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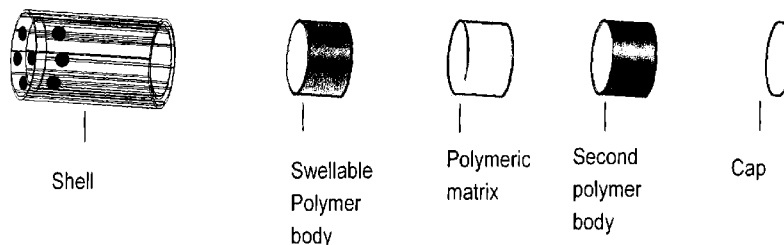


FIG 1

(57) **Abstract:** The invention relates to a pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising a shell defining therein an outlet; a polymeric matrix having at least one API, the polymeric matrix received within the shell; and a swellable polymer body located within the shell, wherein the swellable polymer body is pH responsive, such that in use, exposure of the body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn, facilitates displacement of the matrix through the outlet toward the target site for delivery of the API.



PHARMACEUTICAL DOSAGE FORM

FIELD OF INVENTION

This invention relates to a pharmaceutical dosage form and, more particularly, to a pharmaceutical dosage form for the site specific delivery of at least one active pharmaceutical ingredient (API), preferably the at least one API may be a peptide and/or protein, to a target site of a human or animal body.

BACKGROUND OF INVENTION

The treatment of a number of medical conditions, particularly those that require systemic distribution of peptide and/or protein active pharmaceutical ingredients (APIs) are often delivered by intramuscular, subcutaneous, inhalation or intravenous administration. The peptide and/or protein APIs are typically administered in relatively small amounts since they have extremely toxic effects if administered incorrectly or at high doses. Therefore, a pharmaceutical formulation that reduces the potential toxic effect of peptide and/or protein APIs, but also enables patient compliant administration, which is highly desirable as an alternative to conventional parental administration, is desired.

By way of example, in the treatment of osteoporosis, a peptide compound such as salmon calcitonin may be recommended as a treatment option. Salmon calcitonin is often administered via a subcutaneous injection at least once a day in order to yield the desired pharmaceutical effect. This means that if a patient is diagnosed with osteoporosis and salmon calcitonin is recommended as part of the treatment, the patient will be subjected to chronic injections that may span for a time period of several years. Salmon calcitonin is administered subcutaneously because the drug compound is highly sensitive to external factors (for example temperature, presence of peptidase enzymes, presence of water, pH of solvent medium, and the presence of bacterial agents) and has very poor absorption across epidermal layers in the gastrointestinal tract.

Previously, any condition that required treatment with a peptide and/or protein API was administered via subcutaneous-, intramuscular-, or intravenous injection, or inhalation. Research initiatives were undertaken to design an orally administrable pharmaceutical dosage form for the delivery of a peptide and/or protein as the active pharmaceutical ingredient.

A number of patents and patent applications claiming protection for peptide and/or protein API formulations are known to the applicant. The most relevant of these are the following:

United States patent application having publication number US 2004/0197323, which discloses an oral acid resistant pharmaceutical composition which increases the oral bioavailability of peptides, such as salmon calcitonin, insulin, and vasopressin and other such therapeutic peptides, by utilizing a protease inhibitor and a permeation enhancer in a capsule or tablet form. Once the acid coating has dissolved in the stomach the peptide is released over a large region in the small intestine. Therefore, the peptide is not concentrated in a localized environment causing for poor absorption of the peptide. The acid which is mixed with the peptide to reduce the activity of proteases at the release site may negatively impact on the three dimensional structure, and therefore the activity, of the peptide itself. There exists a need for a dosage form for effective delivery of protein and/or peptide APIs at a target site.

United States patent having publication number US 8,348,930A, which discloses an implantable delivery device which contains two compartments and a water permeable membrane inside a housing, and in use, expels API/drug under pressure due to gas being formed in one compartment in response to generation of electrical current in an ionic solution. The device is not suited to be an oral formulation and requires implantation. The device is mechanical and acts by releasing an active pharmaceutical ingredient. The device itself does not provide any means to enhance absorption of the API at a target site.

United States patent application having publication number US 2009/0317462, which discloses an oral pharmaceutical formulation which contains an acid coated particulate separated from the peptide therapeutic via barrier layers. The API is not released at a localized target site therefore causing poor absorption and poor bioavailability of the API. The lack of localization also increases the risk of pre-systemic degradation of the API.

PCT International Application No. PCT/EP1998/000320 published as WO 98/31712, which discloses a method for covalently bonding a chelatory agent (i.e. ethylenediaminetetraacetate) to a natural polysaccharide (i.e. chitosan) to facilitate enhanced oral absorption of peptide therapeutics by chelating metal ions out of protease enzymes and facilitating enhanced local retention through a mechanism known as mucoadhesion, thus preventing the toxic effects of absorbing the chelatory agent systemically but inhibiting protease enzymatic action of the gastrointestinal tract which increases peptide API/therapeutic bioavailability. However, lack of localization of the API causes poor absorption and poor bioavailability.

Additionally, covalently bonding EDTA to a polymer restricts the ability of the metal chelator to interact with tight junctions located within the epidermal layer of the small intestine. Therefore the permeation enhancing activity of the EDTA is reduced.

Known problems associated with the delivery of peptide and/or protein active pharmaceutical ingredients (APIs) in oral formulations include the fact that the acidic conditions of the stomach denature said peptides and/or proteins and that proteolytic enzymes in the gastric and/or intestinal region of the gastrointestinal tract (GIT) compromise the structural integrity of peptides and/or proteins. Furthermore, the biological architecture of the intestinal wall hinders ready transport of peptides and/or proteins across the intestinal wall into the systemic circulation. Delivery of the peptide and/or protein API over a large region of the target site reduces the probability of the API being absorbed into systemic circulation and increases the risk of the API being biologically deactivated and/or denatured by for example protease enzymes. There exists a need for a dosage form for the effective delivery of protein and/or peptide APIs at a target site wherein the API is concentrated at a localized target site and wherein absorption into the systemic blood stream is efficient.

There is a need for an oral pharmaceutical dosage form, preferably for the delivery of peptide and/or protein active pharmaceutical ingredients (APIs), that at least ameliorates one of the disadvantages known in the prior art.

SUMMARY OF INVENTION

In accordance with a first aspect of this invention there is provided a pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising:

- a shell defining therein an outlet;

- a polymeric matrix having at least one API, the polymeric matrix received within the shell; and

- a swellable polymer body located within the shell, wherein the swellable polymer body may be pH responsive, such that in use, exposure of the swellable polymer body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the polymeric matrix through the outlet out of the shell toward the target site for delivery of the API.

The shell may comprise a substantially non-degradable, biologically inert, non-responsive material, preferably a non-toxic biologically inert, non-responsive material, such that in use, the shell does not substantially biodegrade upon passage through the gastrointestinal tract (GIT). In a preferred

embodiment, the material may be a USP Class VI ISO-10993 US FDA (United States Food and Drug Administration) compliant material.

The shell may comprise a natural and/or synthetic polymer.

5

The natural polymer comprising the shell may be selected from polysaccharide polymers including, but not limited to, at least one of the following group: chitosan, pectin, gellan gum, xanthan gum, sodium alginate, celluloses such as sodium carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), hydroxymethylpropylmethylcellulose (HPMC), and dextrans.

