Abstract:
The present invention relates to liquid formulation of biologically active compound having one or more carboxylic acid groups such as analogues and in particular NSAIDs such as ibuprofen. An organic monocarboxylic acid is used to create interactions that generate a soluble formulation that remains homogenously stable, with substantially no crystallization of the biologically active compound at high concentration for a suitable period of time. The formulation can be used as filling solution for gelatin capsules or various pharmaceutical dosage forms such as syrup or cream, and in certain case, preparations for parenteral administration.
PHARMACEUTICAL SOLUTION FORMULATIONS FOR ENCAPSULATION INTO GELATIN CAPSULES OR OTHER DOSAGE FORMS

FIELDS OF THE INVENTION
The invention relates to a liquid pharmaceutical formulation of a therapeutically active agent, a pharmaceutical dosage form containing same and method for preparing a liquid pharmaceutical formulation.

BACKGROUND OF INVENTION
Many currently marketed drugs, including Non-steroidal anti-inflammatory drugs (NSAIDs), may show various unpleasant effects such as a burning sensation, a bitter taste and aftertaste, and/or an adverse mouth feel when taken orally. NSAIDs such as ibuprofen, naproxen and aspirin (acetyl salicylic acid) have been widely prescribed by physicians in the treatment of pains. These drugs are in general tolerated well by most patients and provide an effective means for control of pain and inflammatory processes, particularly for the rheumatoid arthritis and osteoarthritis patients.

Furthermore, some of these drugs may have a low degree of bioavailability due to their low solubility in gastro-intestinal medium. For example, ibuprofen is a white powder or crystal which is practically insoluble in water. Ibuprofen is absorbed from the gastro-intestinal tract and the peak plasma concentrations occur approximately one to two hours after ingestion of the solid powder or crystal form. A standard dosage form widely in use for the delivery of ibuprofen is the solid dosage form or tablet, which displays a relatively long time to reach the peak plasma concentration because of two significant factors. The first factor is that the tablet needs to dissolve before to be absorbed and the second factor is that absorption is delayed because ibuprofen is practically insoluble in water or the acidic environment of the stomach (Rouffer, US 6,221,391).
Generally, active ingredients with a bitter taste have been the subject of numerous studies in order to formulate stable compositions with the prevention of the bitterness and the quick-activeness.

One member of the class of compounds known as derivative of propionic acid is ibuprofen, namely 2-(4-isobutylphenyl) propionic acid which is an analgesic, anti-inflammatory and anti-pyretic compound. Ibuprofen is a white powder or crystal sparingly soluble in water, has a very bitter taste (Haas, US Pat. No. 4,859,704; Ramachandran et al., US patent application publication 2003/0232097). This medicament is used for the treatment of painful and anti-inflammatory disorders including rhumatoid arthritis, osteoarthritis, post-operative pain, etc. Generally, ibuprofen is administered at doses of up to 3200 mg per day.

In the oral suspensions of bitter active ingredient already described in the literature, the active ingredient is coated with a lipid substance, either directly or after incorporation into a core. The lipid substances used are, for example, a partially hydrogenated vegetable oil, stearic acid and/or palmitic acid, glyceryl tripalmitate, etc. (EP 664 701). The active ingredient is also coated with a polymer intended to mask its bitter taste. This polymer is for example a methacrylic acid copolymer (EP 524 180), a cellulose acetate phthalate (WO 95/05166) or a vinyl acetal (JP 91/83922).

Peck et al. (U.S. 4,316,580) described a pharmaceutical liquid composition of the aluminium salt of ibuprofen comprising of microcrystalline cellulose, sodium carboxymethyl cellulose, magnesium aluminium silicate powder and sucrose, fructose, glucose or mixture thereof.

Gregory et al. (U.S. 5,262,179) describes effervescent water soluble composition of ibuprofen salt in which unpleasant taste of salt is masked by the taste masking agent, comprising an alkali metal carbonate, alkali metal monohydrogen phosphate or alkali metal tribasic citrate.
Suspension of ibuprofen for the encapsulation in the gelatin capsule has also been described in the literature. Since the dosage form is generally swallowed, it is unnecessary to flavor or otherwise mask any unpleasant taste of the active pharmaceutical ingredients. Furthermore, the patient compliance is improved if soft gelatin capsule is used for drug administration, because of its soft, and has an elastic character making it easier to swallow compared to conventional tablets or hard gelatin capsules. Finally, unlike tablets, soft gelatin capsules do not chip or powder (US patent application publication 2003/0232097).

In general, not all liquids are suitable as vehicles or carriers for inclusion in gelatin capsules. In example, certain compounds such as water, propylene glycol, glycerol, alcohols, ketones and esters, etc. can't be used as a carrier in gelatin capsules since they interact with the gel, and can change the mechanical properties of gelatin capsules. Generally, these compounds, if present, can only represent a relatively small amount (US patent application publication 2003/0232097).

Another limitation associated with gelatin capsules is the ability to incorporate a single dose of the pharmaceutically active ingredient in solution in an acceptable fill volume. Often, it is difficult to dissolve the pharmaceutically active ingredient in a volume of solvent small enough to produce a gelatin capsule, which delivers the desired dosage amount, is economically appropriate and comfortable to ingest by the patient. Developing solvent systems for pharmaceutically active ingredients that neither significantly interacts with the active ingredient nor the gelatin capsule casing it self, has proven a difficult art (US patent application publication 2003/0232079).

