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(54) Titre : COMPRIME A COUCHES MULTIPLES POUR L'ADMINISTRATION D'UNE COMBINAISON FIXE DE
TRAMADOL ET DE DICLOFENAC

(54) Title: MULTILAYERED TABLET FOR ADMINISTRATION OF A FIXED COMBINATION OF TRAMADOL AND
DICLOFENAC

(57) **Abrégé/Abstract:**

A multilayered tablet for oral administration, comprising at least one tramadol layer and diclofenac in at least one layer and/or the physiologically acceptable salt thereof. Said layers are separated from each other by means of a separating layer.



Abstract

A multilayered tablet for oral administration, comprising at least one tramadol layer and diclofenac in at least one layer and/or the physiologically acceptable salt thereof. Said layers are separated from each other by means of a separating layer.

**Multilayer Tablet for Administration of a Fixed Combination
of Tramadol and Diclofenac**

The present invention relates to a multilayer tablet
5 containing the active substances Tramadol and Diclofenac
and/or their in each case physiologically compatible salts,
the said active substances being separated from one another
by a separating layer.

10 Tramadol is an analgesic used to treat severe and
moderately severe pain, whose mode of action is not based
on a pure opioid mechanism. Tramadol does not exhibit the
characteristic side effects of an opioid. In some cases
nausea is observed as an undesirable accompanying symptom.

15

Other known, non-opioid analgesics suitable for treating
less severe pain include steroid-free analgesics such as
Diclofenac-Na, acetylsalicylic acid or Ibuprofen.

20 Furthermore, for the treatment of moderate to severe pain
it is recommended by the WHO to combine opioid analgesics
with non-steroidal analgesics in order to produce a more
effective pain relief and possibly reduce the necessary
application amounts.

25

European Patent EP-B 546 676 discloses for example that the
combination of Tramadol-HCl with non-steroidal anti-
inflammatories, such as for example Ibuprofen, in a
composition ratio of 1:1 to 1:200 produces a

30 synergistically enhanced analgesic action and reduces the
undesired accompanying symptoms. Tramadol-HCl and
Diclofenac-Na form a sparingly soluble compound however.
It is therefore to be expected that the bioavailability of

the two active substances is reduced and higher dosages are required in order to compensate for this.

The object of the present invention was accordingly to
5 combine the two active substances Tramadol and Diclofenac and/or their in each case physiologically compatible salts in a common application unit without however impairing the release profiles of the two active substances and reducing their bioavailability.

10

According to the invention this object is achieved by providing a multilayer tablet to be administered orally that contains in at least one layer Tramadol and/or its physiologically compatible salt and in at least one further
15 layer Diclofenac and/or its physiologically compatible salt, a separating layer being present in each case between the layers containing the active substances.

Preferably the tablet consists of seven layers,
20 particularly preferably of five layers and most particularly preferably of three layers.

The following compounds are preferably used as physiologically compatible salts of Tramadol: Tramadol
25 hydrochloride, Tramadol hydrobromide, Tramadol sulfate, Tramadol phosphate, Tramadol fumarate, Tramadol succinate, Tramadol maleate, Tramadol nitrate, Tramadol acetate, Tramadol propionate, Tramadol malonate, Tramadol citrate, Tramadol tartrate, Tramadol benzoate, Tramadol salicylate,
30 Tramadol phthalate and/or Tramadol nicotinate.

Particularly preferably Tramadol hydrochloride is used.

The following compounds are preferably used as physiologically compatible salts of Diclofenac: Diclofenac-

sodium, Diclofenac-potassium, Diclofenac-calcium, Diclofenac-magnesium and/or Diclofenac-cholestyramine. Particularly preferably Diclofenac-sodium is used.

- 5 The multilayer tablet to be used according to the invention may contain the conventional auxiliary substances and additives in the Tramadol-containing layer as well as in the Diclofenac-containing layer.
- 10 Preferably the multilayer tablet to be used contains in one or more layers in each case one of the two active substances, preferably uniformly divided, in a retarding (delayed release) matrix, whereby optimal, individually matched release values can be achieved. By combination
- 15 with the immediately released active substance an initial dose for a rapid pain relief can be achieved. The slow release from the retarded form permits the maintenance of therapeutic blood levels over a prolonged time.
- 20 The layers may also contain a retarded, particulate form of the respective active substance, preferably granules and/or pellets, particularly preferably pellets produced by extrusion and/or spheronisation. Particularly preferably
- 25 active substances will be adjusted so that the tablet has to be administered at most twice, and preferably only once per day.

The proportion of the two analgesics in relation to

30 auxiliary substances in the multilayer tablet is adjusted depending on the desired release duration and amount of the analgesics to be released. Preferably the content of Tramadol is 2 to 60 wt.%, more preferably 5 to 45 wt.% and

most particularly preferably 10 to 35 wt.%, referred to the total weight of the multilayer tablet. Preferably the proportion of Diclofenac is 2 to 30 wt.%, particularly preferably 5 to 25 wt.% and most particularly preferably 6 to 20 wt.%, referred to the total weight of the multilayer tablet. On the basis of the action of the analgesics the person skilled in the art knows what quantitative ratios of these analgesics should be used in order to achieve the desired effect of the active substances.

