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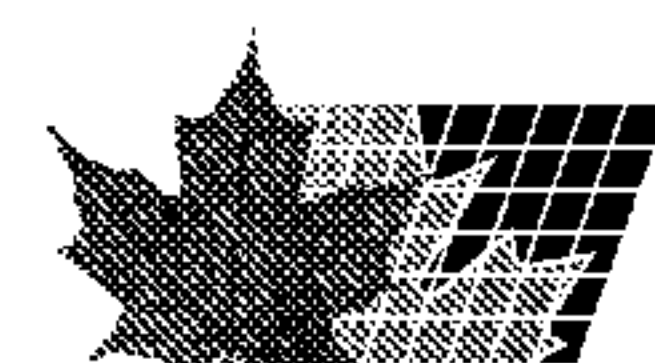
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(54) Titre : GEL BIOADHESIF A BASE D'HYDROXYETHYLCELLULOSE
(54) Title: BIOADHESIVE GEL BASED ON HYDROXYETHYLCELLULOSE

(57) **Abrégé/Abstract:**

Disclosed are compositions in the form of a bioadhesive gel that adheres to the mucous membranes, in particular the vaginal mucosa, for the application of active ingredients and/or principles, comprising hydroxyethylcellulose as the only gelling agent.



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BIOADHESIVE GEL BASED ON HYDROXYETHYLCELLULOSE

This invention relates to compositions in the form of a bioadhesive gel that adheres to the mucous membranes, in particular the vaginal mucosa, for the application of active ingredients and/or principles.

Bioadhesion is the property whereby some hydrogels adhere to
5 biological tissues, in particular to mucous-coated epithelia such as the gastric, buccal, vaginal and rectal mucosae.

This property has been exploited to develop drug delivery systems, especially in order to increase the time over which drugs remain in contact with certain sites or areas of therapeutic interest, giving rise to systemic
10 effects (thus increasing transmucosal absorption) or local effects.

The most commonly used polymers that are capable of forming hydrogels and imparting bio- and/or muco-adhesion are acrylic or methacrylic acid polymers, possibly cross-linked, and chitosan, or its derivatives.

In particular, for drugs designed for gynaecological use, a bioadhesive
15 gel able to ensure prolonged contact between the active ingredient and the vaginal mucosa, and gradual release of that ingredient over time, provides the ideal solution in terms of efficacy and compliance by patients.

Bioadhesive vaginal gels have consequently been disclosed, for example, in US 6159491, US 2002012674, US 2003091642, WO 200047144,
20 WO 200203896, WO 200143720 and WO 9610989. In all these cases, an acrylic acid polymer (Carbomer or polycarbophil) is used as viscosity-controlling or bioadhesive agent.

WO 200015192 describes mucoadhesive formulations in which chitosan is used instead of the acrylic acid polymer.

25 However, the problem of obtaining a bioadhesive formulation that presents the following advantages and properties:

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- release of drug for up to approximately 24 hours;
- absence of gelling/bioadhesive agents, characterised by the presence of acid groups, which are therefore sensitive to the ionic strength of the medium, and sometimes need to be neutralised with bases;
- 5 - the possibility of carrying drugs with different chemico-physical properties, in particular water-soluble drugs and lipophilic drugs which are substantially insoluble in water;
- reduction of the time and cost of the treatment

remains substantially unsolved.

10 It has now been found that said objectives can be achieved by bioadhesive gel formulations that adhere to the mucous membranes, in particular the vaginal mucosa, comprising hydroxyethylcellulose as the only bioadhesive polymer. This gelling excipient has no acid groups and is therefore not dependent on the ionic strength of the medium; it also has a
15 matrix effect which allows particularly slow, gradual release of the active ingredient, for up to 24 hours.

This invention therefore relates to compositions in the form of an aqueous gel for the intravaginal delivery of active ingredients, comprising hydroxyethylcellulose as the only gelling and bioadhesive agent.

20 The compositions of the invention may also contain glycerol, diethylene glycol monoethyl ether, surfactants, preservatives, acidifiers and other excipients in common use for the form of delivery considered herein.

