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(54) NEW PHARMACEUTICAL COMPOSITIONS AND A PROCESS FOR THE PREPARATION THEREOF

(71) We, RICHTER GEDEON VEGYESZETI GYAR RT., a body corporate organised under the laws of Hungary, of 21, Gyomroi ut, Budapest X., Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to pharmaceutical compositions and to a process for the preparation thereof. More particularly, the invention relates to pharmaceutical compositions possessing antiphlogistic effects.

As known, all of the hitherto applied antiphlogistic agents have the common disadvantage of causing gastrointestinal haemorrhages or ulcers. The ulcerogeneous side-effects of 1 - (p - chlorobenzoyl) - 5 - methoxy - 2 - methyl - indol - 3 - yl - acetic acid (indomethacin), 4 - butyl - 1,2 - diphenyl - pyrazolidine - 3,5 - dione (phenylbutazone) and acetylsalicylic acid have been reported in numerous publications (Bonfils et al.: Bull. Mem. Soc. Med. Hosp. Paris, *5*, 114 /1955/; Somogyi et al.: J. Pharm. Pharmacol. *21*, 122 /1969/; R. Nath: Studies on the Pharmacology of Inflammation, M. D. Thesis Lucknow University, Lucknow, India /1970/; Lee et al.: Arch. Int. Pharmacodyn. *19*, 370 /1971/; Bhargava et al.: European J. of Pharmacol. *22*, 191 /1973/; Katz et al.: Clin. Pharm. Ther. *6*, 25 /1965/; Leonard et al.: Clin. Pharmacol. Ther. *14*, No. 1, 62 /1973/).

In prolonged treatments of various arthritic conditions two or more different antiphlogistic agents can sometimes be administered simultaneously to the patients. The antiphlogistic effects arising upon the simultaneous administration of indomethacin and acetylsalicylic acid were investigated first in animal tests (Mielons et al.: J. Pharm. Pharmac. *20*, 567 /1968/; Swingle et al.: J. Pharmacol. Exp. Ther. *172*, 423 /1970/; Yesair et al.: Biochem. Pharm. *19*, 1591 /1970/). Since the oedema tests had not indicated the additivity of antiphlogistic effects, clinical tests were performed in order to elucidate this question (Champion et al.: Clin. Pharm. and Ther. *13*, 239 /1972/; Lindquist et al.: Clin. Pharm. and Ther. *15*, 247 /1974/). These clinical tests have shown that the blood indomethacin level is not affected by the simultaneous administration of acetylsalicylic acid, that is, these two types of antiphlogistic agents do not worsen the effects of one another.

So far only the main effect, i.e. the antiphlogistic activity was investigated in the tests utilizing two different antiphlogistic agents simultaneously, and the gastrointestinal side-effects have not been analysed. Our experiments aimed at investigating both the main antiphlogistic effect and the ulcerogeneous side-effects appearing upon the administration of various combinations of antiphlogistic agents, and preparing a pharmaceutical composition in which the original antiphlogistic effects of the individual components are retained but the gastrointestinal side-effects are decreased to the minimum.

As a result of our experiments we provide a pharmaceutical composition containing as an antiphlogistic agent indomethacin, niflumic acid, phenylbutazone or acetylsalicylic acid or a pharmaceutically acceptable salt of any of these compounds, and 0.2 to 50 parts by weight of salicylic acid or an alkali metal salicylate for one part by weight of the antiphlogistic agent.

Preferably the antiphlogistic agent is used with the alkali metal salicylate, preferred ex-

amples of which are sodium salicylate and lithium salicylate.

The composition of the invention may be associated with a carrier, a diluent or an auxiliary agent.

Details of the experiments on which the present invention is based are given below.