10

As matrix materials there may be used physiologically compatible, hydrophilic materials that are known to the person skilled in the art. There are preferably used as hydrophilic matrix materials polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins. Most particularly preferably ethyl-cellulose, hydroxypropylmethylcellulose, hydroxypropyl-cellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or its derivatives such as its salts, amides or esters, are used as matrix materials.

20

Particularly preferably there is used as physiologically compatible material for a retarding matrix at least one cellulose ether and/or cellulose ester whose 2 wt.% aqueous solution at 20°C has a viscosity of 3,000 to 150,000 mP·as, preferably 10,000 to 150,000 mP·as, optionally in combination with a filler that is not swellable in an aqueous medium, such as for example calcium hydrogen phosphate, or with an insoluble filler that is swellable in an aqueous medium, such as for example microcrystalline cellulose, or a filler that is soluble in aqueous media, such as for example lactose.

30

Also preferred is a matrix material of hydrophobic materials such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or their mixtures. Particularly preferably monoglycerides or diglycerides of C₁₂-C₃₀ fatty acids and/or C₁₂-C₃₀ fatty alcohols and/or waxes or their mixtures are used as hydrophobic materials.

10 It is also possible to use mixtures of the aforementioned hydrophilic and hydrophobic materials as retarding matrix material.

In a preferred embodiment the separating layer is slightly permeable with respect to the two active substances also on contact with aqueous body fluids. This separating layer is preferably based on a polymer, a wax, a fat, a fatty acid, a fatty alcohol or a corresponding ether or ester or a mixture thereof, and has a melting point of $\geq 40^{\circ}\text{C}$.

20 As physiologically compatible polymers there are preferably used cellulose acetate, ethylcellulose, cellulose butyrate, polyethylene or ethylene/vinyl acetate copolymers.

In a further preferred embodiment the separating layer is more specifically readily permeable with respect to the two active substances per se on contact with aqueous body fluids, the thickness of the separating layer then being adjusted however so that the two active substances do not come into contact with one another during the duration of the release.

To this end a permeable separating layer of the tablet may consist of hydroxyethylcellulose, hydroxypropylcellulose,

hydroxymethylcellulose and/or hydroxypropylmethylcellulose.

Furthermore the separating layer as well as the active substance-containing layers may include further auxiliary substances and additives. These may be fillers, preferably lactose, microcrystalline cellulose or calcium hydrogen phosphate, or slip agents, lubricants and/or flow regulating agents and/or plasticisers, preferably highly dispersed silicon dioxide, talcum, magnesium stearate and/or stearic acid.

The individual layers of the multilayer tablet according to the invention may also be formulated so that they dissolve from one another on contact with aqueous body fluids and thus release the active substances in a spatially separated manner. As physiologically compatible release agents that release the layers from one another on contact with aqueous body fluids, there may be used Crospovidon, Croscarmellose, sodium starch glycolate, starch and/or hydroxypropylcellulose having a low degree of substitution.

The present invention accordingly provides multilayer tablets that contain at least one release layer that effects a separation of the different layers from one another on contact with aqueous body fluids. It is however also possible for the layers to remain combined with one another on contact with aqueous body fluids and to release the active substances, separated by the separating layer, independently of one another.

With the multilayer tablet according to the invention a controlled release of both active substances can also be achieved by means of a coating that permits a controlled,

as a rule delayed release of the active substance in an aqueous medium. Suitable retard coatings include water-insoluble waxes or polymers, such as for example acrylic resins, preferably poly(meth)acrylates, or water-insoluble
5 celluloses such as ethylcellulose. These materials are known from the prior art, e.g. Bauer, Lehmann, Osterwald, Rothgang "Überzogene Arzneiformen" ("Coated Medicament Forms"), Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1988, p. 69 ff. They are introduced here by way
10 of reference.

In addition to the water-insoluble polymers, in the coating there may optionally also be used non-retarded, preferably water-soluble polymers in order to adjust the release rate
15 of the active substance, in amounts of up to 30 wt.%, such as polyvinylpyrrolidone or water-soluble celluloses, preferably hydroxypropylmethylcellulose or hydroxypropyl-cellulose, or water-soluble pore-forming agents such as for example lactose, NaCl, sucrose, and/or the known
20 plasticisers.

In addition to the retarding coating the multilayer tablet according to the invention may also be provided with further coatings. One such further coating may for example
25 dissolve in a manner dependent on the pH value. In this way a specific amount of active substance can pass undissolved through the stomach and be released only in the intestinal tract.

30 The multilayer tablet according to the invention may also have at least one score mark that enables the dose being administered to be subdivided, preferably halved. This permits the dosage to be matched to the individual

requirements of the patient, corresponding to the amount of the analgesics to be administered individually.