10

The synthetic polymer comprising the shell may be selected from, but not limited to, at least one of the following group: high density polyethylene (HDPE), ultra high molecular weight polyethylene (UHMWPE), polytetrafluoroethylene, polymethmethacrylate, polydimethylsiloxane, and poly(sulphone).

15 The synthetic polymers may include a polymer having a water absorption percentage over 24 hours of 0.05% when expressed in mL, or less; tensile strength of about 16 700 (pounds per square inch) psi; a melting temperature of about 340°C; being sterilizable with steam at 121°C or sterilizable with gamma irradiation.

20 In a preferred embodiment of the invention the shell may comprise a polyetheretherketone.

The shell may further define an inlet at a region proximate the location of the swellable polymer body, such that in use, the medium may penetrate into the shell through the inlet to contact the swellable polymer body causing the swellable polymer body to swell, which in turn facilitates the displacement of
25 the matrix through the outlet out of the shell to the target site.

In an embodiment of the invention the shell may be substantially cylindrically shaped having the outlet and inlet located at opposing first and second end regions of the shell respectively. It is to be understood that the shape and/or dimensions of the shell may vary. For example the shell may be shaped to be
30 substantially, but not limited to, at least one of the following group: spherical, cylindrical, elongate, oval, discoid, geoid, rectangular, square, triangular and polygonal.

The shell facilitates concentrating the at least one API at the target site and facilitates in generating a steep concentration gradient of the at least one API at the target site, which in turn, facilitates translocation of the at least one API across a wall of the target site into the systemic circulation.

5 The polymeric matrix may be a natural and/or synthetic polymer. Preferably the polymeric matrix is a natural polymer and may be biodegradable being responsive to specific enzymes in the gastrointestinal tract (GIT). Further preferably, the polymeric matrix may be responsive to colonic enzymes including, but not limited to, at least one of the following group: β -glycosidases, pectinases, and polysaccharidases. The colonic enzymes, in use, causing digestion and/or chemical cleavage and/or
10 degradation of the polymeric matrix such that the at least one API is released for delivery at the target site.

The polymeric matrix may be mucoadhesive, such that in use, the matrix adheres at the target site. The target site may be the wall of the small intestine of the human or animal body. Mucoadhesion facilitates
15 concentrating the at least one API at the target site and facilitates in generating a steep concentration gradient of the at least one API at the target site, which in turn, facilitates translocation of the at least one API across a wall of the target site into the systemic circulation.

The polymeric matrix may be at least one polymer including, but not limited to, at least one of the
20 following group: chitosan, trimethyl chitosan, EDTA-g-chitosan, 2-mercaptoethylamine-g-chitosan, polyacrylic acid-cysteine. The polymer trimethyl chitosan is a polysaccharide chitosan derivative and has demonstrated permeation enhancing, mucoadhesive, biodegradable and biocompatible properties. Further preferably, the polymeric matrix may comprise trimethyl chitosan chloride (TMC:Cl). These aforementioned cationic polymers interact with negatively charged residues on the cell surface which
25 induces a change in the cell membrane structure and this induces a change in the tight junctions. EDTA-g-chitosan demonstrates no permeation enhancing ability but does demonstrate a reduction in divalent cation species within the localized environment which may reduce the degradation of the protein and/or peptide API within a localized environment and allow a greater mass of the API to be absorbed into the systemic circulation.

30 The polymeric matrix may further include a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot

fragment); AT-1002; Zot (45kDa), zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, and bile salts.

5 The polymeric matrix may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of peptide and/or protein API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

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The polymeric matrix may further include at least one pharmaceutical excipient, preferably the excipient may be a lubricant, further preferably the lubricant may be magnesium stearate.

15

The polymeric matrix may further include a glidant, preferably the glidant may be amorphous fumed silica.

20

There is provided that the polymeric matrix may be crosslinked by at least one of, but not limited to, the following group of processes: microwave radiation, ultra violet radiation and chemical crosslinking, such that in use, crosslinking facilitates controlled release of the at least one API.

25

The polymeric matrix may be shaped and/or dimensioned to be receivable into the shell. It is to be understood that the shape and/or dimensions of the polymeric matrix may vary. For example the polymeric matrix may be shaped to be substantially, but not limited to, at least one of the following group: spherical, cylindrical, elongate, oval, discoid, geoid, rectangular, square, triangular and polygonal, so as to be receivable into the shell.

30

The at least one API may be a peptide and/or protein therapeutic. The peptide and/or protein therapeutic may be selected from, but not limited to, at least one of the following group: salmon calcitonin, eel calcitonin, chicken calcitonin, rat calcitonin, human calcitonin, porcine calcitonin or any gene-variant of calcitonin, parathyroid hormone, parathyroid hormone analogue PTH 1-31NH₂, parathyroid hormone analogue PTH 1-34NH₂, insulin of any gene variant, vasopressin, desmopressin, luteinizing hormone-releasing factor, erythropoietin, tissue plasminogen activators, human growth factor, adrenocorticotropin, various interleukins, and enkephalin.

The at least one API may further be an API selected from, but not limited to, at least one of the following group of classes of APIs: anti-inflammatories, immunosuppressives, antibiotics, antifungals, antivirals, antimalarials, antiretrovirals, antihypertensives, chemotherapeutics, diagnostic agents, probiotics and prebiotics.

5

The swellable polymer body may be a natural and/or synthetic polymer. The swellable polymer body may be pH responsive, such that in use, exposure of the swellable polymer body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body. In use, the swellable polymer body optimally swells upon exposure to pH conditions of the small intestine in the gastrointestinal tract (GIT). Preferably, the pH conditions of the small intestine vary between pH 5 and pH 7.

10

The synthetic polymer for the swellable polymer body may be selected from, but not limited to, at least one of the following group: poly(hydroxyethyl methacrylate), polyethylene glycol methacrylate, polyethylene glycol dimethacrylate, polyethylene diacrylate, polyethylene oxide, polyethylene glycol-poly ϵ caprolactone-polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, polyimide, polyacrylate, polyurethane and derivatives thereof.

15

The natural polymer for the swellable polymer body may be selected from, but not limited to, at least one of the following group: alginate, hyaluronic acid, chitosan and derivatives thereof.

20

The swellable polymer body may comprise a hydrogel.

Preferably, the swellable polymer body comprises acrylamide (AAm), methacrylic acid (MAA), N-N'-methylenebisacrylamide (MBA) and Pluronic F-127. Instead of Pluronic F-127 a poloxamer may be utilized, alternatively another non-ionic surfactant.

25

The swellable polymer body may further include a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the target site, preferably the small intestine, allowing the at least one API to pass through the wall into systemic circulation.

30

The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -

cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, and bile salts.

The swellable polymer body may further include a metal chelator, such that in use, the metal chelator
5 chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of peptide and/or protein API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

10 There is provided that the polymeric matrix may be crosslinked by at least one of, but not limited the following group of processes: microwave radiation, ultra violet radiation and chemical crosslinking, such that in use, crosslinking facilitates controlled release of the at least one API.

The swellable polymer body may further include at least one API. Preferably, the API may be at least one
15 API selected from, but not limited to, the following group: theophylline, metronidazole, zidovudine, indomethacin, sulfamethoxazole, ciprofloxacin, sulpiride, and naproxen.

The at least one API may further be an API selected from, but not limited to, the following group of
20 classes of APIs: anti-inflammatories, immunosuppressives, antibiotics, antifungals, antivirals, antimalarials, antiretrovirals, antihypertensives, chemotherapeutics, diagnostic agents, probiotics and prebiotics.

