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(54) Title: SOLID DOSAGE FORMS OF ALMOKALANT AND PROCESSES FOR MANUFACTURE THEREOF

(57) Abstract: Orally administrable pharmaceutical compositions of almokalant comprising a complex of almokalant with polystyrene sulphonate, and optionally one or more pharmaceutical excipients. The compositions are manufactured by reacting almokalant with polystyrene sulphonic acid to form a complex, optionally mixing with one or more pharmaceutical excipients and forming into orally administrable solid dosage form.

AP 258

(56) Documents cited: EP 0 322 390

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Field of the invention

This invention relates to solid dosage forms of the antiarrhythmic drug almokalant (p-INN) formulated as immediate release (IR) tablets and extended release (ER) tablets as well as processes for manufacture thereof.

Specifically the invention relates to the use of the polystyrene sulphonate complex of almokalant in solid dosage forms.

Background of the invention

No solid dosage forms containing the polystyrene sulphonate complex of almokalant have been reported. The polystyrene sulphonate complex of almokalant is described in European patent application EP 90840242.0 (Publication No. 0404747 A1), which was not publicly available at the time of filing the basic application in Sweden, but was published shortly thereafter.

Almokalant (p-INN), 4-[3-[ethyl[3-(propylsulfinyl)-propyl]amino]-2-hydroxypropoxy]-benzonitrile free base is a viscous, sticky substance, problematic to handle in the manufacture of solid dosage forms. It has pronounced tendency to give a repellent odorous degradation product with a smell resembling old onions.

Several different method of preparing a solid dosage form of almokalant have been tested. Commonly used methods had the following disadvantages.

Due to the instability of the base and its tendency to

worsen tablet binding properties, solid dosage forms of the free base are difficult to produce. See further reference example III.

Tablets prepared by conventional technique, with almokalant dissolved in an acidic granulating solution, have inferior stability properties and develop a repelling onion-like odour. See further reference examples I and III.

The use of complexes of drug substances with ion exchange resins in pharmaceutical formulations has been described previously. A way to obtain a controlled release suspension containing codeine is described by Amsel L.P. et al "Unique Oral Controlled Release Systems": In-Vivo Drug Release Pattern pp 83-93 where a complex between codeine and an ion exchange resin is coated with a diffusion membrane and then formulated into a suspension. In addition, Pennwalt Corporation has published a series of patents describing the use of ion exchange resins having pharmacologically active substances absorbed thereon for use in controlled release preparations either as such or further coated with diffusion membranes (US Pat 4,221,778, EP 0171 528, EP 0 254 811). Other uses of ion exchange resin complexes with drugs in pharmaceutical formulations are for example summarized by Raghunathan et al. J Pharm Sci 1981, 70, (No 4), 379-384.

Description of the invention

The aim of the present invention is to provide solid dosage forms of the antiarrhythmic drug almokalant, formulated as IR-tablets and ER-tablets with improved stability and minimal odour. ER-tablets can be formulated by a variety of formulation principles, such as for instance hydrophilic gel-matrix tablets, matrix tablets, membrane diffusion controlled formulations, osmotic pressure controlled dosage forms etc.

As the use of solid substances in tablet manufacture in general is advantageous and facilitates the production, different ways of preparing solid dosage forms have been investigated.

As it was noticed that the compound almokalant as such in acidic solutions has a good stability, which makes it possible to autoclave it without noteworthy degradation, the addition of acid compounds was tested.

Although complex-binding to ion-exchange resins of viscous, unstable, pharmacologically active agents, to form a stable solid complex suitable for pharmaceutical processing has not been previously described, this was tested with almokalant.

Thus, it was tested to use the polystyrene sulfonate complex of almokalant in the formulation of pharmaceutical dosage forms. It was then unexpectedly found that almokalant polystyrene sulphonate complex (A-PSS) had a much better stability, less repelling odour and was much easier to handle in tablet manufacture.

To form ER tablets it is necessary to mix the formed complex with e.g. a hydrophilic matrix. It is especially preferable to use hydroxypropyl methylcellulose as the gel forming substance. It is further preferred to use a mixture of HPMC containing both low and high molecular weight HPMC.

The use of different mixtures of HPMC gives according to known technics (Journal of Controlled release, 5 (1987) 159-172), different release rates of the active ingredient almokalant.

EXAMPLES

Example 1

Immediate release tablets of almokalant were prepared by mixing A-PSS 90 parts, lactose 85 parts, microcrystalline cellulose 91 parts and polyvinyl pyrrolidone 27 parts and then granulating the mixture with purified water.

