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(54) **Title:** TASTE MASKING OF WATER SOLUBLE DRUGS USING POLOXAMERS

(57) **Abstract:** Use of poloxamers as taste masking agents of water-soluble drugs, wherein the water-soluble drug and poloxamer are in direct contact in granules.



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Taste masking of water soluble drugs using poloxamers

FIELD OF THE INVENTION

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The invention relates to taste-masked solid, semi-solid and liquid pharmaceutical formulations containing a water soluble drug and poloxamer, and a new use of poloxamers as taste masking agents for water-soluble drugs.

10 BACKGROUND OF THE INVENTION

Appropriate dosage form is one of the key factors of effective pharmacotherapy. Soluble or effervescent granules, orodispersible tablets, tablets for preparation of oral solutions and suspensions, liquid drug formulations (solutions, suspensions) allow for desirable patient compliance mainly among
15 paediatric and geriatric populations, where difficulties in swallowing are most common. Important limitation in development of such products is unacceptable (often bitter or salty) taste of numerous drugs. Different taste masking techniques have been described in literature; however they are usually effective only for selected drugs, many of which are used in low doses. Taste masking of bitter drugs might be achieved by different solutions. This is often used in orodispersible and chewable tablets, oral
20 suspensions and solutions. In order to suppress bitter taste of sumatriptan succinate, microspheres manufactured by spray-drying technique may be applied (Sheshala et al, 2011). Similar approach was also used in taste masking of donepezil hydrochloride and ondansetron hydrochloride; however Eudragit EPO (Yan et al. 2010) or Eudragit E 100 (Bora et al. 2008) was the taste masking component. Except from microspheres formation, complexation as a method of taste masking has been described
25 for metoclopramide (Randale et al. 2010) and metformin (Bhoyar, Amgaonkar 2011). Frequently also coating with soluble Eudragits is applied, e.g. for cetirizine hydrochloride (Douroumis et al. 2011).

Model drug:

30 Ibuprofen, (*RS*)-2-(4-(2-methylpropyl) phenyl)propanoic acid is a nonsteroidal anti-inflammatory drug (NSAID) used for its analgesic, antipyretic and anti-inflammatory effects mainly in relief of symptoms of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, fever, as an analgesic in mild to moderate pain, especially where there is an inflammatory component, vascular headache and dysmenorrhea. It is used in different pharmaceutical dosage forms (such as tablets, suppositories, oral suspensions)
35 both in adults and in paediatrics.

Most commonly Ibuprofen is used in pharmaceutical formulations in a form of free acid, which is poorly soluble in water (less than 1 mg/ml), thus for increasing solubility it can be used as a basic salt, namely ibuprofen lysinate.

Ibuprofen lysinate, the lysine salt of Ibuprofen, ($\pm$)-2-[4-(2-methylpropyl)phenyl]propanoic acid lysinate or ($\pm$)-Benzeneacetic acid, α -methyl-4-(2-methylpropyl) lysinate or ($\pm$)-p-Isobutylhydratropic acid lysinate or ($\pm$)-2-(p-Isobutylphenyl)propionic acid lysinate, is a nonsteroidal anti-inflammatory drug (NSAID) used for treatment of the same conditions as Ibuprofen. Ibuprofen lysinate is commercially available as racemic Ibuprofen lysinate. The main advantage of Ibuprofen lysinate is its superior solubility in neutral media (solubility in water 71 mg/ml) in comparison to the free acidic form, thus providing a fast absorption period from stomach and small intestine. However, due to improved solubility, Ibuprofen lysinate expresses even stronger bitter taste than ibuprofen.

Organoleptic properties are important considerations for development of oral dosage forms that can influence consumer compliance. In the case of bitter drugs, acceptable taste is one of the most important parameters assuring patient compliance.

Taste masking of ibuprofen and its lysinate salt is described in several patents/ patent applications.

US 2012101159 claims oral suspension with ibuprofen lysinate in which cyclodextrines are used as taste-masking compound.

SK 2932001 claims composition containing ibuprofen lysinate and cyclodextrines in a form of single dose sachets for dissolving in water.

US 5552152 describes masking of bitter taste of ibuprofen by fluid-bed coating technique.

US 5269179 claims taste masking of ibuprofen salts in aqueous solutions by incorporating in the solution alkali metal bicarbonate.

Poloxamers have been widely used as wetting and solubilizing agents, and surface adsorption excipients (Collett and Popli 2000). They have been employed to enhance the solubility, dissolution and bioavailability of many poorly water soluble drugs including ibuprofen using various techniques including melting agglomeration and melting (Passerini et al., 2002; Rouchotas et al., 2000; Seo et al., 2003). In formulations comprising ibuprofen or its derivatives, poloxamers are used as emulsifiers (KR 20120082061), solubility enhancing agents (US 2006013871) or binders (Newa et al. 2008).