The at least one API may further be a peptide and/or protein therapeutic. The peptide and/or protein
25 therapeutic may be selected from, but not limited to, the following group: salmon calcitonin, eel calcitonin, chicken calcitonin, rat calcitonin, human calcitonin, porcine calcitonin or any gene-variant of calcitonin, parathyroid hormone, parathyroid hormone analogue PTH 1-31NH₂, parathyroid hormone analogue PTH 1-34NH₂, insulin of any gene variant, vasopressin, desmopressin, luteinizing hormone-releasing factor, erythropoietin, tissue plasminogen activators, human growth factor, adrenocorticotropin, various interleukins, and enkephalin.

30 The swelleable polymer body may be shaped and/or dimensioned to be receivable into the shell. It is to be understood that the shape and/or dimensions of the swellable polymer body may vary. For example the swelleable polymer may be shaped to be substantially, but not limited to, at least one of the following group: spherical, cylindrical, elongate, oval, discoid, geoid, rectangular, square, triangular and polygonal,

so as to be receivable into the shell. It is also to be understood that in a particular embodiment of the invention the swellable polymer body is coated on a portion of an interior surface of the shell.

5 The pharmaceutical dosage form may further comprise a coating at least partially enveloping the shell. Preferably, the coating totally envelopes the shell. The coating may be optional.

10 The coating may comprise an enteric coating. The stability and structural integrity of the enteric coating may increase with a corresponding decrease in pH, such that in use, the enteric coating is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

15 In a preferred embodiment of the invention, the enteric coating may comprise at least one polymer selected from, but not limited to, the group consisting of: cellulose acetate phthalate, a Eudragit combination and/or derivative, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxyl propyl methyl cellulose phthalate, hydroxyl propyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, methyl methacrylate-methacrylic acid copolymers, sodium alginate and stearic acid.

20 The pharmaceutical dosage form may further comprise a cap closing the outlet of the shell. The cap may be optional.

The cap may further extend to cover an exterior surface of the shell, in so doing, forming the coating.

25 The cap may comprise a pH responsive polymer. The stability and structural integrity of the cap may increase with a corresponding decrease in pH, such that in use, the cap is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT). The cap may comprise a polymer(s) selected from, but not limited to, at least one of the following group: cellulose acetate phthalate, a Eudragit combination and/or derivative, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxyl propyl methyl cellulose phthalate, hydroxyl propyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, 30 methyl methacrylate-methacrylic acid copolymers, sodium alginate and stearic acid. Preferably, the cap may be chitosan phthalate.

The cap may further include a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the

at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, and bile salts.

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The cap may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of the API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

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The pharmaceutical dosage form may further comprise a spacer to space apart the swellable polymer body and the polymeric matrix, the spacer located within the shell. The spacer preferably comprises methyl cellulose. The spacer may be optional.

15

The pharmaceutical dosage form may further comprise a second polymeric body located proximal the outlet of the shell, such that in use, the second polymeric body is released through the outlet of the shell at a target site prior to the polymeric matrix. Preferably, the second polymeric body is located between the cap and the polymeric matrix. The second polymeric body preferably comprises methyl polyethylene glycol (mPEG).

20

The second polymeric body may further include a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, and bile salts.

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The second polymeric body may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation the API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

30

In a first example embodiment of the invention there is provided a pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising:

a cylindrical shell defining an outlet and an inlet at opposing first and second end regions of the shell;

a polymeric matrix having at least one API, the polymeric matrix received within the shell; and

a swellable polymer body located within the shell, wherein the swellable polymer body may be pH responsive, such that in use, exposure of the swellable polymer body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the matrix through the outlet out of the shell toward the target site for delivery of the API.

The shell may define a hollow chamber extending along a major portion of the length of the cylindrical shell.

The inlet may be defined as a series of apertures through the shell located at the second end region of the shell, such that in use, the medium may penetrate into the shell through the apertures to contact the swellable polymer body located proximal the second end region of the shell, causing the body to swell, which in turn facilitates the displacement of the matrix out through the outlet of the shell to the target site.

In use, the swelling swellable polymer body urges the polymeric matrix out through the outlet of the shell toward the target site.

The medium is a biological medium, typically the biological medium of the small intestine.

The polymeric matrix may be shaped and/or dimensioned to in register with the shell. The polymeric matrix may be shaped and/or dimensioned to be a tablet having a generally circular shape when viewed from top or bottom so as to be operatively received within the shell. The polymeric matrix may be located adjacent to the swellable body, such that in use, the medium penetrates the shell through the inlet causing the body to swell, which in turn causes displacement of the polymeric matrix out of the outlet of the shell toward the target site.

It is to be understood that the polymeric matrix may comprise a plurality of tablets, each of which may be generally discoid in shape and having a generally circular shaped when viewed from top or bottom so as to be operatively received into, and in register with, the shell.

The swellable polymer body may be shaped and/or dimensioned to be in register with the shell. The swellable polymer body may be shaped and/or dimensioned to be a tablet having a generally circular shape when viewed from top or bottom so as to be operatively received within the shell. The swellable
5 polymer body may be located distal relative to the first end region of the shell and substantially proximal the second end region and inlet.

In a second example embodiment of the invention there is provided a pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said
10 pharmaceutical dosage form comprising:

an elongate cylindrical shell defining an outlet and an inlet at opposing first and second end regions of the shell;

a mucoadhesive polymeric matrix having at least one API, the polymeric matrix received within and in register with the shell, the mucoadhesive polymeric matrix being shaped and/or dimensioned to
15 form a tablet; and

a swellable polymer body located within the shell, wherein the swellable polymer body may be pH responsive, such that in use, exposure of the swellable polymer body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the matrix through the outlet out of the shell toward the target site for delivery
20 of the API.

The shell may define a hollow chamber extending along a major portion of the length of the cylindrical shell.

The second example embodiment may have the swellable polymer body located proximal the second end region within and in register with the shell and the polymeric matrix distal the second end region within and in register with the shell, wherein the swellable polymer body may be pH responsive, such that in use, exposure of the swellable polymer body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the
25 polymeric matrix through the outlet out of the shell toward the target site for delivery of the API.
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The second example embodiment may further comprise a spacer to space apart the swellable polymer body and the polymeric matrix located within the shell.

The second example embodiment may further comprise a pH responsive polymer cap closing the outlet of the shell, wherein the stability and structural integrity of the cap may increase with a corresponding decrease in pH, such that in use, the cap is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

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The second example embodiment may further comprise an enteric polymer coating at least partially enveloping the shell, wherein the stability and structural integrity of the enteric coating may increase with a corresponding decrease in pH, such that in use, the enteric coating is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

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The shell may comprise polyetheretherketone. The polymeric matrix may comprise trimethyl cellulose (TMC), preferably, the polymeric matrix may comprise trimethyl chitosan chloride (TMC:Cl). The swellable polymer body may comprise acrylamide (AAm), methacrylic acid (MAA), N-N'-methylenebisacrylamide (MBA) and Pluronic F-127. The coating may comprise cellulose acetate phthalate. The cap may comprise Eudragit. The spacer may comprise methyl cellulose.

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The second example embodiment of the pharmaceutical dosage form may further comprise a second polymeric body located between the cap and the polymeric matrix, such that in use, the second polymeric body is released from the shell at the target site prior to the polymeric matrix. The second polymeric body preferably comprises methyl polyethylene glycol (mPEG).

