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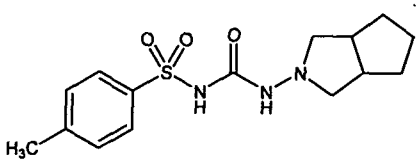
(54) Title: EXTENDED RELEASE GLICLAZIDE TABLET

(57) Abstract: The present invention relates to prolonged release tablets. Tablets which are the subject of invention have not content excipients which have a high glisemic index and show uniformity release profile in pH 6.4 -7.2.

EXTENDED RELEASE GLICLAZIDE TABLET

DESCRIPTION

Gliclazide, a compound of formula (N-[[(Hexahydrocyclopenta[c]pyrol-2(1H) yl)amino]carbonyl]-4-methyl benzene sulfonamide) is a sulphonylurea compound having an antidiabetic property. Gliclazide compound which is disclosed in patents US 3,501,495 and FR 1.510.714 , its chemical formula is as follows (Formula I).



(I)

An extended release product comprising gliclazide is marketed as Diamicron MR.

The invention relates to a tablet formulation for an extended release tablet formulation comprising gliclazide without the pH influencing the in vitro dissolution kinetics between pH 6.4 and pH 7.2 of dissolution medium. The tablet formulation comprises one or more controlled release polymer, one or more buffer agent, one or more polar wetting agent and one or more lublicant. Since the tablet formulation is used for diabetic patients, it does not contain any excipients which has a high glycemic index.

Solubility of the gliclazide active ingredient is respective to pH conditions and it is practically insoluble in water up to pH 5.8. Minor changes within a pH range of from 5.8 to 8, alter the solubility of active ingredient pretty much. The characteristic of pH dependent solubility, causes the absorption problems for the active ingredient.

Indeed, in certain patients an immediate-release gliclazide tablet form can result in high short-term concentrations in the blood. This undesirable plasma levels of the

active ingredient "gliclazide" causes some advers effects including hydroelectrolytic- and metabolic- disorders.

To remove these side effects a dosage form is disclosed in patent aplications WO 2000/018373 (TR 2001 02002 B) that enables the active ingredient that it contains, gliclazide, to be released in a a extended and controlled manner, irrespective of the pH conditions of the dissolution medium.

According to this patent, the release of gliclazide between pH 6.2 and 7.4 has been controlled by the characteristic combination of polymer and glucose syrup in tablet composition.

However glucose syrup and sugar based additives have not been desired in compounds of formulation which is used for the treatment of diabetic patients. Whereas, the glycemic index of maltodextrine in the prolonged release glycazide tablets which has been disclosed in the patent application WO 2000/018373 (TR 2001 02002 B) is 105 and it is higher than the glycemic index of glucose which is 96.

It was thus important, for this active ingredient, to develop a new galenic form that makes gliclazide release that is independent of the pH of the dissolution medium possible and has lower gylicemic index than the prior prolonged tablet formulation comprising the combination of polymer and glucose syrup in order to enable pH-independent dissolution kinetics.

The desired formulation which does not contain glucose syrup, is formulated with at least one controlled release cellulose polymer, at least one buffering agent, at least one wetting agent and at least one lubricant. Although it is not formulated with glucose syrup, surprisingly between pH 6.4 and pH 7.2 values a constant dissolution profile was observed.

In comparative dissolution studies, the formulation which is the subject of invention gives a similar dissolution profile with the reference product Diamicron MR .

One or more cellulose polymer can be used as a controlled release agent in present invention. Cellulose polymers which are used can be at the same or different

viscosity of hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium carboxymethycellulose or mixtures thereof. The percentage of controlled release agent or agents is from about 10 % to about 50 % of the total weight of the tablet. It is preferred to use two hydroxypropyl methylcelluloses together (HPMC 4000 cps ve HPMC 100cps) which have different viscosity as a controlled release polymer in the formulation which is the subject of invention.

