Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2131350 C 2005/08/16

(11)(21) 2 131 350

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1994/09/01

(41) Mise à la disp. pub./Open to Public Insp.: 1995/03/04

(45) Date de délivrance/Issue Date: 2005/08/16

(30) Priorité/Priority: 1993/09/03 (P 43 29 794.3) DE

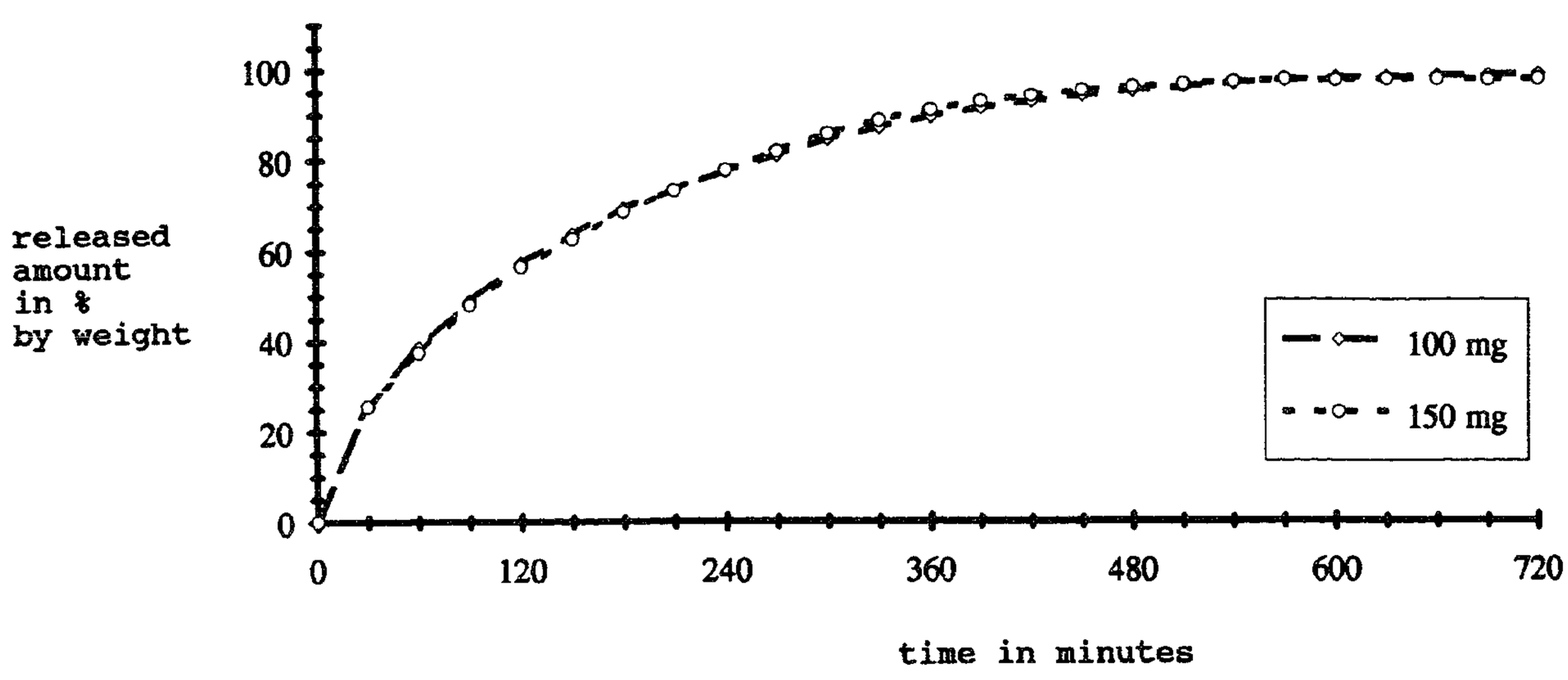
(51) Cl.Int.^{7}/Int.Cl.^{7} A61K 31/135, A61K 47/38, A61K 9/22

(72) Inventeur/Inventor:
BARTHOLOMAUS, JOHANNES HEINRICH ANTONIUS, DE

(73) Propriétaire/Owner:
GRUNENTHAL GMBH, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : FORMULATION MEDICAMENTEUSE A LIBERATION CONTINUE CONTENANT UN SEL TRAMADOL
(54) Title: SUSTAINED RELEASE DRUG FORMULATION CONTAINING A TRAMADOL SALT



(57) Abrégé/Abstract:
Drug formulations in tablet form for oral administration are disclosed from which a non-moisture sensitive, physiologicaloly acceptable tramadol salt is sustained released containing at least one pharmaceutically acceptable matrixing agent.

21

Abstract

Drug formulations in tablet form for oral administration are disclosed from which a non-moisture sensitive, physiologicaloly acceptable tramadol salt is sustained released containing at least one pharmaceutically acceptable matrixing agent.