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The second polymeric body may further include a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, and bile salts.

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The second polymeric body may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein

hindering pre-systemic enzymatic degradation of API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

- 5 According to a second aspect of the invention there is provided a pharmaceutical dosage form for use in delivering at least one active pharmaceutically ingredient (API) to an animal or human in need thereof, the pharmaceutical dosage form being that described in the first aspect of the invention.

According to a third aspect of the invention there is provided a method of delivering at least one pharmaceutically active ingredient (API) to human or animal in need thereof comprising orally
10 administering to said human or animal the pharmaceutical dosage form according to the first aspect of the invention.

According to a fourth aspect of the invention there is provided for a method of manufacturing the pharmaceutical dosage form according to the first aspect, the method comprising the following steps:

- (a) manufacturing a shell defining an outlet;
- 15 (b) manufacturing a polymeric matrix having at least one API, the polymeric matrix inserted into the shell; and
- (c) manufacturing a swellable polymer body being and placing said swellable polymer body into the shell.

There is provided for a pharmaceutical dosage form and/or a method of manufacturing the same and/or
20 use of said dosage form and/or method of delivering at least one API, substantially as herein described, illustrated and/or exemplified with reference to any one of the drawings and/or examples.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a schematic of the components and mechanism of action within the gastrointestinal tract for the pharmaceutical dosage form according to the invention. The Eudragit® cap becomes soluble as the pH increases within the gastrointestinal tract. The dynamically equilibrating hydrogel swellable polymer body dramatically increases in volume in response to increasing pH of the gastrointestinal tract. The increase in volume of the hydrogel swellable body displaces the EDTA second polymeric body and the peptide loaded trimethyl chitosan polymeric matrix tablet substantially at a position along the small intestine. EDTA is released from the second polymeric body and a peptide therapeutic is released from the trimethyl chitosan polymeric matrix tablet and is transported across the intestinal wall into the systemic circulation.

Figure 2 shows a scatter plot and fitted regression curve of matrix hardness and is represented with squares, the scatter plot and fitted regression curve for deformation energy is represented as diamonds, and the scatter plot and fitted regression curve for matrix resilience is represented with a circle. The plots and curves shown in (a) to (e) are for different ratios of EDTA-mPEG.

Figure 3 shows a scatter plot and fitted regression curve of matrix hardness and is represented with squares, the scatter plot and regression curve for deformation energy is represented as diamonds, and the scatter plot and regression curve for matrix resilience is represented with a circle. The plots and curves shown in (a) to (e) are for different ratios of Avicel-EDTA-mPEG.

Figure 4 shows a scatter plot and regression curve for total disintegration time (solid circle), the scatter plot and regression curve for primary disintegration rate (solid square), the scatter plot and regression curve for secondary disintegration rate (diamond), and the scatter plot and regression curve for pellet/tablet thickness (solid hexagon). The plots and curves shown in (a) to (e) are for different EDTA-mPEG ratios.

Figure 5 shows a scatter plot and regression curve for total disintegration time (solid circle), the scatter plot and regression curve for primary disintegration rate (solid square), the scatter plot and regression curve for secondary disintegration rate (diamond), and the scatter plot and regression curve for

pellet/tablet thickness (solid hexagon). The plots and curves shown in (a) to (e) are for different Avicel-EDTA-mPEG ratios.

Figure 6 (a) to (i) show gravimetric swelling profiles of AAm-MAA hydrogel swellable body having different composition ratio in different biological and/or simulated biological media.

Figure 7 (a) to (d) show swelling velocities of AAm-MAA stimuli responsive hydrogel swellable body in formulation biorelevant media and USP simulated fluids (a, b, c) and within isolated porcine fluids (d) with respect to sequential time points. F2, F6 and F8 are AAm-MAA stimuli responsive hydrogel (10:90), AAm-MAA stimuli responsive hydrogel (50:50) and AAm-MAA stimuli responsive hydrogel (70:30), respectively.

Figure 8 shows an in vitro dissolution of theophylline (an example API) from AAm-MAA stimuli responsive hydrogel (50:50) within United States Pharmacopeia simulated gastric fluid (USP pH 1.2), United States Pharmacopeia simulated intestinal fluid (USP pH 6.8), Fasted State Simulated Gastric Fluid pH 1.6 (FaSSGF pH 1.6) and Fasted State Simulated Intestinal Fluid Version 2 pH 6.5 (FaSSIF-V2 pH 6.5). The Area Under Curve (AUC), Mean Dissolution Time at 90 minutes (MDT90) and Mean Dissolution Time at 1440 minutes (MDT1440) was determined for each dissolution profile. Five fitted dissolution modelling protocols (a) to (e) are represented for each dissolution profile.

Figure 9 shows an in vitro dissolution profiling of theophylline (an example API) from AAm-MAA stimuli responsive hydrogel swellable body (50:50) Fed State Simulated Intestinal Fluid pH 5.0 (FeSSIF pH 5.0) and Fasted State Simulated Gastric Fluid canine pH 1.5 (FaSSGFc pH 1.5), Fasted State Simulated Gastric Fluid canine pH 6.5 (FaSSGFc pH 6.5) and Fasted Stated Simulated Intestinal Fluid canine pH 7.5 (FaSSIFc pH 7.5). The Area Under Curve (AUC), Mean Dissolution Time at 90 minutes (MDT90) and Mean Dissolution Time at 1440 minutes (MDT1440) was determined for each dissolution profile. Five fitted dissolution modelling protocols (a) to (e) are represented for each dissolution profile

Figure 10 shows an in vitro dissolution of indomethacin (an example API) from AAm-MAA stimuli responsive hydrogel swellable body (50:50) within United States Pharmacopeia simulated gastric fluid (USP pH 1.2), United States Pharmacopeia simulated intestinal fluid (USP pH 6.8), Fasted State Simulated Gastric Fluid pH 1.6 (FaSSGF pH 1.6) and Fasted State Simulated Intestinal Fluid Version 2 pH 6.5 (FaSSIF-V2 pH 6.5). The Area Under Curve (AUC), Mean Dissolution Time at 90 minutes

(MDT90) and Mean Dissolution Time at 1440 minutes (MDT1440) was determined for each dissolution profile. Five fitted dissolution modelling protocols (a) to (e) are represented for each dissolution profile.

Figure 11 shows an in vitro dissolution profiling of indomethacin (an example API) from AAm-MAA stimuli responsive hydrogel swellable body (50:50) Fed State Simulated Intestinal Fluid pH 5.0 (FeSSIF pH 5.0) and Fasted State Simulated Gastric Fluid canine pH 1.5 (FaSSGFc pH 1.5), Fasted State Simulated Gastric Fluid canine pH 6.5 (FaSSGFc pH 6.5) and Fasted Stated Simulated Intestinal Fluid canine pH 7.5 (FaSSIFc pH 7.5). The Area Under Curve (AUC), Mean Dissolution Time at 90 minutes (MDT90) and Mean Dissolution Time at 1440 minutes (MDT1440) was determined for each dissolution profile. Five fitted dissolution modelling protocols (a) to (e) are represented for each dissolution profile.