Radhakrishnan et al. (US patent application publication 2003/0232097) describe an oily wax matrix pharmaceutical suspension for encapsulation in gelatin capsules in embedding the active ingredient (i.e. Ibuprofen) in an oily wax (i.e. mixture of soybean oil and beeswax) which is blended with a surfactant (i.e. lecithin).
Hu et al. (US patent application publication 2005/0137262) describe ibuprofen liquid composition comprising potassium ibuprofen, water and alcohol for which is suitable for use as liquid-filled soft gelatin capsules.

Kato et al (US patent application publication 2003/0187070) describe a fill liquid composition for capsules which is produced by mixing ibuprofen, polyethylene glycol, water and terpenoid selected from menthol, limonene, borneol, etc.

Guillapalli (US 4,859,704) describes a formulation including polyethylene glycol, polyvinylpyrrolidone and alpha-tocopherol.

As indicated by Kato et al. (U.S. patent application publication 2003/ 0187070) in the ibuprofen preparations, the surfactant agents (i.e. lecithin, miglyol, polyoxyethylene sorbitan mono-oleate, etc.) were considered as an indispensable component, so that the softening of the capsule is jeopardized because of the interaction of the surfactant with the capsule membrane. Moreover, there has been consistent reports in the literature that the addition of solubilizer agent such as propylene glycol, ethylene glycol and glycerol (U.S. patent application publication 2003/ 0187070), of thickening (viscosity) agent including xanthan gum, hydroxypropylmethyl cellulose (U.S. patent application publication 2003/ 0187070), of complexing agents comprising polyvinyl pyrrolidone (US 6,221,391), and certain terpenoids such as menthol, limonene, borneol, etc. (Kato et al., US patent application publication 2003/0187070) were necessary to stabilize the ibuprofen suspension.

Therefore, formulations previously described in the literature requires, in addition to an active ingredient, a solvent (e.g. alcohol) a liposoluble (e.g. soybean oil) or hydrosoluble (e.g. polyethylene glycol) suspending agents, emulsifying agents or surfactants (e.g. Tween), a thickening agent (e.g. Carbomer) and in the certain cases, terpenoids (e.g. menthol).
SUMMARY OF INVENTION
In one aspect, there is provided a liquid pharmaceutical formulation comprising:
- a therapeutically active agent having at least one carboxylic acid group or its salt thereof;
- an organic monocarboxylic acid or its salt thereof; and
- a suspending agent;
wherein said organic monocarboxylic acid or its salt is present in an amount suitable to produce the formulation having substantially no visible precipitated or crystallized therapeutically active agent.

In another aspect, there is provided a method for preparing a liquid pharmaceutical formulation of a therapeutically active agent comprising:
i) mixing the therapeutically active agent with a suspending agent until substantial dispersion is achieved;
ii) mixing a suitable amount of an organic monocarboxylic acid or its salt thereof with the mixture obtained from step i),
or
i') mixing a suitable amount of an organic monocarboxylic acid or its salt thereof with a suspending agent until substantial dispersion is achieved;
ii') mixing the therapeutically active agent with the mixture obtained from step i'),
to obtain the liquid pharmaceutical formulation having substantially no visible precipitated or crystallized therapeutically active agent.

In a further aspect, there is provided a pharmaceutical dosage form comprising a liquid pharmaceutical formulation as defined herein.

BRIEF DESCRIPTION OF THE DRAWINGS
Having thus generally described the nature of the invention, reference will now be made to the accompanying drawing and in which:

Fig. 1 is a FTIR spectra of three mixtures of ibuprofen/ sodium acetate, as well as FTIR spectra of ibuprofen, acetic acid and sodium acetate.
DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the invention, there is provided a liquid pharmaceutical formulation for a therapeutically active agent having at least one carboxylic acid group or its salt.

Without being bound to theory, it is believed that the carboxylic acid group of the therapeutically active agent can associate with the carboxylic acid group of an organic monocarboxylic acid or its salt thereof (e.g. acetic acid or sodium acetate) via dipole-dipole attraction and others polar interactions generating a complex «active agent / organic monocarboxylic acid» which has increased solubility is soluble in a suitable suspending agent without substantially precipitating crystals of the active agent.

The therapeutically active agent advantageously used in the present invention is not particularly limited; however they must possess at least one carboxylic acid group or its corresponding carboxylate salt. Therapeutically active agents having more than one carboxylic acid group are also contemplated within the scope of the invention. The carboxylate salts of those active agents are also contemplated as useful active agent in the present invention. Esters, amides or other derivatives preventing the carboxylic (or carboxylate) function from interacting with the organic monocarboxylic acid and may not benefit from the solubility increasing effect of organic monocarboxylic acid. Example of classes of those therapeutically active agents includes NSAIDs and certain antibiotics.

Non limiting examples of NSAIDs for use, as the active agent having at least a free carboxylic acid group (either as a single agent or as a mixture of active agents), in the pharmaceutical formulation, dosage forms and processes of the present invention include the following categories:

The acetic acid derivatives:
Indomethacin, Sulindac, Diclofenac, Fenclofenac, Bromfenac, Ibufenac, Aceclofenac, Tolmetin, Zomepirac, Nabumetone, Oxaprofen, Acemetacin, Fentiazac, Clidanac, Etodolac, Oxpimac, Acetyl salicylic acid, or their salts.

The propionic acid derivatives
Ibuprofen, Naproxen, Ketoprofen, Fenoprofen, Indoprofen, Carprofen, Pranoprofen, Tioxaprofen, Alminoprofen, Flurprofen, Benoxaprofen, Fenbufen, Flurbiprofen, Pirprofen, Oxaprofen, Miroprofen, Suprofen, Tiaprofenic acid, Bucloxic acid, Loxoprofen, or their salts.