Sustained release drug formulation containing a tramadol salt

~~G 2302~~

The invention relates to drug formulations in form of tablets for oral administration from which a non-moisture sensitive, physiologically acceptable salt of tramadol is released in a sustained manner and which contain at least one pharmaceutically acceptable matrixing agent.

Tramadolhydrochloride - (1RS;2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, hydrochloride - is an analgesic effective in severe and moderate severe pain. All drug formulations available on the market are immediate release forms resulting in a 3 to 4 times intake per day to get a good therapeutic effectiveness in chronic pain. Therefore it would be a desirable relief to the patients if the frequency of administration could be reduced to once or twice daily.

Several principles of sustained release formulations are known to a person skilled in the art. For example US patent No. 3,065,143 filed already on April 19, 1960 discloses a sustained release tablet containing at least one-third part by weight of the weight of the tablet of a pharmaceutically acceptable hydrophilic gum which rapidly absorbs water and swells at 37°C to form a soft mucilaginous gel barrier on the surface of the tablet when brought into contact with the aqueous fluids of the gastro-intestinal tract which prevents rapid disintegration of the tablet and release of the medicament contained therein when taken orally, but allows slow disintegration of the tablet and release of medicament over a period of at least four hours. However, the examples show that the release of the medicament is influenced by the pH value. For the release mechanism it is further described that the soft mucilaginous gum gel barrier is worn away by the motion of

the tablet in the gastro-intestinal tract, and some of the admixed medicinal agent is carried away with it and released. At the same time the protective coating at the surface of the tablet is renewed. This means that the release of the medicament is also influenced by mechanical stress. Further it is described that the velocity of release depends on the weight ratio of active ingredient to gum as well as on the content of hydrophilic gum in the tablet.

In US 4,389,393 (Reexamination Certificate B1 4,389,393) a carrier base material for moisture sensitive active ingredients is disclosed which is shaped and compressed to a solid unit dosage form and has a regular and prolonged release pattern upon administration. The carrier base material consists of one or more hydroxypropylmethylcelluloses or a mixture of one or more hydroxypropylmethylcelluloses and up to 30% by weight of the mixture of methylcellulose, sodium carboxymethylcellulose and/or other cellulose ether, wherein at least one of the hydroxypropylmethylcelluloses has a methoxy content of 16 - 24 % by weight, a hydroxypropyl content of 4 - 32 % by weight and a number average molecular weight of at least 50,000. The carrier base material constitutes 30% by weight or less of the solid unit dosage form and causes that at least four hours are required for the release of 94,4% of the moisture sensitive active ingredient from the dosage form following administration.

In Int. J. Pharm. Tech. & Prod. Mfr. 5, 1 (1984) hydrophilic matrices, especially hydroxypropylmethylcelluloses, are described for oral dosage forms with controlled release. At pages 4 to 6 it is explained that the velocity of drug release depends on the viscosity as well as on the amount of the employed polymer. Furthermore size and shape of the dosage unit influence the release, whereas practically no dependence on the manufacturing process by granu-

lation or by direct tabletting is observed. On the other hand different fillers show a pronounced influence on the drug release. According to Figures 16 and 18 insoluble excipients cause an acceleration of the release up to complete supression of the controlled release effect, independent on whether these compounds are swellable such as microcrystalline cellulose or are not swellable such as calcium hydrogen phosphate.

From Int. J. Pharm. 40, 223 (1987) it is known that the velocity of drug release from a sustained release tablet containing hydroxypropylmethylcellulose as the matrixing agent depends on the weight ratio of active substance to hydroxypropylmethylcellulose. The more this ratio is shifted in the favour of the active substance the higher is the velocity of release. In formulations having a filler content which is more than 50 % by weight the velocity of release is influenced by the type of the employed adjuvants. A partly exchange of hydroxypropylmethylcellulose by a filler and related to that a reduction of the hydroxypropylmethylcellulose content in the dosage form leads to an increase in the release velocity.

The matrix sustained release tablets described in J. Pharm. Sci. 57, 1292 (1968) lead to an increased release velocity when increasing the soluble portions in the hydrophilic matrix.

Object of the present invention was to provide a drug in tablet form for oral administration from which a non-moisture sensitive, well tolerated salt of tramadol is released in a prolonged manner independent on the pH value of the release environment and on the type and amount of the fillers. Further the release profile should be independent on the content of active ingredient and on the amount of the matrixing agent for a given mass and shape of the tablet. "Release profile" means the amount of ac-

tive ingredient released in % by weight of the total content of active ingredient plotted versus the examination time.

It has been found that the high requirements put on a tramadol salt containing sustained release formulation are fulfilled by a tablet formulation containing a non-moisture sensitive salt of tramadol and a selected pharmaceutically acceptable matrixing agent.