Figure 12 shows an in vitro dissolution of metronidazole (an example API) from AAm-MAA stimuli responsive hydrogel swellable body (50:50) within United States Pharmacopeia simulated gastric fluid (USP pH 1.2), United States Pharmacopeia simulated intestinal fluid (USP pH 6.8), Fasted State Simulated Gastric Fluid pH 1.6 (FaSSGF pH 1.6) and Fasted State Simulated Intestinal Fluid Version 2 pH 6.5 (FaSSIF-V2 pH 6.5). The Area Under Curve (AUC), Mean Dissolution Time at 90 minutes (MDT90) and Mean Dissolution Time at 1440 minutes (MDT1440) was determined for each dissolution profile. Five fitted dissolution modelling protocols (a) to (e) are represented for each dissolution profile.

Figure 13 shows an in vitro dissolution profiling of metronidazole (an example API) from AAm-MAA stimuli responsive hydrogel swellable body (50:50) Fed State Simulated Intestinal Fluid pH 5.0 (FeSSIF pH 5.0) and Fasted State Simulated Gastric Fluid canine pH 1.5 (FaSSGFc pH 1.5), Fasted State Simulated Gastric Fluid canine pH 6.5 (FaSSGFc pH 6.5) and Fasted Stated Simulated Intestinal Fluid canine pH 7.5 (FaSSIFc pH 7.5). The Area Under Curve (AUC), Mean Dissolution Time at 90 minutes (MDT90) and Mean Dissolution Time at 1440 minutes (MDT1440) was determined for each dissolution profile. Five fitted dissolution modelling protocols (a) to (e) are represented for each dissolution profile.

Figure 14 shows Scanning Electron Microscopy (SEM) images of the crosslinked AAm-MAA hydrogel swellable body of Formulation 6 within Millipore® water, United States Pharmacopeia simulated intestinal fluid (USP pH 6.8) and United States Pharmacopeia simulated.

Figure 15 shows a schematic representation of a manufacturing process for a non-responsive non-degradable shell of the pharmaceutical dosage form according to the invention: (a) ultra molecular weight polyethylene rods were lathed to obtain a diameter of about 6 mm, and cut into segments of 14 mm in length; (b) a milling press was utilized to hollow out the centre of the rod segments to contain a hollow chamber with an internal diameter of about 5.5 mm and an internal length of about 12 mm; (c) a series of apertures were drilled through the shell at a second end region of the shell.

Figure 16 shows a noncompartmental analysis of orally administered salmon calcitonin (an example API) being part of the pharmaceutical dosage form according to the invention, and conventional IV administration of salmon calcitonin (Micalicin[®]).

Figure 17 shows an in vitro dissolution modeling of salmon calcitonin (an example API) within FaSSGF-FeSSIF V2 and isolated porcine gastrointestinal fluid dissolution set.

Figure 18 shows a predicted noncompartmental analysis derived from the in vitro-in vivo correlation utilizing isolated porcine gastrointestinal fluids of salmon calcitonin (an example API) in the pharmaceutical dosage form according to the invention, and observed plasma drug concentration-time derived noncompartmental analysis.

Figure 19 shows a predicted noncompartmental analysis derived from the in vitro-in vivo correlation utilizing FaSSGF-FeSSIF V2 dissolution fluid set of salmon calcitonin (an example API) in the pharmaceutical dosage form according to the invention and observed plasma drug concentration-time derived noncompartmental analysis.

Figure 20 shows a flow diagram describing the order the order of events occurring for the release of peptide or protein APIs from the pharmaceutical dosage form according to the invention when in use.

DESCRIPTION OF THE REFERRED EMBODIMENTS

Drug delivery is a dynamic field which encompasses the formulation of new and known active pharmaceutical ingredients (APIs) into forms which can be absorbed or targeted within the body at specific target sites. In drug delivery, different routes of API or drug administration that are commonly utilized include transdermal, intranasal, intravenous, intramuscular, subcutaneous and oral (Katzung, 2007) routes. Small molecular drugs are relatively easily absorbed via the oral route. However, the oral absorption of peptide and/or protein therapeutics or peptide and/or protein APIs requires consideration of the stability of the peptide and/or protein, the aqueous environment in which the peptide and/or protein will be suspended, absorption of the peptide and/or protein and the means that enable these processes to be unified.

The oral route is considered the most common and convenient route for patients since it enhances patient compliance (Fasano, 2008; Grabovac et al., 2008; Sastry et al., 2000). Oral delivery of therapeutic peptides and/or proteins can be deceptively difficult as each API molecule has a unique level of absorption/bioavailability and therefore a tablet or capsule needs to be formulated so that the API is absorbed at a useful therapeutic index level (He et al., 2013). Oral administration of therapeutic peptides and/or proteins may also be the most economically viable option for therapeutics which are used on a daily basis as special training of personal is not required, patients can take tablets or capsules at their convenience and some drugs in oral formulations do not have to be produced under sterile conditions (Sastry et al. 2000). The main hurdle in the oral formulation of peptide therapeutics is ensuring that drug concentrations in the plasma reach the desired therapeutic index (He et al., 2013). There are limitations to the oral administration of peptide therapeutics. These limitations include the potential for toxicity of peptide and/or protein APIs which do not follow zero-order kinetics; the fact that biolabile compounds can be degraded during the ingestion process due to environmental conditions (i.e. pH and free ions) or biological elements (i.e. proteases or bacteria); and the fact that macromolecules are rarely localized in a specific part of the gastrointestinal tract (GIT).

The pharmaceutical dosage form according to the invention was designed to overcome at least one of the abovementioned challenges in a unified manner. The first limiting factor of oral protein and/or peptide drug delivery is the hostile environment of the stomach. In the stomach, protein and/or peptide therapeutics are degraded through the combination of an acidic pH of 1-2 and the presence of enzymes such as for example trypsin (Hwang et al., 1998). The dosage form according to a preferred embodiment

of the invention was designed with a non-degradable shell component and an enteric cap that limits the access of the gastric fluids to the protein and/or peptide API. The next hurdle is the lumen environment of the intestine which contains proteolytic enzymes (Carino et al., 2000; Nakamura et al., 2004; Peppas and Carr, 2009). The inclusion of trimethyl chitosan and an EDTA-mPEG component was utilized to reduce degradation of a protein and/or peptide API. The intestinal wall is also a significant barrier where paracellular transport allows for the transport of larger protein and/or peptide APIs but should retain an intact secondary and tertiary peptide structure (Salama et al., 2006; Fasano, 2008; Makhlof et al., 2010). Intracellular transport of protein and/or peptide APIs is very challenging due to extensive digestion mechanisms within the cell during endocytosis (Fasano, 2008; Makhlof et al., 2010). Once a protein and/or peptide API enters the systemic circulation, it should retain tertiary and secondary structure in order to maintain function and reduce the antigen presenting profile of the protein and/or peptide API. Classical examples of peptide APIs include salmon calcitonin and insulin (Kutsung 2007, Peppas and Carr 2009). Oral vaccines have also been considered as a route of delivery but similar to therapeutic peptides, these agents often have a specific peptide sequence that once disrupted, the presenting antigen site will no longer elicit a desired antibody driven immune response (Fasano 2008). A targeted release of the peptide API from the dosage form according to the invention, within the small intestine, is facilitated by the pH responsive hydrogel through a physicommechanical mechanism as explained in more detail below.