The fenamic acid derivatives:
Meclofenamic acid, Flufenamic (Nifluminic) acid, Tolfenamic acid or their salts.

The biphenyl carboxylic acid derivatives:
Diflunisal, Flufenisal or their salts.

Further examples of active agents suitable for use in the present invention include certain antibiotic derived from penicillanic acid:
Penicillin, Carbenicillin, Ampicillin, Cephalosporin, Ceftriaxone, Amoxicillin, Imipenem, Clavulanate, Carbapenem, Para-aminosalicylic acid.

Organic monocarboxylic acid or its salt suitable for use in the present invention includes without limitation those having a non polar acyl chain (lipophile) such as acetic acid (pKa 4.76), propanoic acid (pKa 4.87), butanoic acid (pKa 4.82), etc. or a polar acyl chain such as lactic acid (pKa 3.86), glycolic acid (pKa 3.83), pyruvic acid (pKa 2.49), etc. These organic acids are accepted by the U.S. Food and Drug Administration (FDA) and often used in food preservation with no limitation as generally recognized as safe (GRAS). Short chain acyclic acids having 8 carbon atoms or less or a mixture of those, such as formic acid, pyruvic acid, gluconic acid, ascorbic acid, caprylic acid, caproic acid, sorbic acid and their salts and derivatives, are also suitable. Organic polycarboxylic acid compounds (i.e. those with more than one -COOH groups) are susceptible to
cause crystallization of the active agents in the formulation and may not be useful as solubility increasing agent in the formulation.

In accordance with the invention, for the pharmaceutical formulation, one of the therapeutically active agent or the organic monocarboxylic acid is provided as its salt while the other is provided as carboxylic acid. More preferably, the pharmaceutical formulation is provided using a therapeutically active agent as its carboxylic acid and an organic monocarboxylic acid salt. More preferably, the organic monocarboxylic acid salt is an alkali salt such as sodium or potassium and their mixtures thereof. Most preferably, the organic monocarboxylic acid salt is a salt of sodium or potassium of acetic acid or propionic acid and their mixtures thereof.

In a general manner, the organic monocarboxylic acid may be described by formula

\[
\text{RCOO}_2^X
\]

in which \( R \) is an alkyl, and \( X_2 \) is a hydrogen atom or an alkali salt. In one embodiment, \( R \) is an alkyl of 1 to 7 carbon atoms, preferably of 1 to 6 carbon atoms and more preferably 1 or 2 carbon atoms, the alkyl being optionally substituted with a hydroxyl or an oxo group. In one embodiment \( X_2 \) is a hydrogen, a sodium of potassium salt.

The term «suspending agent» described here is used as a means a pharmaceutically acceptable diluent miscible or dissolvable material that yields a clear suspension or solution for the complex drug/acid. According to the nature of active agent, the suitable suspending agent could be a hydrophobic compound. Suitable suspending agent include vegetal oil such as Coconut oil, Corn oil, Cottonseed oil, canola oil, Olive oil, Palm oil, Peanut oil, Safflower oil, Sesame
oil, Soybean oil, or Sunflower oil, preferably canola oil; mineral oil, mint natural oil or compounds including polyalkylene glycol such as polyethylene glycol (PEG), polypropylene glycol (PPG) and glycerol.

A preferred polyalkylene glycol is PEG. Polyethylene glycols are soluble in water and many organic solvents. These polymers correspond to the general formula: \( H(OCH_2CH_2)_nOH \) preferably having an average molecular weight between about 200 to 800, and most preferably having an average molecular weight between about 400-600. The polyethylene glycols useful herein are those which are liquids at room temperature or have a melting point slightly thereabove. Moreover, mixtures of two or more polyethylene glycols of different average molecular weight range or \( n \) value can also be employed in the present invention. Liquid and low-melting polyethylene glycols are commercially available from various sources.

The term "alkyl" represents a linear or branched hydrocarbon moiety having 1 to 7 carbon atoms preferably 1 to 3 carbon atoms. The alkyl may have one or more unsaturations in the chain, preferably one or two and is optionally substituted by an oxo (in which two hydrogen of the chain are replaced by a = O group), or hydroxyl. The term alkyl is also meant to include alkyls in which one or more hydrogen atom is replaced by a halogen, i.e. an alkylhalide. The term alkyl may also mean cyclic alkyls including for example cyclopropyl and cyclohexyl.

In the present invention, the use of the surfactant agent, thickening agent, polysaccharides or terpenoid are not necessary to increase solubility of the active agent and its homogeneous stability in the formulation. Also, the addition of solvent such as ethanol or complexing agent such as PVP, previously used in the art to increase solubility of an active agent, is not necessary to increase solubility of the active agent and its homogeneous stability in the formulation of the present invention.

Generally, the liquid formulation is comprising:
i) about 20-90% wt combined amount of therapeutically active agent and organic monocarboxylic acid or its salt; and

ii) about 10-80% wt suspending agent.

The amount of the organic monocarboxylic acid or its salt with regard to the amount of therapeutically active agent must be an amount suitable to produce the formulation having substantially no visible precipitated or crystallized therapeutically active agent for a suitable period of time at a storage temperature. Typical storage temperature is from room temperature (about 22°C) to about 0°C. The suitable period of time during which substantially no visible precipitated or crystallized therapeutically active agent is produced in the formulation is not particularly limited and depends on the required or desired shelf life. It may vary generally from months to years.

