the process described in United States Patent No. 3,652,589, which is herein incorporated by reference.

Tramadol N-oxide is prepared by treating tramadol as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol, with, but preferably without heating. See, "Reagents For Organic Synthesis", 1, 471, Fieser & Fieser eds., Wiley N.Y; (1987), B. Kelentey et al., Arzneim. Forsch., 7, 594 (1957). With heating, the reaction takes about 1 hour, whereas without heating the reaction takes about 3 days. Following the oxidation, the mixture is treated with an agent, e.g. PtO_2 or preferably Pt/C, for about a day, to destroy the excess hydrogen peroxide. The mixture is filtered, followed by the evaporation of the filtrate and then the residue is recrystallized from an organic solvent mixture, e.g., methylene chloride/ethyl acetate.

O-desmethyl tramadol is prepared by treating tramadol as a free base under O-demethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH, thiophenol and diethylene glycol (DEG) with heating to reflux. See, Wildes et al., J. Org. Chem., 36, 721 (1971). The reaction takes about an hour, followed by cooling and then quenching in water of the reaction

mixture. The quenched mixture is acidified, extracted with an organic solvent such as ethyl ether, basified and then extracted with a halogenated organic solvent such as methylene chloride. The extract is then dried and the solvent evaporated to yield the O-desmethyl product, which may then be short-path distilled, converted to its corresponding salt, e.g., treated with an acidified (HCl/ethanol) solution, and recrystallized from an organic solvent mixture, e.g., ethanol/ethyl ether.

NSAIDs according to the present invention are non-opioid analgesics characterized in that they are nonsteroidal drugs which act as antiinflammatory, analgesic and anti-pyretic agents. This class of drugs is well known in the art. See for example, Goodman, L. and Gilman, A., supra, in Chapter 26 (1990). These drugs share certain therapeutic actions and side effects. Within this broad class of drugs are salicylates, such as aspirin; pyrazolone derivatives such as phenylbutazone, onyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone; indomethacin; sulindac; fenamates such as mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamice acids; aryl acetic acid and propionic acid compounds such as 2-(p-isobutylphenyl)propionic acid (generic name ibuprofen); alphamethyl-4-(2-thienylcarbonyl) benzene acetic acid (generic name suprofen); 4,5-diphenyl-2-oxazole propionic acid (generic name oxprozin); rac-6-chloro-alphamethyl-carbazole-2-acetic acid (generic name carprofen); 2-(3-phenyloxyphenyl)-propionic acid, particularly the calcium salt dihydrate thereof (these compounds being referred to generically as fenoprofen and fenoprofen calcium); 2-(6-methoxy-2-naphthyl) propionic acid (generic name naproxen; the generic name of the sodium salt is naproxen sodium); 4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-α–methylbenzene acetic acid (generic name indoprofen); 2-(3-benzoylphenyl)propionic acid (generic name ketoprofen); and 2-(2-fluoro-4-biphenylyl) propionic acid (generic name flurbiprofen) and 1-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid (generic name tolmetin). Also included within NSAIDs are compounds within the class including sodium 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate dihydrate (generically referred to as zomepirac sodium); 4-hydroxy-2-methyl-N-(2-pyridyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (generic name piroxicam); 2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid (generic name diflunisal) or 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinozolinone (generic name proquazone), phenylacetic acid derivatives such as diclofenac; etodolac and nabumetone. For the purposes of this invention, para-aminophenol derivatives such as acetaminophen are not considered NSAIDs because of their general

lack of antiinflammatory activity. All of the NSAIDs are commercially available materials. A particularly preferred class of NSAIDs for use in the composition of the present invention are the propionic acid derivatives. Within this class of compounds ibuprofen is the most preferred.

In the compositions of the present invention, the NSAID portion of the composition may either be a single NSAID or a combination of one or more NSAIDs. Accordingly, as used herein, NSAID includes all of these possibilities.

The NSAID and the tramadol material are generally present in a weight ratio of tramadol material to NSAID from about 1:1 to 1:200. Certain ratios result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising a tramadol material and an NSAID, the ratio of the tramadol material: NSAID is preferably from about 1:1 to 1:200; and, more preferably, from about 1:2 to 1:200. The most preferred ratios are from about 1:2 to 1:20. Compositions of a tramadol material and an NSAID within these weight ratios have been shown to exhibit synergistic analgesic effects.

A particularly preferred composition according to the present invention is a tramadol material and ibuprofen. The ratio of the tramadol material to ibuprofen in this preferred combination is from about 1:1 to 1:200, more preferably from about 1:2 to 1:200 and most preferably from about 1:2 to 1:20.