Poloxamer 188 is suitable to prepare solid dispersions and to improve the solubility, absorption and bioavailability of low solubility active agents in solid oral dosage forms.

Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations, and are generally regarded as nontoxic and non-irritant materials which do not undergo metabolism in human body. Because of their amphiphilic structure, the polymers have surfactant properties that make them useful in industrial applications. Poloxamers are used in pharmaceutical technology mainly due to their amphiphilic properties allowing for solubility enhancement. No data on taste masking properties of these excipients has been published so far.

It might be presumed that due to hydrophilic properties of both ibuprofen lysinate and poloxamer taste masking effect will not be pronounced. Surprisingly, it has been found, that granules comprising

ibuprofen lysinate and Poloxamer 188 prepared according to the invention demonstrate acceptable taste while bitterness of pure ibuprofen lysinate at the same concentration is significant. This property of the formulation remains also in case the granules are dissolved which might be due to micelle formation or chemical interaction between ibuprofen salt with the polymer in solution.

- 5 The resulting solid, semi-solid or liquid formulation is obtained by granulation, if necessary followed by converting the granules into the desired dosage form. The granulation process results in stable granules showing taste masking properties even if administered in high dose. This is crucial property since the invention is aimed at water soluble drugs which demonstrate their taste directly after application into the oral cavity.

10 SUMMARY OF THE INVENTION

The present invention relates to the use of poloxamers for effective taste masking of water-soluble drugs (examples are listed below) wherein poloxamer and the water-soluble drug are in direct contact in granules.

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The present invention further relates to pharmaceutical compositions comprising a water soluble drug and poloxamer demonstrating improved taste. The pharmaceutical composition is in the form of granules, tablets, capsule, syrup, oral gel, suspension or solution.

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The present invention further relates to a process for manufacturing the taste masked pharmaceutical composition by granulation (such as dry granulation, wet granulation, hot-melt granulation, hot-melt extrusion), lyophilisation (freeze granulation) or spray drying of the water soluble drug and poloxamer and optionally one or more pharmaceutically acceptable excipient(s), and if required conversion the granules into the desired dosage form.

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The invention is demonstrated by successful use of poloxamer as taste masking agent in pharmaceutical compositions containing ibuprofen lysinate as water soluble compound. Said compound was selected as a model active pharmaceutical agent due to the fact that it is well soluble in water, possesses unpleasant bitter taste and requires high dosing (200 - 600 mg in a dosage form).

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of efficient taste masking of water soluble drugs in different dosage forms.

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It has been found that granulation of a water soluble drug with particular amount of poloxamer and optionally one or more pharmaceutically acceptable excipient(s) results in effective taste masking of a bitter taste of the water soluble drug. Contrarily, direct mixing of a water soluble drug with poloxamer

has been found insufficient to mask the bitter taste of the water soluble drug. We have observed that the phenomenon of taste masking is linked to the coverage of water soluble drug particles with poloxamer as it is visible in Fig 1 showing a microscopic picture of a physical mixture of ibuprofen lysinate with poloxamer 188 (left side) and granulated ibuprofen lysinate with poloxamer 188 (right side).

Different methods of granulation have been investigated including dry granulation (roller compaction), wet granulation (high-shear granulation and fluid-bed granulation), hot-melt granulation and hot-melt extrusion. Efficient taste masking was confirmed for all granules which may be used as final dosage form or processed into tablets disintegrating in oral cavity (including chewable and orodispersible tablets), tablets for preparation of oral solution (including effervescent tablets, dispersible tablets), syrups, gels, suspensions and solutions resulting from dispersion or dissolution of granules in orally acceptable liquids. Similar taste masking effect has been observed for granules obtained by lyophilisation of aqueous solution of poloxamers with water soluble drugs and for spray-dried granules obtained by spray drying of aqueous solution of poloxamers with water soluble drugs.

The present invention further relates to a taste masked pharmaceutical composition comprising a water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s).

The expression "water soluble drug" or "water soluble active agent", which are interchangeable in the context of the invention, means any drug selected from the BCS (Biopharmaceutics Classification System) class I or III, or salt of any drug from BCS class II and IV with a solubility in water from very soluble (less than 1 ml of solvent per gram of solute) to soluble (10-30 ml of solvent per gram of solute), most preferably very soluble and freely soluble according to European Pharmacopoeia 5.0. Suitable water soluble drugs are selected from the group comprising, but are not limited to, acyclovir, alendronic acid, alprazolam, amiloride, amitriptyline, amlodipine, atenolol, benazepril, bisoprolol, captopril, cetirizine, cimetidine, ciprofloxacin, citalopram, clomipramine, desloratadine, diclofenac sodium, digoxin, diltiazem, dolasetron, donepezil, doxazosin, ergotamine, enalapril, fexofenadine, finasteride, fluconazole, fluoxetine, fluvastatin, fluvoxamine, gabapentin, hydralazine, ibuprofen lysinate, ibuprofen sodium, indapamide, ketotifen, lamivudine, levetiracetam, levothyroxine, limaprost, lisinopril, lorazepam, losartan, metformine, metoprolol, mirtazapine, montelukast, morphine, neostigmine, ondansetron, oxybutynin, paroxetine, perindopril, promethazine, propranolol, quetiapine, quinapril, ramipril, ranitidine, rivastigmine, salbutamol, sertraline, sildenafil, sumatriptan, terbinafine, theophylline, topiramate, tramadol, verapamil, venlafaxine, zolmitriptan, zolpidem.