The compositions of the invention will preferably contain 1 to 5% by weight of hydroxyethylcellulose, 25 to 90% by weight of water, 5 to 25% by
25 weight of glycerol, 5 to 50% by weight of diethylene glycol monoethyl ether, 0.01 to 10% by weight of surfactants, 0.05 to 1% by weight of preservatives, and 0.01 to 1% by weight of acidifiers.

Preferably, the hydroxyethylcellulose content is higher than 2% and less than 4%.

Hydroxyethylcellulose is commercially available from many sources: it is preferred an hydroxyethylcellulose having a degree of substitution of about 1.5 (corresponding to 3 hydroxyethyl groups every two saccharide units) and a molecular weight estimated from intrinsic viscosity measurements ranging from 1.0 to 1.3×10^6 . Hydroxyethylcellulose having said characteristic is available under the trade-mark Natrosol 250 HX by Hercules Inc. UK.

The percentage of active ingredient will obviously depend on the characteristics of the selected drug, and may vary within a wide range, for example from 0.01 to 10% by weight.

Active ingredients which can be advantageously formulated according to the invention include antifungals, antiseptics and antimicrobials, antibiotics, analgesics, local anaesthetics, antihistamines, anti-inflammatory agents, contraceptives, hormones, and combinations thereof.

Examples of these active ingredients include, in particular, econazole, miconazole, fluconazole, ciclopiroxolamine, nifuratel, nystatin, chlorhexidine, ibuprofen, ketoprofen, naproxen, benzydamine, benzalkonium chloride or other quaternary ammonium antiseptics, nonoxynol-9 and all other active ingredients of interest for gynaecological applications.

The following examples illustrate the invention in greater detail.

EXAMPLE 1

Composition	Percentage
Purified water	81.9%
Glycerol	12.9%
Chlorhexidine digluconate, 20% solution w/v	2.7%
Hydroxyethylcellulose (Natrosol 250 HX)	2.5%

EXAMPLE 2 - Ibuprofen vaginal gel

	Composition	Percentage
	Ibuprofen	0.100%
	Benzalkonium chloride	0.150%
5	Polyoxyethylen-20-monocetyl ether (Brij 58)	0.500%
	Hydroxyethylcellulose (Natrosol 250 HX)	2.500%
	Diethylene glycol monoethyl ester (Transcutol P)	10.000%
	Purified water	86.750%

EXAMPLE 3 - Econazole nitrate vaginal gel

10	Composition	Percentage
	Econazole nitrate	1.000%
	Benzalkonium chloride	0.150%
	Hydroxyethylcellulose (Natrosol 250 HX)	2.500%
	Polysorbate 80 (Tween 80)	4.000%
15	Glycerol	10.000%
	Diethylene glycol monoethyl ester (Transcutol P)	40.000%
	Purified water	42.350%

EXAMPLE 4 - Study of bioadhesion of vaginal gels

Bioadhesion was measured *in vitro* using a suitably modified Lloyd
 20 dynamometer. The measurement substrate (rabbit gastric mucosa or
 polypropylene) was fixed with an adhesive to the upper support, which in turn
 was connected to the mobile crossbar, and 200 mg of the test formulation
 were placed on the lower support so as to cover the surface evenly. After
 effecting close contact between the formulation and the substrate (30 s), the
 25 crossbar was raised at a defined, constant speed until the two surfaces separated.

A 20 N load cell was used for the measurements [J.Y. Chang, Y-K. Oh,
 H.S. Kong, E.J. Kim et al., J. Control. Release 82 (2002) 39-50; S. Skulason,

T. Kristmundsdottir, W.P. Holbrook, Bio-Gels Pharmaceuticals].

Five measurements were taken for each sample; the parameters considered were the maximum breaking load (ML) and the adhesion work (W).

The operating conditions used in the study are reported below.

5

Apparatus	Lloyd LRX Tensiometer
	Equipped with clamps for adhesion tests
Test conditions	Crossbar speed 0.1mm/s
	Load cell 20 N
	Contact time between substrate and gel 30 s
	Contact surface rabbit gastric mucosa/ polypropylene

RESULTS

The results are shown in Table 1.