The antiphlogistic effects were studied on Wistar rats of both sexes, each weighing 100 to 150 g. The animals were starved for 24 hours, and then 0.1 ml portions of a 1% by weight carrageenin solution were injected under mild ether anaesthesia into the plantar region of one of the hind paws in order to provoke inflammation (oedema). The antiphlogistic agent or composition was introduced into the stomach of the animals via a stomach tube immediately before injecting the carrageenin solution. 4 hours after this treatment the animals were sacrificed, and both hind paws were amputated above the ankles. The paws were weighed, and the oedema weight was calculated from the weight difference of the treated and untreated paws.

The gastrointestinal ulcerogeneous side-effects of the individual active agents and their combinations were also examined on Wistar rats weighing 100 to 150 g. The animals were starved for 24 hours, and the substances to be tested were administered to them via a stomach tube. 4 hours after the treatment the animals were sacrificed, the stomach was removed, incised along the greater curvature, washed, and the haemorrhages (brown spots) appearing on the glandular part were counted. The results were subjected to Student's "t"-test.

The ulcerogeneous side-effects of the individual antiphlogistic agents were examined first by these tests. The results are summarized in Table 1. As it appears from the data of the Table, all the compounds examined possess more or less pronounced ulcerogeneous side-effects.

TABLE 1

Ulcerogeneous side-effects of various antiphlogistic agents

Compound	No. of test animals	Dosage mg/kg p.o.	No. of ulcer/ stomach	Ulcer-free animals	
				No.	%
Indomethacin	20	5	1.1	15	72
,,	28	10	6.5	5	18
,,	120	20	15.0	6	5
,,	41	30	24	0	0
Niflumic acid	18	12.5	0.6	14	78
,,	16	25	10.2	2	12
,,	15	50	19.0	0	0
,,	15	100	23.0	0	0
Phenylbutazone	18	25	0.5	13	73
,,	16	50	0.6	4	25
,,	17	100	6.5	4	23
,,	15	200	20.0	1	7
Aspirin	25	25	4.7	2	8
,,	25	50	5.4	3	10
,,	120	100	6.5	18	14
,,	58	400	11.0	7	12

TABLE 1 (Continued)

Ulcerogeneous side-effects of various antiphlogistic agents

Compound	No. of test animals	Dosage mg/kg p.o.	No. of ulcer/ stomach	Ulcer-free animals	
				No.	%
Sodium salicylate	45	50	0.1	37	82
,,	28	100	0.1	27	96
,,	64	200	1.2	37	50
,,	45	400	1.1	32	71

The following tests aimed at investigating the effects which appear upon the administration of a composition comprising two different antiphlogistic agents. In the first tests compositions of indomethacin and sodium salicylate were studied. It has been found, unexpectedly, that these compounds mutually suppress the ulcerogeneous side-effects of one another, while leaving the main antiphlogistic effects unchanged. This fact could not be foreseen at all, since it is well known that the above two compounds possess marked ulcerogeneous side-effects when added separately.

In the tests the animals received the same dosages of indomethacin, and the amount of sodium salicylate administered was varied. It has been found that the number of ulcer-free animals increases proportionally to the increase in the amount of sodium salicylate added, and when sodium salicylate is administered in a 20-fold amount with respect to indomethacin, the ulcerogeneous effect disappears completely, i.e. sodium salicylate antagonises entirely the deleterious side-effect of indomethacin. Table 2 shows the ulcerogeneous effects and Table 3 shows the antiphlogistic effects of compositions containing varying amounts of sodium salicylate besides indomethacin.