The invention accordingly also provides multilayer tablets
5 that have at least one score mark that enables the dose to be subdivided, preferably halved.

The multilayer tablets are produced according to known methods, such as are described for example in R. Voigt,
10 "Lehrbuch der pharmazeutischen Technologie", 6th Edition, p. 225 ff. They are introduced here by way of reference.

Preferably the production of the multilayer tablets is carried out by combining the constituents of the individual
15 layers first of all separately by mixing the individual constituents in a mixer, optionally followed by granulation. The different layers are then compressed in succession in a tablet press, preferably in a rotary pelleting machine to form a tablet, in such a way that due
20 to the separating layer the active substance-containing layers do not come into contact with one another.

The multilayer tablets according to the invention may be of the usual shapes and sizes. If the multilayer tablet
25 according to the invention contains coatings, then these may be applied by conventional processes, such as for example dragée coating, spraying of solutions, dispersion or suspensions, by melt processes or by powder application processes.

30

If the multilayer tablet according to the invention is intended to be administered twice a day, the release profile for the active substance Tramadol from the

multilayer tablet according to the invention is preferably controlled so that the released amount of Tramadol in percent referred to the total amount is 2 to 40%, preferably 5 to 30% after 30 minutes, 5 to 80%, preferably 20 to 60% after 120 minutes, 30 to 90%, preferably 35 to 75% after 240 minutes, 50 to 95%, preferably 60 to 90% after 360 minutes, 60 to 100%, preferably 70 to 100% after 480 minutes, and 70 to 100%, preferably 75 to 100% after 600 minutes. The release profile for the active substance Tramadol from the multilayer tablet according to the invention for a single daily application is preferably controlled so the released amount of Tramadol in percent referred to the total amount is 2 to 40%, preferably 5 to 30% after 60 minutes, 5 to 80%, preferably 20 to 60% after 240 minutes, 30 to 90%, preferably 35 to 75% after 480 minutes, 50 to 95%, preferably 60 to 90% after 720 minutes, 60 to 100%, preferably 70 to 100% after 960 minutes, and 70 to 100%, preferably 75 to 100% after 1200 minutes.

The release profile for the active substance Diclofenac from the multilayer tablet according to the invention for a twice daily application is preferably controlled so that so that the released amount of Diclofenac in percent referred to the total amount is 0% after 30 minutes, $\leq 5\%$ after 120 minutes, 5 to 50%, preferably 10 to 35% after 240 minutes, 30 to 95%, preferably 35 to 80% after 480 minutes, and 45 to 100%, preferably 60 to 100% after 600 minutes. The release profile for the active substance Diclofenac from the multilayer tablet according to the invention for a single application per day is preferably controlled so that the released amount of Diclofenac in percent referred to the total amount is $\leq 5\%$ after 120 minutes, 5 to 40%, preferably 10 to 30% after 240 minutes, 15 to 60%,

preferably 15 to 50% after 480 minutes, 30 to 80%,
preferably 35 to 80% after 720 minutes, and 50 to 100%,
preferably 60 to 100% after 1,200 minutes.

- 5 The present invention accordingly provides multilayer
tablets that are characterised in that in the case where
they are administered twice a day, in each case $\geq 70\%$ of the
Tramadol and $\geq 60\%$ of the Diclofenac is released within 8
hours. The invention furthermore provides multilayer
10 tablets that are characterised in that in the case where
they are administered once a day $\geq 70\%$ of the Tramadol and
 $\geq 60\%$ of the Diclofenac are released within 16 hours.

The release profiles were determined according to the
15 following method.

With gastric juice-resistant tablets the aforementioned
release profiles with regard to the Tramadol release times
as well as the residence time in the stomach should be
20 appropriately readjusted.

The release profiles of the multilayer tablets according to
the invention were determined as follows:

- 25 The tablets according to the invention were added to
600 ml of enzyme-free artificial gastric juice (pH 1.2) in
a release apparatus equipped with a paddle stirrer
according to the European Pharmacopoeia at a temperature of
the release medium of 37°C and a rotational speed of the
30 paddle stirrer of 75 m^{-1} , for 2 hours. The preparations
were then treated for a further 8 hours in 900 ml of
enzyme-free artificial intestinal juice (pH 7.2). The

amount of the respective active substance Tramadol or Diclofenac released in each case over time is determined by HPLC. The illustrated values and curves are the mean values of in each case 6 samples. The following examples
5 serve to illustrate the invention further without however restricting the general inventive concept.

