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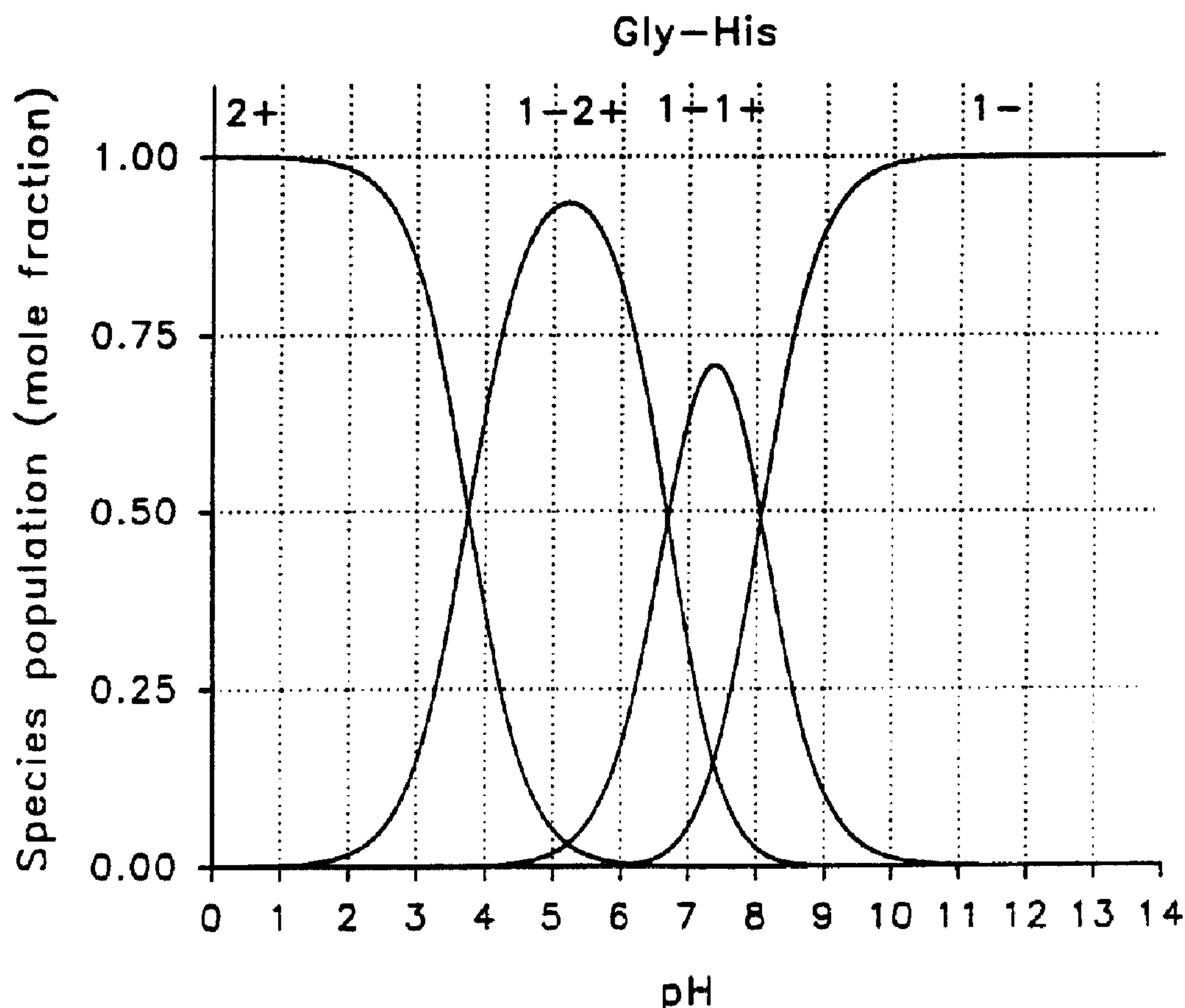
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(54) Title: BUFFERED DRUG FORMULATIONS FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY



(57) Abrégé/Abstract:

Buffered drug formulations for transdermal electrotransport delivery are disclosed. The formulations utilize a dipeptide as a buffer and allow for more efficient electrotransport delivery of drugs, e.g., polypeptide drugs, via the transdermal route.

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(54) Title: BUFFERED DRUG FORMULATIONS FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY		
Gly-His		
(57) Abstract Buffered drug formulations for transdermal electrotransport delivery are disclosed. The formulations utilize a dipeptide as a buffer and allow for more efficient electrotransport delivery of drugs, e.g., polypeptide drugs, via the transdermal route.		

1 BUFFERED DRUG FORMULATIONS FOR TRANSDERMAL**2 ELECTROTRANSPORT DELIVERY****3 ELECTROTRANSPORT DELIVERY**
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TECHNICAL FIELD

The invention relates generally to drug formulations used in transdermal electrotransport drug delivery. More particularly, the invention relates to buffered drug formulations for transdermal electrotransport delivery using buffers which minimally compete with the drug for carrying electric current and which have greater stability and a longer shelf life.

BACKGROUND OF THE INVENTION

Transdermal (i.e., through the skin) delivery of therapeutic agents affords a comfortable, convenient and noninvasive technique for administering drugs. The method provides several advantages over conventional modes of drug delivery. For example, variable rates of absorption and (e.g., hepatic) metabolism encountered in oral treatment are avoided, and other inherent inconveniences -- e.g., gastrointestinal irritation and the like -- are eliminated. Transdermal delivery also allows a high degree of control over blood concentrations of a particular drug and is an especially attractive administration route for drugs with narrow therapeutic indexes, short half-lives and potent activities.

Transdermal delivery can be either passive or active. Many drugs are not suitable for passive transdermal drug delivery because of their size, ionic charge characteristics and hydrophilicity. One method of overcoming this limitation is the use of low levels of electric current to actively transport drugs into the body through skin. This technique is known as "electrotransport" or "iontophoretic" drug delivery. The technique provides a more controllable process than passive transdermal drug delivery since the amplitude, timing and polarity of the applied electric current is easily regulated using standard electrical components. In this regard, electrotransport drug

1 flux can be from 50% to several orders of magnitude greater than passive
2 transdermal flux of the same drug.

3 Electrotransport devices generally employ at least two
4 electrodes. Both of these electrodes are positioned in intimate electrical
5 contact with some portion of the skin of the body. One electrode, called the
6 active or donor electrode, is the electrode from which the therapeutic agent is
7 delivered into the body. The other electrode, called the counter or return
8 electrode, serves to close the electrical circuit through the body. In
9 conjunction with the patient's skin, the circuit is completed by connection of
10 the electrodes to a source of electrical energy, e.g., a battery, and usually to
11 circuitry capable of controlling the current applied by the device through the
12 patient.

13 Depending upon the electrical charge of the species to be
14 delivered transdermally, either the anode or cathode may be the active or
15 donor electrode. Thus, if the ionic substance to be driven into the body is
16 positively charged, the positive electrode (the anode) will be the active
17 electrode and the negative electrode (the cathode) will serve as the counter
18 electrode, completing the circuit. On the other hand, if the ionic substance to
19 be delivered is negatively charged, the cathodic electrode will be the active
20 electrode and the anodic electrode will be the counter electrode.
21 Alternatively, both the anode and the cathode may be used to deliver drugs of
22 appropriate charge into the body. In this case, both electrodes are
23 considered to be active or donor electrodes. In other words, the anodic
24 electrode can deliver positively charged agents into the body while the
25 cathodic electrode can deliver negatively charged agents into the body.

26 Existing electrotransport devices additionally require a reservoir
27 or source of the therapeutic agent that is to be delivered into the body. Such
28 drug reservoirs are connected to the anode or the cathode of the
29 electrotransport device to provide a fixed or renewable source of one or more
30 desired species or agents. Examples of reservoirs and sources include a
31 pouch as described in U.S. Patent No. 4,250,878 to Jacobsen; a pre-formed

1 gel body as disclosed in U.S. Patent No. 4,383,529 to Webster; and a glass
2 or plastic container holding a liquid solution of the drug, as disclosed in the
3 figures of U.S. Patent No. 4,722,726 to Sanderson et al.

4 Of particular interest herein is the transdermal delivery of
5 peptides, polypeptides, and proteins because of the problems encountered
6 with more common drug administration routes such as oral delivery.
7 Polypeptide and protein molecules are highly susceptible to degradation by
8 proteolytic enzymes in the gastrointestinal tract and are subjected to an
9 extensive hepatic metabolism when taken orally. Thus, these substances
10 usually require parenteral administration to achieve therapeutic levels in the
11 patient's blood. The most conventional parenteral administration techniques
12 are hypodermic injections and intravenous administration. Polypeptides and
13 proteins are, however, inherently short acting in their biological activity,
14 requiring frequent injections, often several times a day, to maintain the
15 therapeutically effective levels needed. Patients frequently find this treatment
16 regimen to be inconvenient and painful. Such therapy also includes risk of,
17 e.g., infection.

18 Much effort has been expended to find other routes (other than
19 parenteral injections) for effective administration of pharmaceutical agents,
20 including polypeptides and proteins. Administration routes with fewer side
21 effects as well as better patient compliance have been of particular interest.
22 Such alternative routes have generally included "shielded" oral administration
23 wherein the polypeptide/protein is released from a capsule or other container
24 after passing through the low pH environment of the stomach, delivery
25 through the mucosal tissues, e.g., the mucosal tissues of the lung with
26 inhalers or the nasal mucosal tissues with nasal sprays, and implantable
27 pumps. Unfortunately, these alternative routes of polypeptide/protein delivery
28 have met with only limited success.

29 A number of investigators have disclosed electrotransport
30 delivery of polypeptides and proteins. An early study by R. Burnette et al. J.
31 Pharm. Sci. (1986) 75:738, involved in vitro skin permeation of thyrotropin

1 releasing hormone, a small tripeptide molecule. The electrotransport flux was
2 found to be higher than passive diffusional flux. Chien et al. J. Pharm. Sci.
3 (1988) 78:376, in both in vitro and in vivo studies, showed that transdermal
4 delivery of vasopressin and insulin via electrotransport was possible. See,
5 also, Maulding et al., U.S. Statutory Invention Registration No. H1160, which
6 discloses electrotransport delivery of calcitonin in minipigs.

7 However, transdermal delivery of polypeptide and protein drugs
8 has also encountered technical difficulties. For example, skin irritation can
9 occur due to water hydrolysis at the interface between the electrode and the
10 drug solution or electrolyte salt solution. The products of such hydrolysis,
11 hydronium ions at the anode and hydroxyl ions at the cathode, compete with
12 drug ions of like charge for delivery into the skin, altering skin pH and causing
13 irritation. U.S. Patent No. 5,533,971, to Phipps et al., describes this problem
14 in more detail and reports the use of amino acid buffers, including histidine
15 buffers, for adjusting the pH of electrotransport device reservoirs to levels
16 which cause less irritation. Histidine as well as Asp, Glu and Lys have been
17 used for buffering (U.S. Patent 5,624,415). Additionally, certain polypeptide
18 and protein drugs, particularly those that are not native to the animal being
19 treated, may cause skin reactions, e.g., sensitization or irritation. Many
20 polypeptide and protein drugs are also unstable and degrade rapidly. In this
21 regard, International Publication No. WO 93/12812, published 8 July 1993,
22 describes the use of histidine buffers to chemically stabilize growth hormone
23 formulations. Unfortunately, histidine is not a commercially viable buffer in
24 many electrotransport drug formulations due to its instability in aqueous
25 solution, thereby making the shelf-life of the drug formulation unacceptably
26 short.

27 Controlling pH and assuring conductivity of electrotransport
28 formulations is a dilemma that has not been solved to date. Control of pH in
29 electrotransport systems is usually achieved by introduction of classic buffers
30 such as TRIS, acetate or phosphate buffers in the formulation. This results in
31 introduction of competing ions (i.e., ions having the same sign charge as the

1 drug ions) into the drug formulation. In addition, in these formulations, donor
2 reservoir pH drifting (i.e., during device operation) and reduced conductivity
3 occurs during transport due to depletion of the charged species. This is of
4 particular concern when the electrotransport delivery of therapeutically active
5 polypeptide drugs is considered. Because these compounds are present at
6 low concentration in the donor reservoir formulation, the detrimental effects
7 caused by competing ions, i.e., decreasing conductivity of the formulation,
8 decreasing transdermal drug flux, formulation pH drifting, and local skin
9 irritation, are likely to be more severe. Recently, crosslinked ion exchange
10 polymers have been used in an attempt to solve this deadlock. To date, their
11 use has raised additional problems. In addition to regulatory concerns linked
12 to the presence of small molecular weight degradants in these polymers, it is
13 now evident that they do not provide adequate electrical conductivity and their
14 usefulness in controlling pH is still subject to debate. What is still needed is a
15 method which provides pH control and conductivity of the electrotransport
16 drug formulation without introduction of competing ions and which is
17 accomplished with the use of small molecular weight compounds that are
18 easy to characterize.

19 Although histidine has been used to buffer protein formulations
20 (WO 93/12812), the use of histidine to buffer electrotransport drug
21 formulations is problematic due to the poor chemical stability of histidine in
22 aqueous solutions. Water is by far the most preferred liquid solvent for
23 electrotransport drug formulations due to its excellent biocompatibility when
24 in contact with skin. The aqueous stability of histidine is so poor that the
25 formulations are not able to achieve the minimum stable shelf life required by
26 drug regulatory agencies.

27 Thus, alternative methods for buffering aqueous electrotransport
28 drug formulations, and in particular polypeptide drug or protein formulations,
29 would be desirable.

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Summary of the Invention

According to one aspect of the present invention, there is provided a transdermal electrotransport drug delivery device having a reservoir containing a reservoir
5 formulation comprising an aqueous solution of a drug or an electrolyte and a buffer, the buffer comprising a peptide chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's which are separated by no more than
10 about 3.5 pH units, the solution having a pH which is within 1.0 pH unit of the isoelectric pH. Preferably, the transdermal electrotransport device is a transdermal patch.

According to another aspect of the present invention, there is provided a method of buffering an
15 aqueous solution of a drug or an electrolyte used for transdermal electrotransport delivery, comprising buffering the solution with a peptide comprising a chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's
20 which are separated by no more than about 3.5 pH units, the solution having a pH which is within about 1.0 H unit of the isoelectric pH.

According to still another aspect of the present invention, there is provided a transdermal electrotransport
25 drug delivery device for delivering an analgesic through a body surface of a patient, said device having a reservoir containing a reservoir formulation comprising an aqueous solution of a drug or an electrolyte and a buffer, the buffer comprising a peptide chain of 2 to 5 amino acids and
30 having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution

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having a pH which is within about 1.0 pH unit of the isoelectric pH. Preferably, the analgesic is fentanyl, fentanyl hydrochloride, sufentanil, carfentanil, lofentanil, alfentanil, hydromorphone, oxycodone, propoxyphene, 5 pentazocine, methadone, tilidine, butorphanol, buprenorphine, levorphanol, codeine, oxymorphone, meperidine, dihydrocodeinone, an opioid, cocaine, an analgesic analogue or an analgesic combination.

According to yet another aspect of the present 10 invention, there is provided a transdermal electrotransport drug delivery device for delivering insulin or insulinotropin through a body surface of a patient, said device having a reservoir containing a reservoir formulation comprising an aqueous solution of a drug or an electrolyte 15 and a buffer, the buffer comprising a peptide chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution having a pH which is within about 1.0 pH 20 unit of the isoelectric pH.