TABLE 2

Inhibition of indomethacin-induced ulcer by the simultaneous administration of sodium salicylate

No. of animals tested	Dosage mg/kg p.o. Indomethacin	Sodium salicylate	Ulcerogeneous side-effect		Ulcer-free animals	
			No. of ulcer/stomach	Inhibition %	No.	%
120	20	–	15.0±0.5 ^{xx}	–	6	5
17	20	25	6.1±1.3 ^{xx}	60^{x}	2	12
18	20	50	7.5±1.4 ^{xx}	50^{x}	2	10
22	20	100	4.0±0.8 ^{xx}	73^{x}	3	13
58	20	200	0.27±0.1 ^{xx}	98^{x}	51	88
22	20	400	0	100^{x}	22	100

x $p < 0.01$ (significance level determined by Student's "t"-test
xx corrected with the mean standard error

TABLE 3

Antiphlogistic effects of sodium salicylate, indomethacin and combinations thereof determined by carrageenin-oedema test

Dosage of the compounds tested mg/kg p.o.		No. of animals tested	Oedema-inhibiting effect %
Sodium salicylate	Indomethacin		
50	–	31	15
100	–	28	43[x]
–	5	21	40[x]
–	10	28	45[x]
50	5	29	40[x]
200	5	10	41[x]

x p 0.05 (significance level determined by Student's "t"-test)

In the following tests animals treated for 3 days with various compositions of indomethacin and sodium salicylate were examined. The non-starved test animals were treated orally for 3 days with compositions containing 20 mg/kg of indomethacin and increasing amounts of sodium salicylate. 73% of the animals receiving only indomethacin died on the 3rd day in peritonitis resulting from intestinal perforation and clearly visible ulcers appeared in the intestines of the survivals. In contrast, when indomethacin was administered in combination with sodium salicylate, this severe side-effect could be antagonized completely. The results were summarized in Table 4.

TABLE 4

Antagonizing the gastrointestinal side-effects of indomethacin by sodium salicylate administered simultaneously

(tests performed for 3 days on non-starved animals)

No. of animals tested	Dosage mg/kg p.o.		Dead animals		Ulcerous animals	
	Indo-methacin	Sodium salicylate	No.	%	No.	%
45	3×20	–	33	73	45	100
20	3×20	3×50	5	25	11	55
20	3×20	3×100	3	15	3	15
45	3×20	3×200	0	0	0	0

It has also been studied whether sodium salicylate also antagonizes the ulcerogeneous side-effects of antiphlogistic agents other than indomethacin. These tests have shown that the ulcerogeneous side-effects of phenylbutazone, niflumic acid 2 - (3 - trifluoromethyl - anilino)nicotinic acid and acetylsalicylic acid of its salts can also be antagonized effectively by administering them together with sodium salicylate, and the main antiphlogistic effects of these compounds remain unchanged, or even the antiphlogistic effects of the two active agents are superimposed. It is particularly surprising that the salts of salicylic acid exert a protective effect even against ulcers provoked by acetylsalicylic acid, i.e. two different salicylic acid derivatives mutually suppress the harmful side-effects of each other. The results of these test are summarized in Tables 5 to 7.

(12)

TABLE 5

Antagonizing the ulcerogeneous side-effects of phenylbutazone and niflumic acid by sodium salicylate administered simultaneously

No. of animals tested	Dosage, mg/kg p.o.		Ulcerogeneous side-effect		Ulcer-free animals	
	Phenyl-butazone	Sodium salicylate	No. of ulcer/stomach	Inhibi-tion %	No.	%
17	100	–	6.5	–	4	23
30	100	50	4.4	32	8	27
20	100	100	3.3	50	8	40
18	100	200	2.8	57	10	56
	Niflumic acid					
25	50	–	19	–	0	0
20	50	50	21	–	0	0
20	50	100	13	40	0	0
20	50	200	5.5	73	6	30

TABLE 6

Antagonizing the ulcerogeneous side-effects of acetylsalicylic acid by sodium salicylate administered simultaneously

No. of animals tested	Dosage, mg/kg p.o.		Ulcerogeneous side-effect		Ulcer-free animals	
	Acetylsali-cylic acid	Sodium salicylate	No. of ulcer/stomach	Inhibi-tion %	No.	%
120	100	–	6.5±0.7	–	18	14
22	100	25	2.5±0.5 x	58	3	15
36	100	50	2.4±0.6 x	60	16	45
31	100	100	0.2±0.1 x	99	29	97
40	100	200	0.3±0.1 x	98	36	90

x $p < 0.01$ (significance level determined by Student's "t"-test)