Example 1:

10 The layers of the multilayer tablet according to the invention were first of all produced individually. For this purpose the active substance layer containing Tramadol hydrochloride was prepared by mixing Tramadol hydrochloride, microcrystalline cellulose,
15 hydroxypropylmethylcellulose, highly dispersed silicon dioxide and magnesium stearate in a cube mixer. The separating layer was prepared by mixing microcrystalline cellulose, hydroxypropylmethylcellulose, highly dispersed silicon dioxide and magnesium stearate in a cube mixer.
20 The active substance layer containing Diclofenac-Na was prepared by mixing micronised Diclofenac-Na, microcrystalline cellulose, hydroxypropylmethylcellulose, highly dispersed silicon dioxide and magnesium stearate in a cube mixer. The two layers containing the active
25 substances together with the interposed separating layer were then compressed in one workstage to form a three-layer tablet of diameter 12 mm. For this purpose in each case the successive layer amounts were lightly compressed in a matrix by means of an eccentric tableting machine,
30 following which the whole layer sequence was compressed. The tablet had a hardness of 100 to 130 N according to the Erweka breaking resistance tester.

Composition of the 3-layer tablet

Tramadol hydrochloride	100.00	mg	
Microcrystalline cellulose			
(Avicel PH 101, FMC)	82.00	mg	
Hydroxypropylmethylcellulose,			
100,000 mP·as (Metolose 90 SH			
100,000, ShinEtsu)	63.00	mg	
Highly dispersed silicon dioxide			
(Aerosil, Degussa)	2.50	mg	
Magnesium stearate	2.50	mg	1 st layer: 250 mg
Microcrystalline cellulose			
(Avicel PH 101, FMC)	71.00	mg	
Hydroxypropylmethylcellulose,			
100,000 mP·as (Metolose 90 SH			
100,000, ShinEtsu)	27.00	mg	
Highly dispersed silicon dioxide			
(Aerosil, Degussa)	1.00	mg	
Magnesium stearate	1.00	mg	Separating layer: 100 mg
Diclofenac-Na, micronised	50.00	mg	
Microcrystalline cellulose			
(Avicel PH 101, FMC)	132.00	mg	
Hydroxypropylmethylcellulose,			
100,000 mP·as (Metolose 90 SH			
100,000, ShinEtsu)	63.00	mg	
Highly dispersed silicon dioxide			
(Aerosil, Degussa)	2.50	mg	
Magnesium stearate	2.50	mg	3 rd layer: 250 mg
Total	600.00	mg	

The release profile was as follows and is shown in Fig. 1:

Time in mins.	Released Fraction in %	
	Diclofenac	Tramadol
30	0	21
120	0	40
240	11	54
360	14	59
480	32	72
600	48	77

Fig. 2 shows the release profile of a matrix tablet of diameter 12 mm containing 100 mg of Tramadol and 50 mg of Diclofenac compressed jointly in a hydrophilic matrix consisting of hydroxypropylmethylcellulose. A comparison of Figs. 1 and 2 shows that the amounts of the active substances Tramadol and Diclofenac released from the 3-layer tablet according to the invention after 8 hours are substantially larger than the release from the so-called joint matrix tablets.

Fig. 3 shows the release profile of retarded matrix tablets of diameter 10 mm containing as active substance only 100 mg of Tramadol in a hydrophilic matrix consisting of hydroxypropylmethylcellulose. A comparison of Figs. 1 and 3 shows that the amounts of Tramadol released from the 3-layer tablets according to the invention ($\geq 75\%$) correspond to the release from the Tramadol tablets per se ($\geq 80\%$).

Example 2

The preparation of the individual layers was carried out in a similar manner to Example 1. The two active substance-containing layers together with the interposed separating

layer were then compressed in a similar manner to form a 3-layer tablet of diameter 16 mm.

Composition of the 3-layer tablet

5

Tramadol hydrochloride	100.00	mg	
Microcrystalline cellulose			
(Avicel PH 101, FMC)	82.00	mg	
Hydroxypropylmethylcellulose,			
100,000 mP·as (Metolose 90 SH			
100,000, ShinEtsu)	63.00	mg	
Highly dispersed silicon dioxide			
(Aerosil, Degussa)	2.50	mg	
Magnesium stearate	2.50	mg	1 st layer: 250 mg
Microcrystalline cellulose			
(Avicel PH 101, FMC)	94.00	mg	
Crosslinked polyvinylpyrrolidone			
(Kollidon CL, BASF)	5.00	mg	
Magnesium stearate	1.00	mg	Separating layer: 100 mg
Diclofenac-Na, micronised	50.00	mg	
Microcrystalline cellulose			
(Avicel PH 101, FMC)	132.00	mg	
Hydroxypropylmethylcellulose,			
100,000 mP·as (Metolose 90 SH			
100,000, ShinEtsu)	63.00	mg	
Highly dispersed silicon dioxide			
(Aerosil, Degussa)	2.50	mg	
Magnesium stearate	2.50	mg	3 rd layer: 250 mg
Total	600.00	mg	

The release profile was as follows:

Time in mins.	Released Fraction in %	
	Diclofenac	Tramadol
30	0	35
120	0	71
240	14	85
360	18	90
480	37	95
600	56	99

5 Example 3

Tramadol hydrochloride and Diclofenac-Na were in each case mixed in a similar manner to Example 1 with microcrystalline cellulose, hydroxypropylmethylcellulose, highly dispersed silicon dioxide and magnesium stearate in a suitable mixer and were then compressed in a suitable tableting press together with an active substance-free intermediate layer of microcrystalline cellulose, crosslinked polyvinylpyrrolidone and magnesium stearate to form 3-layer tablets of size 7 mm x 14 mm with a score mark. The tablets have a hardness of 100-130 N.