According to a further aspect of the present invention, there is provided a transdermal electrotransport drug delivery device for delivering a polypeptide, protein, macromolecule or combination thereof, through a body surface 25 of a patient, said device having a reservoir containing a reservoir formulation comprising an aqueous solution of a drug or an electrolyte and a buffer, the buffer comprising a peptide chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, 30 the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution having a pH which is within about 1.0 pH unit of the isoelectric pH.

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Disclosure of the Invention

The present invention provides a buffered aqueous formulation for transdermal electrotransport delivery exhibiting excellent stability characteristics. The reservoir formulation may be a donor reservoir formulation containing a drug or other therapeutic agent to be transdermally delivered. Alternatively, the reservoir formulation may be a counter reservoir formulation containing an electrolyte (e.g., saline). The formulation comprises an aqueous solution of the drug or electrolyte buffered with a buffer, the buffer comprising a peptide chain of two to five amino acids, and has an isoelectric pH at which the peptide carries no net charge. The aqueous solution has a pH which is within about 1.0 pH unit of the isoelectric pH. Preferably, the peptide has at least two pKa's which are separated by no more than about 3.5 pH units. Most preferably, the isoelectric pH of the peptide is between about 3 and 10. The concentration of the peptide buffer in the solution is preferably at least about 10mM. Preferably, the buffer is a dipeptide buffer selected from the group consisting of Asp-Asp, Gly-Asp, Asp-His, Glu-His, His-Glu, His-Asp, Glu-Arg, Glu-Lys, Arg-Glu, Lys-Glu, Arg-Asp, Lys-Asp, His-Gly, His-Ala, His-Asn, His-Citruline, His-Gln, His-Hydroxyproline, His-Isoleucine, His-Leu, His-Met, His-Phe, His-Pro, His-Ser, His-Thr, His-Trp, His-Tyr, His-Val, Asn-His, Thr-His, Try-His, Gin-His, Phe-His, Ser-His, Citruline-His, Trp-His, Met-His, Val-His, His-His, Isoleucine-His, Hydroxyproline-His, Leu-His, Ala-His, Gly-His, Beta-Alanylhistidine, Pro-His, Carnosine, Anserine, Tyr-Arg, Hydroxylysine-His, His-Hydroxytyrosine, Ornithine-His, His-Lys, His-Ornithine and Lys-His. A particularly preferred dipeptide buffer is Gly-His.

The present invention also provides a method of buffering an aqueous solution of a drug or an electrolyte used for transdermal electrotransport delivery. The method includes providing in the solution a pH buffering amount of a peptide comprising a peptide chain of two to five amino acids, and having an isoelectric pH at which the peptide carries no net charge. The aqueous solution has a pH which is within about 1.0 pH unit

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of the isoelectric pH. Preferably, the peptide has at least two pKa's which are separated by no more than about 3.5 pH units. Most preferably, the isoelectric pH of the peptide is between about 3 and 10. The concentration of the peptide buffer in the solution is preferably at least about 10mM. Preferably, the buffer is a dipeptide buffer selected from the group consisting of Asp-Asp, Gly-Asp, Asp-His, Glu-His, His-Glu, His-Asp, Glu-Arg, Glu-Lys, Arg-Glu,, Lys-Glu, Arg-Asp, Lys-Asp, His-Gly, His-Ala, His-Asn, His-Citruline, His-Gln, His-Hydroxyproline, His-Isoleucine, His-Leu, His-Met, His-Phe, His-Pro, His-Ser, His-Thr, His-Trp, His-Tyr, His-Val, Asn-His, Thr-His, Try-His, Gin-His, Phe-His, Ser-His, Citruline-His, Trp-His, Met-His, Val-His, His-His, Isoleucine-His, Hydroxyproline-His, Leu-His, Ala-His, Gly-His, Beta-Alanylhistidine, Pro-His, Carnosine, Anserine, Tyr-Arg, Hydroxylysine-His, His-Hydroxytlysine, Ornithine-His, His-Lys, His-Ornithine and Lys-His. A particularly preferred dipeptide buffer is Gly-His.

Brief Description of the Drawings

Figure 1 is a graph showing ionic charge versus pH for the dipeptide buffer Gly-His.

Figure 2 is a graph showing charged ion species distribution versus pH for the dipeptide buffer Gly-His.

Figure 3 is a graph showing ionic charge versus pH for two prior art buffers.

Figure 4 is a graph showing charged ion species distribution versus pH for phosphoric acid, a prior art buffer.

Figure 5 is a graph of charged ion species distribution versus pH for 3-[N-morpholino]propanesulphonic acid (MOPS), a prior art buffer.

Figure 6 is a graph of charged ion species distribution versus pH for the dipeptide buffer Glu-His.

Figure 7 is a graph of charged ion species distribution versus pH for the dipeptide buffer His-Glu.

1 Figure 8 is an exploded view of a representative electrotransport
2 drug delivery device which can be used with the present invention.

3 Figure 9 is a graph of human growth hormone degradation
4 versus time using a Gly-His dipeptide buffer.

5 Figure 10 is a graph of human growth hormone degradation
6 versus time using His, a non-dipeptide buffer.

7 Figure 11 is a graph of transdermal flux of a model decapeptide
8 at varying Gly-His concentrations.

9

10 **Modes for carrying out the invention**

11 The practice of the present invention will employ, unless
12 otherwise indicated, conventional methods of protein chemistry,
13 electrochemistry and biochemistry within the skill of the art. Such techniques
14 are explained fully in the literature. See, e.g., T.E. Creighton, Proteins:
15 Structures and Molecular Properties (W.H. Freeman and Company, 1993);
16 A.L. Lehninger, Biochemistry (Worth Publishers, Inc., 1975); J.S. Newman,
17 Electrochemical Systems (Prentice Hall, 1973); and A.J. Bard and L.R.
18 Faulkner, Electrochemical Methods, Fundamentals and Applications (John
19 Wiley & Sons, 1980).

20 It must be noted that, as used in this specification and the
21 appended claims, the singular forms "a", "an" and "the" include plural
22 referents unless the content clearly dictates otherwise. Thus, for example,
23 reference to "a polypeptide" includes a mixture of two or more polypeptides,
24 and the like.

25 The following amino acid abbreviations are used throughout the
26 text:

27 Alanine: Ala (A)	Arginine: Arg (R)
28 Asparagine: Asn (N)	Aspartic acid: Asp (D)
29 Cysteine: Cys (C)	Glutamine: Gln (Q)
30 Glutamic acid: Glu (E)	Glycine: Gly (G)
31 Histidine: His (H)	Isoleucine: Ile (I)

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1	Leucine: Leu (L)	Lysine: Lys (K)
2	Methionine: Met (M)	Phenylalanine: Phe (F)
3	Proline: Pro (P)	Serine: Ser (S)
4	Threonine: Thr (T)	Tryptophan: Trp (W)
5	Tyrosine: Tyr (Y)	Valine: Val (V)

6

7 I. Definitions

8 In describing the present invention, the following terms will be
9 employed, and are intended to be defined as indicated below.

10 The term "peptide" denotes any peptide chain of 2 to 5
11 amino acid residues. The term encompasses dipeptides, tripeptides,
12 tetrapeptides, and pentapeptides, and particularly includes dipeptides and
13 tripeptides which contain His, such as but not limited to, His-Gly, Gly-His, Ala-
14 His, His-Ser and His-Ala.

15 The term "drug" and "therapeutic agent" are used
16 interchangeably and are intended to have their broadest interpretation as any
17 therapeutically active substance which is delivered to a living organism to
18 produce a desired, usually beneficial, effect. In general, this includes
19 therapeutic agents in all of the major therapeutic areas including, but not
20 limited to, anti-infectives such as antibiotics and antiviral agents, analgesics
21 including fentanyl, sufentanil, buprenorphine and analgesic combinations,
22 anesthetics, anorexics, antiarthritics, antiasthmatic agents such as
23 terbutaline, anticonvulsants, antidepressants, antidiabetic agents,
24 antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine
25 preparations, antmotion sickness preparations such as scopolamine and
26 ondansetron, antinauseants, antineoplastics, antiparkinsonism drugs,
27 antipruritics, antipsychotics, antipyretics, antispasmodics, including
28 gastrointestinal and urinary, anticholinergics, antiulceratives such as
29 ranitidine, sympathomimetics, xanthine derivatives, cardiovascular
30 preparations including calcium channel blockers such as nifedipene,
31 beta-blockers, beta-agonists such as dobutamine and ritodrine,

1 antiarrhythmics, antihypertensives such as atenolol, ACE inhibitors such as
2 enalapril, benzodiazepine antagonists such as flumazenil, diuretics,
3 vasodilators, including general, coronary, peripheral and cerebral, central
4 nervous system stimulants, cough and cold preparations, decongestants,
5 diagnostics, hormones such as parathyroid hormone, hypnotics,
6 immunosuppressives, muscle relaxants, parasympatholytics,
7 parasympathomimetics, prostaglandins, proteins, peptides,
8 psychostimulants, sedatives and tranquilizers.

9 The invention is also useful in the controlled delivery of
10 polypeptide and protein drugs and other macromolecular drugs. These
11 macromolecular substances typically have a molecular weight of at least
12 about 300 daltons, and more typically a molecular weight in the range of
13 about 300 to 40,000 daltons. Specific examples of peptides, and proteins
14 and macromolecules in this size range include, without limitation, LHRH,
15 LHRH analogs such as buserelin, gonadorelin, napharelin and leuprolide,
16 GHRH, GHRF, insulin, insulotropin, heparin, calcitonin, octreotide, endorphin,
17 TRH, NT-36 (chemical name: $N=[[(s)-4\text{-oxo-2-azetidiny}]carbonyl]-L\text{-histidyl-}$
18 $L\text{-prolinamide}$), liprecin, pituitary hormones (e.g., HGH, HMG, HCG,
19 desmopressin acetate, etc.), follicle luteoids, α ANF, growth factors such as
20 growth factor releasing factor (GFRF), β MSH, somatostatin, atrial natriuretic
21 peptide, bradykinin, somatotropin, platelet-derived growth factor,
22 asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic
23 gonadotropin, corticotropin (ACTH), epidermal growth factor, erythropoietin,
24 epoprostenol (platelet aggregation inhibitor), follicle stimulating hormone,
25 glucagon, hirulog, and other analogs of hirudin, hyaluronidase, interferon,
26 insulin-like growth factors, interleukin-1, interleukin-2, menotropins
27 (urofollitropin (FSH) and LH), oxytocin, streptokinase, tissue plasminogen
28 activator, urokinase, vasopressin, desmopressin, ACTH analogs, ANP, ANP
29 clearance inhibitors, angiotensin II antagonists, antidiuretic hormone agonists,
30 antidiuretic hormone antagonists, bradykinin antagonists, CD4, ceredase,
31 CSF's, enkephalins, FAB fragments, IgE peptide suppressors, IGF-1,

1 neuropeptide Y, neurotrophic factors, oligodeoxynucleotides and their
2 analogues such as antisense RNA, antisense DNA and anti-gene nucleic
3 acids, opiate peptides, colony stimulating factors, parathyroid hormone and
4 agonists, parathyroid hormone antagonists, prostaglandin antagonists,
5 pentigetide, protein C, protein S, ramoplanin, renin inhibitors, thymosin alpha-
6 1, thrombolytics, TNF, vaccines, vasopressin antagonist analogs, alpha-1
7 anti-trypsin (recombinant), and TGF-beta. With electrotransport delivery
8 devices, it has been recognized that the agents should generally be soluble in
9 water. It is generally believed that the pathways for electrotransport drug
10 delivery are hydrophilic pathways or pores such as those associated with hair
11 follicles and sweat glands. The preferred form of an agent for electrotransport
12 delivery is hydrophilic (e.g., water soluble salt form).

13 The term "transdermal delivery" refers to the delivery through a
14 body surface (e.g., skin) of one or more pharmaceutically active agents to be
15 available for either a local or systemic pharmacological effect. Penetration
16 enhancers can be used to facilitate absorption through the skin. Such
17 penetration enhancers include solvents such as water, alcohols including
18 methanol, ethanol, 2-propanol, dodecanol, dodecanediol and the like, alkyl
19 methyl sulfoxides, pyrrolidones, laurocapram, acetone, dimethylacetamide,
20 dimethyl formamide, tetrahydrofurfuryl; surfactants including fatty acids/salts
21 such as laurates; and chemicals such as urea, N,N-diethyl-m-toluamide, and
22 the like.

23 The terms "electrotransport", "iontophoresis", and
24 "iontophoretic" are used herein to refer to the delivery through a body surface
25 (e.g., skin) of one or more pharmaceutically active agents by means of an
26 applied electromotive force to an agent-containing reservoir. The agent may
27 be delivered by electromigration, electroporation, electroosmosis or any
28 combination thereof. Electroosmosis has also been referred to as
29 electrohydrokinesis, electro-convection, and electrically induced osmosis. In
30 general, electroosmosis of a species into a tissue results from the migration of
31 solvent in which the species is contained, as a result of the application of

1 electromotive force to the therapeutic species reservoir, i.e., solvent flow
2 induced by electromigration of other ionic species. During the
3 electrotransport process, certain modifications or alterations of the skin may
4 occur such as the formation of transiently existing pores in the skin, also
5 referred to as "electroporation". Any electrically assisted transport of species
6 enhanced by modifications or alterations to the body surface (e.g., formation
7 of pores in the skin) are also included in the term "electrotransport" as used
8 herein. Thus, as used herein, the terms "electrotransport", "iontophoresis"
9 and "iontophoretic" refer to (1) the delivery of charged agents by
10 electromigration, (2) the delivery of uncharged agents by the process of
11 electroosmosis, (3) the delivery of charged or uncharged agents by
12 electroporation, (4) the delivery of charged agents by the combined
13 processes of electromigration and electroosmosis, and/or (5) the delivery of a
14 mixture of charged and uncharged agents by the combined processes of
15 electromigration and electroosmosis.

16 Transdermal electrotransport flux can be assessed using a
17 number of in vivo or in vitro methods, well known in the art. In vitro methods
18 include clamping a piece of skin of an appropriate animal (e.g., human
19 cadaver skin) between the donor and receptor compartments of an
20 electrotransport flux cell, with the stratum corneum side of the skin piece
21 facing the donor compartment. A liquid solution or gel containing the drug to
22 be delivered is placed in contact with the stratum corneum, and electric
23 current is applied to electrodes, one electrode in each compartment. The
24 transdermal flux is calculated by sampling the amount of drug in the receptor
25 compartment. Two successful models used to optimize transdermal
26 electrotransport drug delivery are the isolated pig skin flap model of Riviere,
27 Heit et al, J. Pharm. Sci. (1993) 82:240-243, and the use of isolated hairless
28 skin from hairless rodents or guinea pigs. See, Hadzija et al., J. Pharm.
29 Pharmacol. (1992) 44:387-390. See, also, Ogiso et al., Biol. Pharm. Bull.
30 (1996) 19:1049-1054, for a description of a method for evaluating
31 percutaneous absorption of insulin.