TABLE 7

Antiphlogistic effects of sodium salicylate, acetylsalicylic acid and mixtures thereof determined by carrageenin-oedema test

Dosage mg/kg p.o.		No. of animals tested	Inhibition of oedema %
Sodium salicylate	Acetylsalicylic acid		
50	–	31	15
100	–	28	43[x]
–	50	13	15
–	100	23	20[x]
50	50	50	21[x]
100	100	100	39[x]

x $p < 0.05$ (significance level determined by Student's "t" test)

The results listed above prove unambiguously that sodium salicylate antagonizes the gastrointestinal haemorrhagic or ulcerogeneous side-effects of other non-steroidal antiphlogistic agents, without affecting the main antiphlogistic effect. Similar effects are shown by compositions which contain other salicylic acid salts, or in certain cases even salicylic acid itself, instead of sodium salicylate.

Pharmaceutical dosage forms containing the active composition of the invention can be prepared by methods commonly applied in the pharmaceutical industry by compounding the antiphlogistic agent and salicylic acid or alkali metal salt thereof with conventional carriers, diluents and/or auxiliary agents. The pharmaceutical compositions can be presented e.g. in the form of tablets, sugar-or film-coated tablets, capsules, suppositories, and injectable solutions.

The pharmaceutical compositions according to the invention can be administered orally, rectally and/or parenterally either in a single dosage or in subdivided forms. For oral administration the compositions are presented preferably in the form of tablets, sugar- or film-coated tablets, or capsules. Film-coated tablets are particularly preferable unit dosage forms. These orally administerable compositions contain generally no filler, but in some cases conventional filling agents, e.g. lactose or starch can also be admixed to them. As binding or granulating agent e.g. gelatine, sodium carboxymethylcellulose, methyl cellulose, polyvinylpyrrolidone or gellified starch can be used. The most appropriate disintegrating agents are potato starch and microcrystalline cellulose, but other disintegrating agents, such as ultraamylopectin, and formaldehyde-casein condensates can be used as well. As lubricating and antiadhesive substances e.g. talc, colloidal silicic acid, stearin, calcium or magnesium stearate can be applied.

The tablets can be prepared e.g. by the conventional wet granulation - compression method. In this instance a dry blend of the active agents, fillers and optionally a part of the disintegrating agents is kneaded with an aqueous alcoholic or aqueous-alcoholic solution of the appropriate binding agent, the mass is granulated, and the obtained granules are dried. Thereafter the other additives (e.g. the remaining part of the disintegrating agents, lubricants, and antiadhesive substances are blended with the granular substance, and the blend is compressed into tablets. If desired, the tablets can be provided with parting incisions in order to facilitate their division at administration. If desired, the tablets can be film-coated with substances resistant towards gastric juice, such as Shellac, cellulose-acetate phthalate or Eudragit-L. These film-forming substances are usually deposited onto the tablet from an alcohol, particularly isopropanol solution.

From the appropriate combinations of the active agents and additives the tablets can also be prepared by direct pressing method, and, if desired, the resulting tablets can be provided with an enteric coating.

If desired, the tablets can be coated with conventional protecting, flavouring and/or colouring agents, such as sugar, cellulose derivatives (methyl or ethylcellulose, and sodium carboxymethylcellulose), polyvinylpyrrolidone, calcium phosphate, calcium carbonate, colouring agents and varnishes commonly used in the food and pharmaceutical

industry, iron oxide pigments, and aroma substances. For the sake of convenience the thus-obtained coated tablets are referred to in the specification and claims as "sugar-coated tablets", with the understanding that this term also covers coated tablets which contain no sugar in the coating layer.

Capsules are prepared by filling the mixture of the active agents into hard gelatine capsules.

