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(54) Title: EFFERVESCENT COMPOSITIONS COMPRISING NIMESULIDE

(57) Abstract: An effervescent Pharmaceutical composition comprising the drug Nimesulide, one or more acids and one or more carbonate source wherein the ratio between Nimesulide and the total carbonate source is between 1:17 to 1:2 w/w.

Effervescent Compositions Comprising Nimesulide

The present invention relates to a effervescent compositions of Nimesulide. The compositions are very useful in providing rapid analgesic and anti-inflammatory action.

Technical background of the invention

Nimesulide is a nonsteroidal anti-inflammatory dug(NSAID) that also has antipyretic and analgesic properties. The compound is weakly acidic(pka=6.5) and differs from other NSAIDs in that its chemical structure contains a sulfonanilide moeity as the acidic group.(fig.1) (Magni E, Nimesulide an overview, Drug Invest 1991; 3 suppl. 2:1-3)

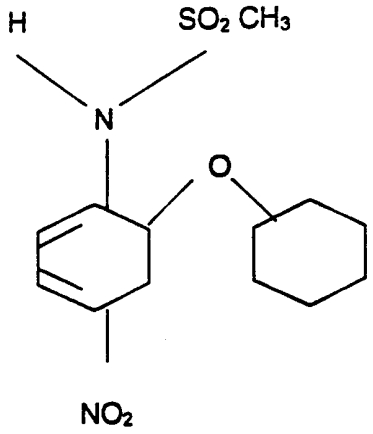

Fig. 1

The therapeutic effects of NSAIDs are largely the result of their ability to inhibit prostaglandin synthesis via inhibition of cyclo-oxygenase. Unfortunately, this effect is also responsible for the inhibition of gastroprotective prostaglandins, which leads to gastrointestinal intolerance. In vitro, Nimesulide is a relatively weak inhibitor of prostaglandin synthesis and appears to exert its effects through a variety of mechanisms. (Magni E. The effect of Nimesulide on prostanoid formation. Drugs 1993; 46 Suppl. 1:10-4). Indeed, mechanism of action of this drug is more complex than previously thought and may involve interference with the production/action of mediators other than prostaglandins such

as enzymes, toxic oxygen derivatives, cytokines, platelet-activating factor(PAF) and histamine.

The anti-infalmmatory, analgesic and antipyretic activities of Nimesulide, a non-steroidal anti-inflammatory drug (NSAID) of the sulfonanilide class, have been demonstrated in a number of experimental models and in numerous clinical trials. Nimesulide has exhibited potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation such as carrageenin-induced rat paw oedema and inflammation, ultraviolet light-induced erythema in guinea-pigs and adjuvant arthritis in rats. The analgesic potency in nimesulide was similar to that of ibuprofen and less than that of indomethacin in an acetic acid writing test in rats, and acetic acid and acetycholine writhing tests in mice. Nimesulide has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin and paracetamol (acetaminophen) in rats with yeast-induced fever.

Nimesulide is a relatively weak inhibitor of prostaglandin synthesis in vitro and appears to exert its effects through a variety of mechanisms including free-radical scavenging, effects on histamine release, the neutrophil mycloperoxidase pathway, bradykinin activity, tumour necrosis factor-α release, cartilage degradation, metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation and synthesis of platelet activating factor. Animal studies have suggested that Nimesulide is less ulcergenic than aspirin, indomethacin, naproxen, piroxicam and ibuprofen. Nimesulide appears to have little effect or renal prostaglandin synthesis in rats.

Nimesulide dose dependently (0/3 to 15.4 mg/L) and at near therapeutic plasma drug concentrations affects neutrophil activity in vitro during inflammatory reactions in at least 2 steps of the cell response. It is also reported to inhibit the release of histamine by 50% during immunological reaction in the perfused sensitised guinea pig lung model at 0.93 mg/L level(Berti F, et al., Arzeneimittel Forschung 1990;40: 1011-6). Further, when added to human articular cartilage explant in vitro, nimesulide, at a therapeutic concentration (3 mg/L), reduced the degradation of the matrix by inhibiting the synthesis of

metalloproteinases such as collagenase and stromelysin (Pelletier JP, Martel-Pelletier J, Drugs 1993; 46 Suppl. 1:34-9).