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II. Modes of Carrying Out the Invention

The present invention concerns the use of peptides, particularly dipeptides, to buffer transdermal electrotransport reservoir formulations, particularly drug-containing donor reservoir formulations and more particularly donor reservoir formulations used for electrotransport delivery of a polypeptide or protein drug. The method therefore permits increased efficiency of the transdermal delivery of a large number of substances, and allows for the transdermal delivery of molecules that would not otherwise be amenable to such delivery.

In performing electrotransport experiments in animals, it has surprisingly been discovered that some buffers are better suited for pH control. In particular, dipeptide buffers such as Gly-His and His-Glu at their pI are capable of assuring pH control of electrotransport formulations for several hours. Peptide buffers for use in the present invention include dipeptides, tripeptides, tetrapeptides, and pentapeptides which contain His, such as His-Gly, Gly-His, Ala-His, L-carnosine (also known as L-Ala-His), His-Ser, His-Ala, Gly-Gly-His (pI = 7.5), His-Gly-Gly (pI = 6.9), Gly-Gly-Gly-His (pI = 7.5), His-Gly-Gly-Gly (pI = 6.9), Gly-Gly-Gly-Gly-His (pI = 7.55), and His-Gly-Gly-Gly-Gly (pI = 6.0).

The peptide should have at least two pKa's separated by no more than about 3.5 pH units. Beyond this range, pH control will be poor and conductivity of the solution will be minimal. The pI range of the peptide should be between 3 and 10 and the pH of the formulation should be no more than about 1 pH unit away from the isoelectric pH (i.e., the pI) of the peptide. Generally, the formulation pH will be from about pH 3 to about pH 9.5. However, the preferred formulation pH will depend on the particular drug and peptide buffer used in the formulation. Beyond these pH limits (i.e., less than pH 3 and greater than pH 10), the formulation is likely to be irritating or will result in unacceptable skin resistance. In addition, if the formulation pH is more than 1 pH unit away from the pI of the peptide buffer, the effects described above will be inefficient as the peptide will start behaving like a conventional buffer (high transport efficiency of charged species and pH

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1 drifting). When the peptide is used in a solution having a pH at or close to
2 the pI of the peptide (i.e., $pI \pm 1.0$ pH unit), minimum competition with the
3 drug ions (i.e., for electrotransport into the patient) will occur because the
4 buffer is at or close to electrical (i.e., ionic) neutrality and therefore it can be
5 used with good results (i.e., little or no ionic competition with the drug ions) in
6 either the anode or the cathode reservoir formulations. If for technical
7 reasons it is decided to use the peptide at a pH between 0.5 to 1.0 pH unit
8 away from the pI, the use of the buffer at a pH slightly higher than its pI is
9 preferred in the cathodic formulation in order to minimize ionic competition
10 with the drug being delivered. Conversely, and for the same reason, the use
11 of the peptide buffer at a pH slightly below (i.e., between 0.5 to 1.0 pH unit
12 below) its pI is preferred in the anodic formulation. In the counter reservoir
13 formulation (i.e., the non-drug containing reservoir) this preference is not as
14 important as there is no concern over the buffer ions competing with drug ions
15 for delivery into the patient from the counter reservoir. The peptide buffer
16 will generally be present in the formulation at a concentration of from about 10
17 mM to 1 M, more preferably from about 10 mM to about 250 mM, and most
18 preferably from about 25 mM to about 250 mM.

19 Table 1 lists conductivities and solubilities of selected dipeptides
20 useful in the present invention, at their pI.

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TABLE 1

Dipeptide	pI	Conductivity at 10 ⁻² Molar (μS*/cm)	Solubility (Moles/l)
His-Glu	5.20	40	0.40
His-Asp	5.22	28	0.05
Glu-Lys	6.00	6	1.00
Lys-Glu	6.06	8	0.50
Lys-Asp	6.08	6	1.00
His-Gly	6.90	40	1.00
His-Ala	6.95	60	0.50
Val-His	7.38	94	0.20
Gly-His	7.55	52	1.00
*micro Siemens			

The peptide buffer preferably includes at least one amino acid selected from His, Asp, Glu, Lys, Tyr, Arg and Cys; more preferably includes at least one amino acid selected from His, Asp, Glu, and Lys; and most preferably includes at least one amino acid selected from His and derivatives thereof (e.g., methyl-His).

This invention can be practiced in many different ways. In its simplest form, the peptide provides pH control to the formulation containing no drug contained in the counter electrode (cathode or anode) reservoir of the electrotransport system. The peptide may also be incorporated in the donor (i.e., drug-containing) reservoir formulation (cathodic or anodic).

The buffering of the anodic and/or cathodic reservoirs of a transdermal electrotransport drug delivery device is particularly important because these reservoirs must contain a liquid solution of a drug or other electrolyte. The liquid solvent used for the drug/electrolyte solutions is usually water due to water's excellent biocompatibility. During operation of an electrotransport device, an oxidation reaction takes place at the interface between the anodic electrode and the solution contained in the anodic reservoir. Similarly, an electrochemical reduction reaction takes place at the

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1 interface between the cathodic electrode and the solution in the cathodic
2 reservoir. When the electrodes are composed of electrochemically non-
3 reactive materials, such as platinum or stainless steel, the water tends to be
4 the primary species which is either oxidized or reduced, thereby causing a pH
5 drop in the anodic reservoir and a pH rise in the cathodic reservoir. See for
6 example, Phipps, et al., U.S. Patent 4,744,787; Phipps, et al., U.S. Patent
7 4,747,819; and Petelenz, et al., U.S. Patent 4,752,285. Although the use of
8 electrochemically reactive electrode materials, such as a silver anode and/or
9 a silver chloride cathode substantially reduces the oxidation and reduction of
10 water in electrotransport reservoirs as taught in the above-identified Phipps,
11 et al. and Petelenz, et al. patents, there is still some tendency for the water in
12 these reservoirs to be oxidized or reduced during operation of the device,
13 leading to undesirable pH changes. Thus, while the peptide buffers of the
14 present invention have particular utility in those electrotransport devices
15 utilizing electrodes composed of materials which are electrochemically non-
16 reactive, the buffers of the present invention can still find utility even in those
17 electrotransport devices utilizing electrodes composed of electrochemically
18 reactive materials.

19 Many dipeptides present adequate characteristics for use in
20 electrotransport formulation. Table 2 includes a non-exhaustive list of the
21 dipeptide buffers ranked by increasing pI. Dipeptides
22 and peptides having up to five amino
23 acids and containing the amino acids histidine, lysine, aspartic acid or
24 glutamic acid in combination or with other amino acids are particularly useful
25 to this invention.

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TABLE 2

Dipeptide	pka A	pka A	pka A	pka B	pka B	pka B	pl	% salt
Asp-Asp	2.70	3.40	4.70	8.26			3.05	43
Gly-Asp	2.81	4.45		8.60			3.60	23
Asp-His	2.45	3.02		6.81	7.98		4.90	3
Glu-His	2.45	3.45		6.81	8.20		5.20	5
His-Glu	2.30	4.19		6.32	8.07		5.20	15
His-Asp	2.28	3.99		6.45	8.19		5.22	11
Glu-Arg	2.66	4.01		7.94	12.50		6.00	2
Glu-Lys	2.85	4.01		7.94	11.07		6.00	2
Arg-Glu	2.74	4.18		7.92	12.50		6.06	3
Lys-Glu	2.74	4.18		7.92	11.12		6.06	3
Arg-Asp	2.64	4.10		8.05	12.50		6.08	2
Lys-Asp	2.64	4.10		8.05	11.20		6.08	2
His-Gly	2.41			5.90	7.91		6.90	16
His-Ala	2.48			6.10	7.80		6.95	22
His-Asn	2.62			6.10	7.80		6.95	22
His-Citrulline	3.05			6.10	7.80		6.95	22
His-Gln	2.93			6.10	7.80		6.95	22
His-Hydroxyproline	2.42			6.10	7.80		6.95	22
His-Isoleucine	3.13			6.10	7.80		6.95	22
His-Leu	3.10			6.10	7.80		6.95	22
His-Met	2.89			6.10	7.80		6.95	22
His-Phe	2.88			6.10	7.80		6.95	22
His-Pro	2.62			6.10	7.80		6.95	22
His-Ser	2.65			6.10	7.80		6.95	22
His-Thr	2.98			6.10	7.80		6.95	22
His-Trp	3.07			6.10	7.80		6.95	22

His-Tyr	2.13	9.97		6.10	7.80		6.95	22
His-Val	3.18			6.10	7.80		6.95	22
Asn-His	2.42			6.71	7.30		7.00	44
Thr-His	2.42			6.71	7.60		7.15	39
Tyr-His	2.42	9.90		6.71	7.60		7.15	39
Gln-His	2.42			6.71	7.70		7.20	36
Phe-His	2.42			6.71	7.70		7.20	36
Ser-His	2.42			6.71	7.70		7.20	36
Citrulline-His	2.42			6.71	7.90		7.30	32
Trp-His	2.42			6.71	7.90		7.30	32
Met-His	2.42			6.71	7.97		7.35	30
Val-His	3.09			6.83	7.94		7.38	34
His-His	2.25			5.40	6.80	7.95	7.40	32
Isoleucine-His	2.42			6.71	8.20		7.44	25
Hydroxyproline-His	2.42			6.71	8.23		7.45	25
Leu-His	2.42			6.71	8.25		7.50	24
Ala-His	2.42			6.71	8.37		7.55	22
Gly-His	2.42			6.71	8.39		7.55	22
Beta-Alanylhistidine	2.60			6.70	8.70		7.70	16
Pro-His	2.42			6.71	9.10		7.90	11
Carnosine	2.64			6.83	9.51		8.17	8
Anserine	2.64			7.04	9.49		8.27	10
Tyr-Arg	2.64	9.36		7.39	11.62		8.40	17
Hydroxylysine-His	2.42			6.71	7.40	9.70	8.60	13
His-Hydroxylysine	3.05			6.10	7.80	9.70	8.75	17
Ornithine-His	2.42			6.71	7.30	11.00	9.20	3

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His-Lys	3.05			6.10	7.80	11.00	9.40	5
His-Ornithine	2.82			6.10	7.80	11.00	9.40	5
Lys-His	2.42			6.71	8.00	11.00	9.50	5

pKa A = acidic pKa

pKa B = basic pKa

% salt = fraction of the dipeptide that is ionized and carries a net positive and/or negative charge, but not including the ionized species carrying a net neutral charge, in an aqueous solution having a pH equal to the pI

The pH buffering capacity of the peptide buffers of the present invention can be explained by using Gly-His at pH 7.5 as an example (the pI of Gly-His is 7.55). At this pH, the net charge of the molecule is essentially zero (see Figure 1). At the pI, three species coexist. The bulk of the molecule (70%) consists of the neutral species which bears two internal charges, one positive and one negative resulting in a net charge of zero. The remaining (30%) consists of the salt form of the positively charged species (1-2+, net charge = +1) and the negatively charged species (-1); see Figure 2). The existence of this salt can be demonstrated by measuring the conductivity of the solution of a Gly-His solution at its pI (Table 1). Although there are small percentages of species presenting a net positive or negative charge in solution, there is minimal ionic transport of these charged species due to charge equilibrium between the three species (i.e., a positive charge migrating in the electric field will revert almost instantly to its neutral form and lose momentum or to its negative form and migrate backward). Due to the same principle of charge equilibrium, any depletion of the charged molecules will be compensated immediately by dissociation of the neutral form to its charged species thereby providing a reservoir insuring long term pH stability. In addition, if loss of the molecule occurs by electroosmosis of the neutral species, this will not result in any pH changes.

The pH buffering capacity of dipeptides at or near their isoelectric pH contrasts sharply with the lack of pH stability observed with

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1 conventional buffers such as phosphate or 3-[N-morpholino] propane sulfonic
2 acid (MOPS) at the same or higher ionic strength as shown in Table 3. The
3 decrease of pH observed in the presence of phosphate (a triacid: pKa's of
4 2.12, 7.2 and 12.32) and MOPS (a zwitterion: pKa's of <1 and 7.2) can be
5 explained by the fact that these buffers are used at a pH close to their pKa.
6 The net charge of phosphoric acid and MOPS at pH 7 is respectively -1/5 and
7 -0.5 (see Figure 3). For phosphoric acid, half of the molecules have a -2
8 valence and the other half have a -1 valence (see Figure 4). For MOPS, half
9 of the molecules have a -1 valence and the other half are the neutral form of
10 the molecule which bears two internal charges, one positive and one negative
11 (see Figure 5). In an electric field these negative species move in the
12 opposite direction of their positive associated counterions. This migration will
13 result in depletion of the charged species and accumulation of the neutral
14 species in the reservoir resulting in a pH drop. At its pI, MOPS (pI = 4) does
15 not present any buffering capacity and MOPS solutions at this pH are non-
16 conductive.

17 Figures 6 and 7 present examples of the charge distribution for
18 two dipeptides (Glu-His and His-Glu) both having a pI of 5.2. At the pI, the
19 species presenting a net charge (which assure electrical conductivity)
20 represent respectively about 5% and 15% of the molecules. Choice of the
21 peptide buffer will be on a case-by-case basis depending on the drug
22 compound and the desired level of pH control and conductivity of the
23 formulation. For example with a non-peptidic drug such as fentanyl,
24 conductivity of the buffer and tight pH control is not essential because the
25 drug itself is present at high concentration which provides adequate
26 conductivity and because the charge of the drug is constant in the pH range
27 zero to seven. For this drug, the buffer Glu-His is a perfect choice. The pI of
28 this buffer is 5.2 (this pH assures solubility of the drug) and the conductivity of
29 the buffer is minimal. If more pH control and more conductivity is required, as
30 with most polypeptide and protein drugs such as goserelin, the buffer His-Glu
31 is a judicious choice. The pI of this buffer is 5.2 (this pH assures that the

1 goserelin has optimal charge) and about 15% of the buffer is charged at its pI
2 assuring good conductivity of the formulation.

3 When used to buffer electrotransport donor (i.e., drug-
4 containing) reservoir formulations, the present invention is useful for any
5 number of categories of therapeutic agents (i.e., drugs) and the invention is
6 not limited thereby. The invention has particular utility in buffering aqueous
7 polypeptide and protein drug formulations because these drugs are typically
8 present at low concentration in the donor reservoir formulation, the
9 detrimental effects caused by competing ions, i.e., decreasing conductivity of
10 the formulation, decreasing transdermal drug flux, formulation pH drifting, and
11 local skin irritation, are likely to be more severe. Such protein and
12 polypeptide drugs include those derived from eucaryotic, procaryotic and viral
13 sources, as well as synthetic polypeptide drugs. Such polypeptide drugs
14 include without limitation, polypeptide drugs which are antibiotics and antiviral
15 agents, antineoplastics, immunomodulators, polypeptide hormones such as
16 insulin, proinsulin, growth hormone, GHRH, LHRH, EGF, Somatostatin, SNX-
17 111, BNP, insulinotropin, ANP, and glycoprotein hormones such as, FSH, LH,
18 PTH and hCG.

19 Examples of protein drugs for use with the present methods
20 include any commercially available insulins, such as, for example,
21 recombinant human insulin from Sigma, St. Louis, MO, formulated as neutral
22 solutions or suspensions of zinc insulin. Such preparations of insulin contain
23 a minimum of two zinc ions bound per hexamer and have an insulin
24 concentration from about 0.2 to about 3.0 mM (1 mg mL⁻¹ to 18 mg mL⁻¹).
25 However, insulin preparations including higher concentrations of insulin, up to
26 about 17 mM insulin will also find use herein.