Table 1

FORMULATION	Rabbit gastric mucosa		Polypropylene	
	ML (N)	W (Nmm)	ML (N)	W (Nmm)
EXAMPLE 1	0.088 ± 0.017	0.095 ± 0.030	0.101 ± 0.019	0.099 ± 0.014
EXAMPLE 2	0.076 ± 0.012	0.069 ± 0.010		
EXAMPLE 3	0.179 ± 0.032	0.155 ± 0.032		

10

EXAMPLE 5 - pH 4.0 diffusion test of gels of Examples 1, 2 and 3

Diffusion medium: lactate buffer, pH 4.0

Diffusion volume: 50 mL

Temperature: 37 ± 0.5°C

Agitation speed: 50 rpm

Quantity of sample: 1.5 g

Release area: 4.5 cm²

Release membrane: cellulose acetate 0.45 µm.

5 The test for release of the drug from the gel was performed using diffusion cells, with cellulose acetate membranes having a 4.5 cm² surface. The quantity of gel applied was 1.5 g. At given times, an automated system took predetermined sample aliquots, with immediate UV spectrophotometer reading at 254 nm.

10 Figure 1 shows the diffusion profile of chlorhexidine as the mean of 8 samples ± standard deviation.

Figure 2 shows the diffusion profile of chlorhexidine from the 8 samples.

Table 2 shows the percentages released for the 8 chlorhexidine samples.

Table 2

15

time	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	sample 7	sample 8	mean	SD
0	0	0	0	0	0	0	0	0	0	0
10	12.89	8.532	11.94	10.37	11.54	4.473	12.28	9.514	10.19	2.74
20	20.05	19.09	19.92	19.39	18.9	17.3	20.35	18.51	19.19	0.98
30	25.29	23.73	26.29	24.53	23.49	22.86	25.73	24.65	24.57	1.17
40	29.94	28.16	31.35	29.54	27.11	27.24	29.5	27.47	28.79	1.53
60	37.63	33.33	39.02	38.09	34.48	35.99	37.73	35.43	36.46	1.97
90	48.43	45.46	51.11	50.36	42.11	40.69	45.84	43.93	45.99	3.76
120	57.25	53.77	59.81	60.04	49.54	51.69	53.37	51.09	54.57	4.01
150	64.1	60.13	65.16	64.99	56.34	60.75	62.1	60.35	61.74	2.99
180	69.83	65.88	70.99	72.06	59.42	64.05	65.88	63.19	66.41	4.31
210	75.2	72.57	76.17	79.41	66.23	70.77	71.62	69.9	72.73	4.10
240	78.71	74.61	79.33	82.52	69.9	73.52	74.98	73.03	75.83	4.07
270	81.79	78.38	81.54	84.88	72.61	77.04	77.86	74.84	78.62	3.99
300	84.36	81.24	83.65	87.96	76.38	79.6	80.6	79.33	81.64	3.58

Figure 3 shows the diffusion profile of ibuprofen as the mean of 8 samples $\pm$ standard deviation.

Table 3 shows the percentages released for the 8 ibuprofen samples.

Table 3

time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	sample 7	sample 8	mean	SD
0	0	0	0	0	0	0	0	0	0	0
30	15.56	17.83	18.96	18.96	4.18	3.22	17.06	11.26	13.38	6.05
60	24.34	26.60	26.88	19.53	33.15	24.14	26.71	19.95	25.16	4.06
90	30.56	28.02	32.26	28.02	34.44	36.37	30.57	37.01	32.16	3.28
120	40.19	33.39	45.28	30.56	36.05	44.74	42.16	39.59	38.99	4.94
150	47.26	47.54	45.56	56.60	47.63	44.74	43.77	43.77	47.11	3.89
180	57.45	41.60	53.49	46.69	47.31	44.74	44.09	44.41	47.47	4.99
240	57.73	54.62	54.62	59.71	52.11	51.81	53.03	52.11	54.47	2.70
300	68.20	61.69	59.99	63.67	68.88	61.87	69.49	62.17	64.49	3.52
360	70.18	66.79	64.24	59.71	76.80	74.67	69.79	71.31	69.19	5.17
420	61.98	74.99	65.65	73.30	77.41	84.72	77.71	76.50	74.03	6.73
480	78.39	72.16	71.60	71.31	81.98	84.72	81.07	80.15	77.67	4.93

Figure 4 shows the diffusion profile of econazole as the mean of 8 samples $\pm$ standard deviation.