Compositions for rectal administration are presented in the form of suppositories. The suppositories contain, besides the active agents, conventional carriers, such as vegetable fats (e.g. hardened vegetable oils) or triglycerides of C_{12-18} fatty acids. Witepsol (Registered Trade Mark) proved to be a particularly preferable carrier for the preparation of suppositories. The active agents are homogenized with the molten carrier, and the mass is cast into suppository moulds.

Compositions for parenteral administration are presented in injectable forms. To prepare injectable solutions the active agents are dissolved e.g. in distilled water and/or various organic solvents, such as lower aliphatic alcohols or glycol ethers (particularly ethyleneglycol monoethyl ether), optionally containing dissolution aids, such as polyoxyethylene sorbitan monolaurate, monooleate or monostearate (Tween 20, Tween 60 or Tween 80; Tween is a Registered Trade Mark). The injectable solutions may contain various other additives, such as preserving agents (e.g. benzyl alcohol, methyl or propyl p-hydroxybenzoate, phenylmercuric borate or benzalkonium chloride), antioxidants (e.g. sodium pyrosulfate, ascorbic acid, and tocoferol), complexing agents for binding traces of heavy metals (e.g. ethylenediamine tetraacetate), substances for adjusting the pH, buffers, and optionally local anaesthetic agents (e.g. lidocaine).

The injectable solutions are filtered, filled into vials, the vials are closed and sterilized.

The invention is elucidated in detail by the aid of the following non-limiting Examples.

Example 1.

Film-coated tablets containing indomethacin and sodium salicylate as active agents

Composition of one tablet:	
indomethacin	20 mg
sodium salicylate	200 mg
magnesium stearate	3 mg
polyvinyl pyrollidone	8 mg
Eudragit-L	10 mg
talc	12 mg
potato starch	157 mg
total	410 mg

The tablets are prepared by the conventional wet granulation-compression technique, and film-coated with Eudragit-L.

In the above composition sodium salicylate can be replaced by another alkali metal salicylate, such as lithium salicylate to obtain tablets with the same effect.

Example 2.

Suppositories containing indomethacin and sodium salicylate as active agents

Composition of one suppository:	
indomethacin	0.02 g
sodium salicylate	0.20 g
Witepsol H-15	1.78 g
total	2.00 g

The above components are admixed with each other and the mixture is cast into suppository moulds.

In the above composition sodium salicylate can be replaced by lithium salicylate.

Example 3.

Film-coated tablets containing acetylsalicylic acid and sodium salicylate as active agents

Composition of one tablet:	
acetylsalicylic acid	200 mg
sodium salicylate	200 mg
magnesium stearate	4 mg
Eudragit-L	15 mg
talc	18 mg
polyvinylpyrrolidone	20 mg
potato starch	58 mg
microcrystalline cellulose	100 mg
total	615 mg

The tablets are prepared by direct pressing and film-coated with Eudragit-L[2] to obtain enteric compositions.

Tablets containing another alkali metal salicylate instead of sodium salicylate, or containing a pharmaceutically acceptable salt (e.g. calcium salt) of acetylsalicylic acid instead of the free acid can be prepared by similar methods.

Example 4.

Suppositories containing acetylsalicylic acid and sodium salicylate as active agents

Composition of one suppository:	
acetylsalicylic acid	0.2 g
sodium salicylate	0.2 g
Witepsol H-15	1.6 g
total	2.0 g

The suppositories are prepared as described in Example 2. Suppositories containing cal-

cium acetylsalicylate instead of the free acid, or another alkali metal salicylate instead of sodium salicylate can be prepared by completely analogous methods.

Example 5.

Film-coated tablets containing acetylsalicylic acid and sodium salicylate as active agents

Composition of one tablet:

acetylsalicylic acid	200 mg
sodium salicylate	300 mg
magnesium stearate	5 mg
talc	20 mg
Eudragit-L	20 mg
polyvinyl pyrrolidone	25 mg
potato starch	100 mg
microcrystalline cellulose	150 mg
total	820 mg

The enteric tablets are prepared as described in Example 3.