27 The drug and dipeptide buffer are present in an aqueous
28 solution since water is by far the most preferred liquid solvent for transdermal
29 electrotransport drug delivery due to its excellent biocompatibility. In
30 addition to water, other pharmaceutically acceptable excipients such as
31 dextrose, glycerol, ethanol, and the like may also be present. If desired, the

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1 pharmaceutical composition to be administered may also contain minor
2 amounts of nontoxic auxiliary substances such as wetting or emulsifying
3 agents, preservatives, ion-binding agents and the like, for example, sodium
4 acetate, sorbitan monolaurate, triethanolamine sodium acetate,
5 triethanolamine oleate, etc. The choice of an appropriate excipient and
6 additives is determined largely by the drug being delivered. For a discussion
7 of drug formulations, see, e.g., Remington: The Science and Practice of
8 Pharmacy, Mack Publishing Company, Easton, Pennsylvania, 19th edition,
9 1995. For protein drug formulations, such excipients include, without
10 limitation, preservatives such as methylparaben and phenol (m-cresol);
11 isotonic agents such as glycerol or salts, including but not limited to NaCl
12 (generally at a concentration of about 1 to about 100 mM NaCl); and the like.
13 For a discussion of insulin formulations, see, e.g., Brange, J., Stability of
14 Insulin (Kluwer Academic Publishers); Brange, J. Galenics of Insulin, The
15 Physico-chemical and Pharmaceutical Aspects of Insulin and Insulin
16 Preparations (Springer-Verlag); and Remington: The Science and Practice of
17 Pharmacy, Mack Publishing Company, Easton, Pennsylvania, 19th edition,
18 1995.

19 Once the desired drug formulation with the peptide buffer is
20 prepared, it can be used with any of several transdermal electrotransport drug
21 delivery systems and use is not limited to any one particular electrotransport
22 system. Examples of electrotransport drug delivery systems are described in,
23 e.g., U.S. Patents 5,312,326 to Myers et al., 5,080,646 to Theeuwes et al.,
24 5,387,189 to Gyory et al., and 5,169,383 to Gyory et al..

25 Figure 8 illustrates a representative electrotransport delivery
26 device that may be used in conjunction with the present method. Device 10
27 comprises an upper housing 16, a circuit board assembly 18, a lower housing
28 20, anode electrode 22, cathode electrode 24, anode reservoir 26, cathode
29 reservoir 28 and skin-compatible adhesive 30. When the drug to be delivered
30 is cationic, anodic reservoir 26 will be the donor reservoir and cathodic
31 reservoir 28 will be the counter reservoir. Conversely, when the drug to be

1 delivered is anionic, cathodic reservoir 28 will be the donor reservoir and
2 anodic reservoir 26 will be the counter reservoir.

3 Upper housing 16 has lateral wings 15 which assist in holding
4 device 10 on a patient's skin. Upper housing 16 is preferably composed of an
5 injection moldable elastomer (e.g., ethylene vinyl acetate). Printed circuit
6 board assembly 18 comprises an integrated circuit 19 coupled to discrete
7 components 40 and battery 32. Circuit board assembly 18 is attached to
8 housing 16 by posts (not shown in Figure 2) passing through openings 13a
9 and 13b, the ends of the posts being heated/melted in order to heat stake the
10 circuit board assembly 18 to the housing 16. Lower housing 20 is attached to
11 the upper housing 16 by means of adhesive 30, the upper surface 34 of
12 adhesive 30 being adhered to both lower housing 20 and upper housing 16
13 including the bottom surfaces of wings 15.

14 Shown (partially) on the underside of circuit board assembly 18
15 is a button cell battery 32. Other types of batteries may also be employed to
16 power device 10.

17 The device 10 is generally comprised of battery 32, electronic
18 circuitry 19,40, electrodes 22,24, and drug/chemical reservoirs 26,28, all of
19 which are integrated into a self-contained unit. The outputs (not shown in
20 Figure 2) of the circuit board assembly 18 make electrical contact with the
21 electrodes 24 and 22 through openings 23,23' in the depressions 25,25'
22 formed in lower housing 20, by means of electrically conductive adhesive
23 strips 42,42'. Electrodes 22 and 24, in turn, are in direct mechanical and
24 electrical contact with the top sides 44',44 of drug reservoirs 26 and 28. The
25 bottom sides 46',46 of drug reservoirs 26,28 contact the patient's skin through
26 the openings 29',29 in adhesive 30.

27 Device 10 optionally has a feature which allows the patient to
28 self-administer a dose of drug by electrotransport. Upon depression of push
29 button switch 12, the electronic circuitry on circuit board assembly 18 delivers
30 a predetermined DC current to the electrodes/reservoirs 22,26 and 24,28 for
31 a delivery interval of predetermined length. The push button switch 12 is

1 conveniently located on the top side of device 10 and is easily actuated
2 through clothing. A double press of the push button switch 12 within a short
3 time period, e.g., three seconds, is preferably used to activate the device for
4 delivery of drug, thereby minimizing the likelihood of inadvertent actuation of
5 the device 10. Preferably, the device transmits to the user a visual and/or
6 audible confirmation of the onset of the drug delivery interval by means of
7 LED 14 becoming lit and/or an audible sound signal from, e.g., a "beeper".
8 Drug is delivered through the patient's skin by electrotransport, e.g., on the
9 arm, over the predetermined delivery interval.

10 Anodic electrode 22 is preferably comprised of silver and
11 cathodic electrode 24 is preferably comprised of silver chloride. Both
12 reservoirs 26 and 28 are preferably comprised of polymer hydrogel materials.
13 Electrodes 22,24 and reservoirs 26,28 are retained within the depressions
14 25',25 in lower housing 20.

15 The push button switch 12, the electronic circuitry on circuit
16 board assembly 18 and the battery 32 are adhesively "sealed" between upper
17 housing 16 and lower housing 20. Upper housing 16 is preferably composed
18 of rubber or other elastomeric material. Lower housing 20 is preferably
19 composed of a plastic or elastomeric sheet material (e.g., polyethylene) which
20 can be easily molded to form depressions 25,25' and cut to form openings
21 23,23'. The assembled device 10 is preferably water resistant (i.e., splash
22 proof) and is most preferably waterproof. The system has a low profile that
23 easily conforms to the body, thereby allowing freedom of movement at, and
24 around, the wearing site. The reservoirs 26 and 28 are located on the skin-
25 contacting side of the device 10 and are sufficiently separated to prevent
26 accidental electrical shorting during normal handling and use.

27 The device 10 adheres to the patient's body surface (e.g., skin)
28 by means of a peripheral adhesive 30 which has upper side 34 and body-
29 contacting side 36. The adhesive side 36 has adhesive properties which
30 assures that the device 10 remains in place on the body during normal user
31 activity, and yet permits reasonable removal after the predetermined (e.g., 24-

1 hour) wear period. Upper adhesive side 34 adheres to lower housing 20 and
2 retains lower housing 20 attached to upper housing 16.

3 The reservoirs 26 and 28 generally comprise a gel matrix, with
4 the drug solution uniformly dispersed in at least one of the reservoirs 26 and
5 28. Drug concentrations in the range of approximately 1×10^{-4} M to 1.0 M or
6 more can be used, with drug concentrations in the lower portion of the range
7 being preferred. Suitable polymers for the gel matrix may comprise
8 essentially any nonionic synthetic and/or naturally occurring polymeric
9 materials. A polar nature is preferred when the active agent is polar and/or
10 capable of ionization, so as to enhance agent solubility. Optionally, the gel
11 matrix will be water swellable. Examples of suitable synthetic polymers
12 include, but are not limited to, poly(acrylamide), poly(2-hydroxyethyl acrylate),
13 poly(2-hydroxypropyl acrylate), poly(N-vinyl-2-pyrrolidone), poly(n-methylol
14 acrylamide), poly(diacetone acrylamide), poly(2-hydroxyethyl methacrylate),
15 poly(vinyl alcohol) and poly(allyl alcohol). Hydroxyl functional condensation
16 polymers (i.e., polyesters, polycarbonates, polyurethanes) are also examples
17 of suitable polar synthetic polymers. Polar naturally occurring polymers (or
18 derivatives thereof) suitable for use as the gel matrix are exemplified by
19 cellulose ethers, methyl cellulose ethers, cellulose and hydroxylated cellulose,
20 methyl cellulose and hydroxylated methyl cellulose, gums such as guar,
21 locust, karaya, xanthan, gelatin, and derivatives thereof. Ionic polymers can
22 also be used for the matrix provided that the available counterions are either
23 drug ions or other ions that are oppositely charged relative to the active
24 agent.

25 Thus, the drug/dipeptide formulations of the present invention
26 will be incorporated into the drug reservoir, e.g., a gel matrix as just
27 described, and administered to a patient using an electrotransport drug
28 delivery system, as exemplified hereinabove. Incorporation of the drug
29 solution can be done any number of ways, i.e., by imbibing the solution into

1 the reservoir matrix, by admixing the drug solution with the matrix material
2 prior to hydrogel formation, or the like.

3 Optionally, the outermost layer of the skin may be punctured
4 with a microblade array before electrotransport delivery therethrough. The
5 mechanical cutting/puncturing of the stratum corneum is beneficial when
6 transdermally delivering high molecular weight drugs such as polypeptides
7 and proteins. Examples of microblade arrays, for either skin pretreatment or
8 as an integrated feature of a transdermal electrotransport drug delivery
9 device, are disclosed in Lee et al. U.S. Patent 5,250,023; Cormier et al. WO
10 97/48440; and Theeuwes et al. WO 98/28037.

11 While the invention has been described in conjunction with the
12 preferred specific embodiments thereof, it is to be understood that the
13 foregoing description as well as the examples which follow are intended to
14 illustrate and not limit the scope of the invention. Other aspects, advantages
15 and modifications within the scope of the invention will be apparent to those
16 skilled in the art to which the invention pertains.

17

18

Example 1

19 A sufficient quantity of His-Gly from BACHEM Bioscience was
20 added to distilled water to make a 12.5 mM buffer solution having a pH of
21 6.75. A human growth hormone (hGH) formulation obtained from BresaGen
22 contained growth hormone, mannitol and glycine in the following proportions:
23 1:5:1 (w/w). The original hGH formulation was subjected to purification
24 (diafiltration against 12.5 mM His-Gly buffer to remove the mannitol and
25 glycine) and the hGH concentration was adjusted to about 20 mg/ml via
26 ultrafiltration.

27 Aliquots of 250 μ l of the resulting hGH stock solution were
28 placed into Eppendorf tubes, each containing 5 mg (2%) of hydroxyethyl
29 cellulose (HEC) as a gelling agent and the samples were carefully mixed.
30 After gelation, the samples were tested for stability at body temperature. The
31 samples were warmed to 32 °C (ie, skin temperature) and assayed at 0, 1, 2,

1 3, 4, 5, and 6 hours to determine the percent of hGH remaining intact in the
2 gel. hGH from the gels was extracted by dissolving the gel in 25 ml of His-Gly
3 buffer. All hGH samples were analyzed by reverse-phase high performance
4 liquid chromatography (RP), size-exclusion high performance liquid
5 chromatography (SEC), and ion-exchange high performance liquid
6 chromatography (IE) to determine percentage of intact hGH remaining (%LS
7 in Figure 9). The percent of hGH remaining was calculated by measuring the
8 concentration of the hGH (as determined using one of three high performance
9 liquid chromatography methods) and dividing that by the initial hGH
10 concentration. The results of the His-Gly buffered hGH stability tests are
11 shown in Figure 9.

12 When analyzed by these methods, no significant loss of protein
13 through degradation was observed in the hGH gel formulations stored at 32
14 °C. No extra degradation products were discovered.

15 As a comparison, hGH stability studies were run under identical
16 conditions to those described above, except histidine buffer was substituted
17 for His-Gly. The results of the histidine stability tests are shown in Figure 10.
18 Figure 10 shows that after only 6 hours, approximately 50% of the His
19 buffered hGH remained intact, whereas about 80% of the hGH remained
20 intact using the His-Gly buffer. As is clearly shown by comparing Figures 9
21 and 10, substitution of histidine buffer with His-Gly buffer considerably
22 improved human growth hormone formulation stability.

23

24

EXAMPLE 2

25 In vivo iontophoresis experiments were performed using custom
26 built electrotransport systems. The anodic compartment comprised a skin-
27 contacting gel containing the aqueous solution of the buffering agent at the
28 indicated concentration and 3% of the gelling agent hydroxyethyl cellulose
29 (HEC). This formulation was separated from the anode electrode by a
30 Sybron ion exchange membrane. A gel containing 0.15M sodium chloride
31 (which acted as the chloride source) was placed between the anode and the

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1 ionic exchange membrane. Alternatively, the anodic compartment comprised
2 a skin-contacting gel containing the aqueous solution of the buffering agent at
3 the indicated concentration and 3% HEC as well as 10% of the chloride
4 source cholestyramine. The cathode-compartment comprised a skin-
5 contacting gel containing the aqueous solution of the buffering agent at the
6 indicated concentration and 3% HEC. This formulation was separated from
7 the cathode electrode by a Nafion ion exchange membrane. A gel containing
8 0.15M sodium chloride was placed between the cathode and the ionic
9 exchange membrane.

10 The systems had a silver foil anode and a silver chloride
11 cathode. The reservoir gel (i.e., both the anodic and cathodic skin-contacting
12 gels) sizes were each approximately 350 μ L and had a skin contacting
13 surface area of about 2 cm². The electrodes were connected to a DC power
14 source which supplied a constant level of electric current of 0.1 mA/cm².

15 Experiments were performed in vivo in hairless guinea pigs.
16 Three animals were used for each condition studied. The electrotransport
17 systems were applied to and removed from the flank of the animals. The two
18 reservoirs were generally spaced about 5 cm apart. The application site was
19 wiped with water prior to system application. pH of the gels was measured
20 prior to application and after removal of the systems using a HORIBA*
21 compact pH meter (Cardy).

22 Table 3 shows that Gly-His and His-Glu at their pI were capable of
23 assuring pH control of an anodic electrotransport formulation for several
24 hours. This contrasts with the lack of stability observed with buffers such as
25 phosphate or MOPS at the same or higher ionic strength.

26 Table 4 shows that Gly-His and His-Glu at their pI were capable of
27 assuring pH control of a cathodic electrotransport formulation for at least 5
28 hours. This contrasts with the lack of stability observed with buffers such as
29 phosphate or MOPS at the same or higher ionic strength.

*Trade-mark

1 Table 5 shows that Gly-His and His-Glu at their pI were capable of
 2 assuring pH control of anodic and cathodic electrotransport formulations for
 3 up to 24 hours.