In this present invention the light alkaline additives such calcium carbonate, dibasic calcium phosphate, aluminium hydroxide can be used as buffering agent. Dibasic calcium phosphate dihydrate is preferred for the simplicity of the compression and the characteristic of calcium phosphate as a filler in the formulation which is the subject of invention. The amount of buffering agent is from about 5 % to about 45% of the total weight of the tablet.

The solution of dibasic calcium phosphate in water has a stable value between pH 6 and pH 7.2. When the tablet formulation which is the subject of invention is confronted with the solvent, the gel is performed as a result of the swelling of a hydrophilic polymer. In this gel, Dibasic calcium phosphate acts as a buffer and enables the control release of the active substance.

One or more polar wetting agent can be used in the present invention. The wetting agent or agents can be from the different types of polyethylene glycol and polyvinylpyrrolidone.

In this present extended tablet invention, Polyethylene glycol 4000 (PEG 4000) which has limited absorption due to its high molecular weight is preferred. The amount of wetting agent or agents is from about 3 % to about 15 % of the total weight of the tablet.

In this present formulation, magnesium stearate and colloidal silicon dioxide (Aerosil 200) is used as lubricants.

According to this present invention, gliclazide is blended with dibasic calcium phosphate and granuled with the water solution of Polyethylene glycol. Wet granules

which are dried are sieved and mixed with hydroxypropyl methylcellulose. Tablets are compressed after adding colloidal silicon dioxide and magnesium stearate.

The following examples explain the invention but do not limit it in any way.

EXAMPLE :

According to the present invention, two different formulations are developed and the contents thereof are given on Table 1.

TABLE 1

	FORMULA 1 mg/Tablet	FORMULA 2 mg/Tablet
Gliclazide	30.00	30.00
Dibasic calcium phosphate dihydrate	75.88	82.88
PEG 4000	19.00	12.00
HPMC 4000cps	20.00	20.00
HPMC 100 cps	14.00	14.00
Aerosil 200	0.32	0.32
Magnesium Stearate	0.80	0.80
Tablet weight	160.00	160.00

In this present formulation, Dibasic calcium phosphate dihydrate and Gliclazide are mixed. The mixture is granulated with water solution of PEG 4000. Dried granules are screened through 40 mesh size screen and mixed with aerosil and HPMC having two different viscosity grade which have been screened through 40 mesh size screen. After blending with magnesium stearate short time, tablet is then compressed.

Dissolution tests of reference product, Formula 1 and Formula 2 have been done until 12 hours regarding to British Pharmacopoeiae 2005 "Gliclazide" tablet monograph with pedale method at 100 rpm and pH mediums which are suitable with ICH directives. Diamicron (batch no: 4D5288) has been used as reference product.

If the value of similarity factor (f2) which is known as the measurement of similarity of comparative dissolution profiles is 50 or more, two dissolution profiles are accepted similar.

Dissolution profiles of Formula 1 and Formula 2 with reference product in pH 7.2 are shown on Table 2.

TABLE 2

Time (hr)	Formula 1 % Gliclazide	Formula 2 % Gliclazide	Diamicron % Gliclazide
1	7.6	10.7	8.2
2	16.8	19.7	18.7
4	38.5	38.0	40.3
6	60.8	56.2	58.7
8	84.5	77.8	74.1
10	100.2	96.7	83.8
12	103.6	102.0	93.8

Formula 1 and Formula 2 have pointed out linear dissolution profiles during 10 hours whose dissolution profiles are similar in pH 7.2 (the similarity factor,f2=70.48) (FIG1).

As it shown on Table 2, released gliclazide quantity from the Formula 1 and Formula 2 with reference product are very similar to each other . The similarity factor of dissolution profile (f2) of Formula 2 and reference product is 60.22 in pH 7.2 (FIG 2).

Dissolution profiles of Formula 2 and reference product Diamicron in pH 6.4 are shown on Table 3. The similarity factor (f2) of the dissolution profiles of Formula 2 with reference product in pH 6.4 is 59 (FIG 3).