Composition of the 3-layer tablet

Tramadol hydrochloride	100.00	mg	
Microcrystalline cellulose			
(Avicel PH 101, FMC)	82.00	mg	
Hydroxypropylmethylcellulose,			
100,000 mP·as (Metolose 90 SH			
100,000, ShinEtsu)	63.00	mg	
Highly dispersed silicon dioxide			
(Aerosil, Degussa)	2.50	mg	
Magnesium stearate	2.50	mg	1 st layer: 250 mg
Microcrystalline cellulose			
(Avicel PH 101, FMC)	94.00	mg	
Crosslinked polyvinylpyrrolidone			
(Kollidon CL, BASF)	5.00	mg	
Magnesium stearate	1.00	mg	Separating layer: 100 mg
Diclofenac-Na, micronised	50.00	mg	
Microcrystalline cellulose			
(Avicel PH 101, FMC)	132.00	mg	
Hydroxypropylmethylcellulose,			
100,000 mP·as (Metolose 90 SH			
100,000, ShinEtsu)	63.00	mg	
Highly dispersed silicon dioxide			
(Aerosil, Degussa)	2.50	mg	
Magnesium stearate	2.50	mg	3 rd layer: 250 mg
Total	600.00	mg	

5 The release profile was determined similarly to Example 1 and is shown in the following Table, the individual layers of the tablet dissociating from one another during the course of the first few hours of the release process and then in each case being present as separate units in the release apparatus and released.

Time in mins.	Released Fraction in %	
	Diclofenac	Tramadol
30	0	22
120	0	45
240	15	60
360	31	70
480	50	80
600	72	96

Patent Claims

1. Multilayer tablet containing in at least one layer Tramadol and in at least one layer Diclofenac and/or their in each case physiologically compatible salt, the active substance-containing layers in each case being separated from one another by a separating layer.
2. Multilayer table according to claim 1, characterised in that it contains as physiologically compatible salt of Tramadol: Tramadol hydrochloride, Tramadol hydrobromide, Tramadol sulfate, Tramadol phosphate, Tramadol fumarate, Tramadol succinate, Tramadol maleate, Tramadol nitrate, Tramadol acetate, Tramadol propionate, Tramadol malonate, Tramadol citrate, Tramadol tartrate, Tramadol benzoate, Tramadol salicylate, Tramadol phthalate and/or Tramadol nicotinate, particularly preferably Tramadol hydrochloride, and as physiologically compatible salt of Diclofenac: Diclofenac-sodium, Diclofenac-potassium, Diclofenac-calcium, Diclofenac-magnesium and/or Diclofenac-cholestyramine, preferably Diclofenac-sodium.
3. Multilayer tablet according to claim 1 or 2, characterised in that it consists of seven layers, preferably of five layers and particularly preferably of three layers.
4. Multilayer tablet according to one or more of claims 1 to 3, characterised in that the content of Tramadol-HCl is 2 to 60 wt.%, preferably 5 to 45 wt.% and

particularly preferably 10 to 35 wt.%, referred to the total weight of the multilayer tablet.

5. Multilayer tablet according to one or more of claims 1 to 4, characterised in that the content of Diclofenac-Na is 2 to 30 wt.%, preferably 5 to 25 wt.% and particularly preferably 6 to 20 wt.%, referred to the total weight of the multilayer tablet.
6. Multilayer tablet according to one or more of claims 1 to 5, characterised in that the Tramadol-containing and/or Diclofenac-containing active substance layer has in each case a layer thickness of 0.05 mm to 5 mm, preferably 0.1 mm to 4 mm and particularly preferably 1 mm to 3 mm.
7. Multilayer tablet according to one or more of claims 1 to 6, characterised in that at least one of the active substance-containing layers contains the active substance, preferably uniformly divided, in a retarding matrix.
8. Multilayer table according to claim 7, characterised in that the matrix contains at least a polymer, a wax, a fat, a fatty acid, a fatty alcohol or a corresponding ester or ether.
9. Multilayer table according to claim 8, characterised in that cellulose ethers, cellulose esters and/or acrylic resins are used as polymers.
10. Multilayer tablet according to one or more of claims 7 to 9, characterised in that ethylcellulose,

hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, monoglycerides and diglycerides of fatty acids with C₁₂-C₃₀ and/or fatty alcohols with C₁₂-C₃₀ or their mixtures are used as matrix material.