Orally administered protein and/or peptide APIs are required to be absorbed via the intestinal wall. The intestinal wall offers a significant barrier to the absorption of large macromolecules such as proteins and/or peptides, as well as hydrophobic compounds (Groschwitz and Hogan 2009; Peppas and Carr 2009). Permeation enhancers are substances which cause transient disruption of the intestinal wall and therefore allow large macromolecules and/or hydrophobic substances to pass through the cell layer into the systemic circulation (Peppas and Carr 2009). However, small molecule permeability enhancers have significant toxic side-effects such as pancreatic hypertrophy or hyperplasia and may provide a means for pathogenic bacteria, viruses or endotoxins to enter the systemic circulation (Peppas and Carr 2009). Therefore the application of permeability enhancers to facilitate the transport of therapeutic agents into systemic circulation from the intestine has to be considered carefully so as to decrease the toxicity (Peppas and Carr 2009). Trimethyl chitosan is a polysaccharide chitosan derivative which has demonstrated permeation enhancer, mucoadhesive, biodegradable and biocompatible properties. These are ideal properties of a bulk excipient for the oral administration of protein and/or peptide therapeutics.

Metal chelation has been utilized as a means to reduce the pre-systemic proteolytic enzyme activity during the administration of peptide therapeutics. EDTA-mPEG components were designed to facilitate the reduction of proteolytic enzymes in a tuneable manner. These components were designed to undergo disintegration in a mathematically predictive manner. The non-specific chelation of metal ions within an oral peptide therapeutic application has the benefit of chelating enzymatic cofactors, such as zinc and calcium therein hindering pre-systemic proteolytic enzyme activity.

Stimuli responsive hydrogels have been extensively investigated for drug delivery applications because they offer tuneable characteristics to internal and external stimuli that translate into a controlled release of a drug/API (Grabovac et al. 2008). Hydrogels are synthetic and/or organic polymeric monomers that collectively form network structures that are maintained by polyelectrolyte or covalent interactions and have the ability to retain large quantities of solvent without immediately dissociating into monomer components (Peppas and Carr 2009; Sajeesh et al. 2010). Hydrogels can be engineered to be stimuli responsive to, for example, temperature, pH, magnetic fields and/or electrical current (Bawa et al. 2009). Stimuli responsive hydrogels can undergo swelling in response to a triggering stimulus such as an increase in pH, and facilitate the accelerated diffusion or degradation mediated release of an entrapped or entrained therapeutic compound (Chiappetta and Sosnik 2007, Sajeesh et al. 2010). The utilization of a pH responsive hydrogel as a physicommechanical means to target the release of a protein and/or peptide therapeutic to a specific location within the gastrointestinal tract is a novel approach to drug delivery. A pH responsive hydrogel was designed that can withstand a constant exerted pressure within an aqueous environment and undergo significant swelling. The swelling hydrogel has the physical and/or mechanical strength to facilitate the displacement of the API containing tablets out from the shell.

In accordance with a first aspect of this invention there is provided a pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising: a shell defining therein an outlet; a polymeric matrix having at least one API, the polymeric matrix received within the shell; and a swellable polymer body located within the shell, wherein the swellable polymer body is pH responsive, such that in use, exposure of the swellable polymer body to a medium, such as a biological medium, of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the matrix through the outlet out of the shell toward the target site for delivery of the API. The medium is typically a biological medium located in and/or around the target site. The target site is typically the wall of the small intestine of a human or animal.

The shell typically comprises a substantially non-degradable, biologically inert, non-responsive material, preferably a non-toxic biologically inert, non-responsive material, such that in use, the shell does not substantially biodegrade upon passage through the gastrointestinal tract (GIT). In a preferred embodiment, the material may be a USP Class VI ISO-10993 US FDA (United States Food and Drug Administration) compliant material. The shell may comprise a natural and/or synthetic polymer.

If the shell is a natural polymer, the natural polymer may be selected from polysaccharide polymers including, but not limited to, at least one of the following group: chitosan, pectin, gellan gum, xanthan gum, sodium alginate, celluloses such as sodium carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), hydroxymethylpropylmethylcellulose (HPMC), and dextrans.

If the shell is a synthetic polymer, the synthetic polymer may be selected from, but not limited to, at least one of the following group: high density polyethylene (HDPE), ultra high molecular weight, polyethylene (UHMWPE), polytetrafluoroethylene, polymethmethacrylate, polydimethylsiloxane, and poly(sulphone).

The synthetic polymers may include a polymer having a water absorption percentage over 24 hours of 0.05% when expressed in mL, or less; tensile strength of about 16 700 (pounds per square inch) psi; a melting temperature of about 340°C; being sterilizable with steam at 121°C or sterilizable with gamma irradiation. In a preferred embodiment of the invention the shell may comprise a polyetheretherketone.

The shell typically further defines an inlet at a region proximate the location of the swellable polymer body, such that in use, the medium may penetrate into the shell through the inlet to contact the swellable polymer body causing the swellable polymer body to swell, which in turn facilitates the displacement of the matrix through the outlet out of the shell to the target site.

In an embodiment of the invention the shell may be substantially cylindrically shaped having an outlet and inlet located at opposing first and second end regions of the shell respectively. It is to be understood that the shape and/or dimensions of the shell may vary. For example the shell may be shaped to be substantially, but not limited to, at least one of the following group: spherical, cylindrical, elongate, oval, discoid, geoid, rectangular, square, triangular and polygonal. In a preferred embodiment of the invention the shell is an elongate and cylindrical.

The shell facilitates concentrating the at least one API at the target site and facilitates in generating a steep concentration gradient of the at least one API at the target site, which in turn, facilitates translocation of the at least one API across a wall of the target site into the systemic circulation.

- 5 The polymeric matrix may be a natural and/or synthetic polymer. Preferably the polymeric matrix is a natural polymer and is biodegradable being responsive to specific enzymes in the gastrointestinal tract (GIT). Further preferably, the polymeric matrix is responsive to colonic enzymes including, but not limited to, at least one of the following group: β -glycosidases, pectinases, and polysaccharidases. The colonic enzymes, in use, causing digestion and/or chemical cleavage and/or degradation of the polymeric
10 matrix such that the at least one API is released for delivery at the target site.

The polymeric matrix may be mucoadhesive, such that in use, the matrix adheres at the target site. The target site may be the wall of the small intestine of the human or animal body. Adhesion of the polymeric matrix facilitates in delivery of the API at the target site, and prevents an amount of API being release
15 substantially away from the target site and being subsequently digested and/or rendered pharmaceutically inactive.

The polymeric matrix may be at least one polymer including, but not limited to, the following group: chitosan, trimethyl chitosan, EDTA-g-chitosan, 2-mercaptoethylamine-g-chitosan, and polyacrylic acid-
20 cysteine. Trimethyl chitosan is a polysaccharide chitosan derivative which has demonstrated permeation enhancer, mucoadhesive, biodegradable and biocompatible properties. Further preferably, the polymeric matrix may comprise trimethyl chitosan chloride (TMC:Cl). These cationic polymers interact with negatively charged residues on the cell surface which induces a change in the cell membrane structure and this induces a change in tight junctions. EDTA-g-chitosan demonstrates no permeation enhancing ability
25 but does demonstrate a reduction in divalent cation species within the localized environment which may reduce the degradation of the protein and/or peptide API within a localized environment and allow a greater mass of the API to be absorbed into the systemic circulation.

The polymeric matrix may further include a permeation enhancer, such that in use, the permeation
30 enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation.