TABLE 3

Time (hr)	Formula 2 % Gliclazide	Diamicron % Gliclazide
1	7.7	6.1
2	16.7	16.2
4	34.6	40.4
6	52.5	63.1
8	69.9	80.2
10	84.5	91.1
12	95.6	96.5

Dissolution profiles of Formula 2 and reference product Diamicron in pH 6.8 are shown on Table 4. Dissolution profiles of Formula 2 and reference product in pH 6.8 is similar (the similarity factor,f2=55.1) (FIG 4).

TABLE 4

Time (hr)	Formula 2 % Gliclazide	Diamicron % Gliclazide
1	8.8	8.0
2	18.3	19.5
4	36.2	45.2
6	53.7	67.1
8	70.9	83.0
10	91.5	92.4
12	101.2	96.5

The dissolution profiles of pilot production product of Formula 2 in three different pH mediums product are shown on Table 5.

As it is shown , dissolution of the tablet which is the subject of invention is independent of the pH conditions between 6.4 and 7.2. (FIG 5).

TABLE 5

Time (hr)	pH = 6.4 % Gliclazide	pH = 6.8 % Gliclazide	pH = 7.2 % Gliclazide
0.5	3,80	4,40	7,11
1	7,77	8,80	12,15
2	16,70	18,28	21,49
4	34,58	36,15	38,89
6	52,48	53,65	55,39
8	69,85	70,92	73,38
10	84,53	91,52	90,31
12	95,57	101,28	99,35

DESCRIPTION OF THE DRAWINGS

FIG. 1 - Dissolution profiles of Formula 1 and Formula 2 in pH 7.2

FIG. 2 - Dissolution profiles of reference product and Formula 2 in pH 7.2

FIG. 3 - Dissolution profiles of reference product and Formula 2 in pH 6.4

FIG. 4 - Dissolution profiles of reference product and Formula 2 in pH 6.8

FIG. 5 - Dissolution profiles of pilot production of Formula 2 in three different pH mediums product are shown

CLAIMS

1. An extended release tablet formulation of gliclazide, comprises at least one or more controlled release cellulose polymers, one or more buffering agents, one or more wetting agents and one or more lubricants.

2. An extended release tablet formulation of gliclazide according to claim 1; wherein the cellulose polymer which control the release is selected from the list comprising hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium carboxymethycellulose or mixtures thereof either having same or different viscosity.

3. An extended release tablet formulation of gliclazide according to claim 1; wherein the amount of the cellulose polymer or polymers which control the release is between about 10% and about 50% based on the weight of the tablet.

4. An extended release tablet formulation of gliclazide according to claim 1; wherein two hydroxypropyl methylcelluloses having viscosities of 4000 cps and 100 cps are used as cellulose polymers which control the release.

5. An extended release tablet formulation of gliclazide according to claim 1; wherein the buffering agent is selected from the list comprising calcium carbonate, dibasic calcium phosphate and aluminium hydroxide.

6. An extended release tablet formulation of gliclazide according to claim 1; wherein dibasic calcium phosphate dihydrate is used as the buffering agent.

7. An extended release tablet formulation of gliclazide according to claim 1; wherein the amount of buffering agent or agents is between about 5% and about 45% based on the weight of the tablet.

8 An extended release tablet formulation of gliclazide according to claim 1; wherein the wetting agent is selected from the list which comprises different types of polyethylene glycol ve polyvinylpyrrolidone.

9. An extended release tablet formulation of gliclazide according to claim 1; wherein polyethylene glycol 4000 is used as a wetting agent.

10. An extended release tablet formulation of gliclazide according to claim 1; wherein the amount of wetting agent or agents is between about 3% and about 15 % based on the weight of the tablet.