The solubility of preferred drugs in water is from 0.1 g/ml to freely water soluble. In the preferred embodiment of the invention the water soluble drug is ibuprofen salt, such as lysinate or sodium salt.

Poloxamer, α -hydro- ω -hydroxyl poly-(oxyethylene) poly-(oxypropylene) poly-(oxyethylene) block copolymer is represented by the following chemical structure: $-\text{HO} (\text{C}_2\text{H}_4\text{O})_a (\text{C}_3\text{H}_6\text{O})_b (\text{C}_2\text{H}_4\text{O})_a \text{H}$, wherein a and b blocks have the following values:

Lutrol	Poloxamer	a	b	Pour/melt point [°C]
L 44	124	12	20	16
F 68	188	80	27	52
F 87	237	64	37	49
F 108	338	141	44	57
F 127	407	101	56	56

Poloxamers are known also as poloxalkols, polyethylene–propylene glycol copolymers, polyoxyethylene–polyoxypropylene copolymers and are commercially available as Lutrol, Monolan, Pluronic, Supronic and Synperonic. They are readily soluble in water, in polar and non-polar organic solvents.

The taste masked pharmaceutical composition according to the invention comprises the water soluble drug and poloxamer in a weight ratio from 1:5 to 5:1, preferably from 1:2 to 5:1. The pharmaceutical composition is in the form of granules, which are used as such or for preparation of tablet, gel, syrup, suspension or solution.

In a preferred embodiment of the invention the pharmaceutical composition is a tablet having a two-phase structure consisting of an inner granular phase and an outer phase. The inner granular phase comprises the water-soluble active agent, poloxamer and optionally at least one pharmaceutically acceptable excipient. The outer phase is formed by at least one other pharmaceutically acceptable excipient suitable for preparation of tablets.

In other preferred embodiment of the invention the pharmaceutical composition is in liquid form as syrup, suspension or solution, wherein the granules are suspended or dissolved in a pharmaceutically acceptable liquid medium, preferably water, aqueous solution of sugar alcohols, saccharose, or aqueous solution of water soluble polymers.

In other preferred embodiment of the invention the pharmaceutical composition is in semi-solid form as a gel, wherein the granules are suspended or dissolved in a pharmaceutically acceptable semi-liquid medium, preferably aqueous solution of water soluble polymers.

Granules containing the water soluble drug and poloxamer

The granules include the water soluble drug, poloxamer, and optionally at least one pharmaceutically acceptable excipient selected from fillers, binders, disintegrants, sweeteners, surfactants, effervescent agents, flavours and aromas, glidants, lubricants, or any combinations thereof.

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Fillers are selected from lactose, glucose, cellulose and its derivatives, starch, mannitol or other sugar alcohols, binders are selected from water soluble polymers such as povidone, water-soluble cellulose derivatives (preferably methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), sugar alcohols (preferably mannitol, sorbitol), calcium sulphate, calcium phosphate, starch, disintegrant is preferably selected from sodium croscarmellose, sodium starch glycolate, crospovidone, alginates, sweeteners are preferably selected from sucrose, sucralose, sodium saccharin, saccharin, aspartame, surfactants are preferably selected from polysorbates, sodium dodecylsulphate, effervescent agents preferably selected from citric acid, fumaric acid, tartaric acid and sodium or potassium inorganic salt (preferably carbonates such as sodium carbonate, potassium carbonate), flavours and aromas are preferably selected from orange, strawberry, cherry, banana, vanilla, raspberry, glidants are preferably selected from colloidal silicon dioxide, corn starch, lubricants are preferably selected from magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, talc, polyethyleneoxide.

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Solid taste masked pharmaceutical compositions

- a. Granules comprise the water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s) selected from binders, fillers, disintegrants, sweeteners, flavours and aromas, optionally surfactants, glidants, lubricants listed above,
- b. Tablets, including orodispersible tablets, chewable tablets, effervescent tablets, tablets for preparation of solution and suspension, comprising granules described in point a) and optionally one or more pharmaceutically acceptable excipient(s) selected from glidants, effervescent agents and lubricants, disintegrant, surfactant, sweetener, flavours and aromas listed above.