In yeast induced febrile rats, the ED_{50} (producing a 5° C decrease in rectal temperature) of nimesulid is reported to be 0.21 mg/kg, indicating more potency than indomethacin (ED_{50} – 1.8 mg/kg) and aspirin (ED_{50} – 25 mg/kg) [Tanaka K. et al. Arzeneimittel Forschung 1992; 42:935-44]. Using the same animal model, Ceserani et al. (drugs 1993; 46 Suppl. 1:48-51) observed that orally and rectally administered nimesulide (ED_{50} range 0.22 to 0.47 mg/kg) displayed more antipyretic potency than paracetamol (ED_{50} range 10 to 118 mg/kg) and maintained its potency througout the observation period (6 to 9 hours after administration of yeast).

After oral administration of nimesulide 50 to 200 mg to healthy adult volunteers, peak serum concentrations of 1.98 to 9.85 mg/L are achieved within 1.22 to 3.17 hours. Compared with values obtained with oral drug administration, peak serum concentrations are slightly lower (2.14 to 2.32 mg/L) and are achieved more slowly (3 to 4.58h) after rectal administration of nimesulide 100 and 200 mg. Oral drug absorption is nearly complete and concomitant administration of food may decrease the rate, but not the extent of absorption of nimesulide. The drug is extensively bound (99%) to plasma proteins and has an estimated apparent volume of distribution of 0.19 to 0.35 L/kg following oral administration.

Nimesulide is extensively metabolized (1 to 3% of a dose is excreted unchanged in the urine) to several metabolites which are excreted mainly in the urine (≈70%) or the faeces (≈20%). The drug is almost completely biotransformed into 4-hydroxy-nimesulide in both free and conjugated forms and this metabolise appears to contribute to the anti-inflammatory activity of the compound. Peak concentration of 4-hydroxy-nimesulide ranged from 0.84 to 3.03 mg/L and were attained within 2.61 to 5.33 hours after oral administration of Nimesulide 50 to 200 mg to healthy adult volunteers. The elimination half-life of 4-hydroxy-nimsulide ranges from 2.89 to 4.78 hours and is generally similar to or slightly higher than that of the parent compound (1.56 to 4.95h).

The pharmacokinetic profile of nimesulide is not significantly altered in children, elderly volunteers and patients with moderately impaired renal function [creatinine clearance 1.8 to 4.8 L/h (30 to 80 ml/min)]. Slight accumulation of 4-hydroxy-nimesulide was noted in patients with moderate renal impairment; however, the clinical significance of this finding is unknown.

Clinical studies have established the analgesic, anti-inflammatory and antipyretic effectiveness of orally (mostly 200 mg/day) or rectally (400 mg/day) administered nimesulide in the treatment of a variety of painful inflammatory conditions, including those associated with osteoarthritis, oncology, postoperative trauma, sports injuries, ear nose and throat disorders, dental surgery, bursitis/tendinitis, thrombophlebitis. Upperairways inflammation and gynaecological disorders. In these indications, nimesulide is more effective than placebo and is at least as effective as therapeutic dosages of other NSAIDs, including piroxicam, ketoprofen, naproxen, etodolac, mefenamic acid, dicofenac, niflumic acid, fentiazae, feprazone and flurbiprofen. Nimsulide therapy was characterised by a rapid onset of analgesia and symptomatic relief in studies where as significant difference in clinical efficacy between active treatment was observed. However, most of theses studies evaluated small numbers of patients and were probably too small to identify any small differences in effectiveness.