The amount of organic monocarboxylic acid or its salt that can be used may vary depending on the nature of the therapeutically active agent, however when the active agent has one carboxylic acid group, the molar ratio is more than about 1 : 8 (organic monocarboxylic acid : therapeutically active agent), preferably about 1 : 6, alternatively about 1 : 4 and more preferably about 2 : 5. Typical ranges include from more than about 1 : 8 to about 1 : 1, preferably about 1 : 6 to about 2 : 5.

When the active agent contains more than one carboxylic acid group, the molar ratio should be adjusted accordingly. For instance, an active agent possessing two carboxylic acid groups, should have a molar ratio of more than about 2 : 8 (organic monocarboxylic acid : therapeutically active agent). The molar ratio could be changed in the case that therapeutic agent is a polycarboxylic acids.

Furthermore, the active agent concentration in the formulation, in certain case, could reach up to 80 wt% of the total weight of the formulation without visible precipitation or crystallization. In certain cases (e.g. ibuprofen) up to 90 wt% can
be reached if required. In one embodiment, the liquid formulation as comprises about 20%, 40%, 60% or 80% wt of the therapeutically active agent; and the molar ratio of said organic monocarboxylic acid or its salt with regard to therapeutically active agent is about 2:5. Moreover, the composition remained homogenously stable at various temperatures (-10 to 22 °C) and different pH values (3-10).

When using a formulation in accordance with the present invention, the active agent is likely to remain soluble in acidic media, particularly in gastric acid, so that the active agent is quickly released which can favor the resorption.

Another advantage of using the organic monocarboxylic acids or their salts is for their antibacterial and antifungal effects. For example, sodium propionate is one of the food preservatives that used alone or in combination with other agents as a preservative to inhibit mold production in bakery, dairy products or other foods and in pharmaceuticals. It is also used as a topical antifungal in the treatment of various mycoses. Consequently, the addition of the preservatives, in the certain case, is not necessary.

A feature of this invention is that the therapeutically active agent possesses at least a free carboxylic group which can be protonated (acid form) or non-protonated (salt form). As mentioned previously by Yu et al. (US 5,071,643), the pH value of filling liquid used to encapsulate into gelatin capsules should not be below 2.5 or above 7.5 due to the gelatin hydrolysis causing leakage. For this purpose, in the case of active agent having protonated carboxylic groups (acid form), the organic monocarboxylic acid is preferably used under salt form (potassium acetate, sodium propionate, sodium gluconate, etc.) and vice versa for the active agent possessing non-protonated carboxylic group, the stabilizer is preferably in acidic form (acetic acid, propionic acid, gluconic acid, etc.).

Without being bound to theory, it is believed that for example, when the sodium acetate was added in the salicylic solution, there is initially a phenomenon of
protonation (proton coming from salicylic acid) converting a part of acetate in acetic acid (which can interact with salicylic acid via dipole-dipole attractions as hypothesized previously). The remaining part is comprised the salt form which could be interacted by other polar interactions. In this case, the addition of acetate was permitted not only to increase the pH value in acceptable range, but also use as stabilizer. Generally, the pH final values of solution could be varied between of 3-7 which are compatible with the gelatin capsules. Good results were obtained when the molar ratios of active agent and organic monocarboxylic acid are as described herein.

The liquid formulation of the instant invention can also combine with one or more additional therapeutically active agents. Useful classes of additional therapeutically active agents include antipyretics, expectorants, decongestants and antitussives. Examples include, but are not limited to dextromethorphan and its salts such as dextromethorphan hydrobromide, pseudoephedrine and its salts such as pseudoephedrine hydrochloride, phenylephrine and its salts such as phenylephrine hydrochloride, diphenhydramine and it salts such as diphenhydramine hydrochloride, chlorpheniramine and its salts such as chlorpheniramine maleate, and their mixtures thereof. Those additional therapeutically active agents can be added at either of the preparation process steps.

The formulation of the present invention can be encapsulated within any conventional soft gelatin shell that is capable of supporting the formulation for a suitable period of time. The soft gelatin shells can be prepared according to methods known in the art by combining appropriate amounts of gelatin, water, plasticizer, and any optional components. This soft gelatin shell preparation can then be used for encapsulating the formulation of the present invention employing standard encapsulation methodology to produce one-piece soft gelatin capsules.
The size and strength of soft gelatine capsules comprising the formulation of the present invention may vary. This allows for sufficient flexibility to provide the dosage/ strength required. For example, a soft capsule that can accept about a gram (of roughly 1ml) of an approximately 40% wt ibuprofen formulation (which is about 400mg d'Ibuprofen per gram of solution) contains about 400mg ibuprofen/capsule. Alternatively, similar capsule filled up with a 80% wt ibuprofen formulation will provide a 800mg/ capsule.

In one embodiment, there is provided a liquid pharmaceutical formulation comprising ibuprofen; an organic monocarboxylic acid or its salt selected from sodium acetate, potassium acetate, sodium propionate and potassium propionate; and canola oil; wherein the molar ratio of said organic monocarboxylic acid or its salt with regard to ibuprofen is more than about 1 : 8. Preferably, the molar ratio is at least about 1 : 6, alternatively at least about 1 : 4, preferably about 1 : 4, more preferably about 2:5. Typical ranges include from more than about 1 : 8 to about 1 : 1, preferably about 1 : 4 to about 2 : 5. In one embodiment, the formulation comprises about 20 to 90% wt combined amount of ibuprofen and about 10 to 80% wt of the organic monocarboxylic acid.