4

Table 3

Buffer	Ionic strength (approx.)	Initial pH	Anodic pH after 5 h electrotransport
Phosphate 10 mM	0.015	6.9	3.7 to 5.5
Phosphate 33 mM	0.05	6.9	3.3
Phosphate 100 mM	0.15	6.8	6.5
MOPS 20 mM	0.01	7.0	4.1
Gly-His 30 mM	0.007	7.1	7.0
Gly-His 100 mM	0.02	7.4	7.3
Gly-His 250 mM	0.06	7.4	7.3
His-Glu 100 mM	0.015	5.1	5.2
His-Glu 250 mM	0.037	5.2	5.2

5

6

Table 4

Buffer	Ionic strength (approx.)	Initial pH	Cathodic pH after 5 h electrotransport
Gly-His 100 mM	0.02	7.6	7.3
Gly-His 250 mM	0.06	7.5	7.4
His-Glu 100 mM	0.015	5.3	5.0
His-Glu 250 mM	0.037	5.3	5.0
Phosphate 10 mM	0.015	6.9	4.2
MOPS 20 mM	0.01	7.0	5.4

Table 5

Buffer	Electrode	Initial pH	pH after 24 h electrotransport
Gly-His 100 mM	Anode	7.3	7.2
Gly-His 250 mM	Anode	7.2	7.2
Gly-His 100 mM	Cathode	7.6	7.3
Gly-His 250 mM	Cathode	6.9	7.0
His-Glu 100 mM	Anode	5.1	5.5
His-Glu 250 mM	Anode	5.2	5.4
His-Glu 100 mM	Cathode	5.3	5.4
His-Glu 250 mM	Cathode	5.3	5.2

Example 3

The effect of the zwitterionic buffer Gly-His at pH 7.5 (pI) on the transdermal delivery of a synthetic radiolabeled decapeptide (DECAD) in the hairless guinea pig was evaluated. This model polypeptide drug is composed of D-amino acids and is excreted unchanged in urine. At pH 7.5 the net charge of DECAD is about +1.6.

The electrotransport systems used in this study had a silver foil anode and a silver chloride cathode. The anodic and cathodic reservoir gels each had a volume of approximately 350 mL and a skin contacting surface area of about 2 cm². The electrodes were connected to a DC power source which supplied a constant level of electric current of 0.100 mA/cm². The anodic reservoir comprised a skin-contacting gel containing the aqueous solution of the buffering agent and DECAD at the indicated concentrations and 3% hydroxyethyl cellulose (HEC) as well as 10% cholestyramine, a high molecular weight resin in chloride salt form which contributes chloride ions into the donor solution without introducing mobile cations which compete with

1 the DECAD for delivery into the animal. The chloride ions from the
 2 cholestyramine resin are provided to react with any silver ions which are
 3 generated by electrochemical oxidation of the silver foil anode, thereby
 4 removing silver cations (ie, as potentially competing with the DECAD cations)
 5 from the donor solution. The cathodic reservoir contained a 0.15 M aqueous
 6 solution of sodium chloride in an HEC gel.

7 Experiments were performed in vivo in hairless guinea pigs. Three
 8 animals were used for each condition studied. The electrotransport systems
 9 were applied to and removed from the flank of the animals. The two
 10 reservoirs were generally spaced about 5 cm apart. The application site was
 11 wiped with water prior to system application. Flux was estimated over a 5
 12 hour delivery period by analyzing the radioactive content of urine excreted for
 13 48 hours. Donor reservoir gel pH was measured prior to application and after
 14 removal of the systems using a HORIBA compact pH meter (Cardy).

15 At concentrations up to 250 mM, Gly-His did not lower significantly the
 16 flux of the DECAD polypeptide as shown in Figure 11. Table 6 shows that in
 17 all experimental conditions tested, the dipeptide Gly-His was capable of
 18 assuring pH control.

19

20

Table 6

Gly-His conc. (mM)	DECAD conc. (mM)	Wearing time (h)	Initial pH	Final pH
100	0.5	5	7.3	7.2
10	5	5	6.9	7.0
30	5	5	7.1	7.0
100	5	5	7.4	7.3
250	5	5	7.4	7.3
100	5	24	7.4	7.3

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Example 4

The effect of the zwitterionic buffer Gly-His and His-Glu on pH stability of formulations containing small molecular weight drug-like compounds during electrotransport to hairless guinea pigs was studied. Trimethylammonium bromide (TMAB) was used as the cationic model drug and sodium methanesulfate (SMS) was used as the model anionic drug.

The electrotransport systems used in the study had a silver foil anode and a silver chloride cathode. The anodic and cathodic reservoir gels each had a volume of approximately 350 μ L and a skin contacting surface area of about 2 cm^2 . The electrodes were connected to a DC power source which supplied a constant level of electric current of 0.100 mA/cm^2 . The anodic electrode assembly comprised a skin-contacting gel containing the aqueous solution of His-Glu 66 mM or Gly-His 45 mM and TMAB at 50 mM and 3% HEC. This formulation was separated from the silver anode by a Sybron ion exchange membrane. A gel containing 0.15 M sodium chloride (which acted as a chloride source) was placed between the silver anode and the ion exchange membrane. The cathodic electrode assembly comprised a skin-contacting gel containing the aqueous solution of His-Glu 66 mM or Gly-His 45 mM and SMS 50 mM and 3% HEC. The cathodic gel reservoir was separated from the silver chloride cathode by a Nafion ion exchange membrane. A gel containing 0.15M sodium chloride was placed between the cathode and the ion exchange membrane. The ionic strength of the skin-contacting gels was 60 mM.

Experiments were performed in vivo in hairless guinea pigs. Two animals were used for each condition studied. The electrotransport systems were applied to and removed from the backs of the animals. The two reservoirs were generally spaced about 5 cm apart. The application site was wiped with 70% isopropyl alcohol wipes prior to system application. Donor reservoir gel pH was measured prior to application and after removal of the systems using a HORIBA* compact pH meter (Cardy).

*Trade-mark

1 Table 7 shows that in all experimental conditions tested, the dipeptides
2 Gly-His and His-Glu provided good pH control.

3
4
5

Table 7

Drug	Buffer	Electrode	Initial pH	Final pH
TMAB 50 mM	His-Glu 66 mM	Anode	5.1	5.3
SMS 50 mM	His-Glu 66 mM	Cathode	5.2	6.0
TMAB 50 mM	Gly-His 45 mM	Anode	7.4	6.9
SMS 50 mM	Gly-His 45 mM	Cathode	7.5	7.9

6

7 Although preferred embodiments of the subject invention have
8 been described in some detail, it is understood that obvious variations can be
9 made without departing from the spirit and the scope of the invention as
10 defined by the appended claims.

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CLAIMS:

1. A transdermal electrotransport drug delivery device having a reservoir containing a reservoir formulation comprising an aqueous solution of a drug or an electrolyte and a buffer, the buffer comprising a peptide chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution having a pH which is within 1.0 pH unit of the isoelectric pH.
2. The transdermal electrotransport drug delivery device according to claim 1, wherein the peptide is a dipeptide.
3. The transdermal electrotransport drug delivery device according to claim 1 or 2, wherein said reservoir is a drug-containing donor reservoir.
4. The transdermal electrotransport drug delivery device according to any one of claims 1 to 3, wherein said reservoir is an electrolyte-containing counter reservoir.
5. The transdermal electrotransport drug delivery device according to any one of claims 1 to 4, wherein the isoelectric pH of the peptide is between about 3 and 10.
6. The transdermal electrotransport drug delivery device according to any one of claims 1 to 5, wherein the peptide is present in the reservoir formulation at a concentration of at least about 10mM.
7. The transdermal electrotransport drug delivery device according to any one of claims 1 to 6, wherein the peptide includes at least one amino acid selected from the group consisting of His, Tyr, Arg, Cys, Lys, Asp and Glu.

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8. The transdermal electrotransport drug delivery device according to any one of claims 1 to 7, wherein the peptide includes histidine.

9. The transdermal electrotransport drug delivery device according to any one of claims 1 to 8, wherein the peptide is Gly-His.

10. The transdermal electrotransport drug delivery device according to any one of claims 1 to 6, wherein the peptide is selected from the group consisting of Asp-Asp, Gly-Asp, Asp-His, Glu-His, His-Glu, His-Asp, Glu-Arg, Glu-Lys, Arg-Glu, Lys-Glu, Arg-Asp, Lys-Asp, His-Gly, His-Ala, His-Asn, His-Citruline, His-Gln, His-Hydroxyproline, His-Isoleucine, His-Leu, His-Met, His-Phe, His-Pro, His-Ser, His-Thr, His-Trp, His-Tyr, His-Val, Asn-His, Thr-His, Tyr-His, Gln-His, Phe-His, Ser-His, Citruline-His, Trp-His, Met-His, Val-His, His-His, Ile-His, Hydroxyproline-His, Leu-His, Ala-His, Gly-His, Beta-Alanylhystidine, Pro-His, Carnosine, Anserine, Tyr-Arg, Hydroxylysine-His, His-Hydroxylysine, Ornithine-His, His-Lys, His-Ornithine and Lys-His.

11. The transdermal electrotransport drug delivery device according to any one of claims 1 to 10, wherein the drug comprises a polypeptide or a protein.

12. The transdermal electrotransport drug delivery device according to claim 11, wherein the polypeptide or protein is LHRH, a LHRH analog, GHRH, GHRF, insulin, insulinotropin, heparin, calcitonin, octreotide, endorphin, TRH, NT-36, liprecin, a pituitary hormone, a follicile luteoid, α ANF, growth factor releasing factor (GFRF), bradykinin, somatotropin platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin,

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erythropoietin, epoprostenol, glucagon, hirulog, hirudin
 analogs, hyaluronidase, interferon, interleukin-2, a
 menotropin, oxytocin, streptokinase, tissue plasminogen
 activator, urokinase, vasopressin, desmopressin, an ACTH
 5 analog, ANP, an ANP clearance inhibitor, an angiotensin 11
 antagonist, an antidiuretic hormone agonist, an antidiuretic
 hormone antagonist, a bradykinin antagonist, CD4, ceredase,
 a CSF, an enkephalin, a FAB fragment, an IgE peptide
 suppressor, IGF-1, a neurotrophic factor, a colony
 10 stimulating factor, a parathyroid hormone, a parathyroid
 hormone agonist, a parathyroid hormone antagonist, a
 prostaglandin antagonist, pentigetide, protein C, protein S,
 a renin inhibitor, thymosin alpha-1, a thrombolytic, TNF, a
 vaccine, a vasopressin antagonist analog, alpha-1
 15 antitrypsin, or TGF-beta.

13. The transdermal electrotransport drug delivery
 device according to claim 12, wherein the protein is insulin
 or insulinotropin.

14. The transdermal electrotransport drug delivery
 20 device according to any one of claims 1 to 10, wherein the
 drug comprises an analgesic.

15. The transdermal electrotransport drug delivery
 device according to claim 14, wherein the analgesic is
 fentanyl, fentanyl hydrochloride, sufentanil, carfentanil,
 25 lofentanil, alfentanil, oxycodone, propoxyphene,
 pentazocine, methadone, tilidine, butorphanol,
 buprenorphine, levorphanol, codeine, oxymorphone,
 meperidine, dihydrocodeinone, an opioid, cocaine, an
 analgesic analogue or an analgesic combination.

30 16. The transdermal electrotransport drug delivery
 device according to claim 15, wherein the analgesic is
 fentanyl.

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17. The transdermal electrotransport drug delivery device according to claim 15, wherein the analgesic is fentanyl hydrochloride.

18. The transdermal electrotransport drug delivery device according to claim 15, wherein the analgesic is sufentanil.

19. A method of buffering an aqueous solution of a drug or an electrolyte used for transdermal electrotransport delivery, comprising buffering the solution with a peptide comprising a chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution having a pH which is within about 1.0 H unit of the isoelectric pH.

20. The method according to claim 19, wherein the peptide is a dipeptide.

21. The method according to claim 19 or 20, wherein the isoelectric pH of the peptide is between about 3 and 10.

22. The method according to any one of claims 19 to 21, wherein the peptide is present in the solution at a concentration of at least about 10mM.

23. The method according to any one of claims 19 to 22, wherein the peptide contains one or more of His, Tyr, Arg, Cys, Lys, Asp or Glu.

24. The method according to any one of claims 19 to 23, wherein the peptide contains His.

25. The method according to any one of claims 19 to 24, wherein the peptide is Gly-His.

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26. The method according to any one of claims 19 to 22, wherein the dipeptide is selected from the group consisting of Asp-Asp, Gly-Asp, Asp-His, Glu-His, His-Glu, His-Asp, Glu-Arg, Glu-Lys, Arg-Glu, Lys-Glu, Arg-Asp, Lys-
 5 Asp, His-Gly, His-Ala, His-Asn, His-Citruline, His-Gln, His-Hydroxyproline, His-Isoleucine, His-Leu, His-Met, His-Phe, His-Pro, His-Ser, His-Thr, His-Trp, His-Tyr, His-Val, Asn-His, Thr-His, Tyr-His, Gln-His, Phe-His, Ser-His, Citruline-His, Trp-His, Met-His, Val-His, His-His, Ile-His,
 10 Hydroxyproline-His, Leu-His, Ala-His, Gly-His, Beta-Alanylhistidine, Pro-His, Carnosine, Anserine, Tyr-Arg, Hydroxylysine-His, His-Hydroxylysine, Ornithine-His, His-Lys, His-Ornithine and Lys-His.

27. The method according to any one of claims 19 to 26, wherein the drug comprises a polypeptide or a
 15 protein.

28. The method according to claim 27, wherein the polypeptide or protein is LHRH, a LHRH analog, GHRH, GHRF, insulin, insulinotropin, heparin, calcitonin, octreotide,
 20 endorphin, TRH, NT-36, liprecin, a pituitary hormone, a follicle luteoid, α ANF, growth factor releasing factor (GFRF), bradykinin, somatotropin platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin,
 25 erythropoietin, epoprostenol, glucagon, hirulog, hirudin analogs, hyaluronidase, interferon, interleukin-2, a menotropin, oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin, desmopressin, an ACTH analog, ANP, an ANP clearance inhibitor, an angiotensin
 30 antagonist, an antidiuretic hormone agonist, an antidiuretic hormone antagonist, a bradykinin antagonist, CD4, ceredase, a CSF, an enkephalin, a FAB fragment, an IgE peptide suppressor, IGF-1, a neurotrophic factor, a colony

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stimulating factor, a parathyroid hormone, a parathyroid hormone agonist, a parathyroid hormone antagonist, a prostaglandin antagonist, pentiagetide, protein C, protein S, a renin inhibitor, thymosin alpha-1, a thrombolytic, TNF, a vaccine, a vasopressin antagonist analog, alpha-1 antitrypsin, or TGF-beta.

29. The method according to claim 28, wherein the protein is insulin or insulinotropin.

30. The method according to any one of claims 19 to 26, wherein the drug comprises an analgesic.

31. The method according to claim 30, wherein the analgesic is fentanyl, fentanyl hydrochloride, sufentanil, carfentanil, lofentanil, alfentanil, oxycodone, propoxyphene, pentazocine, methadone, tilidine, butorphanol, buprenorphine, levorphanol, codeine, oxymorphone, meperidine, dihydrocodeinone, an opioid, cocaine, an analgesic analogue or an analgesic combination.

32. The method according to claim 31, wherein the analgesic is fentanyl.

33. The method according to claim 31, wherein the analgesic is fentanyl hydrochloride.

34. The method according to claim 31, wherein the analgesic is sufentanil.

35. The method according to any one of claims 19 to 34, wherein the solution is contained in a reservoir of a transdermal electrotransport drug delivery device.

36. The method according to any one of claims 19 to 35, wherein the transdermal electrotransport drug delivery device is a transdermal patch.