11. Multilayer tablet according to one or more of claims 1 to 10, characterised in that at least one layer contains a retarded, particulate form of Tramadol or Diclofenac and/or their corresponding physiologically compatible salts, preferably as granules, microcapsules and/or pellets, particularly preferably pellets produced by extrusion and/or spheronisation.
12. Multilayer tablet according to one or more of claims 1 to 11, characterised in that the separating layer has a layer thickness of 0.05 mm to 10 mm, preferably 0.1 mm to 5 mm and particularly preferably 0.15 mm to 3 mm.
13. Multilayer tablet according to one or more of claims 1 to 12, characterised in that the separating layer consists of physiologically compatible material.
14. Multilayer tablet according to one or more of claims 1 to 13, characterised in that the separating layer is based on a physiologically compatible material, preferably a polymer, a wax, a fat, a fatty acid, a fatty alcohol or a corresponding ether or base, that is not permeable or is only slightly permeable to the separating layer, and that has a melting point of $\geq 40^{\circ}\text{C}$.

15. Multilayer tablet according to claim 14, characterised in that the separating layer is based on a physiologically compatible polymer, preferably cellulose acetate, cellulose butyrate, polyethylene or ethylene/vinyl acetate copolymers.
16. Multilayer tablet according to one or more of claims 1 to 13, characterised in that the separating layer consists more specifically of material that is permeable to the active substances *per se*, but the layer thickness is dimensioned so that the two active substances do not come into contact with one another during the duration of the release.
17. Multilayer tablet according to claim 16, characterised in that the permeable layer is based on cellulose ethers, cellulose esters and/or acrylate resins, preferably on ethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, hydroxymethylpropylcellulose, poly(meth)acrylic acid and/or their derivatives such as their salts, amides or esters.
18. Multilayer tablet according to one or more of claims 1 to 17, characterised in that the separating layer and/or the active substance-containing layers contain further auxiliary substances such as fillers, slip agents, lubricants and flow regulating agents.
19. Multilayer tablet according to one or more of claims 1 to 18, characterised in that it is provided with at least one coating.

20. Multilayer tablet according to claim 19, characterised in that the coating is a delayed release coating.
21. Multilayer tablet according to claim 20, characterised in that the coating is based on a water-insoluble polymer or wax.
22. Multilayer tablet according to claim 21, characterised in that a polyacrylic resin or cellulose derivative, preferably alkylcellulose, is used as polymer.
23. Multilayer tablet according to claim 22, characterised in that ethylcellulose and/or a poly(meth)acrylate is used as polymer.
24. Multilayer tablet for twice-daily application according to one of claims 1 to 23, characterised in that the Tramadol and the Diclofenac are released in an amount of ≥ 70 wt.% and ≥ 60 wt.% respectively within 8 hours.
25. Multilayer tablet for a single daily application according to one or more of claims 1 to 24, characterised in that the Tramadol and the Diclofenac are released in an amount of ≥ 70 wt.% and ≥ 60 wt.% respectively within 16 hours.
26. Multilayer tablet according to one or more of claims 1 to 25, characterised in that it contains at least one release layer that effects the dissociation of the different layers from one another on contact with aqueous body fluids.

27. Multilayer tablet according to one or more of claims 1 to 26, characterised in that the tablet contains at least one score mark that enables the dose being administered to be subdivided, preferably halved.