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Semi-solid taste masked pharmaceutical compositions

- c. Gels comprising granules described in point a) dissolved or suspended in a pharmaceutically acceptable semi-liquid medium, selected from aqueous solutions of water soluble polymers, wherein the polymer is preferably a water soluble cellulose derivative such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and sodium carmellose; alginates, gums or polyvinylpyrrolidones.

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Liquid taste masked pharmaceutical compositions

- 5 d. Syrups comprising granules described in point a) dissolved or suspended in a pharmaceutically acceptable liquid medium, selected from aqueous solutions of sugar alcohols, wherein the sugar alcohol is preferably sorbitol, maltitol, mannitol, xylitol and their mixtures, or aqueous solution of saccharides such as saccharose,
- e. Suspensions comprising granules described in point a) suspended in pharmaceutically acceptable liquid medium, selected from aqueous solutions of water soluble polymers, wherein the polymer is preferably a cellulose derivative such as methylcellulose, hydroxyethylcellulose, sodium carmellose, hydroxypropylcellulose, hydroxypropylmethylcellulose.
- 10 f. Solutions comprising granules described in point a) dissolved in pharmaceutically acceptable liquid medium, preferably water.

The present invention further relates to a process for manufacturing the stable solid, semi-solid or liquid taste masked pharmaceutical composition of water soluble drug which comprises:

- 15 1. preparation of granules: mixing the water-soluble drug with poloxamer, and optionally one or more pharmaceutically acceptable excipient(s), granulation in any suitable means, or lyophilisation or spray-drying resulting in granules, if necessary drying, milling, complementation, homogenisation the obtained the granules, and
2. converting said granules into desired dosage form.

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The process for the preparation of the stable taste masked pharmaceutical composition according to the present invention comprises the following steps:

- a. Preparing a mixture of the water soluble drug, poloxamer, and optionally one or more pharmaceutically acceptable excipient(s) selected from binders, fillers, disintegrants, sweeteners, flavours and aromas, surfactants, glidants, lubricants by direct mixing, followed by granulation in any suitable means, preferably hot-melt granulation, dry granulation (compaction), wet granulation (high-shear granulation, fluid-bed granulation); optionally hot-melt extrusion, spray-drying and lyophilisation.
- 25 b. Admixing one or more pharmaceutically acceptable excipient(s) to the granules obtained in the step a), wherein said pharmaceutically acceptable excipient is selected particularly from sweeteners, flavours, aromas, effervescent agents, lubricants, glidants, surfactants, and disintegrant to obtain a blend.
- 30 c. Compressing the granules obtained in step a) or the blend obtained in step b) into tablets, dissolving or suspending the granules obtained in step a) or the blend obtained in step b) in a pharmaceutically acceptable liquid or semi-liquid media or filling the granules obtained in step a) or the blend obtained in step b) into capsules or sachets.
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Preparation of granules which are used as such or further processed into specific dosage forms:

1. Dry granulation

Mixture of water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s) is blended for at least 3 minutes at speed at least 10 rotations per minute and the obtained blend is granulated by roller compaction using compaction force at least 1 kN/cm². The parameters of the process are adjusted to obtain granules of desirable size (not more than 40% of granules below 100 µm), flowability and miscibility with optional further one or more pharmaceutically acceptable excipient(s). Exact properties of the granules are set depending on the final formulation – tablets, sachets, gels, suspensions, solutions.

2. Wet granulation

Mixture of water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s) is blended for at least 3 minutes at speed at least 10 rotations per minute and further the obtained blend is granulated with water or aqueous solution or suspension of a binder. The granules are dried in a fluid-bed dryer at the temperature not higher than melting point of the used poloxamer, preferably 5-10 °C lower than the melting point of the poloxamer. Alternatively, the process is performed by mixing poloxamer and optionally one or more pharmaceutically acceptable excipient(s) and granulation with aqueous solution of the water soluble drug. The obtained granules are milled and appropriately dried in fluid-bed or tray dryer, and optionally mixed with one or more pharmaceutically acceptable excipient(s) to obtain a blend with desirable physicochemical characteristics depending on the final dosage form.

3. Hot-melt granulation

Mixture of water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s) is blended for at least 3 minutes at speed not lower than 10 rotations per minute and then granulated at the temperature at least equal or higher by maximally 20 °C than the melting point of the used poloxamer, which acts as a binder. After the granules have been cooled down to the temperature not higher than 5°C below melting point of poloxamer, the granules are milled and optionally mixed with one or more pharmaceutically acceptable excipient(s) to obtain a final blend demonstrating physicochemical characteristics allowing for formulation of a final dosage form.

4. Hot-melt extrusion

Mixture of water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s) is blended for at least 3 minutes at speed at least 10 rotations per minute and further extruded at elevated temperature (40 - 120°C) to form granules. The obtained granules are used either as a final formulation, tableted or blended with further excipients to obtain a blend demonstrating properties appropriate to form a final formulation.