Subject matter of the invention are accordingly drug formulations in tablet form with sustained release of the active ingredient containing at least one non-moisture sensitive, physiologically acceptable salt of tramadol as active ingredient and at least one cellulose ether and/or cellulose ester which comprises a viscosity between 3,000 and 150,000 mPas in a 2 % by weight aqueous solution at 20°C as pharmaceutically acceptable matrixing agent.

Cellulose ethers and/or cellulose esters having a viscosity between 10,000 and 150,000 mPas in a 2 % by weight aqueous solution at 20°C are preferred as pharmaceutically acceptable matrixing agents. Particularly suitable pharmaceutically acceptable matrixing agents are selected from the group containing methylhydroxypropylcelluloses, hydroxyethylcelluloses, hydroxypropylcelluloses, methylcelluloses, ethylcelluloses, and carboxymethylcelluloses and most particularly selected from the group containing methylhydroxypropylcelluloses, hydroxyethylcelluloses, and hydroxypropylcelluloses.

In drug formulations according to the invention the content of active ingredient to be released in a prolonged way is in the range of 10 to 85 % by weight and the content of pharmaceutically acceptable matrixing agent in the range of 10 and 40 % by weight. Drug formulations with a content of active ingredient to be released in a prolonged

way in the range of 25 to 70 % by weight and a content of pharmaceutically acceptable matrixing agent in the range of 10 to 40 % by weight are most preferred.

The tablets according to the invention may contain pharmaceutically common excipients like fillers, e.g. lactose, microcristalline cellulose or calcium hydrogen phosphate, as well as parting compounds, lubricants and flow regulators, e.g. colloidal silicon dioxide, talc, magnesium stearate and/or stearic acid, in an amount between 0 and 80 % by weight, preferably between 5 and 65 % by weight.

In many cases the velocity of release of an active ingredient from a drug formulation depends on the pH value. During the gastro-intestinal passage of the drug formulation the pH value may vary from less than 1 to about 8. These fluctuations may be different from one drug taking person to another. There can also be variations in the pH value-versus-time-profile during the gasto-intestinal passage in the same person from one intake to another. A dependency on the pH value of the release velocity of the active ingredient can lead in-vivo to different release velocities. The release profiles of a tramadol salt from a drug formulation according to the invention, however, are surprisingly independent on pH values which may occur during the gastro-intestinal passage. The release profiles at surrounding pH values of 1.2, 4.0 and 6.8 are coincident to each other as well as to the release during a pH value-versus-time-profile starting from pH 1.2 over pH 2.3 and pH 6.8 up to pH 7.2.

In contrast to the mentioned prior art the release velocity of a tramadol salt from a drug formulation according to the invention is independent on the viscosity of the matrixing agent in the range between 3,000 and 150,000 mPas for a 2 % by weight aqueous solution as well as on the content of the matrixing agent and the filler.

Furthermore it is insignificant for the release profile of a tramadol salt containing sustained release tablet according to the invention whether the employed filler is a water soluble one such as lactose, or an insoluble, non-water swellable filler such calcium hydrogen phosphate, or an insoluble, water swellable filler such as microcrystalline cellulose, provided size and shape of the tablet and the composition regarding the active ingredient, the matrixing agent and the optional components are kept constant. All those drug formulations show coinciding release profiles.

Because of the high water-solubility particularly of tramadolhydrochloride and with regard to the teaching of the prior art that the content of soluble compounds in a drug formulation has an influence on the release velocity it has been expected that formulations with different contents of a tramadol salt would possess different release profiles. Further it has been expected that a change in the ratio of tramadol salt to matrixing agent would lead to a change in the release profile as well. Surprisingly it turns out that drug formulations according to the invention with different contents of active ingredient in which the overall content of the non-moisture sensitive, physiologically acceptable tramadol salt and the soluble or insoluble filler is kept constant show coinciding release profiles provided the tablet's size, shape, total mass and composition regarding the matrixing agent and the optional excipients remain unchanged.

Drug formulations according to the invention may be simple tablets as well as coated tablets such as film- or sugar-coated tablets. One or more coating layers can be applied for the coated tablets. Suitable coating materials are e.g. the well known methylhydroxypropylcelluloses which affect the release profile only to a minor extent. Known diffusion coatings e.g. on the basis of swellable, but

water-insoluble poly(meth)acrylates lead to an even more retarded release from drug formulations according to the invention. The active ingredient containing and slow releasing tablet core with an active ingredient content preferably between 10 and 85 % by weight, most preferably between 25 and 70 % by weight, may be coated with additional active ingredient, which is immediately released as an initial dose, by various known methods, e.g. by sugar-coating like methods, by spraying of solutions or suspensions, or by powder layering. Further suitable tablet forms are multi-layer and inlay type tablets. At least one tramadol salt is contained in a range of preferably 10 to 85 % by weight, most preferably 25 to 70 % by weight, in one or more layers of the multi-layer tablet or in the core of the inlay type tablet and is sustained released from this part of the tablet whereas the release of a tramadol salt from one or more layers of the multi-layer tablet respectively from the outer shell of the inlay type tablets is unsustained. Multi-layer and inlay type tablets may have one or more layers, shells or coatings without active ingredient.