5

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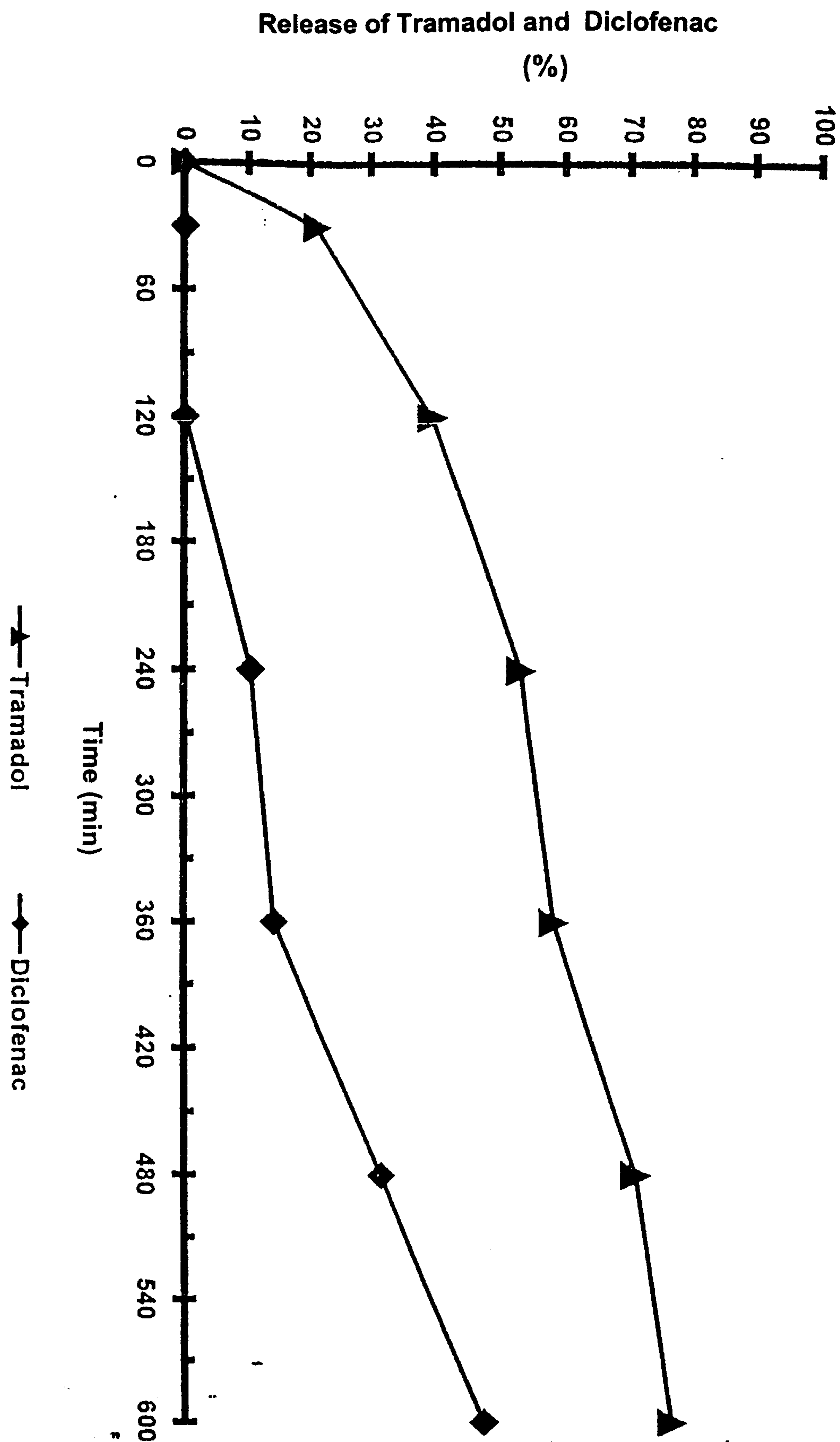