5. Spray-drying

Mixture of water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s) is dissolved in an appropriate liquid medium and spray dried at temperature below melting point of poloxamer to obtain granules which may be used as a final formulation, tableted or blended with one or more pharmaceutically acceptable excipient(s) to form a blend demonstrating appropriate physicochemical characteristics to form final dosage form.

6. Freeze-drying

Mixture of water soluble drug, poloxamer and optionally one or more pharmaceutically acceptable excipient(s) is dissolved or dispersed in an appropriate liquid medium, preferably water, and freeze-dried to obtain granules which may be used as a final formulation or milled and mixed with one or more pharmaceutically acceptable excipient(s) to form a blend used for manufacturing of a final formulation.

The final pharmaceutical formulation

The granules or the blend, obtained as described above in paragraphs 1) to 6), suitable for the preparation of the final pharmaceutical formulation, comprise the water-soluble drug and poloxamer in the weight ratio from 5:1 to 1:5, preferably from 1:2 to 5:1.

As stated above, the water-soluble active agent is granulated, extruded, and spray-dried or freeze-dried together with a poloxamer, wherein the obtained granules optionally further comprise one or more pharmaceutically acceptable excipient(s). Said granules are optionally admixed with one or more pharmaceutically acceptable excipient(s) to form a final blend. The granules or said blend is filled into sachets, compressed into tablets, dispersed or dissolved in liquid or semi-liquid media.

The taste masked pharmaceutical formulation according to the invention is in the form of the following dosage forms:

The above described granules or blend with appropriate flowability are used as such and filled into sachets, or compressed into tablets with suitable hardness and friability and packed into blisters or plastic or glass bottles. In the case of effervescent tablets addition of organic acid and carbonate salt is necessary.

Syrup is a suspension or solution of the above described granules or blend in appropriate pharmaceutically acceptable liquid media is filled into bottles. The pharmaceutically acceptable media is selected from aqueous solution of sugar alcohols, preferably sorbitol, maltitol, mannitol, xylitol and mixtures thereof, or aqueous solution of saccharose,

Suspension is a suspension of above described granules or blend in appropriate pharmaceutically acceptable liquid media filled into bottles. The pharmaceutically acceptable liquid media is aqueous

solutions of water soluble polymers preferably selected from cellulose derivatives (methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose sodium carboxymethyl cellulose).

- 5 Solution is a solution of above described granules or blend in appropriate liquid media, preferably water, filled into bottles.

Gel is a suspension or solution of above described granules or blend in appropriate pharmaceutically acceptable semi-liquid media filled into bottles or single-use sachets. The pharmaceutically acceptable
10 medium is selected from aqueous solutions of water soluble polymers, preferably cellulose derivatives such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and sodium carboxymethylcellulose, alginates, gums or polyvinylpyrrolidones.

Preferred embodiment of the invention

15 The pharmaceutical composition comprises as water soluble active agent ibuprofen salt, preferable lysine or sodium salt, poloxamer, and optionally one or more pharmaceutically acceptable excipient(s).

The granules comprises (w/w % based on granules):

- 20 a/ 15 - 80% ibuprofen salt
b/ 3- 75 % poloxamer
Optionally:
c/ 10-50% filler
25 d/ 4 – 6% binder
e/ 0.1-10% sweetener or sugar
f/ 0.1 – 5% flavour and aroma
g/ 0.5 – 10% disintegrant
h/ 0.1 – 3% surfactant
30 i/ 0.1 – 3% glidant
j/ 0.1 – 3% lubricant
k/ 1-25% effervescent agents

Components of the formulations

35 The taste masking agent which is poloxamer can be selected from the whole range of marketed α -hydro- ω -hydroxyl poly-(oxyethylene) poly-(oxypropylene) poly-(oxyethylene) block copolymers of different block lengths. The weight ratio of ibuprofen salt and poloxamer is limited to the range from 1:5 up to 5:1 (w/w) which allows for effective taste masking.

The composition optionally comprises one or more pharmaceutically acceptable excipient(s) which can be admixed to the mixture of poloxamer and ibuprofen salt before granulation or to the granules containing ibuprofen salt and poloxamer. The one or more pharmaceutically acceptable excipient(s) can be also granulated/extruded/spray-dried/freeze-dried together with poloxamer and ibuprofen salt.

5 These excipients are selected from, but are not limited to the following groups:

1. Fillers - sugars such as lactose, glucose, sucrose, starch or sugar alcohols such as sorbitol, mannitol, xylitol.
2. Binders - cellulose and its derivatives such as hydroxyethylcellulose, hydroxypropylcellulose, sodium carmellose, methylcellulose.
- 10 3. Sweeteners such as sucralose, sodium saccharin, saccharin, aspartame.
4. Effervescent agents - organic acids such as tartaric, citric, fumaric and salts of carbonic acid such as sodium carbonate, potassium carbonate.