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37. A transdermal electrotransport drug delivery device for delivering an analgesic through a body surface of a patient, said device having a reservoir containing a reservoir formulation comprising an aqueous solution of a
5 drug or an electrolyte and a buffer, the buffer comprising a peptide chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution having a pH
10 which is within about 1.0 pH unit of the isoelectric pH.

38. The transdermal electrotransport drug delivery device according to claim 37, wherein the analgesic is fentanyl, fentanyl hydrochloride, sufentanil, carfentanil, lofentanil, alfentanil, hydromorphone, oxycodone,
15 propoxyphene, pentazocine, methadone, tilidine, butorphanol, buprenorphine, levorphanol, codeine, oxymorphone, meperidine, dihydrocodeinone, an opioid, cocaine, an analgesic analogue or an analgesic combination.

39. The electrotransport device according to claim 38,
20 wherein the analgesic is fentanyl.

40. The electrotransport device according to claim 38, wherein the analgesic is fentanyl hydrochloride.

41. The electrotransport device according to claim 38, wherein the analgesic is sufentanil.

25 42. A transdermal electrotransport drug delivery device for delivering insulin or insulinotropin through a body surface of a patient, said device having a reservoir containing a reservoir formulation comprising an aqueous solution of a drug or an electrolyte and a buffer, the
30 buffer comprising a peptide chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net

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charge, the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution having a pH which is within about 1.0 pH unit of the isoelectric pH.

5 43. A transdermal electrotransport drug delivery device for delivering a polypeptide, protein, macromolecule or combination thereof, through a body surface of a patient, said device having a reservoir containing a reservoir formulation comprising an aqueous solution of a drug or an
10 electrolyte and a buffer, the buffer comprising a peptide chain of 2 to 5 amino acids and having an isoelectric pH at which the peptide carries no net charge, the peptide having at least 2 pKa's which are separated by no more than about 3.5 pH units, the solution having a pH which is within
15 about 1.0 pH unit of the isoelectric pH.

44. The transdermal electrotransport drug delivery device according to claim 43 wherein the polypeptide, protein or macromolecule is LHRH, a LHRH analog, GHRH, GHRF, insulin, insulinotropin, heparin, calcitonin, octreotide,
20 endorphin, TRH, NT-36, liprecin, a pituitary hormone, a follicle luteoid, α ANF, growth factor releasing factor (GFRF), bradykinin, somatotropin platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin,
25 erythropoietin, epoprostenol, glucagon, hirulog, hirudin analogs, hyaluronidase, interferon, interleukin-2, a menotropin, oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin, desmopressin, an ACTH analog, ANP, an ANP clearance inhibitor, an angiotensin 11
30 antagonist, an antidiuretic hormone agonist, an antidiuretic hormone antagonist, a bradykinin antagonist, CD4, ceredase, a CSF, an enkephalin, a FAB fragment, an IgE peptide suppressor, IGF-1, a neurotrophic factor, a colony

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stimulating factor, a parathyroid hormone, a parathyroid hormone agonist, a parathyroid hormone antagonist, a prostaglandin antagonist, pentigetide, protein C, protein S, a renin inhibitor, thymosin alpha-1, a thrombolytic, TNF, a vaccine, a vasopressin antagonist analog, alpha-1 antitrypsin, or TGF-beta.

45. The transdermal electrotransport drug delivery device according to any one of claims 1 to 18 and 37 to 44, wherein said device is a transdermal patch.

10 46. Use of the transdermal electrotransport drug delivery device as defined in any one of claims 1 to 11 for delivering an analgesic in the treatment of pain.

47. The use according to claim 46 wherein the analgesic is fentanyl, fentanyl hydrochloride, sufentanil, carfentanil, lofentanil, alfentanil, oxycodone, propoxyphene, pentazocine, methadone, tilidine, butorphanol, buprenorphine, levorphanol, codeine, oxymorphone, meperidine, dihydrocodeinone, an opioid, cocaine, an analgesic analogue or an analgesic combination.

20 48. The use according to claim 47 wherein the analgesic is fentanyl.

49. The use according to claim 47 wherein the analgesic is fentanyl hydrochloride.

50. The use according to claim 47 wherein the analgesic is sufentanil.

51. Use of the electrotransport device as defined in any one of claims 1 to 11 for delivering insulin or insulinotropin in the treatment of diabetes mellitus.

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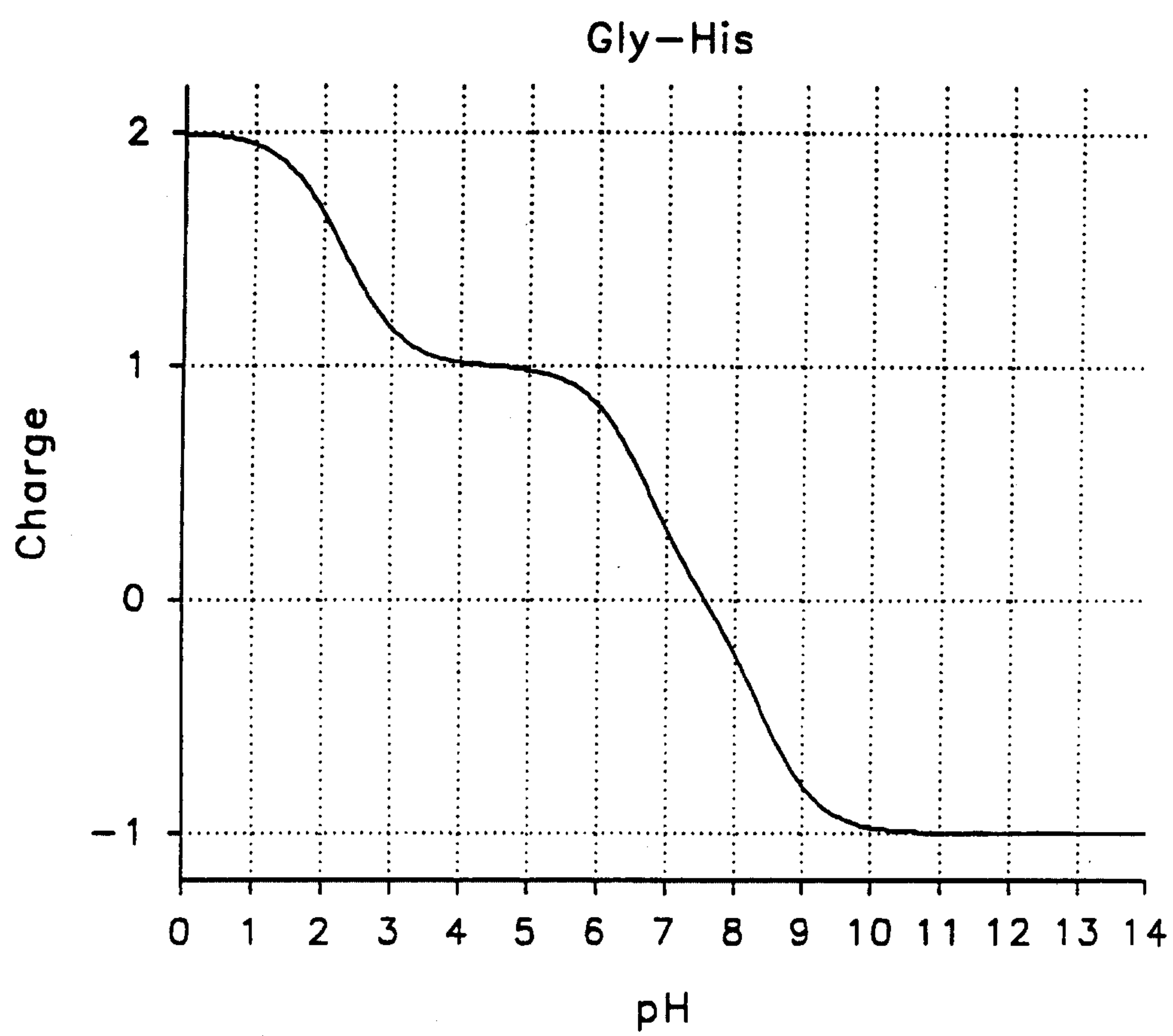


FIG. 1

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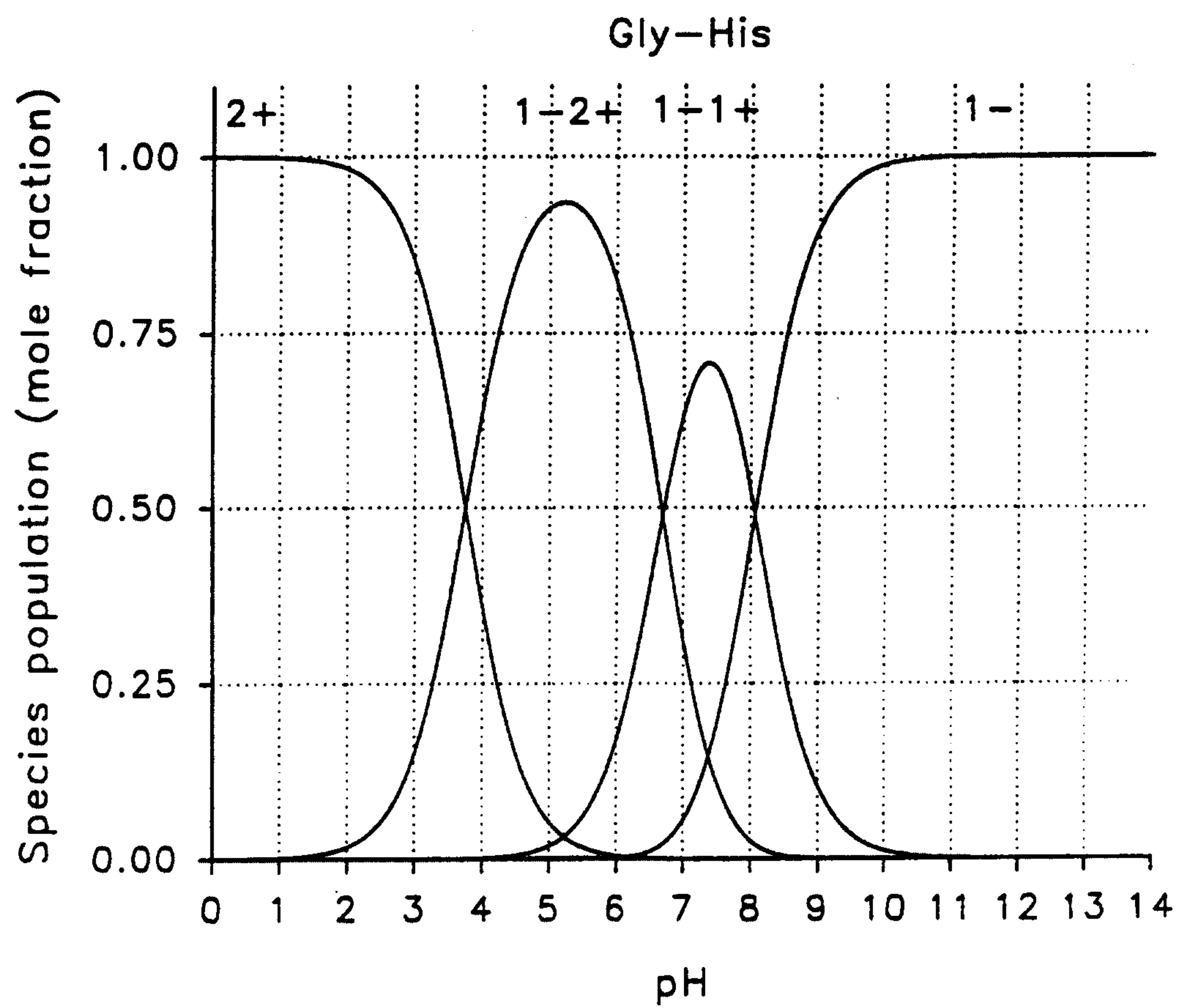