After drying the granulate was milled and then mixed with sodium stearyl fumarate and compressed to tablets.

A reference preparation was produced by dissolving the free base in a 2M hydrochloric acid solution and using this solution to granulate the excipients.

	A-PSS tablet Ex 1	Ref. Ex I
1. A-PSS corresp. to almokalant	50.0	-
Almokalant	-	50.0
2. Lactose pwd	84.5	-
Lactose anhydrous	-	106.8
Avicel® PH 101	91.3	114.0
Povidone® K-25	26.8	-
Polyvinyl pyrrolidone, cross-linked	-	7.1
Aerosil®	-	3.6
3. Water, purified	105	-
Hydrochloric acid 2M	-	71.2
(corresp. to HCl)	-	(5.2)
4. Sodium stearyl fumarate	5.8	-
Magnesium stearate	-	2.9
Talcum	-	11.5
Polyvinyl pyrrolidone, cross-linked	-	5.7

The A-PSS tablet was prepared by first mixing ingredients 1 and 2. The mixture was granulated with 3. After drying and milling 4 was admixed, whereupon compression to

tablets was performed on a Korsch Pharmapress 100.

The reference tablet (Ref. ex. I) was prepared by making a granulating solution of the ingredients 1 and 3. The powders in 2 were mixed and then granulated with the prepared solution. After drying and milling the lubricant, glidant and disintegrant in 4 were admixed and tablets compressed on the same machine.

	A-PSS tablet. Ex. 1	Ref.ex. I
Punches:	9 mm	10 mm
Tablet weight:	298 mg	307 mg
Hardness:	7.5 kP	6.7 kP
Disintegration:	1-2 min.	1-2 min.

		Ex. 1 A-PSS tablet	Ref. Ex. I
Stability data of storage in glass bottles. Degradation measured as area sum of byproducts in a HPLC-system			
0	month	0.81	2.11
1	month in 25°C	0.88	2.83
1	month in 50°C	1.82	3.41
3.5	months in 25°C	0.88	2.87

Example 2

Immediate release tablets of almokalant were prepared by mixing A-PSS 90 parts, lactose 85 parts, microcrystalline cellulose 91 parts and polyvinyl pyrrolidone 27 parts and then granulating the mixture with purified water. After drying the granulate was milled and then mixed with the lubricant sodium stearyl fumarate and then tablets were formed by compression.

A reference preparation (Ref. ex. II) was produced by dissolving the free base in an aqueous tartaric acid solution and using this solution to granulate the excipients.

	A-PSS tablet Ex 2	Ref. tablet Ex II
1. A-PSS corresp. to almokalant	50.0	-
Almokalant	-	50.0
2. Lactose pwd	84.5	-
Lactose anhydrous	-	110.7
Avicel® PH 101	91.3	114.3
Polyvidone® K-25	26.8	-
3. Water, purified	105	57.1
Tartaric acid	-	21.5
4. Sodium stearyl fumarate	5.8	6.0
Talcum	-	12.0
Polyvinyl pyrrolidone, cross-linked	-	12.0
Punches:	9 mm	10mm
Tablet weight:	298 mg	331mg
Hardness:	7.5 kP	5.9kP
Disintegration:	1-2 min.	8min.

The A-PSS tablets were prepared by first mixing ingredients 1 and 2. The mixture was granulated with 3. After drying and milling 4 was admixed, whereupon compression to tablets were performed on a Korsch Pharmapress 100.

The reference tablet (Ref. ex. II) was prepared by making a granulating solution of 1 and 3. The powders 2 were mixed and granulated with the solution. After drying and milling the lubricant, glidant and disintegrant in 4 were admixed and tablets were compressed on the same machine.

The odour intensity of the two formulations were compared

immediately after manufacturing and after 1 month of storage in glass bottles.

	Odour intensity	
	A-PSS tablets Ex. 2	Ref. Ex. II
Freshly prepared	+ (some smell, but not of onions.)	++ (pronounced smell of onions.)
1 month	+ (some smell, but not of onions.)	+++ (strong smell of of onions)

Example 3

Immediate release tablets of almokalant can be prepared in suitable strengths.

In Ex. 1 and 2 a 50 mg preparation was described. Below are examples of 70 mg and 1.8 mg preparations shown.