In children, nimesulide suspension, granules and suppositories are more effective than placebo and are at least as effective as paracetamol, diclofenac, naproxen, lysine acetylsalicylate, mefenamic acid, ketoprofen and diprone in reducing in pain, inflammation and fever associated with respiratory tract infection, postoperative pain and musculoskeletal injury. Nimesulide has been well tolerated by both young and elderly adults and children in 2 large post marketing surveillance surveys. As with other NSAIDs, the most common adverse effects are gastrointestinal disturbances (epigastralgia, heartburn, nausea, diarrhoea, and vomitings 5.1 to 8.5% of patients), dermatological reactions (rash, pruritus; 0.2 to 0.6%) and central nervous system effects (dizziness, somnolence, headache; 0.3 to 0.4%). Withdrawal rates associated with short term (up to 30 days) nimesulide treatment range from 1.1 to 2.2% in adult, elderly and paediatric patients.

Available data indicate that the gastrointestinal tolerability of nimesulide in adults and children is similar to that of other NSAIDs. The rate of endoscopically verified gastroduodenal irritation with nimesulide appears to be similar to that with placebo and diclofenac and less than that with indomethacin. The drug is well tolerated by most patients intolerant of aspirin and/or other NSAIDs and by patients with asthama.

The literature surveys shows that different dosage forms reported for nimesulide are tablets, granules, suppositories and suspension (Drugs 48 (3):431-454, 1994) and lately our group has patented transdermal (US Pat. No. 5688829) and intramuscular injection (US Pat. No. 5716609) formulations. But no effervescent oral solid dosage form of Nimesulide has been reported so far.

Thus the present invention discloses a fast-acting effervescent solid dosage form of Nimesulide. The formulation may be in the form of granules or compressed tablets. Such dosage form, when added to water, produces very fine dispersion of the drug rapidly with simultaneous release of carbon dioxide. The carbon dioxide is released due to chemical reaction between an acid and alkali present in the formulation in presence of water.

Summery of Invention

The composition in accordance with the present invention comprises an effervescent pharmaceutical composition comprising.
Nimesulide as the active drug, one or more acid, one or more carbonate source and pharmaceutical aids. Nimesulide is present in the composition from 1% to 95% w/w, preferably from 2% to 20% w/w and more preferably from 3% to 10% w/w.

The acids are present in the range 5 % to 90% w/w, preferably from 10% to 70% w/w and more preferably from 30% to 60% w/w in the composition.

The carbonate source are present in the range 5% to 90% w/w, preferably from 10% to 70% w/w and more preferably 30 to 60% w/w in the composition.

The pharmaceutical aids may include fillers, binders, suspending agents, wetting agents, sweetening agents, lubricants, flavouring agents, and colouring agents.

Suitable examples of acids include organic acids like citric acid, tartaric acid, malic acid, fumaric acid, adipic acid and succinic acid. Acid salts like sodium dihydrogen phosphate, disodium dihydrogen pyrophosphate, sodium dihydrogen citrate and disodium hydrogen citrate can also be used.

Suitable carbonate sources include sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, sodium sesquicarbonate, sodium glycine carbonate, L-Lysine carbonate, Arginine carbonate, calcium carbonate and the like.
Fillers include, lactose mannitol, dibasic calcium phosphate and celluloses.
Binders include materials like cellulose gums, natural gums like acacia, xanthan gum., guar gum, tragacanth, alginates, silicon dioxide, carbomers, carrageenans, and the like.

Suitable example of wetting agents include:
Reaction products of natural and hydrogenated vegetables oils and ethylene glycol e.g. polyoxyethylene glycolated natural or hydrogenated castor oil such as those available under the trade name Cremophor.

Polyoxyethylene sorbitan fatty acid esters e.g. of the type available under the trade name TWEEN.

Polyoxyethylene fatty acid esters e.g. MYRJ and CETIOLHE.