In one embodiment, there is provided a method for preparing a liquid pharmaceutical formulation of therapeutically active agent comprising: i) mixing the therapeutically active agent with a suspending agent until substantial dispersion is achieved; ii) mixing a suitable amount of an organic monocarboxylic acid or its salt thereof with the mixture obtained from step i) or i') mixing a suitable amount of an organic monocarboxylic acid or its salt thereof with a suspending agent until substantial dispersion is achieved; and ii') mixing the therapeutically active agent with the mixture obtained from step i'), to obtain the liquid pharmaceutical formulation having substantially no visible precipitated or crystallized therapeutically active agent.

Optionally, flavoring, coloring and preservative agents can be added to the formulation obtained previously at either of the preparation process steps to
improve appearance, patient comfort and compliance. As well the pH of the formulation can be adjusted at either of the process steps (using pH adjusting agents such as HCl or NaOH or KOH) to improve compatibility with the dosage formulation used (e.g. soft gel capsule wall, container ect.)

Optionally, it is possible to use polar suspending agents such as Propylene glycol, Glycerol, Sorbitol, etc. or their mixtures thereof, however smaller quantities are required.

The liquid pharmaceutical formulation of the invention may advantageously be presented in various pharmaceutical dosage form known in the art including an oral dosage form selected from i) a soft gelatin shell comprising the liquid formulation, wherein said gelatin shell is compatible with said liquid formulation and ii) syrup. The pharmaceutical dosage form may also advantageously be a topical dosage form.

In one embodiment, there is provided an oral pharmaceutical dosage form comprising a) a liquid pharmaceutical formulation comprising a therapeutically active agent having at least one carboxylic acid group or its salt thereof; an organic monocarboxylic acid or its salt thereof; and a suspending agent; wherein said organic monocarboxylic acid or its salt in an amount suitable to produce the formulation having substantially no visible precipitated or crystallized therapeutically active agent; b) a soft gelatin shell comprising the liquid formulation a), said gelatin shell being compatible with said liquid formulation.

In a preferred embodiment, the soft gelatin shell is comprising a liquid pharmaceutical formulation comprising a therapeutically active agent that is ibuprofen, an organic monocarboxylic acid salt selected from sodium acetate, potassium acetate, sodium propionate, potassium propionate and a mixture thereof, and a suspending agent that is canola oil; wherein the molar ratio of said organic monocarboxylic acid salt with regard to therapeutically active agent is more than about 1 : 8;
Below are examples illustrating several compositions along with several examples of NSAIDs formulations made in accordance with the present invention. The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the specification, including the claims, in any way.

EXAMPLES

As used in the following examples, the following ingredients/ reagents were obtained from commercial sources: Ibuprofen: ALBEMARLE Corporation, Orangeburg, South Carolina (USA); Sodium Acetate: SIGMA-ALDRICH, Inc., St Louis, MO (USA); Canola oil: SOBEYS, Missisauga, Ontario (Canada); PEG 400: FLUKA (Ph Eur, 400), Sigma-Aldrich Canada, Ltd. Oakville ON. CANADA.

Example 1 - Oily formulation for Ibuprofen: Formulation for 200 mg/g of solution

The formulation was prepared by heating 76.5g of canola oil to 60-70°C and an amount of 20.0g of ibuprofen was added under mild stirring until complete dispersion. Thereafter, an amount of 3.5g of sodium or potassium acetate was slowly added, as a solid, to the solution. The mixture was continued to be stirred at the same temperature during at least one hour.

The sodium acetate/propionate could be equally prepared by dissolving in a minimum quantity of water just prior to add in the ibuprofen-oil solution. For example, 3g sodium acetate was dissolved in 6-8ml water, 3g sodium propionate was dissolved in 4-6ml water. In this case, the mixture became slightly turbid. The mixture was continued to be stirred and heated up to 90-95°C at least one hour or until the solution was clear (i.e. evaporation of water).
The evaluation of stability was performed by visually observing of the appearance of the solution immediately after production and after storage at various temperatures (-10-60°C) at different pH values (3 to 10) during 2 weeks. No change of the solutions appearance (no visible precipitation or crystallization) at various temperatures and at different pH values occurred. A solution of ibuprofen was prepared at the desired concentration with the required amount of organic monocarboxylic acid or its salt. The pH was then adjusted in the range of 3 to 10 using HCl or NaOH (or KOH) while the mixture is heated. The resulting mixtures were then left standing at various temperatures (-10, 0, 4, 10 and 22°C). An assessment of the formulation was made every 4 hours during the first 24 hours and then daily for one to two weeks.

It was observed that it is equally possible to dissolve large amounts of ibuprofen (acid form) in canola oil without addition of organic monocarboxylic acid using a process as described above at an elevated temperature; however, crystallization occurred upon cooling of the solution to ambient temperature. Similar phenomenon was observed for the formulations prepared from ibuprofen sodium or potassium salt form into canola oil. This demonstrated the requirement for a suitable organic monocarboxylic acid.

Example 2- Oily formulation for ibuprofen at high concentrations

Similarly, ibuprofen solutions at high concentrations were prepared as described previously in example 1. Indeed, various quantities of 40, 60, and 80g of ibuprofen were introduced in to 55, 32 and 10g of heated canola oil, respectively. Then, suitable sodium acetate amount (5-10g respectively for a total to 100g) was added in corresponding solution.

A control was carried out for each concentration (10-80%) of ibuprofen described above, but in absence of organic monocarboxylic acid (i.e. without sodium acetate). The formation of crystals in these control solutions was observed after 24 h at 4.0°C for concentrations of ibuprofen >20% and after 48-72h at the same temperature for concentrations between 10-20%. In contrast, no precipitate of
crystal was observed for those in presence the organic monocarboxylic acid (i.e. with sodium acetate).