Table 4 shows the percentages released of the 8 econazole samples.

Table 4

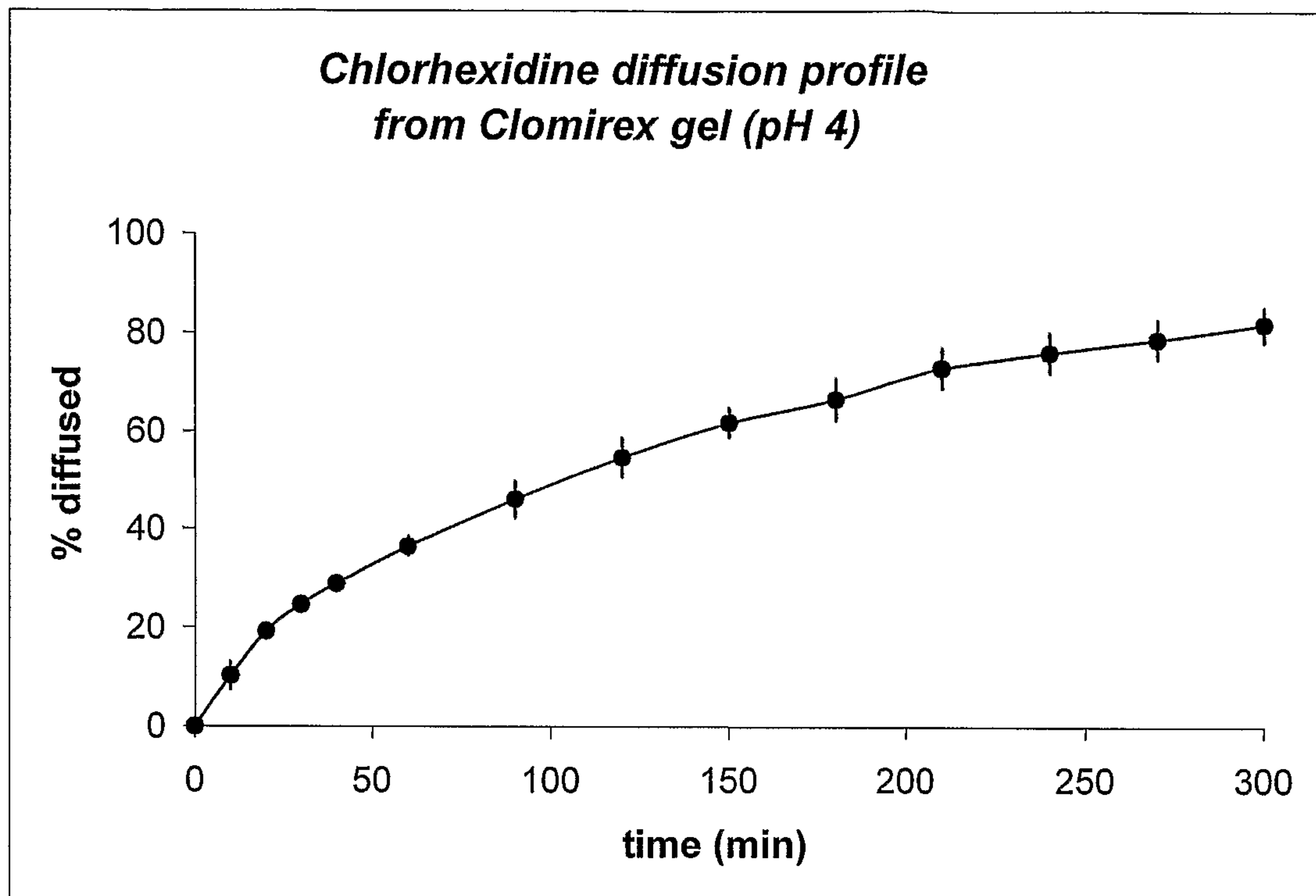
time	sample	sample	sample	sample	sample	sample	sample	sample	mean	SD
	1	2	3	4	5	6	7	8		
1	8.9	8.9	10.7	11.7	9.1	8.8	10.3	12	10.1	1.3
2	12.3	15.5	18.4	19.1	14.4	15	17.3	19.5	16.4	2.5
3	24.1	21.6	24	25	22.1	25.3	21.1	23.6	23.4	1.6
4	29	26.2	28.8	30.1	30.4	28.2	25.8	32.1	28.8	2.1
5	34.1	30.4	32.8	34.5	36	33.4	30.2	33.7	33.1	2.0
6	40	34.2	35.4	37.6	38.4	36.5	34	36.3	36.6	2.1
7	40.5	36.8	37.4	39.9	41	39.2	37	38.4	38.8	1.6
8	44.4	39.3	38.6	41.3	43.2	40.2	39.6	41.2	41.0	2.0
9	45.2	40.6	40	43	45.8	42.1	42.3	44.2	42.9	2.1
10	46.1	41.8	40.9	44	47.3	44	45	45.4	44.3	2.1
11	47.2	42.8	41.4	44.8	48	45.3	46.3	46.7	45.3	2.3
12	48.6	43.6	42.6	45.8	49.2	47.1	48.2	48.1	46.7	2.4
13	49.2	44.3	43.1	46.4	50.3	49.6	50.2	49.2	47.8	2.8
14	50.2	45.2	43.6	46.9	51	49.8	50.8	50.1	48.5	2.8
15	50.7	45.4	43.7	47.6	51.1	50	51.1	50.6	48.8	2.9
16	51.3	46	44.3	47.4	51.3	50.3	51.4	50.8	49.1	2.8
17	51.9	46.3	44.7	47.7	51.5	50.4	51.7	50.9	49.4	2.8
18	52.6	46.3	45	47.7	51.7	50.7	51.9	51.1	49.6	2.9
19	53.1	46.8	46.7	48.2	52	51.1	52	51.3	50.2	2.5
20	53.3	46.9	49.3	50.1	52.2	51.2	52.3	51.5	50.9	2.0
21	53.1	47	52.2	50.3	52.3	51.4	52.6	51.7	51.3	1.9
22	53.9	47.8	54.2	51.2	52.5	51.6	52.7	51.9	52.0	2.0
23	54.1	48.3	55.3	51.9	52.7	51.8	52.9	52.2	52.4	2.0
24	55.2	50.1	56.1	52	53.2	52.4	53.1	52.4	53.1	1.9