11. An extended release tablet formulation of gliclazide according to claim 1; wherein magnesium stearate and colloidal silicon dioxide is used as the lubricant

12. An extended release tablet formulation of gliclazide; wherein the formulation comprises two different viscosity grade hydroxypropyl methylcelluloses between about 10% and about 50%, dibasic calcium phosphate between about 5% and about 45% , colloidal silicon dioxide and magnesium stearate between about 3% and about 15% of the total weight of the tablet.

13. An extended release tablet formulation of gliclazide according to claim 12, wherein two hydroxypropyl methylcelluloses having viscosities of 4000 cps and 100 cps are used together.

14. An extended release tablet formulation of gliclazide according to any of above claims; characterized in that the formulation does not include glucose syrup.

15. An extended release tablet formulation of gliclazide according to any of above claims; characterized in that the formulation has a dissolution profile which is stable between pH 6.4 and pH 7.2 .

FIG. 1

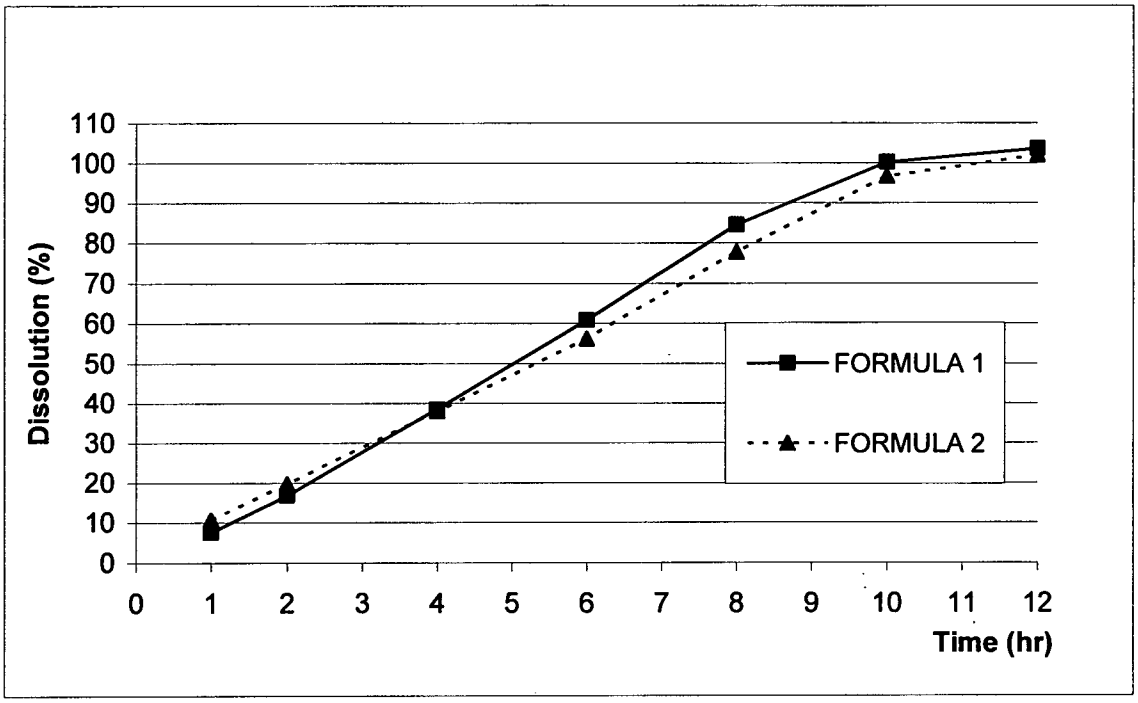

Dissolution (%)
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hr)
FORMULA 1
FORMULA 2