Example 3 - Formulation of ibuprofen in polar medium

The formulation was prepared as described previously for oily formulation, but instead of canola oil, polyethylene glycol (PEG) 400 was used. An amount of 40.0g of ibuprofen was dispersed in 54.0g of PEG 400 which was heated to 70-80°C. When the ibuprofen was completely dispersed, an amount about of 4.0-6.0g of sodium propionate was slowly added and the mixture was continued to be stirred and heated up to 90-95°C during at least 2 hours. A formulation control (without sodium propionate) was equally prepared.

Stability tests of the ibuprofen formulations with sodium propionate showed no visual signs of precipitate or crystals after 2 weeks as described in example 1 at varied pH values and temperatures (0, 10 et 22°C). whereas the control solutions (without sodium propionate) were precipitated with formation crystals from a concentration 20% after 24 h, at 4.0°C. Additionally, the formulations prepared from potassium or sodium ibuprofen were presented the similar phenomenon in the acid solutions at pH values inferior to 3.8. Consequently, the active agent into these compositions is possibly recrystallized in the gastric fluids (pH 1.5) which decrease the quick assimilability.

In order to demonstrate the stabilization of the complex via dipolar interactions, a suitable quantity of copper chloride (CuCb) was added in the ibuprofen preparations. Only the solutions containing of acetate or propionate remain stable, whereas the others are crystallized resulting blue precipitates after a few hours. These results indicate that there are probably interactions between the carboxyl groups of ibuprofen and acetic acid (formed by protonation of acetate) which are not available to complex the copper, as observed by previous study (Trinchero, A., Bonora, S., Tinti, A., Fini, G. 2004. Spectroscopic Behavior of Copper Complexes of Nonsteroidal Anti-Inflammatory Drugs. Biopolymers, 74, 120-124).
Furthermore, FTIR spectra analysis permitted to highlight these interactions as shown in Fig. 1. The various ratios are expressed as weight ratio (w/w) of ibuprofen and sodium acetate. The FTIR spectra shows from top to bottom: a) ibuprofen/ sodium acetate (20/3), b) ibuprofen/ sodium acetate (20/2), c) ibuprofen/ sodium acetate (20/1), d) ibuprofen, e) acetic acid and f) sodium acetate respectively. In fact, pure ibuprofen show mainly a strong carbonyl (C=O) band at 1710 cm⁻¹, which assigns to the carboxylic group (COOH) of ibuprofen. Other smaller bands in the region 1200-1000 cm⁻¹ are contributions from the benzene ring (Socrates, G. 1994. Infrared Characteristic Groups Frequencies. Tables and Charts, 2nd ed., Wiley, New York). In presence of the acetate, the intensity of carbonyl band was decreased and shifted to low wavenumber from 1710 to 1685 cm⁻¹. Furthermore, at the high concentrations of acetate, a new band located at 1593 cm⁻¹ was noticed. It is of interest to mention that the FTIR spectrum of sodium acetate was characterized by absorption bands of carboxylate group located at 1560 and 1407 cm⁻¹, whereas carboxylic group absorption bands of acetic acid were located at 1707 and 1405 cm⁻¹. These distinct changes suggest the formation of complex via dipole-dipole attractions or other polar associations, which agree with previous findings (Azzouz, A.S.P. and Al-Niemi, M.M.H. 2005. Study on association of substituted benzoic acids and other acids by physical methods. Effect of temperature and structure of acids on association process. Zeitschrift für Physikalische Chemie, 219, 1591-1608).

Example 4 - Others formulations based medicines derivatized acids

4-1- Formulation of acetic acid derivatives (salicylic acid).
An amount of 40g of salicylic acid was introduced in 54g of PEG 400 heated at 70-80°C. When the dispersion of salicylic acid was complete, an amount of 4.0-6.0g of sodium acetate was slowly added under stirring and heating at the same temperature for a period between 2-4h.

Others acetic acid derivatives.
Other derivatives (i.e. naproxen, fenbufen, fenoprofen, sulindac, indomethacine, diclofenac, etc.) were obtained by using the same procedure described previously in example 4-1 above.

Although it is possible to prepare exceptionally high concentration of the active agents described herein, it is worth to mention that the highest concentration formulations of certain active agent should take account of their maximum tolerated doses described in the literature to avoid toxicity (e.g. risks of heart failure).

According to Huerta et al. (Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population - Cardiovascular Medicin. Heart, 2006, 92, 1610-1615), for example, it is generally recognized that the following doses may present risks: indomethacin >75mg, diclofenac >100mg, flurbiprofen >150mg, sulindac >200 mg.

4-2 Formulation of biphenyl carboxylic acid derivatives
The solution of biphenyl carboxylic acid derivatives was prepared as described in example 3, but instead of ibuprofen, it was replaced by diflunisal or flufenisal.

4-3 Formulation of penicillanic acid derivatives
The solution of penicillanic acid derivative was prepared as described in example 3, but instead of ibuprofen, it was replaced by amoxicillin.

Example 5 - Combination of NSAIDs liquid with other therapeutic agents for encapsulation into gelatin capsules

5-1 Formulation of ibuprofen (200 mg/g) with pseudoephedrine (30 mg/g)

The ibuprofen solution (20.0 %) was prepared as described previously in example 3. Practically, an amount of 20.0 g of ibuprofen was dispersed into
solution at 60°C containing 67.0g of PEG 400 and 3.0g of sodium acetate. The mixture was continued to stir and heated up to 95°C during at least 2h. In parallel, an amount of 3.0g of pseudoephedrine hydrochloride was gradually dispersed in 7.0g of glycerol. When the pseudoephedrine solution was homogenized, this was slowly added in the ibuprofen solution and was cooled to room temperature.