Polyoxyethylene polyoxypropylene copolymers e.g. PLURONIC and Polyoxyethylene Polyoxypropylene block copolymers e.g. POLOXAMER.
Dioctylsodiumsulfosuccinate, sodium lauryl sulphate.

Propylene glycol mono-and di-fatty acid esters e.g. MIGLYOL 840.

Bile salts e.g. alkali metals salts e.g. sodium taurocholate.

Sweetening agents include sucrose, aspartame, saccharin, acesulfame potassium cyclamates, ammonium glycirrhyzinate and the like.
Lubricants include materials like sodium benzoate, sodium stearate, sodium oleate, liquid parraffin, dimethicone, L-Lycine, stearic acid, magnesium stearate, and colloidal silicon dioxide, talc and the like.

In another preferred embodiment of the invention Nimesulide is given a barrier coating by a suitable treatment. This coating prevents it from coming in contact with the alkali agent e.g. the carbonate source material in the composition. Nimesulide when in contact with the alkaline material gives intense yellow colour due to change in pH of the microenvironment. The yellow coloured particles give rise to a mottled appearance of the compressed tablets which does not look aesthetic.

The barrier coating physically prevents the contact between Nimesulide and the alkali thus preventing mottling. The barrier coating can be given by either coating the Nimesulide powder or by granulating the Nimesulide powder with such material. The coating material are present in the ratio 1:3 of Nimesulide.

Suitable barrier materials include natural, semi-synthetic, synthetic or man-modified. Suitable materials include cellulose, hydroxypropylemethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate.
Polyethylene; polyquaternium-1; Polyvinyl acetate (homopolymer); Polyvinyl acetate phthalate; polyglycolester ; PVP/dimethylaminoethylmethacrylate copolymer PVP dimethylaminoethy
/lmethacrylate/ polycarbamyl polyglycol ester; PVP/polycarbamyl polyglycol ester; PVP/VA copolymer.

Lanolin and lanolin derivatives, glyceryl monostearate, stearic acid, paraffins, beeswax, carnauba wax, Tribehenin.

Polyalkylene polyols like polyethylene glycols.

Gelatin and gelatin derivatives.

Alginates. Carbomers. Polycarbophils.

Methacrylic acid copolymers.

Carrabgeenans, pectins, chitosans, cyclodextrins, lecithins.

Natural and synthetic gums containing galactomannans like xanthan gum, tragacanth, acacia, agar, guar gum etc.

The manufacturing of all the effervescent dosage form is carried out in specially designed areas where relative humidity is below 20% and temperature is below 25 degree C. the finished dosage form is packaged suitably to prevent exposure to atmospheric moisture.

Example 1

1. Nimesulide	:	100.0 mg
2. Sodium Bicarbonate	:	1100.0mg
3. Citric acid (anhydrous, granular)	:	1194.0mg
4. Polyvinyl pyrrolidone	:	6.5mg
5. Polyethylene glycol	:	13.0mg
6. Sodium Benzoate	:	80.0mg
7. Aspartame	:	45.0mg
8. Orange Flavour	:	52.0mg
9. Sodium Lauryl Sulphate	:	0.208mg

Procedure:

(i) Passed 1 and 2 through #100 mesh and 3 through #40 mesh. Mixed uniformly to prepare a homogenous mass.

(ii) Granulated the mixed mass using 4 dissolved in 10, dried, passed through sieve of mesh #16 and mixed with 5 through 9.

(iii) Compressed tablets at 2.5 g per tablet.

Example 2

1. Citric acid (Anhydrous)	-	1385.0mg
2. Sodium Bicarbonate	-	1030.0mg
3. Nimesulide	-	100.0mg
4. Ethylcellulose	-	5.0mg
5. Sodium Carbonate	-	140.0mg
6. Polyethylene Glycol	-	90.0mg
7. Sodium Benzoate	-	90.0mg
8. Aspartame	-	50.0mg
9. Orange Flavour	-	50.0mg
10. Sodium Lauryl Sulphate	-	2.08mg

Procedure:

(i) Passed 3 though #100 mesh and coated with 4 in fluidised bed coater. Passed the dried mass through #60 mesh.