FIG. 2

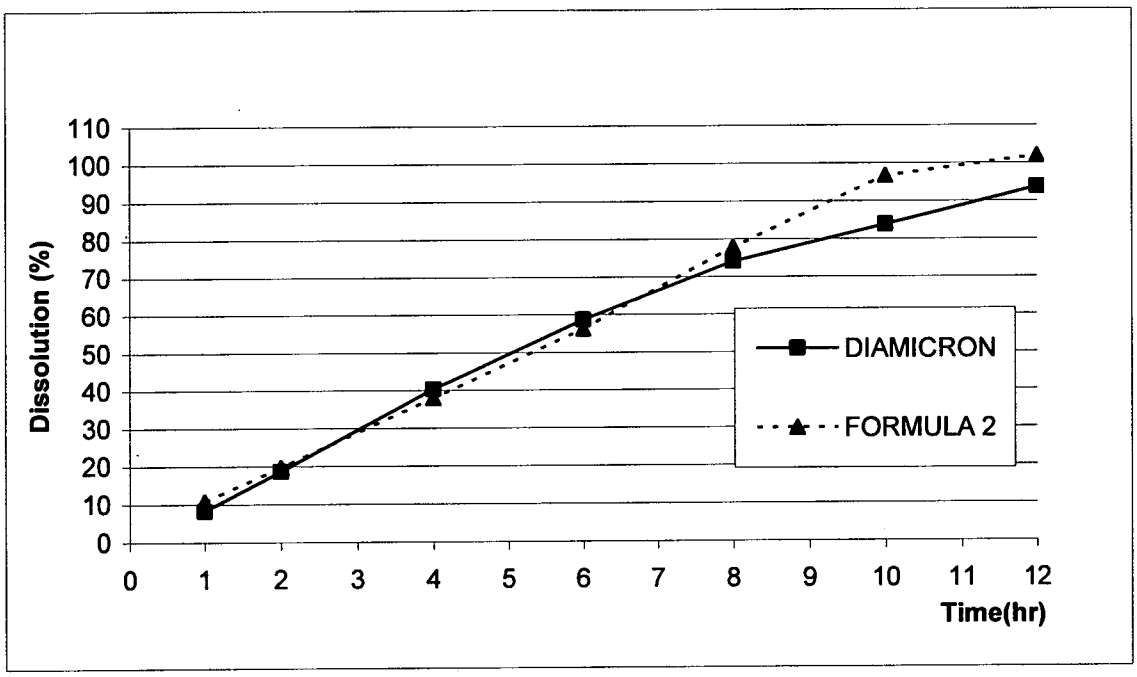
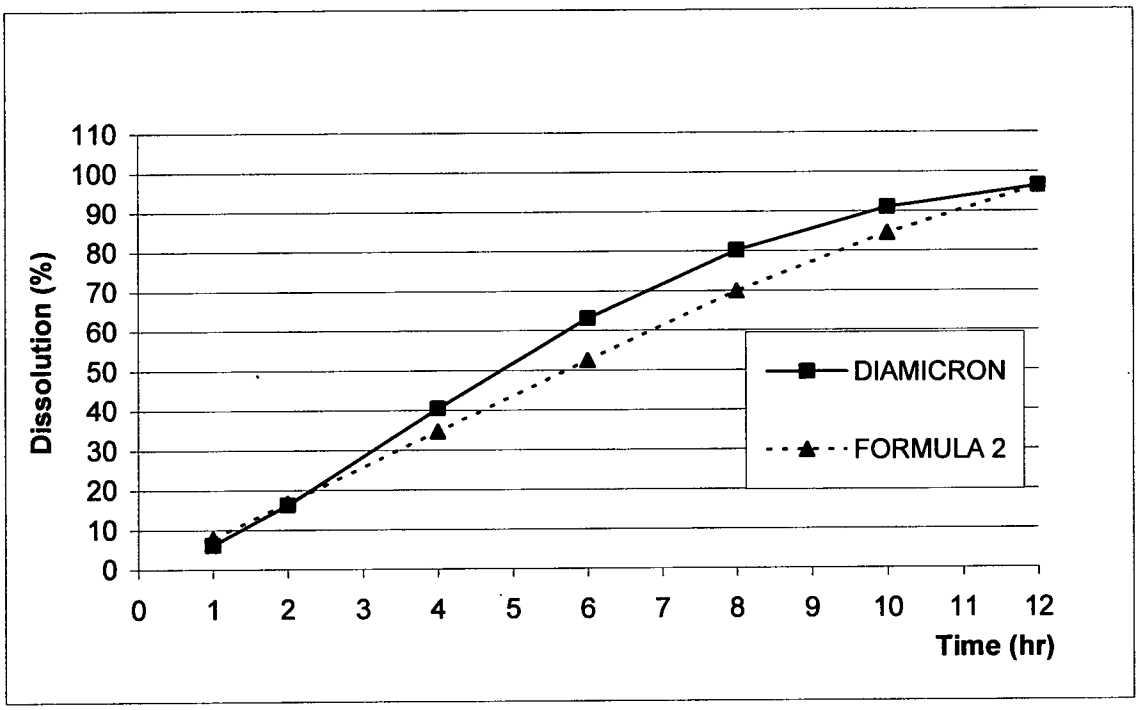