The preparation of drug formulations according to the invention is characterized by a high reproducibility of the release properties of the obtained tramadol salt containing compositions. During a storage of at least one year there is no change in the release profile of drug formulations according to the invention.

Once or twice daily intake of a tablet according to the invention leads to good therapeutical effectiveness in patients with severe chronic pain.

Examples

Example 1

Matrix tablets consisting per tablet of

Tramadolhydrochloride	100 mg
Methylhydroxypropylcellulose type 2208, 100,000 mPas (Manufacturer: Dow Chemical Company, Midland/USA)	85 mg
Calcium hydrogen phosphate	62 mg
colloidal silicon dioxide	5 mg
Magnesium stearate	3 mg

were prepared in a batch size of 200 g by sieving all components through a 0.63 mm sieve, mixing in a cube blender for 10 minutes and pressing into tablets of a diameter of 9 mm, a radius of curvature of 8.5 mm and a mean weight of 255 mg by means of a Korsch EK 0 eccentric press.

By using the same method matrix tablets consisting per tablet of:

Tramadolhydrochloride	150 mg
Methylhydroxypropylcellulose type 2208, 100,000 mPas	85 mg
Calcium hydrogen phosphate	12 mg
colloidal silicon dioxide	5 mg
Magnesium stearate	3 mg

were prepared.

The in-vitro release of tramadolhydrochloride from the tablets was tested according to DAB 10 in a paddle apparatus. The temperature of the dissolution medium was 37°C and the rotation speed of the paddle was 75 r.p.m. At the beginning of the test each tablet was placed in 600 ml of

artificial gastric juice with a pH value of 1.2. After 30 minutes the pH value was raised to 2.3 by adding a sodium hydroxide solution, after further 90 minutes the pH value was raised to 6.5 and after another 60 minutes to 7.2. The amount of released active ingredient in the dissolution medium was measured by means of spectrophotometry. The following release values (mean of n = 3) were determined:

Time in minutes	Amount released in % by weight containing tramadolhydrochloride:	
	100 mg	150 mg
30	26	25
60	39	37
120	57	56
300	84	86
720	99	98

The in-vitro release curves of the tablets containing 100 mg or 150 mg of tramadolhydrochloride are given in Figure 1.

Example 2

Matrix tablets consisting per tablet of

Tramadolhydrochloride	200 mg
Methylhydroxypropylcellulose type 2208, 100,000 mPas (Manufacturer: Shin Etsu, Tokyo/Japan)	105 mg
Calcium hydrogen phosphate	36 mg
colloidal silicon dioxide	5 mg
Magnesium stearate	4 mg

were prepared in a batch size of 525 g in the following manner:

Tramadolhydrochloride, methylhydroxypropylcellulose, calcium hydrogen phosphate and 50 % of the amount of silicon dioxide and magnesium stearate each were sieved through a 0.5 mm sieve and mixed in a cube blender for 10 minutes. The obtained mixture was pressed to briquettes with a diameter of 20 mm by means of a Korsch EK 0 press.

After breaking of the obtained briquettes by means of a 1 mm sieve the remaining amounts of silicon dioxide and magnesium stearate were added and mixed followed by pressing the mixture into tablets of 10 mm diameter, 8 mm radius of curvature and a mean weight of 350 mg by means of a Korsch EK 0 press.

The in-vitro release of the active ingredient was tested according to the procedure of example 1. The following release values (mean of n = 2) were obtained:

Time in minutes	Amount released in % by weight
30	22
60	32
120	48
300	76
720	100

Example 3

The tablets prepared according to example 2 were coated in with a lacquer by means of a Wurster process. The lacquer was composed of

Eudragit RL 30 D (Manufacturer: Röhm, D-Darmstadt)	18.2 % by weight
Talc	8.2 % by weight
Titan dioxide	6.5 % by weight
Polyethylene glycol	1.6 % by weight

(Manufacturer: Hoechst AG, D-Frankfurt)

Triethyl citrate	1.1 % by weight
Demineralized water	64.4 % by weight

The coating caused an increase of the mean weight of the employed tablet cores by 20 mg. The in-vitro release of the active ingredient from the film-coated tablets was tested according to the procedure given in example 1. The following release values (mean of n = 2) were obtained:

Time in minutes	Amount released in % by weight
30	10
60	22
120	39
300	69
720	96

Example 4

As described in example 2 tablets with a mean weight of 350 mg were prepared containing instead of calcium hydrogen phosphate 36 mg of microcrystalline cellulose PH 101 (manufacturer: FMC, Philadelphia/USA) and instead of methylhydroxypropylcellulose either 105 mg of methylhydroxypropylcellulose type 2208 with a viscosity of 15,000 mPas (manufacturer: Shin Etsu) or 105 mg of methylhydroxypropylcellulose type 2208 with a viscosity of 50,000 mPas (manufacturer: Shin Etsu). The in-vitro release of the active ingredient was tested according to the procedure of example 1. The following release values (mean of n = 3) were obtained:

Time in minutes	Amount released in % by weight from the tablet containing the matrixing agent with a viscosity of:	
	15,000 mPas	50,000 mPas
30	23	23
60	35	34
120	51	50
300	79	79
720	103	103

The in-vitro release curves of the tablets containing methylhydroxypropylcellulose with a viscosity of 15,000 and 50,000 mPas respectively are given in Figure 2.

Example 5

As described in example 2 tablets with a mean weight of 350 mg and the following composition per tablet were prepared:

Tramadolhydrochloride	200 mg
Methylhydroxypropylcellulose type 2208, 50,000 mPas (Manufacturer: Shin Etsu)	50 mg
microcrystalline cellulose PH 101	91 mg
colloidal silicon dioxide	5 mg
Magnesium stearate	4 mg

The in-vitro release of the active ingredient was tested according to the procedure of example 1. The following release values (mean of n = 3) were obtained:

Time in minutes	Amount released in % by weight
30	21
60	33
120	49
300	78
720	98

The in-vitro release curves of the tablets containing either 50 mg corresponding to 14 % by weight or 105 mg corresponding to 30 % by weight (see example 4) of methyl-hydroxypropylcellulose with a viscosity of 50,000 mPas are given in Figure 3.

Example 6

Matrix tablets consisting per tablet of

Tramadolhydrochloride	100 mg
Methylhydroxypropylcellulose type 2910, 10,000 mPas (Manufacturer: Dow Chemical Company)	40 mg
microcrystalline cellulose PH 101	26 mg
colloidal silicon dioxide	2 mg
Magnesium stearate	2 mg

were prepared in a batch size of 510 g according to the procedure given in example 2. The tablets obtained had a diameter of 8 mm, a radius of curvature of 7.5 mm and a mean weight of 170 mg.

The in-vitro release of the active ingredient was tested according to the procedure of example 1. The following release values (mean of n = 2) were obtained:

Time in minutes	Amount released in % by weight
30	25
60	40
120	59
300	89
720	105

Example 7

Matrix tablets consisting per tablet of

Tramadolhydrochloride	150 mg
Hydroxypropylcellulose, 30,000 mPas (Klucel® 12, Hercules, Düsseldorf/Germany)	105 mg
microcrystalline cellulose PH 101	86 mg
colloidal silicon dioxide	5 mg
Magnesium stearate	4 mg

were prepared in a batch size of 350 g according to the procedure given in example 2. The in-vitro release of the active ingredient was tested according to the procedure of example 1. The following release values (mean of n = 2) were obtained:

Time in minutes	Amount released in % by weight
30	25
60	35
120	50
300	75
720	100

Example 8

Matrix tablets consisting per tablet of

Tramadolhydrochloride	150 mg
Hydroxyethylcellulose, 100,000 mPas (Natrosol® HHX, Hercules, Düsseldorf/Germany)	105 mg
microcrystalline cellulose PH 101	86 mg
colloidal silicon dioxide	5 mg
Magnesium stearate	4 mg

were prepared in a batch size of 350 g according to the procedure given in example 2. The in-vitro release of the active ingredient was tested according to the procedure of example 1. The following release values (mean of n = 2) were obtained:

Time in minutes	Amount released in % by weight
30	20
60	32
120	48
300	75
720	100

Claims

1) A drug formulation in tablet form with sustained release of the active ingredient containing at least one non-moisture sensitive, physiologically acceptable salt of tramadol as active ingredient and at least one cellulose ether and/or cellulose ester which comprises a viscosity between 3,000 and 150,000 mPas in a 2 % by weight aqueous solution at 20° C as pharmaceutically acceptable matrixing agent.

2) A drug formulation according to claim 1 wherein the matrixing agent is at least one cellulose ether and/or cellulose ester with a viscosity between 10,000 and 150,000 mPas in a 2 % by weight aqueous solution at 20° C.

3) A drug formulation according to claim 1 and/or claim 2 wherein the matrixing agent is selected from the group containing methylhydroxypropylcelluloses, hydroxyethylcelluloses, hydroxypropylcelluloses, methylcelluloses, ethylcelluloses and carboxymethylcelluloses.

4) A drug formulation according to claims 1 to 3 wherein the matrixing agent is selected from the group containing methylhydroxypropylcelluloses, hydroxyethylcelluloses and hydroxypropylcelluloses.