The polymeric matrix may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering

pre-systemic enzymatic degradation of peptide and/or protein API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

5 EDTA and EDTA-mPEG are compounds that chelate divalent and monovalent cations. These cations are utilized within a biological system to facilitate functional tight junction integrity and peptidase enzyme cofactors. For instance divalent cations are utilized by peptidase enzymes to facilitate the degradation of amine bonds between amino acids and allow the peptide to be absorbed into the systemic circulation as a collection of amino acids. If the divalent cationic cofactors are limited/reduced, these peptidase enzymes
10 do not function at full capacity. Thus reducing the rate at which the therapeutic peptides are broken down into non-functional therapeutic compounds. Additionally, divalent cations such as calcium are utilized to crosslink mucin peptides within mucus and increase the viscosity of the substance. If the calcium load within a localized region is reduced, the viscosity of the mucus lining the small intestine is reduced. This allows for a functionalized polymer to gain access to the epidermis of the small intestine more readily
15 (and reduce the integrity of tight junctions) or/and allow the peptide therapeutic to translocate from the small intestinal luminal environment to the small intestinal epidermis layer more rapidly, and therefore, reducing the potential for fully functional peptidase enzymes from degrading the peptide therapeutic to non-functional therapeutic amino acids. Additionally, monovalent and divalent cations have functional roles in maintaining the integrity of tight junctions through biochemical secondary signalling. If the
20 concentration of the available metal ions is reduced, the integrity of the tight junctions could be further reduced. The direct and indirect mechanism of reducing tight junction integrity and the direct mechanism of reducing mucus viscosity, works in synergy to facilitate the accelerated translocation of the peptide therapeutic into the systemic circulation.

25 The polymeric matrix may further include at least one pharmaceutical excipient, preferably the excipient may be a lubricant, further preferably the lubricant may be magnesium stearate. The polymeric matrix may further include a glidant, preferably the glidant may be amorphous fumed silica.

There is provided that the polymeric matrix may be crosslinked by at least one of, but not limited to, the
30 following group of processes: microwave radiation, ultra violet radiation and chemical crosslinking, such that in use, crosslinking facilitates controlled release of the at least one API.

The polymeric matrix may be shaped and/or dimensioned to be receivable into the shell. It is to be understood that the shape and/or dimensions of the polymeric matrix may vary. For example the

polymeric matrix may be shaped to be substantially, but not limited to, at least one of the following group: spherical, cylindrical, elongate, oval, discoid, geoid, rectangular, square, triangular and polygonal, so as to be receivable into the shell.

5 The at least one API may be a peptide and/or protein therapeutic. The peptide and/or protein therapeutic may be selected from, but not limited to, at least one of the following group: salmon calcitonin, eel calcitonin, chicken calcitonin, rat calcitonin, human calcitonin, porcine calcitonin or any gene-variant of calcitonin, parathyroid hormone, parathyroid hormone analogue PTH 1-31NH₂, parathyroid hormone analogue PTH 1-34NH₂, insulin of any gene variant, vasopressin, desmopressin, luteinizing hormone-releasing factor, erythropoietin, tissue plasminogen activators, human growth factor, 10 adrenocorticotropin, various interleukins, and enkephalin. The at least one API may further be an API selected from, but not limited to, the following group of classes of APIs: anti-inflammatories, immunosuppressives, antibiotics, antifungals, antivirals, antimalarials, antiretrovirals, antihypertensives, chemotherapeutics, diagnostic agents, probiotics and prebiotics.

15 The swellable polymer body may be a natural and/or synthetic polymer. The swellable polymer body may be pH responsive, such that in use, exposure of the body to a medium of increasing pH causes an increase in swelling and an increase in volume of the body. In use, the swellable body optimally swells upon exposure to pH conditions of the small intestine in the gastrointestinal tract (GIT). Preferably, the pH 20 conditions of the small intestine vary between pH 5 and pH 7.

The synthetic polymer for the swellable polymer body may be selected from, but not limited to, the following group: poly(hydroxyethyl methacrylate), polyethylene glycol methacrylate, polyethylene glycol dimethacrylate, polyethylene diacrylate, polyethylene oxide, polyethylene glycol-poly ϵ caprolactone- 25 polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, polyimide, polyacrylate, polyurethane and derivatives thereof.

The natural polymer for the swellable polymer body may be selected from, but not limited to, the following group: alginate, hyaluronic acid, chitosan and derivatives thereof.

30 The swellable polymer body may comprise a hydrogel. Preferably, the swellable polymer body comprises acrylamide (AAM), methacrylic acid (MAA), N-N'-methylenebisacrylamide (MBA) and Pluronic F-127. Instead of Pluronic F-127 a poloxamer may be utilized, alternatively another non-ionic surfactant.

The swellable polymer body may further include a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the target site, preferably the small intestine, allowing the at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), Zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), Oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, and bile salts.

The swellable polymer body may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of peptide and/or protein API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

There is provided that the polymeric matrix may be crosslinked by at least one of, but not limited to, the following group of processes: microwave radiation, ultra violet radiation and chemical crosslinking, such that in use, crosslinking facilitates controlled release of the at least one API.

The swellable polymer body may further include at least one API. Preferably, the API may be at least one API selected from, but not limited to, the following group: theophylline, metronidazole, zidovudine, indomethacin, sulfamethoxazole, ciprofloxacin, sulpiride, and naproxen. The at least one API may further be an API selected from, but not limited to, the following group of classes of APIs: anti-inflammatories, immunosuppressives, antibiotics, antifungals, antivirals, antimalarials, antiretrovirals, antihypertensives, chemotherapeutics, diagnostic agents, probiotics and prebiotics. The at least one API may still further be a peptide and/or protein therapeutic. The peptide and/or protein therapeutic may be selected from, but not limited to, the following group: salmon calcitonin, eel calcitonin, chicken calcitonin, rat calcitonin, human calcitonin, porcine calcitonin or any gene-variant of calcitonin, parathyroid hormone, parathyroid hormone analogue PTH 1-31NH₂, parathyroid hormone analogue PTH 1-34NH₂, insulin of any gene variant, vasopressin, desmopressin, luteinizing hormone-releasing factor, erythropoietin, tissue plasminogen activators, human growth factor, adrenocorticotropin, various interleukins, and enkephalin.

The swelleable polymer body may be shaped and/or dimensioned to be receivable into the shell. It is to be understood that the shape and/or dimensions of the swellable polymer body may vary. For example the swelleable polymer may be shaped to be substantially, but not limited to, at least one of the following

group: spherical, cylindrical, elongate, oval, discoid, geoid, rectangular, square, triangular and polygonal, so as to be receivable into the shell. It is also to be understood that in a particular embodiment of the invention the swellable polymer body is coated on a portion of an interior surface of the shell.

5 The pharmaceutical dosage form may further comprise a coating at least partially enveloping the shell. Preferably, the coating totally envelopes the shell. The coating may be optional but preferred. The coating may comprise an enteric coating. The stability and structural integrity of the enteric coating may increase with a corresponding decrease in pH such that the enteric coating is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the
10 gastrointestinal tract (GIT). In a preferred embodiment of the invention, the enteric coating may comprise at least one polymer selected from, but not limited to, the group consisting of: cellulose acetate phthalate, a Eudragit combination and/or derivative, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxyl propyl methyl cellulose phthalate, hydroxyl propyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, methyl methacrylate-methacrylic acid copolymers, sodium alginate and
15 stearic acid.

The pharmaceutical dosage form may further comprise a cap closing the outlet of the shell. The cap may be optional but preferred. The cap may further extend to cover an exterior surface of the shell, in so doing, forming the coating. The cap typically comprises a pH responsive polymer. The stability and structural
20 integrity of the cap increases with a corresponding decrease in pH such that the cap is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT). The cap may comprise a polymer(s) selected from, but not limited to, the following group: cellulose acetate phthalate, a Eudragit combination and/or derivative, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxyl propyl methyl
25 cellulose phthalate, hydroxyl propyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, methyl methacrylate-methacrylic acid copolymers, sodium alginate and stearic acid. Preferably, the cap may be chitosan phthalate.