Dissolution (%)
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time(hr)
DIAMICRON
FORMULA 2

FIG. 3


Dissolution (%)
110
100
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50
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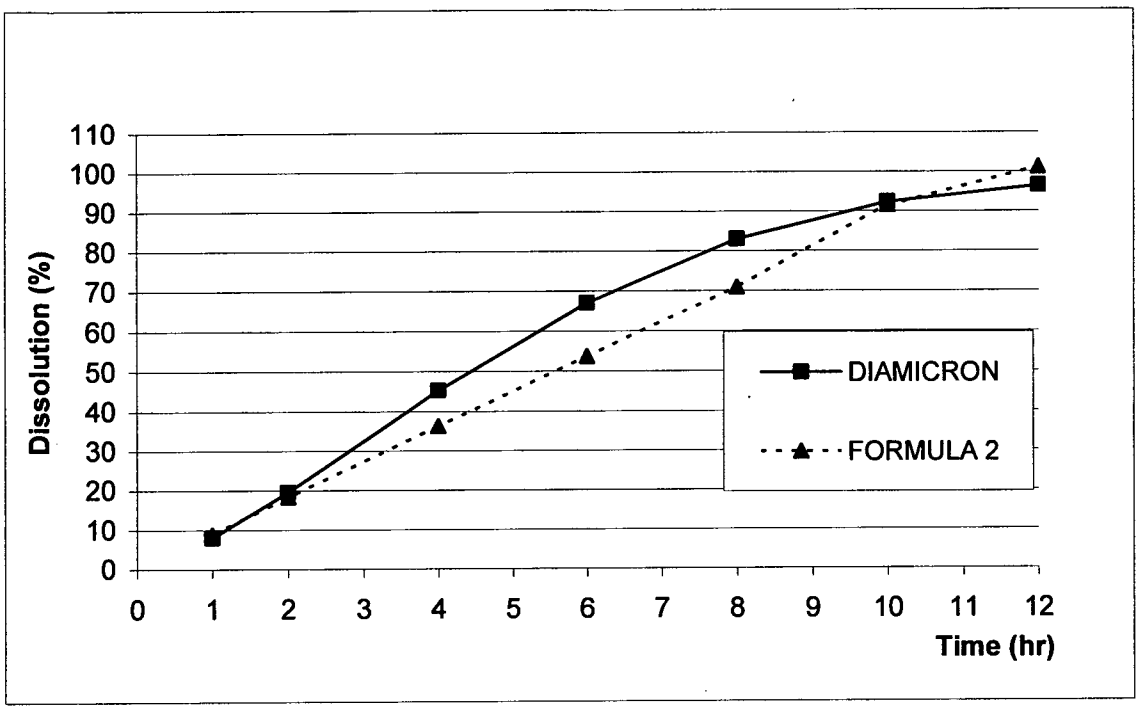
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hr)
DIAMICRON
FORMULA 2