	Ex 3a 70 mg	Ex 3b 1.8 mg
1. A-PSS	127	3.3
Avicel® PH 101	148	29
Polyvidone® K-90	35	-
2. Polyvidone® K-90	10	-
Polyvidone® K-25	-	4.7
Water, purified	161	19
3. Avicel® PH102 coarse grade	-	107
Polyvinyl pyrrolidone, cross-linked	-	4.3
Sodium stearyl fumarate	1.6	1.4

The A-PSS tablets were prepared by first mixing the ingredients 1. The mixture was granulated with a solution made of ingredients 2. After drying and milling ingredients 3 were admixed, whereupon compression to tablets were performed on a Korsch Pharmapress 100.

Punches:	10 mm	5.5x10.5 mm
Tablet weight:	322 mg	150 mg
Hardness:	9-10 kP	9-10 kP
Disintegration (without discs):	0.6-1.0 min.	0.2-0.4 min.

Example 4

Extended release tablets of almokalant were prepared by mixing A-PSS 95 parts, hydroxypropyl methylcellulose (HPMC) 50 cps 40 parts, HPMC 10000 cps 160 parts and hydroxypropyl cellulose (HPC) 50 parts and then granulating the mixture with ethanol 99.5%. After drying the granulate was milled and then mixed with sodium stearyl fumarate whereupon compression to tablets was done.

A reference preparation (Ref. ex. III) was made by dissolving the free base in ethanol (99.5%) and using this solution to granulate the dry excipients, and otherwise following the same way of production.

Ingredient	Example 4 mg/tablet	Ref.ex. III mg/tablet
1. A-PSS corresp. to almokalant	50.0	-
Almokalant	-	50.0
2. HPMC 50 cps (Metolose® 60SH50)	40.0	40.0

3. HPMC 10000 cps (Methocel® E10MCR)	160.0	160.0
4. HPC LF (Klucel® LF)	50.0	50.0
5. Ethanol 99.5%	261	235
6. Sodium stearyl fumarate (Pruv®)	3.3	3.3

Ingredients 1 to 4 were mixed. The mixture was granulated with ethanol. After drying and milling the granulate was mixed with 6.

Compression to tablets was performed on a Korsch Pharmapress 100 with 11 mm circular punches. The tablet machine was equipped with compression force registration.

Tablet weight:	348 mg	303 mg
" compression force:	8.6 kN	12.3 kN
" hardness:	5.5 kP	3.7 kP

Tablets made using the free base have inferior binding properties.

Odour intensity

	A-PSS tablets (Ex. 4)	Reference tablet (Ref.ex. III)
Freshly prepared	+ (some smell, but not of onions.)	+++ (strong smell of onions.)

The release rate was determined from 6 individual tablets using USP dissolution apparatus 2 with the paddle rotating at 100 r/min and the tablet placed in a stationary basket above the paddle, 500 ml buffer solution pH 6.8 kept at 37°C was used as dissolution medium.

hours	A-PSS tablet (Ex. 4) cumulative % released average (min-max)	Ref. tablet (Ref.ex. III) cumulative % released average (min-max)
2	15 (14-15)	28 (28-29)
4	24 (23-25)	43 (42-43)
6	34 (33-35)	55 (54-56)
10	51 (48-52)	74 (72-75)
24	91 (87-93)	102(100-105)

Example 5

Extended release tablets of almokalant can be prepared in suitable strengths and with different release rates.

In Ex. 4 a preparation with 50 mg strength is described. Below follows examples of 10 mg and 100 mg.

Ingredient	10 mg Ex. 5a mg/tablet	100 mg Ex. 5b mg/tablet
1. A-PSS corresp. to almokalant	10.0	100.0
2. Lactose pwd	100.0	40.0
HPMC 50 cps (Metolose® 60SH50)	27.6	39.2
HPMC 10000cps (Methocel® E10MCR)	110.4	146.4
HPC LF (Klucel® LF)	25.0	-
3. Polyethylene glycol 20M (Carbowax® 20M)	30.0	-
Polyethylene glycol 6000 (Carbowax® 6000)	-	42.0
4. Water, purified	70.0	98.1
5. Sodium stearyl fumarate (Pruv®)	1.6	2.3

1 and 2 were mixed. The mixture was granulated with a solution made of 3 and 4. After drying and milling the granulate was mixed with 5.

Compression to tablets was performed on a Korsch Pharmapress 100. The tablet machine was equipped with compression force registration.

Punches, diameter:	10 mm	11 mm
Tablet weight:	314 mg	459 mg
" compression force (kN):	11.0	11.4
" hardness (kP):	8.2	5.4

The release rate was determined from 6 individual tablets using USP dissolution apparatus 2 with the paddle rotating at 100 r/min and the tablet placed in a stationary basket above the paddle. 500 ml buffer solution pH 6.8 kept at 37°C was used as dissolution medium.