Pharmaceutical compositions comprising the tramadol material and the NSAID as the active ingredients in an intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral. The composition may also be administered by means of an aerosol. In preparing the compositions in an oral dosage form, any of the usual pharmaceutical media may be employed. For example, in the case of oral liquid preparations (such as suspensions, elixirs and solution), water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. In the case of oral solid preparations (such as, for example, powders, capsules and tablets), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, may be used. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers

are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, to aid solubility or for preservative purposes, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions will generally be in the form of a dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, containing from 0.1 to about 800 mg/kg, and preferably from about 0.3 to 200 mg/kg of the active ingredients. However, it will be appreciated that the precise dose of the active ingredients will vary depending upon the particular NSAID and tramadol material being used.

The following experimental examples describe the invention in greater particularity and are intended to be a way of illustrating but not limiting the invention.

Example 1: Preparation of the Combined Doses of Tramadol and Ibuprofen

The preparation of different ratios of a tramadol/ibuprofen combination was effected by preparing solutions having concentrations expressed in mg_{drugs} per 10 mL of distilled water. For example, 40 mg of tramadol as the free base and 40 mg of ibuprofen as the free base were added to 10 mL of water with 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the tramadol/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio was prepared separately in a similar manner and injected in a volume of 10 mL/kg per mouse. Similarly, the other ratios of tramadol/ibuprofen listed in Table 1 were prepared at the various concentrations.

Example 2: Preparation of the Combined Doses of Tramadol N-oxide and Ibuprofen

First, tramadol N-oxide was prepared as set forth hereinafter. Tramadol hydrochloride (0.5 mol) was converted to its free base in basified water (pH >9) and then extracted with ether. The ether was evaporated to yield the crystalline hydrate of tramadol. The solid was then heated with steam under a high vacuum to remove as much water as possible to yield 131.5 g of material. The material was dissolved in methanol (500 mL) and 65 g of 30% H_2O_2 was added. The

solution was stirred for 3 hours and then an additional 65 g of the 30% H_2O_2 was added. The reaction was stirred for 2.5 days at room temperature. Approximately 10 mg of PtO_2 on carbon (use of Pt/C is suggested for its ease of removal) was added to the reaction mixture, and very gentle foaming took place. An additional 10 mg of PtO_2 was added and the reaction mixture was stirred overnight and then filtered thru a filter aid. The filtrate was concentrated under vacuum while being heated to a temperature of <40°C. The residue was taken up in methylene chloride. Since the methylene chloride solution contained some colloidial platinum, the solution was diluted with ethyl acetate to 1 L and filtered through a nylon filter membrane (0.45 μ pore size) to yield a clear colorless filtrate. The filtrate was concentrated to 600 mL, and then ethyl acetate was added continuously to maintain a volume of 800 mL while the solution was heated until a vapor temperature of 74°C was reached. The solution was then cooled to room temperature. The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the tramadol N-oxide (mp. 159.5-160°C).

C16H25NO3 Theor.:	C, 68.78; H, 9.27; N, 5.01
Found:	C, 68.65; H, 9.22; N, 4.99

The preparation of different ratios of a tramadol N-oxide/ibuprofen combination is effected by preparing solutions having concentrations expressed in mg_{drugs} per 10 mL of distilled water. For example, 40 mg of tramadol as the free base and 40 mg of ibuprofen as the free base is added to 10 mL of water with 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the tramadol N-oxide/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio is prepared separately in a similar manner.

Example 3: (-) and (+) Enantiomers of O-Desmethyl Tramadol: Their Syntheses and the Preparation of Doses of O-Desmethyl Tramadol-with Ibuprofen

First, O-desmethyl tramadol was prepared as set forth hereinafter. Diethylene glycol (125 mL) was added with cooling to potassium hydride (9.5 g) with the temperature being maintained at <50°C. To the solution was added thiophenol (10 mL) dissolved in diethylene glycol (25 mL), and then (-)-tramadol

as the free base (9.3 g) in diethylene glycol (50 mL) was added. The final reaction mixture was heated slowly to reflux for 45 minutes. The mixture was cooled and then quenched into water. The pH was adjusted to about 3, and the mixture was extracted with ethyl ether. The pH was readjusted to about 8 and the resulting mixture was extracted 5 more times with methylene chloride. The extract was dried and the methylene chloride was evaporated to yield 4.6 g of the title compound as an oil. The oil was distilled (Kugelrohr), dissolved in tetrahydrofuran and treated with an ethanol/HCl solution to give 2.3 g of the salt . The salt was recrystallized from ethanol/ethyl ether and dried to yield 1.80 g of the salt of the (-) enantiomer of O-desmethyl tramadol (mp. 242-3°C), $[\alpha]_D^{25}$ = -32.9 (C=1, EtOH).