CLAIMS

1. Compositions in the form of an aqueous bioadhesive gel for the delivery of active ingredients and/or principles, comprising
5 hydroxyethylcellulose as the only gelling and bioadhesive agent.
2. Compositions in the form of an aqueous gel, as claimed in claim 1, for the intravaginal delivery of active ingredients and/or principles.
3. Compositions as claimed in claim 1 or 2, further containing glycerol, diethylene glycol monoethyl ether, surfactants, preservatives and acidifiers.
- 10 4. Compositions as claimed in claim 3, containing 1 to 5% by weight of hydroxyethylcellulose, 25 to 90% by weight of water, 5 to 25% by weight of glycerol, 5 to 50% by weight of diethylene glycol monoethyl ether, 0.01 to 10% by weight of surfactants, 0.05 to 1% by weight of preservatives, and 0.01 to 1% by weight of acidifiers.
- 15 5. Compositions as claimed in any of claims 1 to 4, containing as active constituents antifungals, antiseptics and antimicrobials, antibiotics, analgesics, local anaesthetics, antihistamines, anti-inflammatory agents, contraceptives, hormones, or combinations thereof.
6. Compositions as claimed in claim 5, wherein the active ingredient is
20 selected from econazole, miconazole, fluconazole, cyclopiroxolamine, nifuratel, nystatin, chlorhexidine, ibuprofen, ketoprofen, naproxen, benzydamine, benzalkonium chloride or other quaternary ammonium antiseptics, and nonoxynol-9.