(ii) Mixed 1 and 2 and dried first at 65 degree C for 30 minutes and then at 95 degree C for 90 minutes.

(iii) Mixed the powder of step (I) and granules of step (ii) with sifted ingradients 5,6,7,8,9, and 10.

(iv) Compressed tablets at 2.5g per tablet.

Example 3:

Nimesulide	-	100.0mg
Mythacrylic Acid Co-polymer (EudragitE)	-	5.0mg
Sodium Bicarbonate	-	1200.0mg
Citric acid (Anhydrous)	-	1185.0mg
Sodium Carbonate	-	200.0mg
Polyethylene Glycol	-	25.0mg
Poly Vinyl Pyrrolidone	-	7.5mg
Sodium Benzoate	-	90.0mg
Simethicone	-	2.0mg
Aspartame	-	50.0mg
Sodium Layryl Sulphate	-	2.08mg
Orange flavour	-	50.0mg

Procedure:

1. Pass Nimesulide through #100 mesh. Dissolve methacrylic acid co-polymer in dichloromethane. Coat Nimesulide with polymer solution in fluidised bed coater. Pass the coated material through #60 mesh.
2. Granulate coated Nimesulide sodium bicarbonate, soudium carbonate and citric acid with Poly Vinyl Pyrrolidon. Dry mix with extra granular lubricants, sweeteners and flavours.
3. Compressed tablets at 2.5g tablet weight.

Example 4:

Nimesulide	-	100.0mg
Carbomer	-	10.0mg
Tartaric acid (Anhydrous)	-	1185.0mg
Sodium Bicarbonate	-	1200.0mg
Poly Vinyl Pyrrolidone	-	7.5mg
Fumaric Acid	-	550.0mg
Sodium Benzoate	-	90.0mg
Orange Flavour	-	50.0mg
Aspartame	-	50.0mg
Sodium Lauryl Sulphate	-	2.08mg
Isopropyl Alcolhol	-	q.s.

Procedure:

(i) Pass 1 through #100 mesh. Disperse 2 in water & granulate 1 with it. Passed the dried granules through #60 mesh.

(ii) Sift 3 through #30 mesh & 4 through #100 mesh. Mix with powder of step (i) and granulate with 5 dissolved in 10.

(iii) Pass granulates of step (ii) through #16 mesh and mix with 6,7,8,9, & 10.

(iv) Compress tablets at a weight of 2.5g.

Example 5

1.	Nimesulide	-	100.00 mg
2.	Anhydrous Citric Acid	-	1247.50 mg
3.	Sodium Bicarbonate	-	1000.00 mg
4.	Anhydrous Sodium carbonate	-	80.00 mg
5.	Povidone (K-30)	-	67.50 mg
6.	Polyethylene Glycol 6000	-	25.00 mg
7.	Sodium Benzoate	-	80.00 mg
8.	Aspartame	-	40.00 mg

9.	Sodium Lauryl Sulphate	-	2.50 mg
10.	Magnesium Stearate	-	7.50 mg
11.	Flavour	-	100.00 mg
12.	Isopropyl Alcohol	-	Lost during processing
13.	Dichloromethane	-	Lost during processing

Procedure :

(i) Mix 1,2,3 and 4 and granulate with solution of 5 in a mixture of 12 and 13.
(ii) Dry the wet granules at 40 to 50° C
(iii) Pass the dried granules through sieve of mesh size 16.
(iv) To the granules of step (iii) add 6,7,8,9,10 and 11. Mix uniformly.
(v) Compress into tablets.