FIG. 4


110
100
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70
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50
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10
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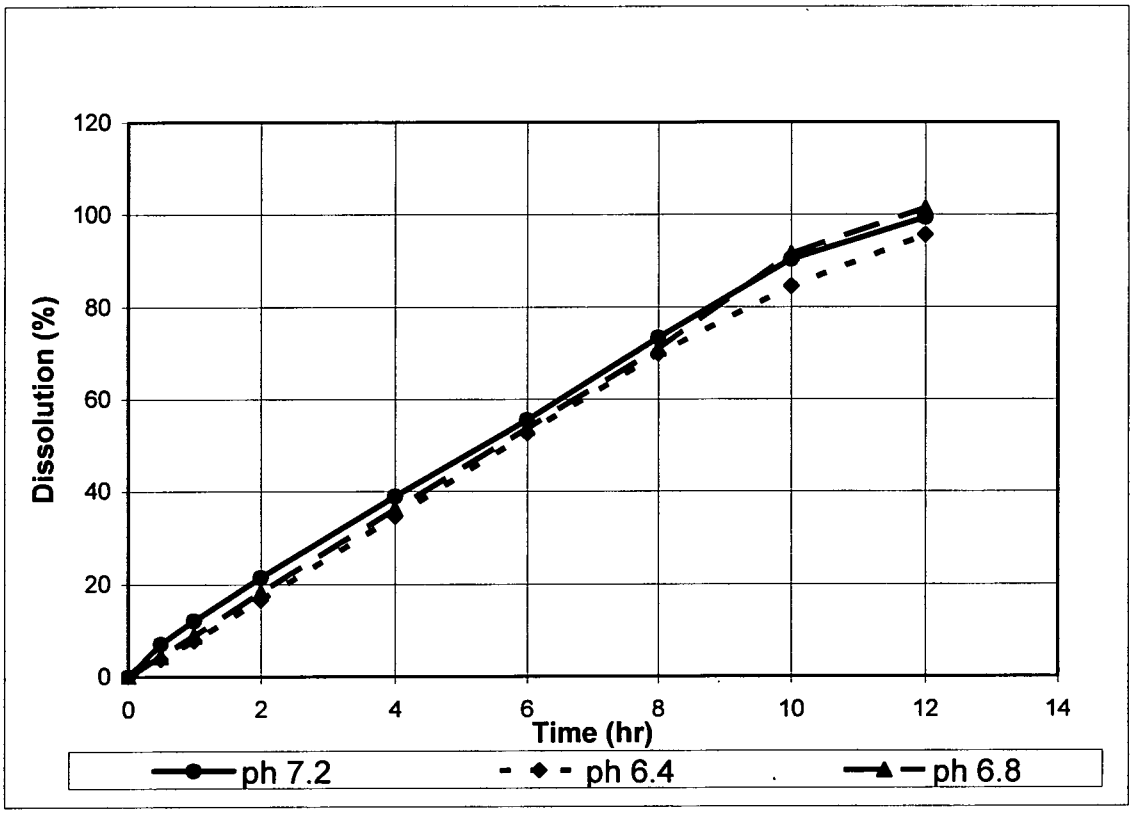
Dissolution (%)
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hr)
DIAMICRON
FORMULA 2

FIG. 5


120
100
80
60
40
20
0
Dissolution (%)
0
2
4
6
8
10
12
14
Time (hr)
ph 7.2
ph 6.4
ph 6.8

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2008/000040

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2008/062470 A (TORRENT) 29 May 2008 (2008-05-29) claims examples	1-15
X	WO 2006/123213 A (RANBAXY) 23 November 2006 (2006-11-23) claims examples 1-7	1-15
A	WO 2006/061697 A (THEMIS) 15 June 2006 (2006-06-15) claims examples	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2008	29/07/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2008/000040

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/18373 A (ADIR) 6 April 2000 (2000-04-06) cited in the application claims examples	1-15

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2008/000040

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