15 The one or more pharmaceutically acceptable excipient(s) improve physicochemical parameters of the granules allowing for further processing and preparation of final dosage form.

When the final formulation is chewable tablet or orodispersible tablet, superdisintegrant such as sodium croscarmellose, sodium starch glycolate, crospovidone may be included. Moreover when the final formulation is tablet, glidants (such as silicon dioxide) and lubricants (such as magnesium stearate, sodium stearyl fumarate) may be included. Furthermore the final formulation optionally also comprises flavouring agents and aromas (such as strawberry flavour, orange flavour, cherry flavour and others).

25 When the final formulation is a suspension/solution, the preferred pharmaceutically acceptable liquid medium is:

	Composition/dose	
	g/100 g	%
Sorbitol 70%	30.0	30
Avicel RC591	1.6	1.6
Sodium croscarmellose	0.3	0.3
Water	68.1	68.1
Total	100.0	100.0

When the final formulation is a gel, the preferred pharmaceutically acceptable semi-liquid medium is:

	Composition/dose	
	g/100 g	%
Hydroxyethylcellulose	4.0	4.0
Water	96.0	96.0
Total	100.0	100.0

BRIEF DESCRIPTION OF DRAWINGS

Fig 1 shows a microscopic picture of a physical mixture of ibuprofen lysinate with poloxamer 188 (left side) and granulated ibuprofen lysinate with poloxamer 188 (right side).

EXAMPLES

Examples 1 - 3: Roller compaction

A first blend was prepared by mixing of micronized ibuprofen lysinate and excipients according to the tables (see examples 1 – 3) below in a blender for 10 min. The blend was compacted with a force of 2-10 kN/cm², preferable between 3-7 KN/cm². The compacts were milled, the obtained granules sieved through 0.8-1.25 mm sieve. The resulted dry granules were lubricated before tableting or filling into sachets. The dry granules may be also used for dissolution/dispersion in liquid or semi-liquid medium to create solution/dispersion or gel.

The granules prepared by compaction had sufficient flowability and can be easily compressed into tablets with suitable hardness and friability.

Example 1: Composition of granules as final formulation

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	45.3
Lactose monohydrate	80.0	5.3
Poloxamer 188	340.0	22.7
Microcrystalline cellulose	340.0	22.7
Sucralose	50.0	3.3
Orange flavour (powdered)	10.0	0.7
Total	1500.0	100.0

Example 2: Composition of two-phase structure tablet

Inner phase - Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	61.8
Lactose monohydrate	80.0	7.3
Poloxamer 188	136.0	12.4
Outer phase		
Microcrystalline cellulose	133.0	12.1
Sucralose	50.0	4.5
Cherry flavour (powdered)	10.0	0.9
Magnesium stearate	11.0	1.0
Total	1100.0	100.0

5 Example 3: Composition of granules for dissolution in liquid media

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	56.7
Glucose	80.0	6.7
Poloxamer 188	380.0	31.7
Sucralose	50.0	4.1
Orange flavour (powdered)	10.0	0.8
Total	1200.0	100.0

Examples 4 - 6: Wet granulation

- 10 Ibuprofen lysinate was blended with lactose and poloxamer in a high shear mixer for 2 minutes, then sweetener and flavouring agent were added and the mixture was blended for additional 2 minutes. The blend was then granulated in high-shear mixer or fluid-bed granulator with water. The obtained granules were dried at 40°C and milled 0.8-1.2 mm sieve. When tablets are prepared, lubricant was admixed for 3 minutes.

Example 4: Composition of granules as final formulation

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	54.9
Lactose monohydrate	160.0	12.9
Poloxamer 188	340.0	27.4
Sucralose	50.0	4.0
Cherry flavour (powdered)	10.0	0.8
Total	1240.0	100.0

Example 5: Composition of two-phase structure tablet

5

Inner phase - Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	61.8
Lactose monohydrate	133.0	12.1
Poloxamer 188	136.0	12.4
Outer phase		
Microcrystalline cellulose	80.0	7.3
Sucralose	50.0	4.5
Strawberry flavour (powdered)	10.0	0.9
Magnesium stearate	11.0	1.0
Total	1100.0	100.0

Example 6: Composition of granules for dissolution in liquid media

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	37.4
Glucose	100.0	5.5
Poloxamer 188	1020.0	56.1
Sucralose	10.0	0.5
Cherry flavour (powdered)	10.0	0.5
Total	1820.0	100.0

Examples 7-9: Hot-melt granulation

Ibuprofen lysinate was granulated together with lactose and poloxamer 188 in fluid-bed granulator. The inlet temperature was set to achieve product temperature slightly, about 2-3 °C, above melting temperature of poloxamer. Granules started to form after reaching the desired temperature. Then the inlet temperature was decreased to achieve product temperature about 47°C, the granules were milled through 1.0 mm sieve and cooled down to the room temperature.