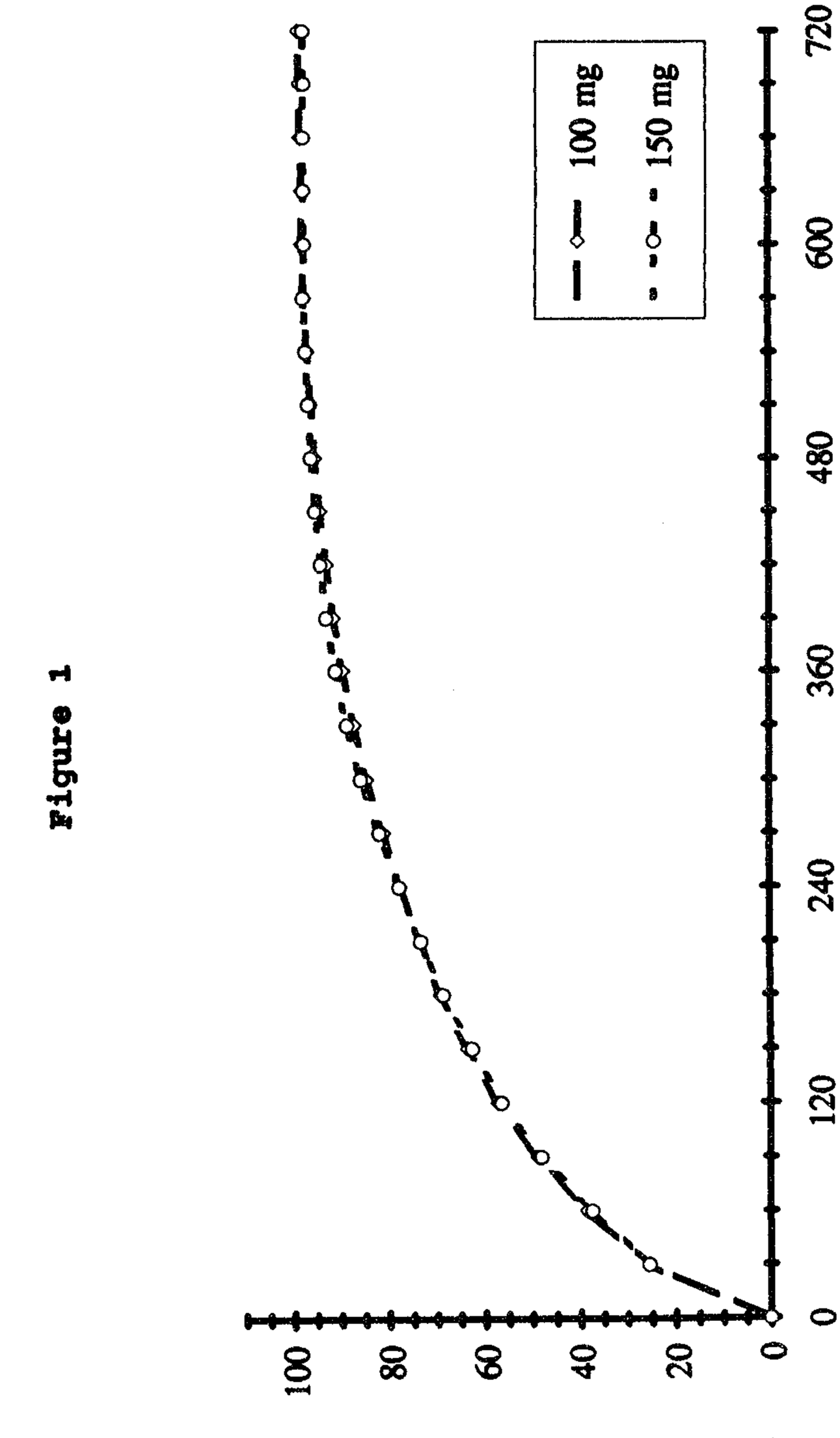
5) A drug formulation according to claims 1 to 4 wherein the content of the active ingredient which is sustained released is between 10 and 85 % by weight and the content of the matrixing agent is between 10 and 40 % by weight.

6) A drug formulation according to claims 1 to 5 wherein the content of the active ingredient which is sustained released is between 25 and 70 % by weight and the

content of the matrixing agent is between 10 and 40 % by weight.

Fetherstonhaugh & Co.,
Ottawa, Canada
Patent Agents

Figure 1



in-vitro release curves of tramadolhydrochloride from tablets prepared according to example 1, containing 100 mg or 150 mg of active ingredient

Figure 1:

Patent Agents
[illegible] & Co.