FIG. 2

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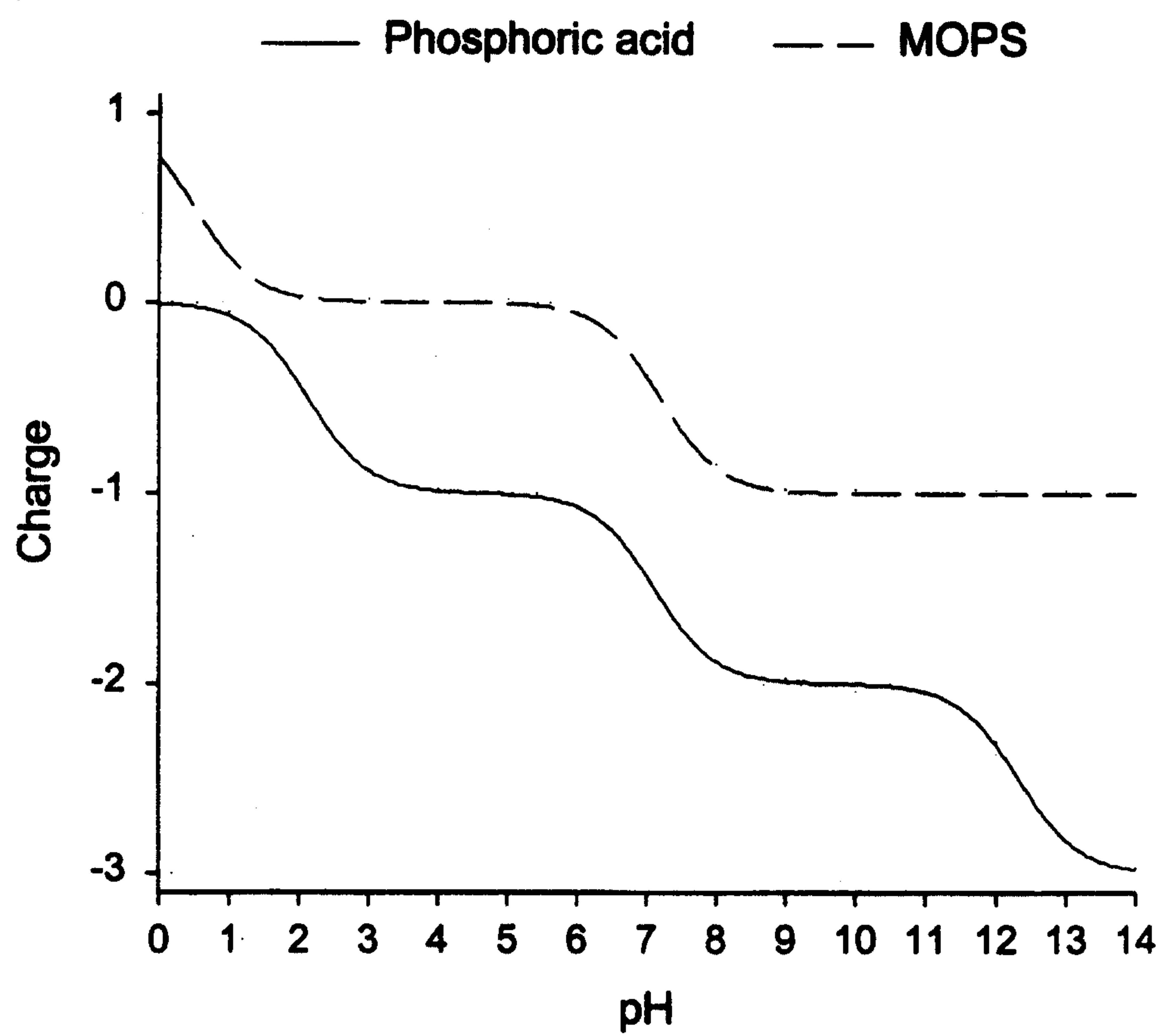
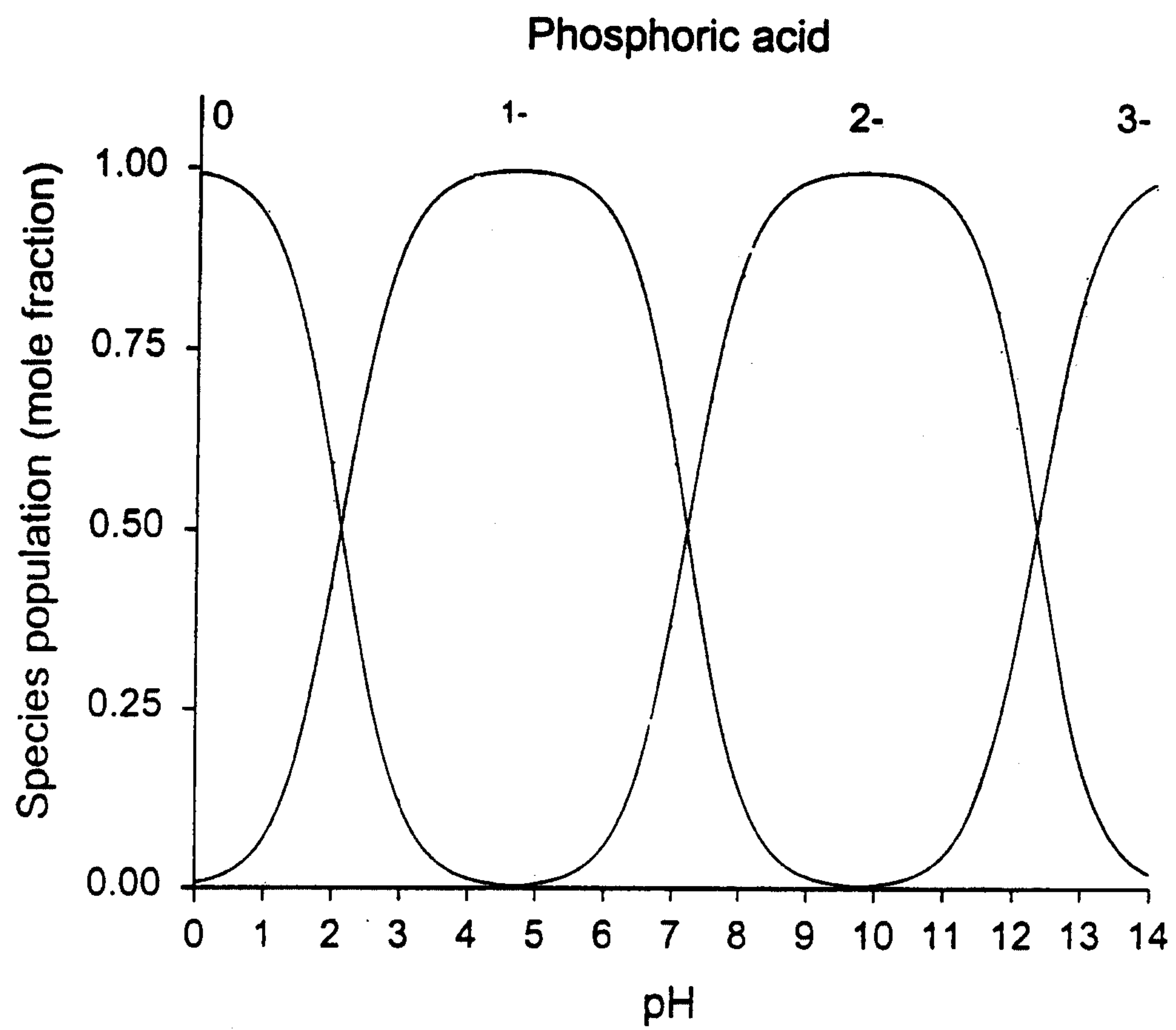


FIG. 3

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**FIG. 4**

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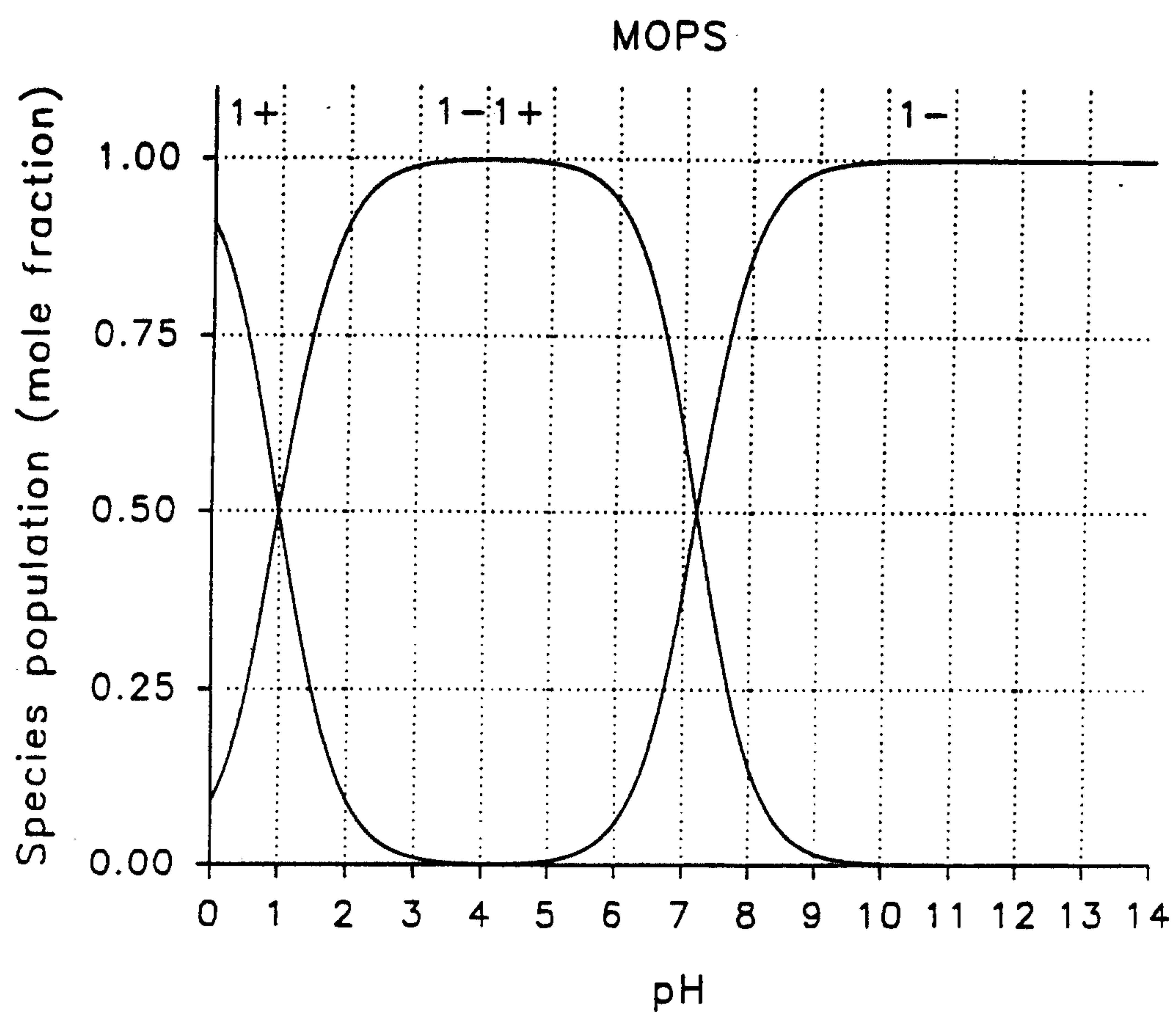


FIG. 5

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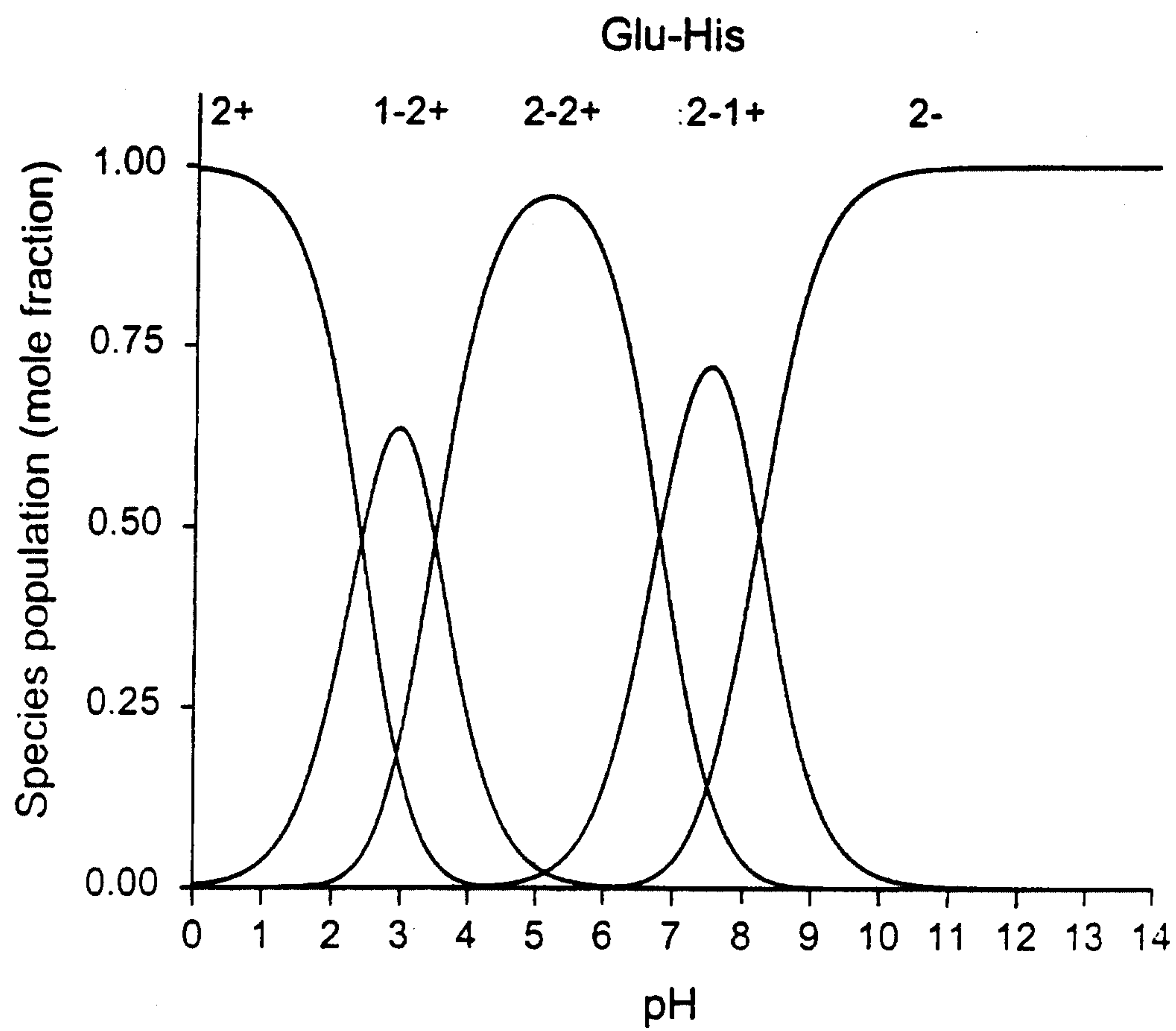


FIG. 6

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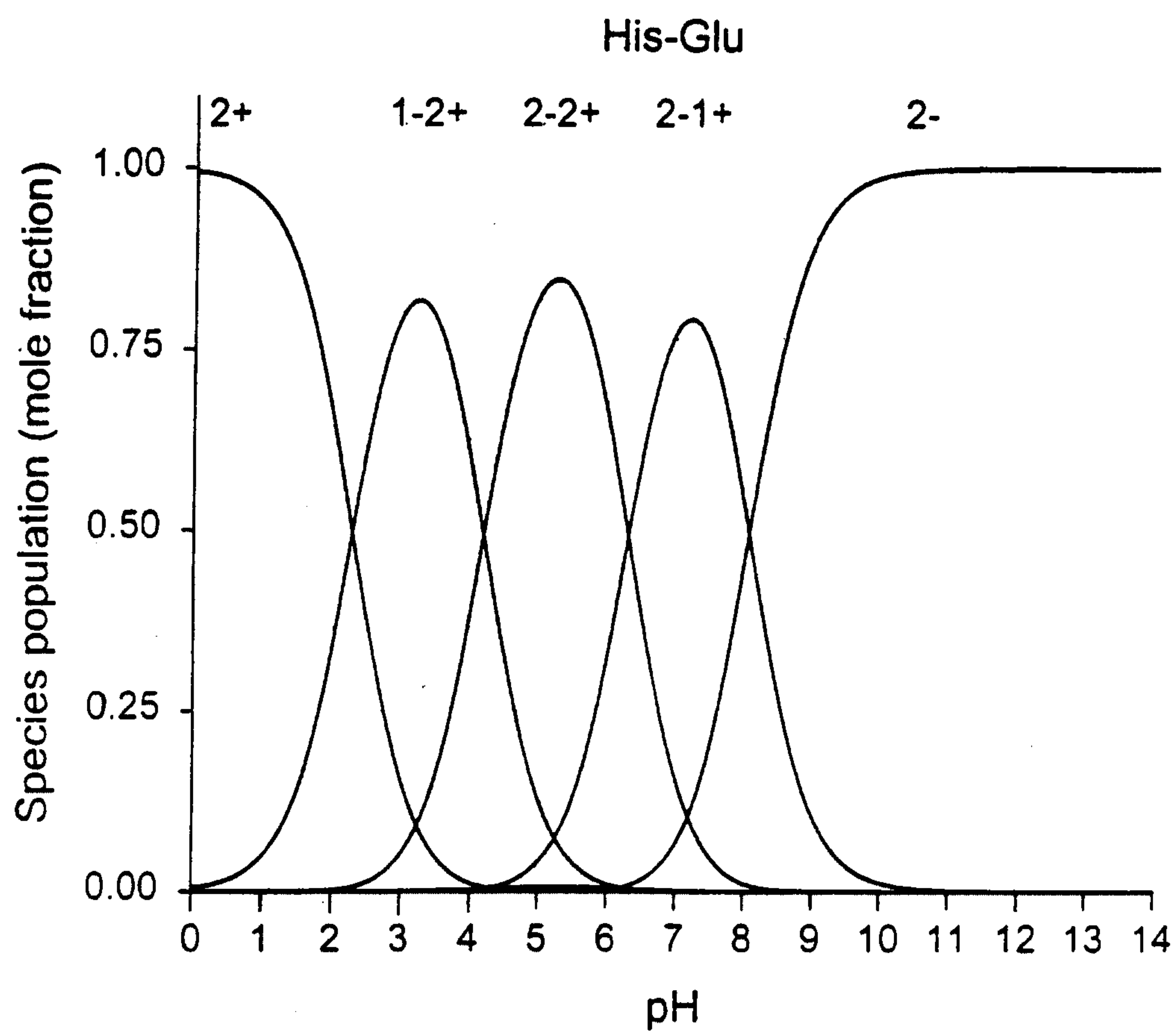