Example 7: Composition of granules as final formulation

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	48.6
Lactose monohydrate	340.0	24.3
Poloxamer 188	360.0	25.7
Sucralose	10.0	0.7
Cherry flavour (powdered)	10.0	0.7
Total	1400.0	100.0

Example 8: Composition of two-phase structure tablet

Inner phase - Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	45.3
Glucose	120.0	8.0
Poloxamer 188	156.0	10.4
Outer phase		
Sucralose	10.0	0.7
Sodium bicarbonate	325.0	21.6
Citric acid	183.0	12.2
Orange flavour (powdered)	10.0	0.7
Magnesium stearate	16.0	1.1
Total	1500.0	100.0

Example 9: Composition of granules for dissolution in liquid media or for gel preparation

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	58.6
Lactose monohydrate	120.0	10.3
Poloxamer 188	340.0	29.3
Sucralose	10.0	0.9
Cherry flavour (powdered)	10.0	0.9
Total	1160.0	100.0

Examples 10 – 12: Hot-melt extrusion

- 5 Ibuprofen lysinate was blended together with poloxamer and Povidone. The mixture was extruded using laboratory hot-melt extruder using temperature within the range 80 – 130 °C. The resulting extrudate was cooled down to room temperature, then milled using laboratory mill, and sieved through 0.8 mm sieve. Depending on final formulation, additional excipients were admixed (see tables below, example 10 – 12).
- 10 Example 10: Composition of granules as final formulation

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	34.0
Lactose monohydrate	120.0	6.0
Poloxamer 188	136.0	6.8
Kollidon VA64	1044.0	52.2
Sucralose	10.0	0.5
Cherry flavour (powdered)	10.0	0.5
Total	2000.0	100.0

Example 11: Composition of two-phase structure tablet

Inner phase - Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	53.5
Lactose monohydrate	80.0	6.3
Poloxamer 188	136.0	10.7
Kollidon VA64	340.0	26.8
Outer phase		
Sucralose	10.0	0.8
Cherry flavour (powdered)	10.0	0.8
Magnesium stearate	14.0	1.1
Total	1270.0	100.0

Example 12: Composition of granules for dissolution in liquid media

5

Granules	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	52.3
Lactose monohydrate	120.0	9.2
Poloxamer 188	136.0	10.4
Kollidon VA64	344.0	26.5
Sucralose	10.0	0.8
Orange flavour (powdered)	10.0	0.8
Total	1300.0	100.0

Comparative examples 13 - 16: Direct mixing

10 The following examples deal with ineffective taste masking using similar composition as described above, but without granulation step.

The mixture which may be used for dissolution or dispersion in liquid media or for tableting was prepared by direct blending. Micronized ibuprofen lysinate, lactose and poloxamer 188 were blended. Then the remaining excipients (see tables below, examples 13 – 16) were added and the mixture was blended for 10 min. If lubricant is present, it was added separately to the mixture and blended for 3-5
15 minutes. Then the mixture was dispersed in water at room temperature or tableted using rotary tablet press.

Example 13: Composition of powder mix for dissolution/dispersion in liquid medium

Powder mix	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	34.0
Lactose monohydrate	460.0	23.0
Poloxamer 188	750.0	37.5
Sucralose	50.0	2.5
Sodium saccharin	50.0	2.5
Cherry flavour (powdered)	10.0	0.5
Total	2000.0	100.0

Example 14: Composition of powder mix for dissolution/dispersion in liquid medium

5

Powder mix	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	45.3
Lactose monohydrate	574.0	38.3
Poloxamer 188	136.0	9.1
Sucralose	50.0	3.3
Sodium saccharin	50.0	3.3
Cherry flavour (powdered)	10.0	0.7
Total	1500.0	100.0

Example 15: Composition of powder mix for direct compression

Powder mix	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	61.8
Lactose monohydrate	82.0	7.5
Poloxamer 188	136.0	12.4
Microcrystalline cellulose	130.0	11.8
Sucralose	50.0	4.5
Cherry flavour (powdered)	11.0	1.0
Magnesium stearate	11.0	1.0
Total	1100.0	100.0

Example 16: Composition of powder mix for direct compression

Powder mix	Composition/dose	
	mg	%
Ibuprofen lysinate	680.0	40.0
Lactose monohydrate	88.0	5.2
Poloxamer 188	340.0	20.0
Sodium bicarbonate	325.0	19.1
Citric acid anhydrous	183.0	10.8
Sucralose	50.0	2.9
Cherry flavour (powdered)	17.0	1.0
Magnesium stearate	17.0	1.0
Total	1700.0	100.0

