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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 9/20, 47/38, 38/55, A61P 7/02

A1

(11) International Publication Number: WO 00/13671

(43) International Publication Date: 16 March 2000 (16.03.00)

(21) International Application Number: PCT/SE99/01471

(22) International Filing Date: 27 August 1999 (27.08.99)

(30) Priority Data:
9802973–9 3 September 1998 (03.09.98) SE

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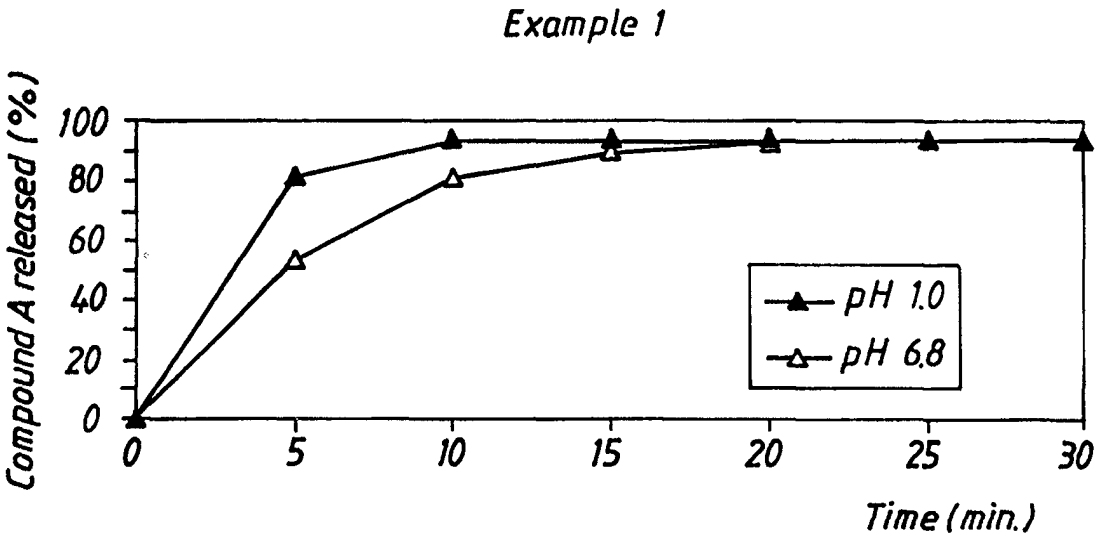
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IMMEDIATE RELEASE TABLET



(57) Abstract

A new oral IR formulation in solid form for a low molecular weight thrombin inhibitor having pH dependent dissolution, characterized in that the formulation comprises a filler or a combination of fillers having disintegrant properties in an amount higher than 35 % w/w of the formulation.

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IMMEDIATE RELEASE TABLET

Field of the invention

The invention relates to a solid dosage form of a low molecular weight thrombin inhibitor formulated as immediate release (IR) tablets as well as a process for manufacture thereof. The invention also relates to the medical use of the formulation in the prophylaxis and / or treatment of thromboembolism.

Background of the invention

The thrombin inhibitor, used in the formulation of the present invention is a low molecular weight drug with pH dependent solubility. It is characterised by a low solubility at basic pH which is dramatically increased in the protonated form at acidic pH. Thus, upon administration in conventional IR formulations, fast dissolution of the drug is obtained in acidic pH while markedly slower dissolution is obtained at more neutral pH. This variability in dissolution is not acceptable for safe, efficient and convenient therapy. The present invention provides an immediate release formulation based on conventional manufacturing processes with careful chosen excipients that provides a dissolution which is not , or very little dependent on pH.

Several different ways have been suggested in order to prepare immediate-release solid dosage forms.

Lachman (The theory and practice of industrial pharmacy 1986, 343, appA) describes the composition and manufacturing of two different standard granulates for IR tablets. These two compositions gave very poor quality of the granulates, which gave unacceptable tablets with very low hardness. These compositions do not work with the low molecular weight thrombin inhibitors used in connection with the present invention. The tablets do

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not answer to the definition of a rapidly dissolving drug product presented in Guidance for Industry. Waiver of in Vivo Bioavailability and Bioequivalens Studies for Immediate Release Solids Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on Biopharmaceutics Classification System. Tablets must release 85% or more of stated amount within 30 min.

Description of the invention

It has now been found that low molecular weight peptide-based thrombin inhibitors with pH-dependent solubility - including their salts - can be formulated as IR tablets with no or very little pH depending dissolution.

Therefore, the object of the present invention is to provide a novel pharmaceutical formulation comprising a low molecular weight peptide-based thrombin inhibitor formulated as an IR-tablet with no or very little pH depending dissolution and a process for the preparation of such formulation.

Thrombin inhibitors referred to in this application are low molecular weight peptide-based thrombin inhibitors with pH dependent solubility. The term "low molecular weight peptide-based thrombin inhibitors" will be well understood by one skilled in the art to include thrombin inhibitors with one to four peptide linkages, and/or with a molecular weight below 1000, and includes those described generically and, more preferably, specifically in the review paper by Claesson in Blood Coagul. Fibrin. (1994) 5, 411, as well as those disclosed in US Patent No. 4,346,078; International Patent Applications WO 97/23499, WO 97/02284, WO97/46577, WO 98/01422, WO 93/05069, WO93/11152, WO 95/23609, WO95/35309, WO 96/25426, WO 94/29336, WO WO 93/18060 and WO 95/01168; and European Patent Applications 623 596, 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317 and 601 459.

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Preferred low molecular weight peptide-based thrombin inhibitors include those known collectively as the "gatrans". Particular gatrans which may be mentioned include HOOC-CH_2(R)Cha-Pic-Nag-H (known as inogatran; see International Patent Application WO 93/11152 and the list of abbreviations therein) and HOOC-CH_2-(R)Cgl-Aze-Pab-H (known as melagatran; see International Patent Application WO 94/29336 and the list of abbreviations therein).

The preferred low molecular weight peptide-based thrombin inhibitor is selected from the group consisting of inogatran, *(Glycine, N-[2-[2-[[[3-[(aminoimino-methyl)amino]propyl]amino]carbonyl]-1-piperidinyl]-1-(cyclohexylmethyl)-2-oxoethyl]-, [2R-[2S]]-)*, melagatran, *(Glycine, N-[2-[2-[[[[4 (aminoiminomethyl)phenyl]-methyl]amino]carbonyl]-1-azetidinyl]-1-cyclohexyl-2-oxoethyl]-, [2R-[2S]]-)* and compound A, *(Glycine, N-[1-cyclohexyl-2-[2-[[[[4-[(hydroxyimino)aminomethyl]-phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]-, ethyl ester, [S-(R*, S*)]-)*.

The particularly preferred low molecular weight thrombin inhibitor Compound A is effective for the treatment of thrombo-embolism. Compound A is described in the International Patent Application WO 97/23499. Compound A is a low molecular weight thrombin inhibitor with good oral bioavaibility, low variability and limited food interaction. No solid dosage forms containing this thrombin inhibitor have been reported.

In order to produce tablets which provides a dissolution which is not or very little dependent on pH compound A should have a particle size less than 300 μm, preferably less than 150 μm and with a preferred mean particle size less than 80 μm. With other low molecular weight thrombin inhibitor with low solubility at basic pH and pH dependent solubility the requirements on the particle size will depend on the level of low solubility.

It has been found that by carefully selecting excipients the pH dependent dissolution could be reduced and giving a tablet release of more than 85% within 30 minutes in acidic as

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