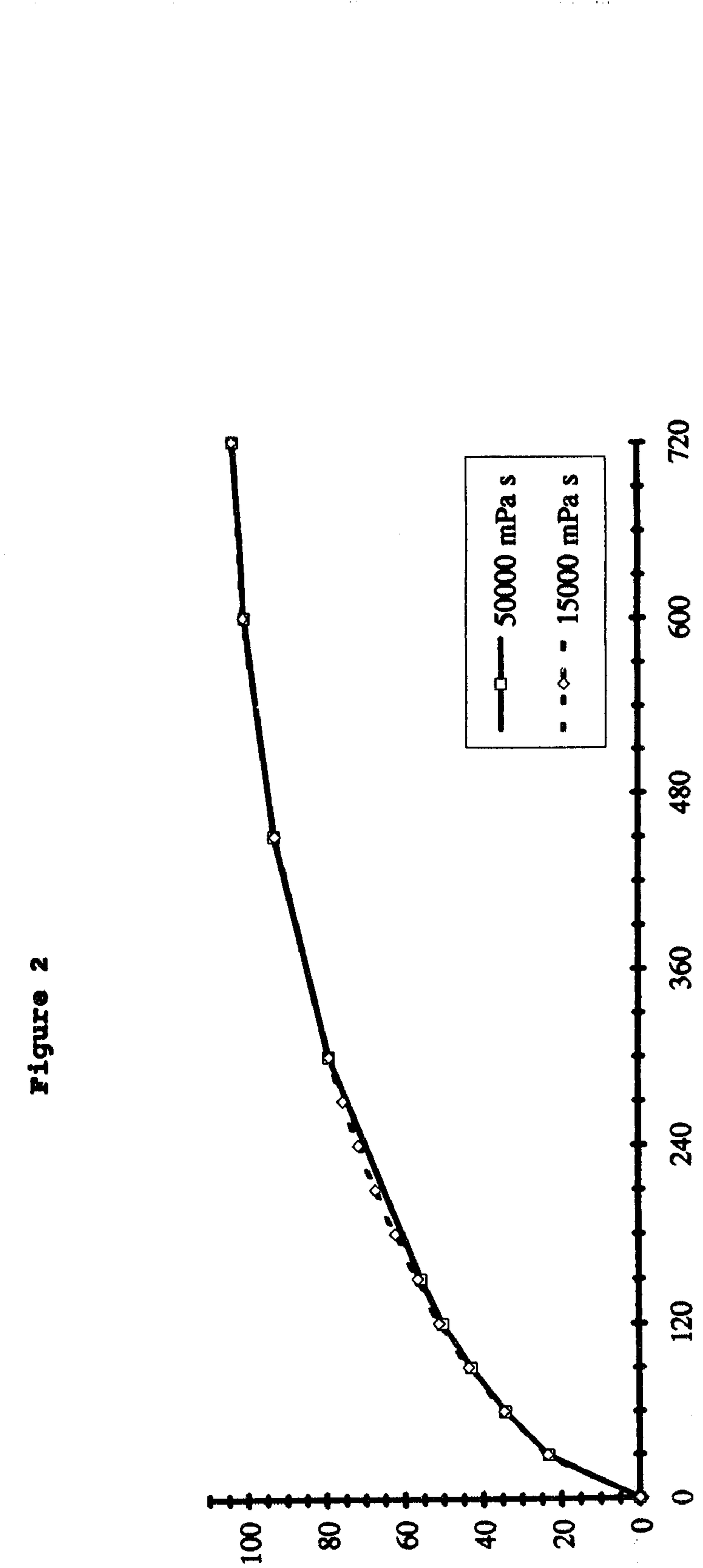
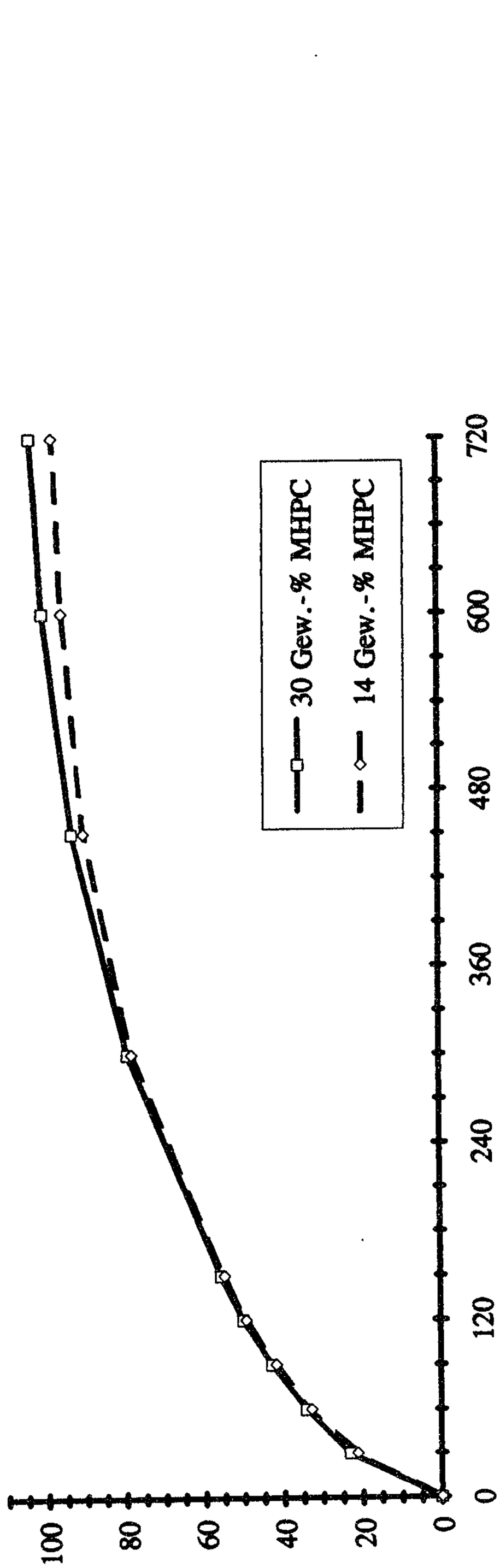