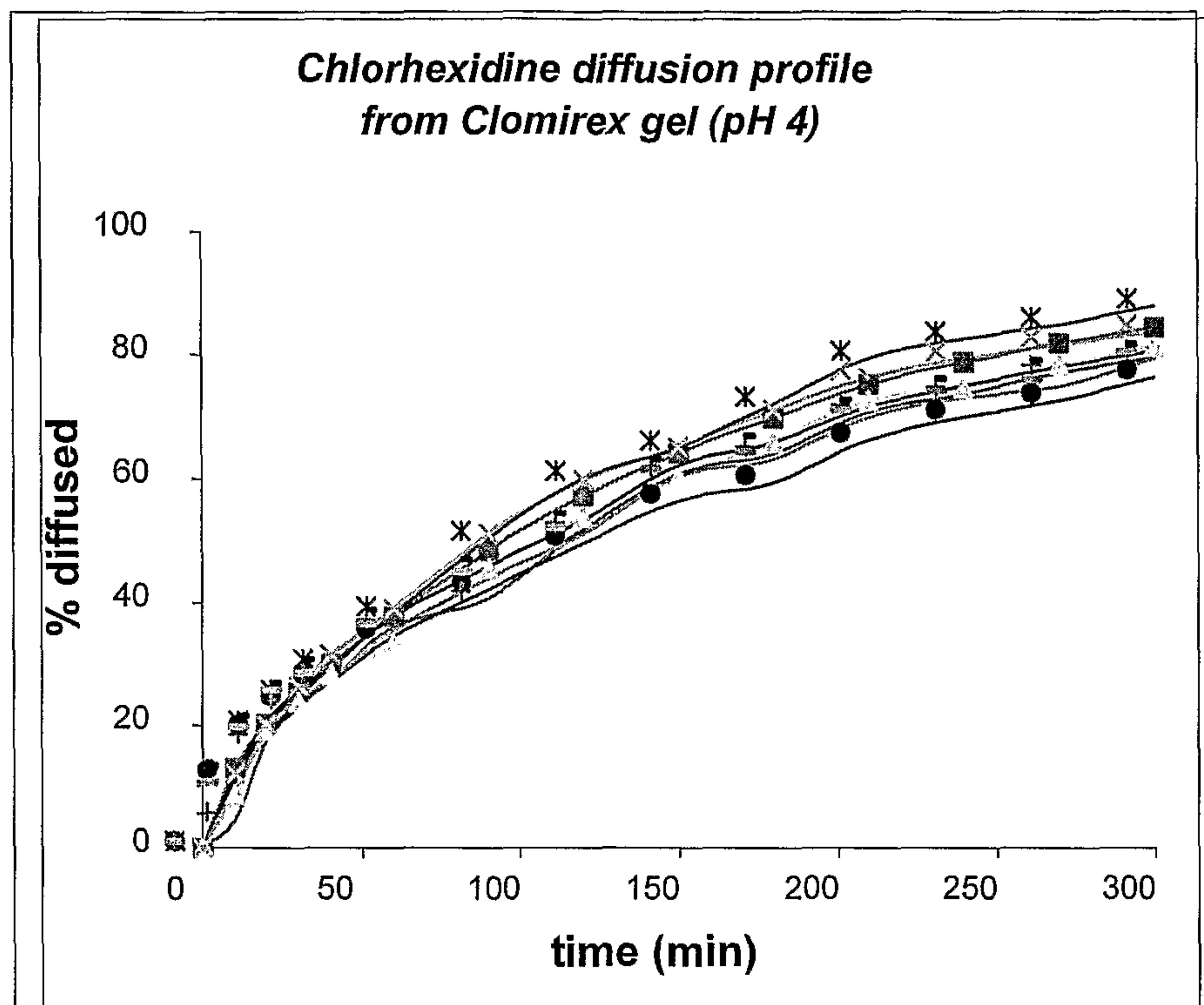
SHEET 1/4

FIGURE 1



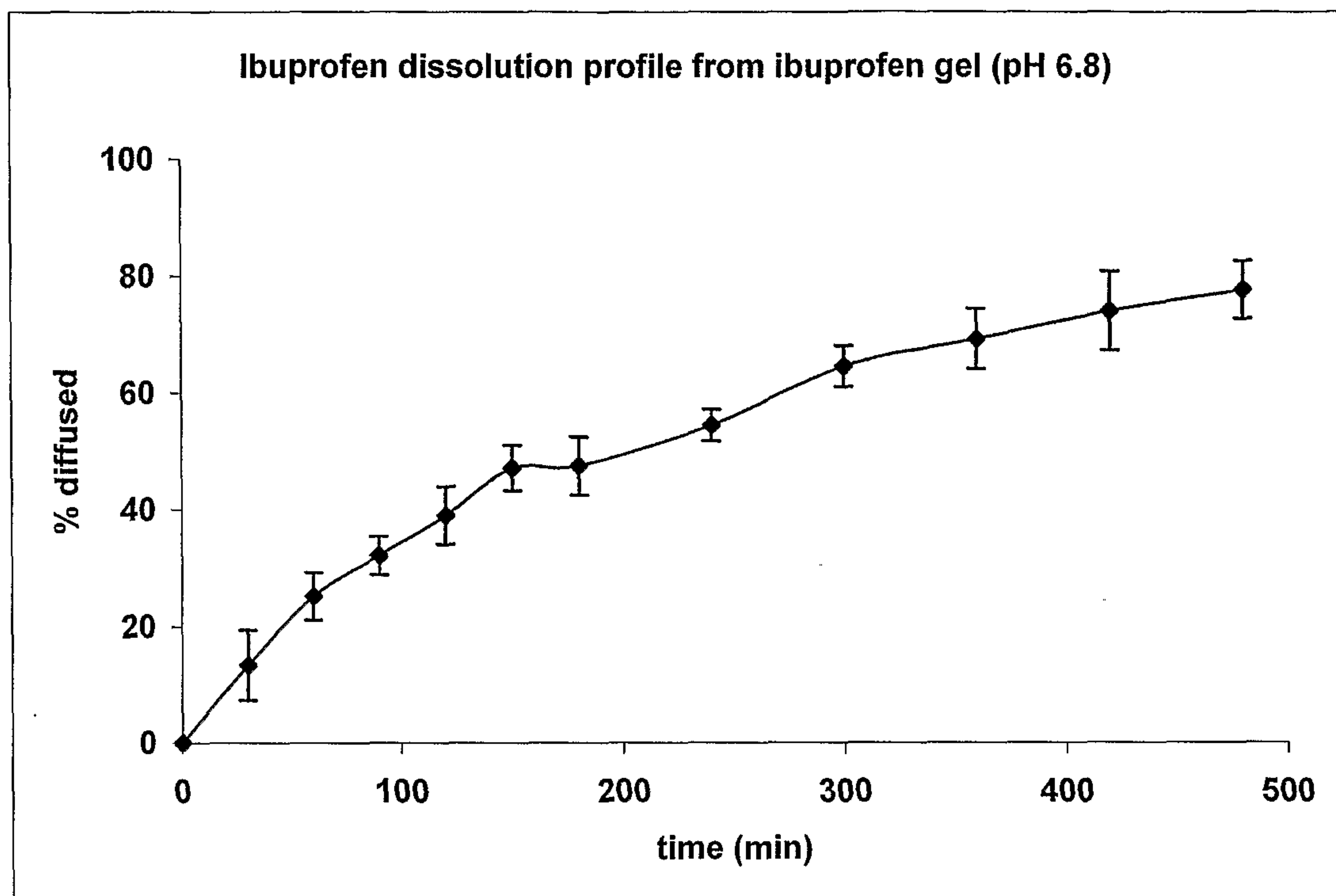
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FIGURE 2



SHEET 3/4

FIGURE 3



SHEET 4/4

FIGURE 4