5-2 Formulation of ibuprofen (200 mg/g) with phenylephrine (10 mg/q)

The formulation was prepared as described above in example 5-1, but 1.0g of phenylephrine hydrochloride was added into the glycerol (4.0-5.0g) instead of pseudoephedrine hydrochloride. The PEG 400 was used to complete at 100g of solution.

5-3 Formulation of ibuprofen (200mg/g) with pseudoephedrine (30mg/q) and dextromethorphan (10.0mg/g)

The formulation was prepared as described above in example 5-1, but 1.0g of dextromethorphan hydrobromide was added at the same time of pseudoephedrine hydrochloride into the glycerol.

Example 6- Liquid ibuprofen syrup (400 mg/5 ml or one teaspoon)

The stabilized liquid ibuprofen syrup was prepared by dispersing 8.0 g of ibuprofen in 52.0g of PEG 400 heating at about of 70-80°C. When the solution was homogenized, an amount of 1.2g of sodium propionate (or acetate) was added and the mixture was continued to stir and heated at the same temperature during at least 1-2h. Thereafter, quantities of 30g of glycerol, 2.0g of sucralose and others ingredients such as citrus lemon flavor (2.0mL), dye (0.05-0.1g) and preservatives (0.05-0.1) were added. The distilled water could be used to complete the volume of solution at 100mL.
Example 7 - Liquid ibuprofen using in other formulation: topical preparation

Preparation of alginate-based cream
The cream was prepared by dispersing 3g of alginate and 3g of glycerol in 37g of purified water at 70°C. In parallel, an amount of 8.0g of Polawax™ and 4.0g of stearic acid were heated at 70°C. Thereafter, the polawax and stearic acid mixture were added in the alginate solution at the same temperature with strong agitation until a uniform suspension.

Preparation of ibuprofen solution
The ibuprofen solution was prepared as described previously in example 1 (200mg/g)

The ibuprofen cream was obtained after addition of 45mL of ibuprofen solution into the cream suspensions with moderate agitation. The addition of Tween is optional to obtain the desired texture and the obtained cream was cooled to room temperature until a uniform suspension.

Example 8 - High concentration liquid ibuprofen formulation.
To prepare a high concentration ibuprofen formulation, 90g of ibuprofen was added to 10ml of ethanol and 5g of mineral oil and the mixture heated to 70°C. Once homogenized, 5g of sodium acetate was added to the mixture followed by heating for 1-2 hours at 95 to 100°C to remove essentially all ethanol. The resulting formulation remained stable (i.e. no visible precipitation or crystallization) once cooled down to room temperature.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary
practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claim. All of the references, either as patent documents or other publications, cited above are herein incorporated by reference.
Claims
1. A liquid pharmaceutical formulation comprising:
- a therapeutically active agent having at least one carboxylic acid group or its salt thereof;
- an organic monocarboxylic acid or its salt thereof; and
- a suspending agent;
wherein said organic monocarboxylic acid or its salt is present in an amount suitable to produce the formulation having substantially no visible precipitated or crystallized therapeutically active agent.

2. The formulation of claim 1, wherein said therapeutically active agent is a NSAID or an antibiotic.

3. The formulation of claim 1, wherein said therapeutically active agent is a NSAID selected from the group acetic acid derivatives, propionic acid derivatives, fenamic acid derivatives and biphenyl carboxylic acid derivatives.

4. The formulation of claim 1, wherein said therapeutically active agent is indomethacin, sulindac, diclofenac, fenclofenac, bromfenac, ibufenac, aceclofenac, tolmetin, zomepirac, nabumetone, oxaprofen, acemetacin, fentiazac, clidanac, etodolac, oxpimac, acetyl salicylic acid, or a mixture or their salts thereof.

5. The formulation of claim 1, wherein said therapeutically active agent is ibuprofen, naproxen, ketoprofen, fenoprofen, indoprofen, carprofen, pranoprofen, tioxaprofen, alminoprofen, flurprofen, benoxaprofen, fenbufen, flurbiprofen, pirprofen, oxaprofen, miroprofen, suprofen, tiaprofenic acid, bucloxic acid, loxoprofen, or a mixture or their salts thereof.

6. The formulation of claim 1, wherein said therapeutically active agent is ibuprofen.
7. The formulation of claim 1, wherein said therapeutically active agent is meclofenamic acid, flufenamic acid, tolfenamic acid or a mixture or their salts thereof.

8. The formulation of any one of claims 1 to 7, wherein said organic monocarboxylic acid or its salt is an acyclic organic monocarboxylic acid having 8 carbon atoms or less, a salt or a mixture thereof.

9. The formulation of any one of claims 1 to 7, wherein said organic monocarboxylic acid or its salt is acetic acid, propanoic acid, butanoic acid, lactic acid, glycolic acid, pyruvic acid, formic acid, pyruvic acid, gluconic acid, ascorbic acid, caprylic acid, caproic acid, sorbic acid or their salts or a mixture thereof.

10. The formulation of any one of claims 1 to 7, wherein said organic monocarboxylic acid or its salt is a sodium or potassium salt of acetic acid or propionic acid or a mixture thereof.

11. The formulation of any one of claims 1 to 7, wherein said organic monocarboxylic acid or its salt has a formula

   \[
   \text{RCO}_2X_2
   \]

   wherein R is an alkyl, and X₂ is a hydrogen atom or an alkali salt.