Example 6.

Film-coated tablets containing phenylbutazone and sodium salicylate as active agents

Composition of one tablet:

phenylbutazone	100 mg
sodium salicylate	250 mg
magnesium stearate	3 mg
polyvinyl pyrrolidone	10 mg
talc	15 mg
Eudragit-L	15 mg
potato starch	122 mg
total	515 mg

The enteric tablets are prepared as described in Example 1.

In the above composition phenylbutazone may be replaced by its sodium or calcium salt, and sodium salicylate may be replaced by salicylic acid or lithium salicylate.

Example 7.

Injectable compositions containing phenylbutazone and sodium salicylate as active agents

Composition of one unit dosage:

phenylbutazone	100 mg
sodium salicylate	250 mg
sodium pyrosulfite	0.3 mg
ethylenediamine tetraacetate	0.6 mg
lidocaine hydrochloride	6.0 mg
sodium hydroxide	14.0 mg
benzyl alcohol	30.0 mg
ethyleneglycol monoethylether	1000.0 mg
distilled water pro inj.	3.0 ml

Phenylbutazone is dissolved in sodium hydroxide solution under heating, and ethyleneglycol monoethylether is added to the solution. In parallel, sodium salicylate, sodium pyrosulfite and ethylenediamine tetraacetate are dissolved in a part of the distilled water (oxygen-free and saturated with nitrogen). The two solutions are combined, then a solution of lidocaine hydrochloride in the remainder of the distilled water, and finally the benzyl alcohol are added. The solution is filtered, filled into dark vials, the vials are closed and sterilized by heating.

In the above composition sodium salicylate can be replaced by another alkali metal salicylate. Similarly, phenylbutazone can be replaced by a pharmaceutically acceptable salt thereof.

Example 8.

Film-coated tablets containing niflumic acid and sodium salicylate as active agents

Composition of one tablet:

niflumic acid	150 mg
sodium salicylate	250 mg
magnesium stearate	3 mg
polyvinyl pyrrolidone	12 mg
Eudragit-L	15 mg
talc	18 mg
potato starch	167 mg
total	615 mg

The enteric tablets are prepared as described in Example 1.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition containing as an antiphlogistic agent indomethacin, niflumic acid, phenylbutazone or acetylsalicylic acid or a pharmaceutically acceptable salt of any of these compounds, and 0.2 to 50 parts by weight of salicylic acid or an alkali metal salicylate for one part by weight of the antiphlogistic agent.

2. A composition as claimed in claim 1 wherein the alkali metal salicylate is used.

3. A composition as claimed in claim 2 wherein the alkali metal salicylate is sodium salicylate or lithium salicylate.

4. A composition as claimed in any one of claims 1 to 3, which further comprises a carrier, a diluent or an auxiliary agent.

5. A composition as claimed in claim 4 in the form of a tablet, a capsule, a suppository or an injectable solution.

6. A composition as claimed in claim 5 wherein the tablet is a sugar coated tablet (as herein defined) or a film-coated tablet.

7. A process for the preparation of a pharmaceutical dosage form wherein an antiphlogistic agent selected from indomethacin, niflumic acid, phenylbutazone or acetylsalicylic acid, or a pharmaceutically acceptable salt of any of these compounds, and 0.2 to 50 parts by weight, based on the weight of

cium acetylsalicylate instead of the free acid, or another alkali metal salicylate instead of sodium salicylate can be prepared by completely analogous methods.

Example 5.

Film-coated tablets containing acetylsalicylic acid and sodium salicylate as active agents

Composition of one tablet:	
acetylsalicylic acid	200 mg
sodium salicylate	300 mg
magnesium stearate	5 mg
talc	20 mg
Eudragit-L	20 mg
polyvinyl pyrrolidone	25 mg
potato starch	100 mg
microcrystalline cellulose	150 mg
total	820 mg

The enteric tablets are prepared as described in Example 3.