FIG. 1

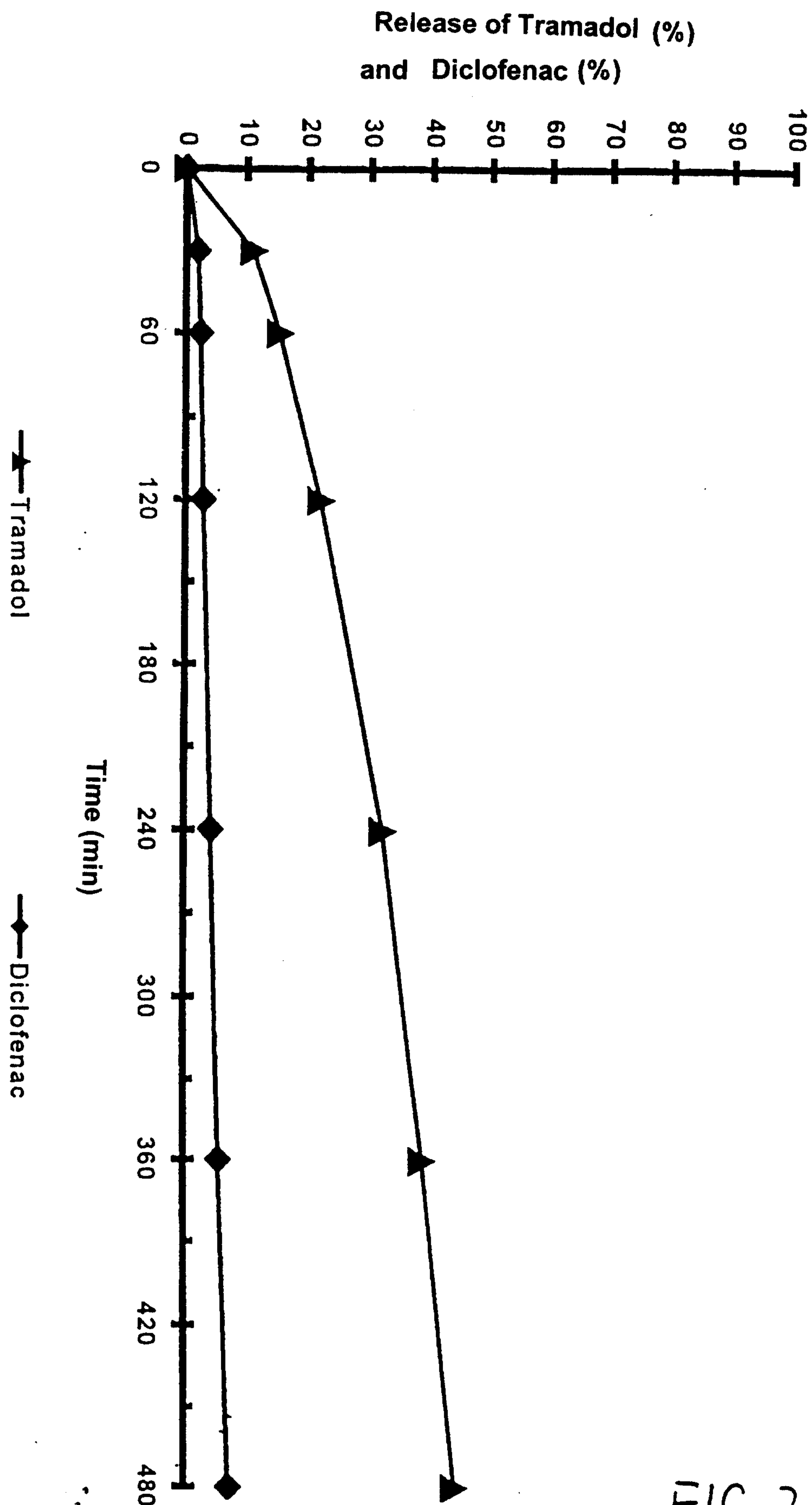


FIG. 2

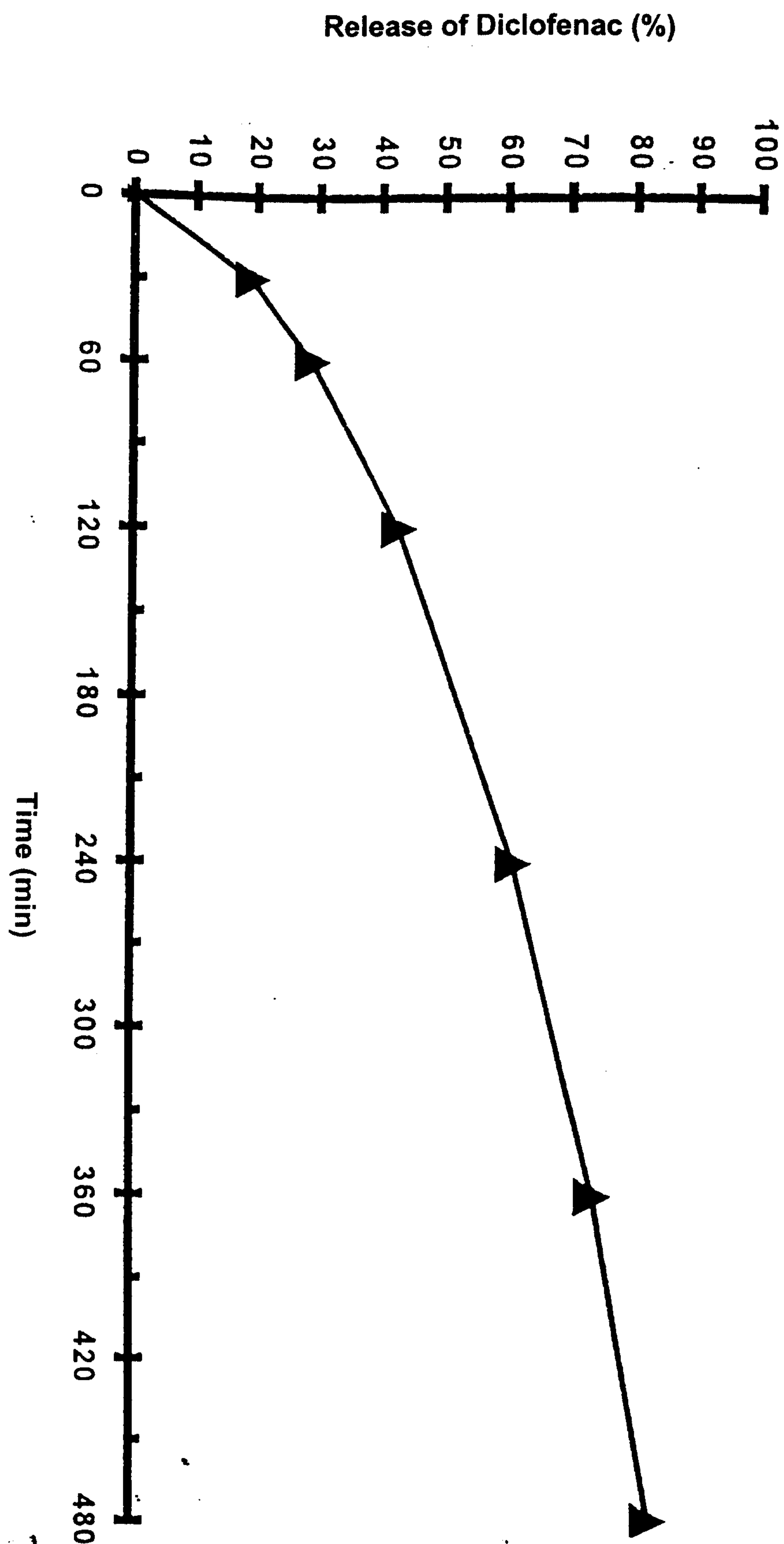


FIG. 3