12. The formulation of any one of claims 1 to 11, wherein said suspending agent is vegetal oil, mineral oil, or a polyalkylene glycol.

13. The formulation of any one of claims 1 to 11, wherein said suspending agent is selected from coconut oil, corn oil, cottonseed oil, canola oil, olive oil, palm oil, peanut oil, safflower oil, sesame oil, soybean oil, and sunflower oil.

14. The formulation of any one of claims 1 to 11, wherein said suspending agent is canola oil.
15. The formulation of any one of claims 1 to 11, wherein said suspending agent is polyethylene glycol or polypropylene glycol.

16. The formulation of any one of claims 1 to 11, wherein said suspending agent is polyethylene glycol.

17. A liquid pharmaceutical formulation comprising:
- a therapeutically active agent that is ibuprofen;
- an organic monocarboxylic acid salt selected from sodium acetate, potassium acetate, sodium propionate, potassium propionate and a mixture thereof; and
- a suspending agent that is canola oil;
wherein the molar ratio of said organic monocarboxylic acid salt with regard to therapeutically active agent is more than about 1:8.

18. The liquid formulation as defined in any one of claims 1 to 17, wherein the formulation comprise about 20 to 90% wt combined amount of therapeutically active agent and the organic monocarboxylic acid and 10 to 80% wt of suspending agent.

19. The liquid formulation as defined in claim 18, wherein the formulation comprise about 20%, 40%, 60% or 80% wt of the therapeutically active agent; and the molar ratio of said organic monocarboxylic acid or its salt with regard to therapeutically active agent is about 2:5.

20. The liquid formulation as defined in any one of claims 1 to 17, wherein, the molar ratio of said organic monocarboxylic acid or its salt with regard to therapeutically active agent is about 1:4.

21. The liquid formulation as defined in any one of claims 1 to 17, wherein, the molar ratio of said organic monocarboxylic acid or its salt with regard to ibuprofen is about 2:5.
22. The liquid formulation as defined in any one of claims 1 to 17, wherein, the molar ratio of said organic monocarboxylic acid or its salt with regard to ibuprofen is from more than about 1 : 8 to about 1 : 1.

23. The liquid formulation as defined in any one of claims 1 to 17, wherein, the molar ratio of said organic monocarboxylic acid or its salt with regard to ibuprofen is from about 1 : 4 to about 2 : 5.

24. The liquid formulation as defined in any one of claims 1 to 23, further comprising one or more additional therapeutically active agents selected from antipyretics, expectorants, decongestants and antitussives.

25. The liquid formulation as defined in any one of claims 1 to 24, further comprising a flavoring, a coloring agent, preservative agents and their mixtures thereof.

26. A method for preparing a liquid pharmaceutical formulation of a therapeutically active agent comprising:
   i) mixing the therapeutically active agent with a suspending agent until substantial dispersion is achieved;
   ii) mixing a suitable amount of an organic monocarboxylic acid or its salt thereof with the mixture obtained from step i),
   or
   i') mixing a suitable amount of an organic monocarboxylic acid or its salt thereof with a suspending agent until substantial dispersion is achieved;
   ii') mixing the therapeutically active agent with the mixture obtained from step i'),

to obtain the liquid pharmaceutical formulation having substantially no visible precipitated or crystallized therapeutically active agent.
27. The method as defined in claim 26, further comprising adding one or more additional therapeutically active agents selected from antipyretics, expectorants, decongestants and antitussives at one of steps i), ii), i') or ii').

28. The method as defined in claim 26 or 27, further comprising adding one or more agents selected from a flavoring, a coloring agent, preservative agents and their mixtures thereof at one of steps i), ii), i') or ii').

29. A pharmaceutical dosage form comprising a liquid pharmaceutical formulation as defined in any one of claims 1 to 25.

30. The pharmaceutical dosage form of claim 29, that is an oral dosage form selected from i) a soft gelatin shell comprising the liquid formulation, wherein said gelatin shell is compatible with said liquid formulation and ii) syrup.

31. The pharmaceutical dosage form of claim 29 that is a topical dosage form.

32. An oral pharmaceutical dosage form comprising
   a) a liquid pharmaceutical formulation comprising a therapeutically active agent that is ibuprofen, an organic monocarboxylic acid salt selected from sodium acetate, potassium acetate, sodium propionate, potassium propionate and a mixture thereof, and a suspending agent that is canola oil; wherein the molar ratio of said organic monocarboxylic acid salt with regard to therapeutically active agent is more than about 1:8;
   b) a soft gelatin shell comprising the liquid formulation a), said gelatin shell being compatible with said liquid formulation.
Fig. 1:
INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/002036

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61K 31/192 (2006.01), A61K 47/12 (2006.01), A61K 9/48 (2006.01), A61P 29/00 (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC: A61K 31, A61K 47/12 (2006.01), A61K 9/48 (2006.01), A61P 29/00 (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, Delphion, Scopus (organic monocarboxylic acid and related terms, NSATDs and related terms, antibiotics and related terms, oil, polyethylene glycol and related terms, soft gel capsules, solvent systems)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>1-12, 15-16, 18-30</td>
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<td>Y</td>
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents
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  "O" document referring to an oral disclosure, use, exhibition or other means
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  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "&" document member of the same patent family

Date of the actual completion of the international search
3 July 2007 (03-0702007)

Date of mailing of the international search report
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Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
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Gatineau, Quebec K1A 0C9
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TaniaNish 819-934-3592
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