Example 6.

Film-coated tablets containing phenylbutazone and sodium salicylate as active agents

Composition of one tablet:	
phenylbutazone	100 mg
sodium salicylate	250 mg
magnesium stearate	3 mg
polyvinyl pyrrolidone	10 mg
talc	15 mg
Eudragit-L	15 mg
potato starch	122 mg
total	515 mg

The enteric tablets are prepared as described in Example 1.

In the above composition phenylbutazone may be replaced by its sodium or calcium salt, and sodium salicylate may be replaced by salicylic acid or lithium salicylate.

Example 7.

Injectable compositions containing phenylbutazone and sodium salicylate as active agents

Composition of one unit dosage:	
phenylbutazone	100 mg
sodium salicylate	250 mg
sodium pyrosulfite	0.3 mg
ethylenediamine tetraacetate	0.6 mg
lidocaine hydrochloride	6.0 mg
sodium hydroxide	14.0 mg
benzyl alcohol	30.0 mg
ethyleneglycol monoethylether	1000.0 mg
distilled water pro inj.	3.0 ml

Phenylbutazone is dissolved in sodium hydroxide solution under heating, and ethyleneglycol monoethylether is added to the solution. In parallel, sodium salicylate, sodium pyrosulfite and ethylenediamine tetraacetate are dissolved in a part of the distilled water (oxygen-free and saturated with nitrogen). The two solutions are combined, then a solution of lidocaine hydrochloride in the remainder of the distilled water, and finally the benzyl alcohol are added. The solution is filtered, filled into dark vials, the vials are closed and sterilized by heating.

In the above composition sodium salicylate can be replaced by another alkali metal salicylate. Similarly, phenylbutazone can be replaced by a pharmaceutically acceptable salt thereof.

Example 8.

Film-coated tablets containing niflumic acid and sodium salicylate as active agents

Composition of one tablet:	
niflumic acid	150 mg
sodium salicylate	250 mg
magnesium stearate	3 mg
polyvinyl pyrrolidone	12 mg
Eudragit-L	15 mg
talc	18 mg
potato starch	167 mg
total	615 mg

The enteric tablets are prepared as described in Example 1.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition containing as an antiphlogistic agent indomethacin, niflumic acid, phenylbutazone or acetylsalicylic acid or a pharmaceutically acceptable salt of any of these compounds, and 0.2 to 50 parts by weight of salicylic acid or an alkali metal salicylate for one part by weight of the antiphlogistic agent.

2. A composition as claimed in claim 1 wherein the alkali metal salicylate is used.

3. A composition as claimed in claim 2 wherein the alkali metal salicylate is sodium salicylate or lithium salicylate.

4. A composition as claimed in any one of claims 1 to 3, which further comprises a carrier, a diluent or an auxiliary agent.

5. A composition as claimed in claim 4 in the form of a tablet, a capsule, a suppository or an injectable solution.

6. A composition as claimed in claim 5 wherein the tablet is a sugar coated tablet (as herein defined) or a film-coated tablet.

7. A process for the preparation of a pharmaceutical dosage form wherein an antiphlogistic agent selected from indomethacin, niflumic acid, phenylbutazone or acetylsalicylic acid, or a pharmaceutically acceptable salt of any of these compounds, and 0.2 to 50 parts by weight, based on the weight of

the antiphlogistic agent, of salicylic acid or an alkali metal salicylate are compounded with conventional carriers, diluents and/or auxiliary agents to produce the required dosage form.

8. A process as claimed in claim 7 wherein the alkali metal salicylate is used.

9. A process as claimed in claim 8 wherein the alkali metal salicylate is sodium salicylate or lithium salicylate.

10. A pharmaceutical composition as claimed in claim 1 substantially as hereinbefore described in any one of the examples.

11. A process as claimed in claim 7 for the preparation of a pharmaceutical composition substantially as hereinbefore described in any one of the Examples.

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