	10 mg ER tablet	100 mg ER tablet
	Ex. 5a	Ex. 5b
	cumulative	cumulative
hours	% released	% released
	average (min-max)	average (min-max)
2	27 (27-28)	17 (17-18)
4	44 (43-45)	28 (26-29)
6	- - - - -	37 (35-39)
8	72 (70-75)	- - - - -
10	- - - - -	55 (52-60)
12	105 (96-109)	- - - - -
20	- - - - -	91 (84-95)
24	- - - - -	100(99-101)

Examples 6-7

Controlled release tablets were prepared by granulating 54.3 parts active substance, 30.0 parts mannitol, 154 parts HPMC 50 cps, 221 parts HPMC 10,000 cps, 37.5 parts HPC, 0.3 parts propyl gallate with a solution of 45 parts PEG 20,000 (Ex. 6) or PVP K-25 (Ex. 7) dissolved in 105 parts of water. The dried granulate was lubricated with 2.7 parts of sodium stearyl fumarate.

Ingredient	Example 6 mg/tablet	Example 7 mg/tablet
1. A-PSS corresp. to almokalant	30.0	30.0
2. Mannitol pwd	30.0	30.0
3. HPMC (Metolose® 60SH50)	154.0	154.0
4. HPMC (Methocel® E10MCR)	221.0	221.0
5. HPC (Klucel® LF)	37.5	37.5
6. Propyl gallate	0.3	0.3
7. PEG (Carbowax® 20M)	45.0	-
PVP (Povidone® K-25)	-	45.0
8. Water	105.0	105.0
9. Sodium stearyl fumarate (Pruv®)	2.7	2.7

Ingredients 1 to 6 were mixed. The mixture was granulated with a solution made of 7 and 8. After drying the granulate was mixed with 9.

Compression to tablets were performed on a Korsch Pharmapress 100 with 11 mm circular punches. The tablet machine was equipped with compression force registration .

	Example 6	Example 7
Tablet weight:	545 mg	545 mg

compression force (kN):	20	19
tablet hardness (kP):	7.7	12.2

The release rate was determined in USP dissolution apparatus 2 with the paddle rotating at 100 r/min and the tablet placed in a stationary basket above the paddle. 500 ml buffer solution pH 6.8 kept at 37°C was used as dissolution medium.

Cumulative % released
Average (min-max)

	Example 6	Example 7
2h	17(17-18)	18(17-18)
4h	28(28-29)	28(28-29)
6h	38(38-39)	38(37-39)
10h	55(54-56)	54(53-56)
16h	74(73-76)	73(71-74)

The examples show that PEG 20000 and PVP K-25 both function in the process.

Discussion

From the examples it can be seen that the use of almokalant free base in pharmaceutical formulations - apart from the inconvenience of handling a sticky, viscous substance - results in dosage forms with inferior stability and palatability as well as in inferior technical properties. The use of almokalant polystyrene sulphonate complex in pharmaceutical formulations eases the handling and results in more stable and more palatable dosage forms.
The best mode of carrying out the invention known at present is to prepare the formulation according to Examples 6-7.

CLAIMS

1. An orally administrable pharmaceutical composition of almokalant in solid dosage form, which comprises a complex of almokalant with polystyrene sulphonate, and optionally one or more pharmaceutical excipients.

2. A composition according to claim 1 which contains, as pharmaceutical excipient, a hydrophilic matrix.

3. A composition according to claim 2 wherein the hydrophilic matrix is hydroxypropyl methylcellulose.

4. A composition according to claim 3 wherein the hydroxypropyl methylcellulose contains both low and high molecular weight hydroxypropyl methylcellulose.

5. A composition according to any one of the preceding claims in tablet form.

6. A composition according to claim 1 substantially as hereinbefore described.

7. A composition according to claim 1 substantially as described in any one of the Examples.

8. A process for the manufacture of a composition as claimed in any preceding claim, which process comprises reacting almokalant with polystyrene sulphonic acid to form a complex, optionally mixing the complex with one or more pharmaceutical excipients, and forming into orally administrable solid dosage form in manner known per se.

9. A process according to claim 8, wherein there is used, as pharmaceutical excipient, a hydrophilic matrix.

10. A process according to claim 9, wherein the hydrophilic matrix is hydroxypropyl methylcellulose.

11. A composition according to claim 1 made by the process claimed in any one of claims 8 to 10.

Dated this 2nd day of DECEMBER 1991

PATENT AGENT FOR THE APPLICANT