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Claims

1. Use of poloxamers as taste masking agents of water-soluble drugs, wherein the water-soluble drug and poloxamer are in direct contact in granules.
2. Use according to claim 1, characterized in that the weight ratio of the water soluble drug to poloxamer is from 1:5 to 5:1.
3. Use according to claim 2, characterized in that the weight ratio of the water soluble drug to poloxamer is from 1:2 to 5:1.
4. Use according to claims 1 and 3, characterized in that the poloxamer is selected from the group consisting of poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.
5. Use according to claim 4, characterized in that the poloxamer is poloxamer 188.
6. Use according to claims 1 to 3, characterized in that the water-soluble drug is selected from drugs with water solubility from 0.1 g/ml to freely soluble.
7. Use according to claim 6, characterized in that the water-soluble drug is selected from ibuprofen salts.
8. Use according to claim 7, characterized in that the water-soluble drug is ibuprofen lysine and ibuprofen sodium.
9. Taste masked pharmaceutical composition in the form of granules containing a water soluble drug and poloxamer, and optionally one or more pharmaceutically acceptable excipient(s).
10. Taste masked pharmaceutical composition according to claim 9, characterized in that the poloxamer is selected from the group consisting of poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.
11. Taste masked pharmaceutical composition according to claim 10, characterized in that the poloxamer is poloxamer 188.
12. Taste masked pharmaceutical composition according to claim 9, characterized in that the water-soluble drug is selected from drugs with water solubility from 0.1 g/ml to freely soluble.

13. Taste masked pharmaceutical composition according to claim 12, characterized in that the water-soluble drug is selected from ibuprofen salts.
14. Taste masked pharmaceutical composition according to claim 13, characterized in that the water-soluble drug is selected from ibuprofen lysine and ibuprofen sodium.
15. Taste masked pharmaceutical composition according to claims 9 to 14, characterized in that the optionally one or more pharmaceutically acceptable excipient(s) is selected from fillers, binders, disintegrants, sweeteners, surfactants, glidants, lubricants, effervescent agents, flavours and aromas, or combinations thereof.
16. Solid taste masked pharmaceutical composition containing granules according to claims 9 to 15 and optionally one or more pharmaceutically acceptable excipient(s).
17. Solid taste masked pharmaceutical composition according to claim 16, characterised in that is in the form of granules or tablets.
18. Solid taste masked pharmaceutical composition according to claim 17 characterised in that is in the form of orodispersible tablets, chewable tablets, effervescent tablets, tablets for preparation of solution or suspension.
19. Liquid taste masked pharmaceutical composition containing granules according to claims 9 to 15 and optionally one or more pharmaceutically acceptable excipient(s).
20. Liquid taste masked pharmaceutical composition according to claim 19 characterised in that is in the form of syrup, suspension or solution.
21. Semi-solid taste masked pharmaceutical composition containing granules according to claims 9 to 15 and optionally one or more pharmaceutically acceptable excipient(s).
22. Semi-solid taste masked pharmaceutical composition according to claim 21, characterised in that is in the form of gel.
23. Process for preparation of granules according to claims 9 to 15, characterised in that the water soluble drug is granulated together with poloxamer, and optionally one or more pharmaceutically acceptable excipient.
24. Process for preparation of granules according to claim 23, characterized in that dry granulation, wet granulation, hot-melt granulation, hot-melt extrusion, spray-drying or lyophilization technique is

used.

25. Process for preparation of granules according to claim 23 or 24, characterized in that the water soluble drug, poloxamer, and optionally one or more pharmaceutically acceptable excipient(s) are dry-mixed and the obtained blend is hot-melt granulated at the temperature equal or higher by 20 °C than the melting point of the used poloxamer.
26. Process for preparation of granules according to claim 23 or 24, characterized in that the water soluble drug, poloxamer, and optionally one or more pharmaceutically acceptable excipient(s) are dry-mixed and the obtained blend is extruded at temperature from 40 °C to 120 °C to form granules.
27. Process for preparation of granules according to claim 23 or 24, characterized in that the water soluble drug, poloxamer, and optionally one or more pharmaceutically acceptable excipient(s) are dry-mixed and the obtained blend is granulated with water or aqueous solution of a binder.
28. Process for preparation of granules according to claim 23 or 24, characterized in that poloxamer and optionally one or more pharmaceutically acceptable excipient(s) is dry-mixed and the obtained blend is granulated with an aqueous solution of a water soluble drug.



Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000071

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/16 A61K31/192
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 403 407 A (BURKE MICHAEL HILARY [IE]) 5 January 2005 (2005-01-05) page 5, lines 1-16 claims 1,8,16	1-28
X	----- US 2006/057207 A1 (ZIEGLER CARL B [US] ET AL) 16 March 2006 (2006-03-16) example 23 claims 1,16,17	1-28
X	----- WO 02/098392 A1 (BOOTS CO PLC [GB]; RHOADES TRACEY JANE [GB]; SHERRY ROBERT ARTHUR [GB]) 12 December 2002 (2002-12-12) page 6, line 1 - line 3 examples 18,19 ----- -/-	1-28



Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000071

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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