C15H23NO2·HCl	Theor.:	C, 63.04; H, 8.46; N, 4.90
	Found:	C, 63.00; H, 8.51; N, 4.94

To prepare the (+) enantiomer of the title compound, the reaction was run under the same conditions except that (+)-tramadol as the free base was used instead of the (-)-tramadol to yield 2.8 g of the (+) enantiomer of O-desmethyl tramadol (mp. 242-3°C) $[\alpha]_D^{25}$ =+32.2 (C=1, EtOH).

C15H23NO2·HCl	Theor.:	C, 63.04; H, 8.46; N, 4.90
	Found:	C, 63.14; H, 8.49; N, 4.86

The preparation of different ratios of a O-desmethyl/ibuprofen combination is effected by preparing solutions having concentrations expressed in mg_{drugs} per 10 mL of distilled water. For example, 40 mg of O-desmethyl as the free base and 40 mg of ibuprofen as the free base were added to 10 mL of water with 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the O-desmethyl tramadol/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio is prepared separately in a similar manner and injected in a volume of 10 mL/kg per mouse.

Example 4: Analgesic Activity

Male CD1 mice (weighing from 18-24 g) were utilized in determining the analgesic effects associated with the compositions of the invention. The mice were all dosed orally with tramadol hydrochloride (calculated as the base), which was completely dissolved in distilled water, and ibuprofen (calculated as the base), which was completely dissolved in distilled water or in distilled water containing 2% by volume of Tween 80 containing 100% polysorbate 80. The dosing volume was 10 mL/kg.

The procedure used in detecting and comparing the analgesic activity of different classes of analgesic drugs for which there is a good correlation with human efficacy is the prevention of acetylcholine-induced abdominal constriction in mice (H. Collier et al., Br. J. Pharmacol., 32, 295 (1968)).

Mice, intubated with various doses of tramadol hydrochloride alone, ibuprofen alone, combined doses of tramadol hydrochloride and ibuprofen, or vehicle such as distilled water, or distilled water containing 2% by volume of Tween 80, were injected intraperitoneally with a challenge dose of acetylcholine bromide. The acetylcholine was completely dissolved in distilled water at a concentration of 5.5 mg/kg and injected at the rate of 0.20 mL/20 g. For scoring purposes an "abdominal constriction" was defined as a contraction of the abdominal musculature accompanied by arching of the back and extension of the limbs. The mice were observed 10 minutes for the presence or absence of the abdominal constriction response beginning immediately after receiving the acetylcholine dose, which was 30 minutes after receiving the oral administration of tramadol hydrochloride, ibuprofen, combined doses of tramadol hydrochloride and ibuprofen, or vehicle. Each mouse was used only once.

The analysis of possible superadditivity for the compositions at each fixed ratio was determined as disclosed by R. J. Tallarida et al., Life Sci., 45, 947 (1989). This procedure involved the determination of the total amount in the mixture that is required to produce a specified level of effect, such as 50% ($ED50_{mix}$), and the corresponding total amount that would be expected under simple additivity ($ED50_{add}$). Where it was established that $ED50_{mix} < ED50_{add}$ for a specific fixed-ratio, then that composition ratio was superadditive. Both the quantities $ED50_{mix}$ and $ED50_{add}$ were random variables; $ED50_{mix}$ was estimated from the dose-response curve for a specific fixed-ratio; $ED50_{add}$ was

obtained by combining the ED50 estimates for the two drugs under additivity. $ED50_{mix}$ was then compared to $ED50_{add}$ via a Student's t-test. The ED50 value for tramadol hydrochloride alone was 5.5(4.8-6.4) mg/kg. The ED50 value for ibuprofen alone was 33.5 (24.1-46.5) mg/kg.

The interaction between tramadol and ibuprofen was determined at precise dosage ratios of tramadol hydrochloride and ibuprofen. Multiple (typically 4-6) coded doses of each selected combination were studied for analgesic effectiveness after 30 minutes using an experimental design which permitted the complete randomization of the separate dosage forms tested.