Example 6

1.	Nimesulide (Micronized)	-	100.00 mg
2.	Tartaric Acid	-	175.0 mg
3.	Sodium Bicarbonate	-	190.0 mg
4.	Lactose	-	70.0 mg
5.	Sodium Benzoate	-	25.0 mg
6.	Flavour	-	10.0 mg
7.	Sodium Carbonate	-	10.0 mg
8.	PEG 6000	-	20.0 mg

Procedure :

(i) Dry 1,2,3,4,5, & 7 at 50° – 60°C
(ii) Mix 1,2,3,4 & 7 and slug – deslug to prepare granules

(iii) Blend the granules of (ii) with 5,6 and 8.

(iv) Compress into tablets

Example 7

1. Nimesulide (Micronized)	-	50.0 mg
2. Citric Acid	-	800.0 mg
3. Sodium Bicarbonate	-	790.0 mg
4. Sodium Bicarbonate	-	60.0 mg
5. Lactose	-	132.0 mg
6. Povidone (K-30)	-	50.0 mg
7. Sodium Benzoate	-	30.0 mg
8. PEG 6000	-	60.0 mg
9. Flavour	-	25.0 mg
10. Magnesium Stearate	-	2.5 mg

Procedure:

(i) Mix 1,2,3,4 & 5 and granulate with solution of 6 in water.

(ii) Dry the granules at $50^{\circ} - 60^{\circ}$ C.

(iii) Size the granules and blend with 7,8,9 and 10.

(iv) Compress into tablets or fill the granules in sachets

We Claim:

1. An effervescent pharmaceutical composition comprising the drug Nimesulide, one or more acids, as herein described and one or more carbonate source, as herein described, wherein the ratio between Nimesulide and the total carbonate source is between 1:17 to 1:2 w/w.

2. The effervescent pharmaceutical composition as claimed in claim 1 wherein the ratio between Nimesulide and the total carbonate source is between 1:15 to 1:7 w/w.

3. The effervescent pharmaceutical composition as claimed in claims 1 to 2 wherein the ratio between Nimesulide and the total carbonate source is between 1:12 to 1:8w/w

4. The effervescent pharmaceutical composition as claimed in claims 1 to 3 wherein the acid is organic acid like citric acid, tartaric acid, malic acid , fumaric acid, adipic acid and succinic acid.

5. The effervescent pharmaceutical composition as claimed in claims 1 to 4 wherein the acid is citric acid.

6. The effervescent pharmaceutical composition as claimed in claims 1 to 5 wherein the carbonate source is sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, sodium sesquicarbonate, sodium glycine carbonate, L-Lysine carbonate, Arginine carbonate, Calcium Carbonate.

7. The effervescent pharmaceutical composition as claimed in claims 1 to 6 wherein the carbonate source is a mixture of sodium carbonate and sodium bicarbonate.

8. The effervescent pharmaceutical composition as claimed in claims 1 to 7 wherein the ratio of sodium carbonate to sodium bicarbonate is between 1:20 1:6 w/w.

9. The effervescent pharmaceutical composition as claimed in claims 1 to 8 wherein the ratio of sodium carbonate to sodium bicarbonate is between 1:14 to 1:10 w/w.

10. The effervescent pharmaceutical composition as claimed in claims 1 to 9 wherein the ratio of sodium carbonate to sodium bicarbonate is between 1:14 to 1:10 w/w.

11. The effervescent pharmaceutical composition as claimed in claims 1 to 10 wherein the drug Nimesulide is present in micronized form having average particle size of less than 5 microns.

12. The effervescent pharmaceutical composition as claimed in claims 1 to 11 wherein in addition, one or more conventional pharmaceutical aids like wetting agents, flavouring agents, sweetening agents, binders, suspending agents, fillers, lubricants and colouring agents, as herein described, are added to the composition.

13. The effervescent pharmaceutical composition as claimed in claims 1 to 12 which is in the form of tablets.

14. The effervescent pharmaceutical composition as claimed in claims 1 to 13 which is not required to be heated to remove the residual moisture after compression into tablets or before packaging.

15. The effervescent pharmaceutical composition substantially as herein described and illustrated by the Example here.