FIG. 7

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FIG. 8

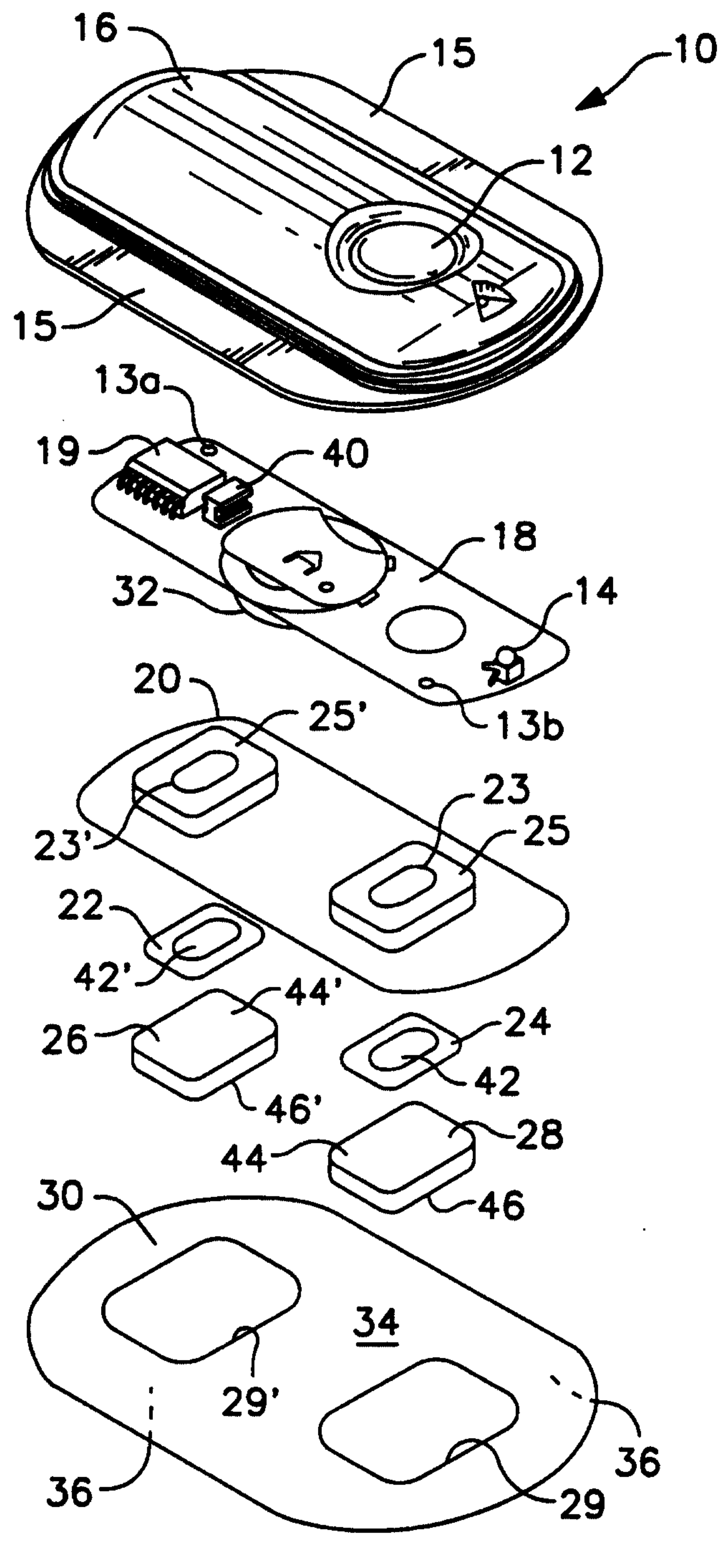


FIG. 9

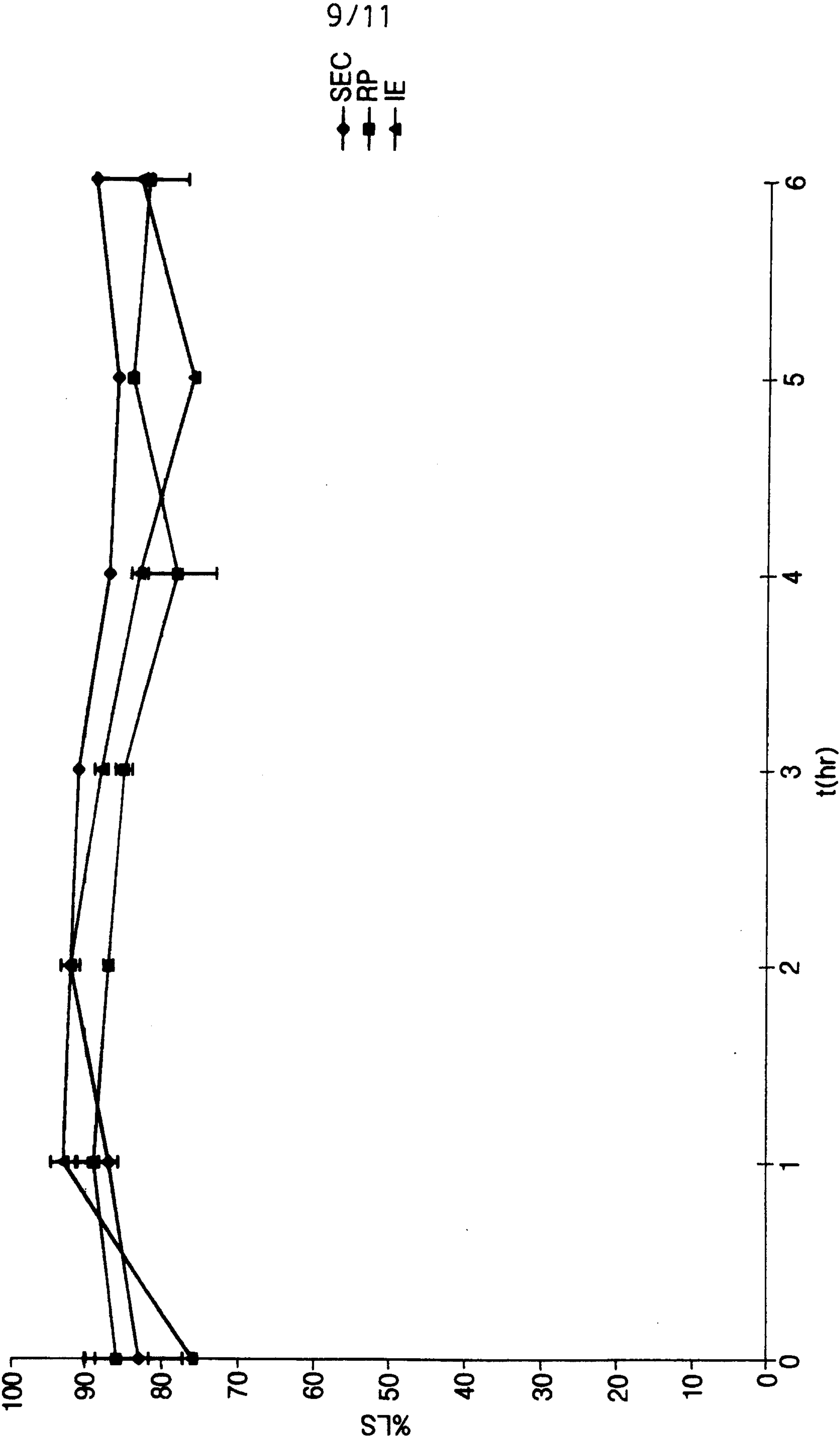
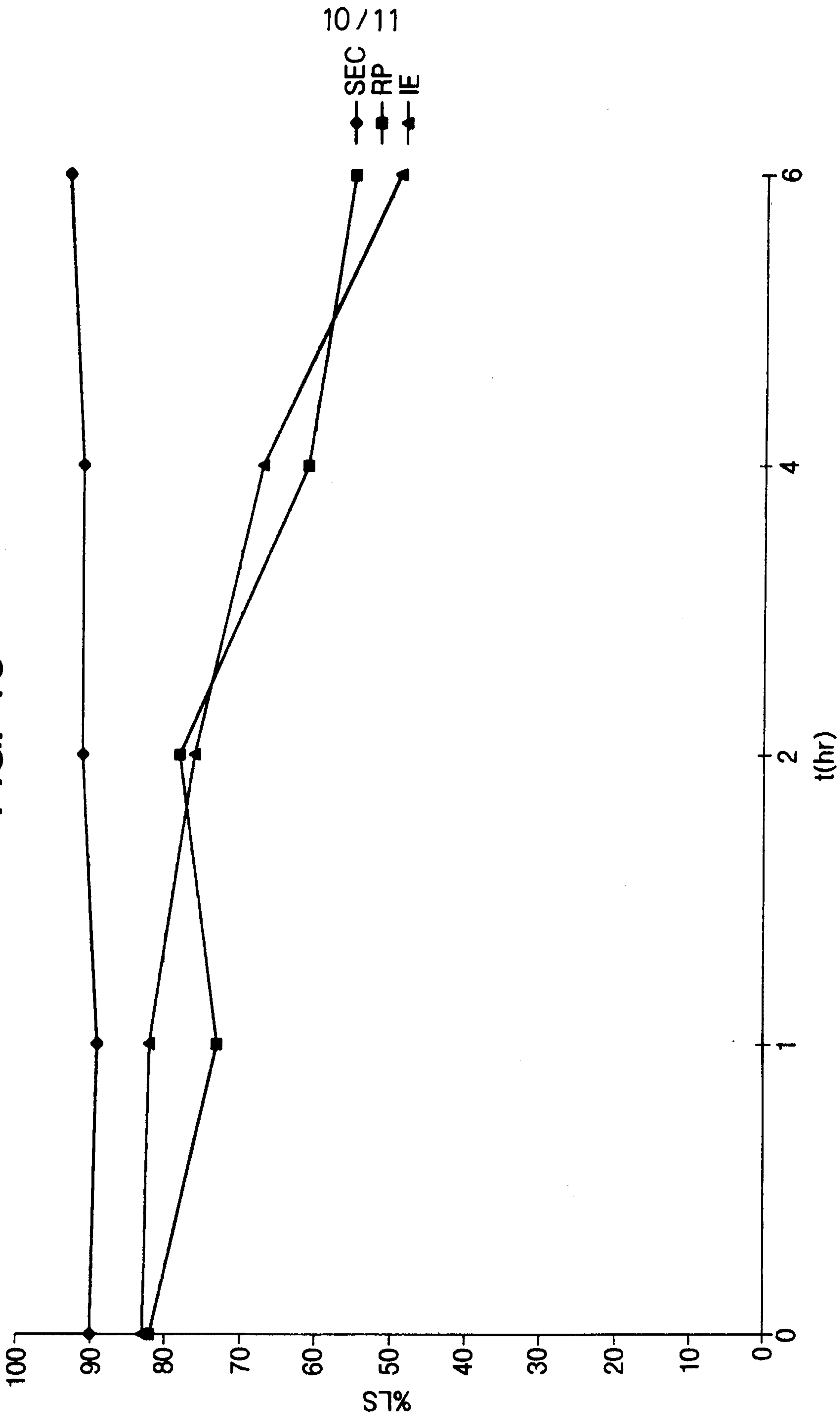


FIG. 10



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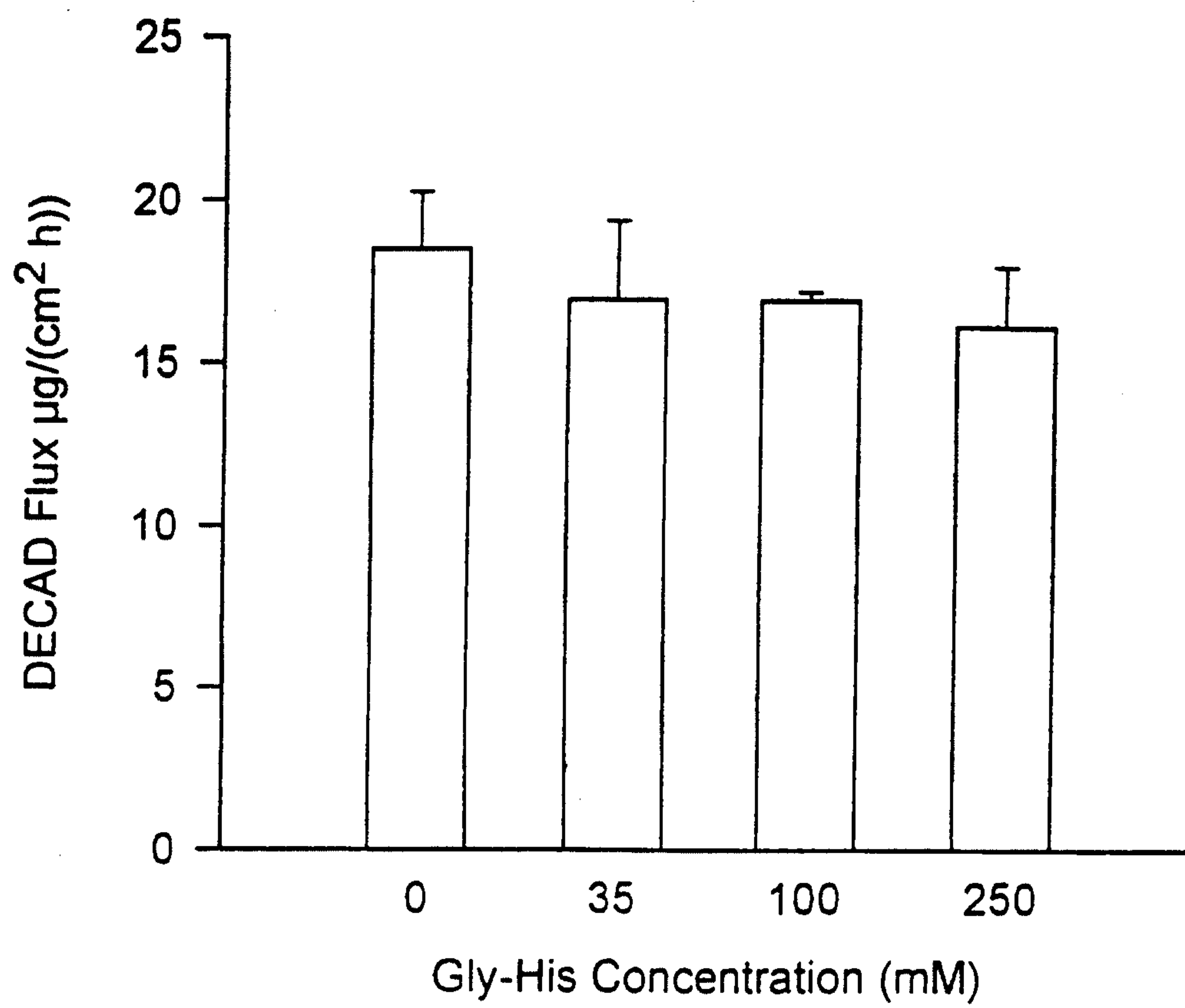


FIG. 11

Gly-His