The interaction of tramadol hydrochloride and ibuprofen on the acetylcholine-induced abdominal constriction in mice was demonstrated by the data in Table I and is shown in the Loewe isobologram, Figure I, (see, S. Loewe, Pharm. Rev., 9; 237 (1957) regarding the preparation and basis of an isobologram). In Figure 1, the diagonal line joining the ED50 values of the two drugs given separately represents the simple additivity of effects at different component ratios. The dotted lines adjacent to the diagonal line define the 95% confidence interval. ED50 values falling under the curve (between the line and the origin) indicate superadditivity, i.e., unexpected enhancement of effects. The diagonal dashed lines radiating from the origin represent the dose ratios of ibuprofen to tramadol hydrochloride used in mice receiving the combined drug dosages. The bars through the ED50 points for the tramadol and ibuprofen composition represent the 95% confidence intervals of the ED50 value. The experimental data as represented in Figure I establish that compositions having a ratio of tramadol to ibuprofen from about 1:1 to 1:200 (represented by the curved line) give unexpectedly enhanced activity since $ED50_{mix}$ is less than $ED50_{add}$.

It is expected that based on these results, other NSAIDs, and particularly the propionic acid derivatives, when combined with a tramadol material, will produce similar synergistic results.

TABLE 1
TRAMADOL:IBUPROFEN

DRUG COMBINATIONS (Tramadol:Ibuprofen)	DOSE (mg/kg, p.o.) Tramadol	Ibuprofen	analgesia	ED_{50} at 30 min (95% CI's) Tramadol	Ibuprofen
Tramadol only	2	0	3/15		
	3	0	4/15		
	4	0	14/45		
	6	0	20/45	5.5	
	8	0	40/60	(4.8-6.4)	
	10	0	15/15		
	16	0	14/15		
2:1	2.5	1.25	2/15		
	5	2.5	7/15	4.8	2.4
	10	5	14/15	(3.8-6.2)	(1.9-3.1)
1:1	1.25	1.25	2/15		
	2.5	2.5	3/15	4.4	4.4
	5	5	6/15	(3.3-5.9)	(3.3-5.9)
	10	10	15/15		
1:2	1.25	2.5	1/15		
	2.5	5	7/15	2.5	5.1
	5	10	14/15	(2.1-3.1)	(4.1-6.3)
	10	20	15/15		
1:20	0.15625	3.125	2/15		
	0.3125	6.25	7/15		
	0.625	12.5	8/15	0.4	9.0
	1.25	25	26/30	(0.3-0.6)	(6.3-12.8)
	2.5	50	13/15		
	5	100	15/15		
1:200	0.05	10	3/15		
	0.1	20	6/15		
	0.2	40	9/15	0.1	25.8
	0.4	80	13/15	(0.1-0.2)	(18.4-36.2)
	0.8	160	15/15		
Ibuprofen only	0	10	2/15		
	0	20	4/15		
	0	40	8/15		33.5
	0	80	13/15		(24.1-46.5)
	0	160	14/15		

CLAIMS:

1. A pharmaceutical composition comprising a tramadol material and a nonsteroidal antiinflammatory drug.

2. The pharmaceutical composition of claim 1 wherein the the tramadol material and the nonsteroidal antiinflammatory drug are in a ratio that is sufficient to provide a synergistic pharmacological effect.

3. The pharmaceutical composition of claim 2 wherein the tramadol material is tramadol hydrochloride.

4. The pharmaceutical composition of claim 3 wherein the tramadol hydrochloride is racemic.

5. The pharmaceutical composition of any preceding claim, wherein the nonsteroidal antiinflammatory drug is selected from any of salicylates, pyrazolone derivatives, indomethacin, sulindac, fenanates, aryl acetic acid derivatives, propionic acid derivatives, phenyl acetic acid derivatives, or mixtures thereof.

6. The pharmaceutical composition of claim 5, wherein the aryl nonsteroidal antiinflammatory drug is the propionic acid derivatives from any of ibuprofen, oxaprozin, naproxen, flurbiprofen, fenoprofen, fenoprofen calcium or ketoprofen.

7. The pharmaceutical composition of claim 6, wherein the propionic acid derivative is ibuprofen.

8. The pharmaceutical composition of any preceding claim, wherein the ratio of the tramadol material to the nonsteroidal antiinflammatory drug is a weight ratio from about 1:1 to about 1:200.

9. The pharmaceutical composition of claim 8 wherein the weight ratio is about 1:2.

10. The pharmaceutical composition of claim 8 wherein the weight ratio is about 1:20.

11. The pharmaceutical composition of claim 8 wherein the weight ratio is from about 1:2 to about 1:200.

12. The pharmaceutical composition of claim 11 wherein the weight ratio is from about 1:2 to about 1:20.

13. The pharmaceutical composition of any preceding claim further comprising a pharmaceutically acceptable carrier.

14. A product comprising a tramadol material and a nonsteroidal antiinflammatory drug as a combined preparation for simultaneous, separate or sequential use in the treatment of a pharmacological condition.

15. Use of a tramadol material and a nonsteroidal antiinflammatory drug in the manufacture of a medicament for use in the relief of pain.