Figure 2: in-vitro release curves of tramadolhydrochloride from tablets prepared according to example 4 containing methylhydroxypropylcellulose of viscosity of 15,000 and 50,000 mPas

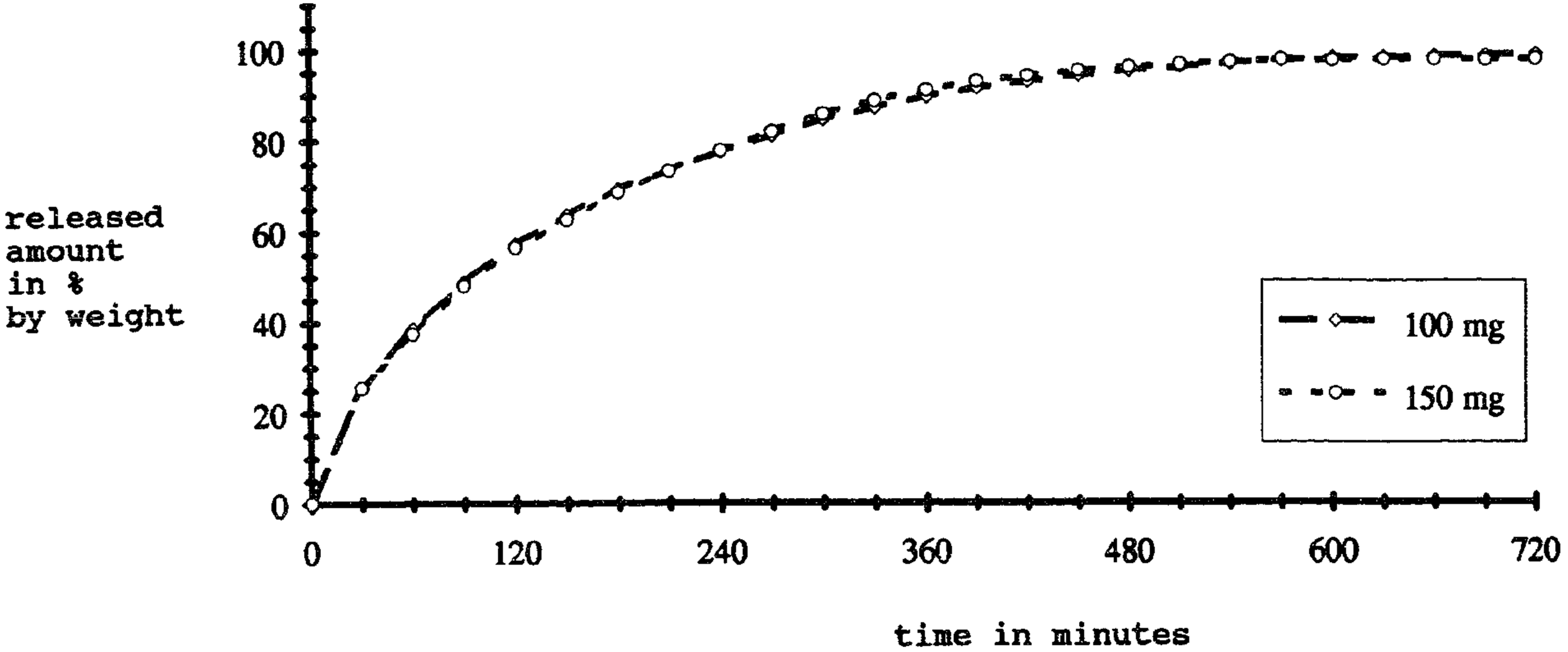
Patent Agents

Figure 3



in-vitro release curves of tramadolhydrochloride from tablets containing 30 weight-% (example 4) or 14 weight-% (example 5) of methylhydroxypropylcellulose (MHPC) of a viscosity of 50,000 mPas

Figure 3:


released amount in % by weight
100
80
60
40
20
0
0
120
240
360
480
600
720
time in minutes
100 mg
150 mg