The cap may further include a permeation enhancer, such that in use, the permeation enhancer facilitates
30 paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), Zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, bile salts. The

cap may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of the API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

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The pharmaceutical dosage form may further comprise a spacer to space apart the swellable polymer body and the polymeric matrix, the spacer located within the shell. The spacer preferably comprises methyl cellulose. The spacer may be optional but preferred.

10 The pharmaceutical dosage form may further comprise a second polymeric body located proximal the outlet of the shell, such that in use, the second polymeric body is released through the outlet of the shell at a target site prior to the polymeric matrix. Preferably, the second polymeric body is located between the cap and the polymeric matrix. The second polymeric body preferably comprises methyl polyethylene glycol (mPEG). The second polymeric body may further include a permeation enhancer, such that in use,
15 the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), Zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin
20 peptide, trimethyl chitosan, and bile salts. The second polymeric body may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation the API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

25

In a first example embodiment of the invention there is provided a pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising:

30 a cylindrical shell defining an outlet and an inlet at opposing first and second end regions of the shell;

a polymeric matrix having at least one API, the polymeric matrix received within the shell; and

a swellable polymer body located within the shell, wherein the swellable polymer body may be pH responsive, such that in use, exposure of the body to a medium of increasing pH causes an increase in

swelling and an increase in volume of the body, which in turn facilitates displacement of the matrix through the outlet out of the shell toward the target site for delivery of the API.

5 The shell may define a hollow chamber extending along a major portion of the length of the cylindrical shell.

10 The inlet may be defined as a series of apertures through the shell located at the second end region of the shell, such that in use, the medium may penetrate into the shell through the apertures to contact the swellable polymer body located proximal the second end region of the shell, causing the body to swell, which in turn facilitates the displacement of the matrix out through the outlet of the shell to the target site. In use, the swelling swellable polymer body urges the polymeric matrix out through the outlet of the shell toward the target site.

15 The polymeric matrix may be shaped and/or dimensioned to in register with the shell. The polymeric matrix may be shaped and/or dimensioned to be a tablet having a generally circular shape when viewed from top or bottom so as to be operatively received within the shell. The polymeric matrix may be located adjacent to the swellable body, such that in use, the medium penetrates the shell through the inlet causing the body to swell, which in turn causes displacement of the polymeric matrix out of the outlet of the shell toward the target site.

20 It is to be understood that the polymeric matrix may comprise a plurality of tablets, each of which may be generally discoid in shape and having a generally circular shaped when viewed from top or bottom so as to be operatively received into, and in register with, the shell.

25 The swellable polymer body may be shaped and/or dimensioned to be in register with the shell. The swellable polymer body may be shaped and/or dimensioned to be a tablet having a generally circular shape when viewed from top or bottom so as to be operatively received within the shell. The swellable polymer body may be located distal relative to the first end region of the shell and substantially proximal the second end region and inlet.

30 In a second example embodiment of the invention there is provided a pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising:

an elongate cylindrical shell defining an outlet and an inlet at opposing first and second end regions of the shell;

a mucoadhesive polymeric matrix having at least one API, the polymeric matrix received within and in register with the shell, the mucoadhesive polymeric matrix being shaped and/or dimensioned to form a tablet; and

a swellable polymer body located within the shell, wherein the swellable polymer body may be pH responsive, such that in use, exposure of the body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the polymeric matrix through the outlet out of the shell toward the target site for delivery of the API.

The shell may define a hollow chamber extending along a major portion of the length of the cylindrical shell.

The second example embodiment may have the swellable polymer body located proximal the second end region within and in register with the shell, wherein the swellable polymer body may be pH responsive such that in use exposure of the swellable polymer body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the polymeric matrix through the outlet out of the shell toward the target site for delivery of the API.

The second example embodiment may further comprise a spacer to space apart the swellable polymer body and the polymeric matrix located within the shell.

The second example embodiment may further comprise a pH responsive polymer cap closing the outlet of the shell, wherein the stability and structural integrity of the cap may increase with a corresponding decrease in pH such that the cap is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

The second example embodiment may further comprise an enteric polymer coating at least partially enveloping the shell, wherein the stability and structural integrity of the enteric coating may increase with a corresponding decrease in pH such that the enteric coating is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

The shell may comprise polyetheretherketone. The polymeric matrix may comprise trimethyl cellulose (TMC), preferably, the polymeric matrix may comprise trimethyl chitosan chloride (TMC:Cl). The swellable polymer body may comprise acrylamide (AAm), methacrylic acid (MAA), N-N'-methylenebisacrylamide (MBA) and Pluronic F-127. The coating may comprise cellulose acetate phthalate. The cap may comprise Eudragit. The spacer may comprise methyl cellulose.

The second example embodiment of the pharmaceutical dosage form may further comprise a second polymeric body located between the cap and the polymeric matrix, such that in use, the second polymeric body is released from the shell at the target site prior to the polymeric matrix. The second polymeric body preferably comprises methyl polyethylene glycol (mPEG).

The second polymeric body may further include a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation. The permeation enhancer may be selected from, but not limited to, at least one of the following group: Δ G (Zot fragment); AT-1002; Zot (45kDa), zonulin (47kDa), C-CPE, sodium caprate, dimethyl- β -cyclodextrin, NO donors (NOC5, NOC12 and SNAP), oleic acid, occludin peptide, FSH-fusion occludin peptide, trimethyl chitosan, and bile salts.

The second polymeric body may further include a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of API. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

According to a second aspect of the invention there is provided a pharmaceutical dosage form for use in delivering at least one active pharmaceutically ingredient (API) to an animal or human in need thereof, the pharmaceutical dosage form being that described in the first aspect of the invention.

According to a third aspect of the invention there is provided a method of delivering at least one pharmaceutically active ingredient (API) to human or animal in need thereof comprising orally administering to said human or animal the pharmaceutical dosage form according to the first aspect.

According to a fourth aspect of the invention there is provided for a method of manufacturing the pharmaceutical dosage form according to the first aspect, the method comprising the following steps:

- (a) manufacturing a shell defining an outlet;
- (b) manufacturing a polymeric matrix having at least one API, the polymeric matrix inserted into the shell; and
- (c) manufacturing a swellable polymer body being and placing said swellable polymer body into the shell.

There is provided for a pharmaceutical dosage form and/or a method of manufacturing the same substantially as herein described, illustrated and/or exemplified with reference to any one of the drawings and/or examples.

Certain examples of the pharmaceutical dosage form and method of manufacturing the same will now be described and/or illustrated and/or exemplified below.

MATERIALS AND METHODS

Materials

Chitosan (medium molecular weight) with a degree of deacetylation of 77.0% was purchased from Aldrich (Schnelldorf, Germany). GMP grade salmon calcitonin was purchased from Bachem (Bachem AG, Bubendorf, Switzerland). A salmon calcitonin immunoassay kit (S-1166) was purchased from Bachem (Bachem AG, Bubendorf, Switzerland). Trimethyl chitosan was prepared through reductive methylation. Acrylamide ($\geq 98\%$ pure, MW 71.08 g/mol) was purchased from Fluka (Sigma-Aldrich, Buchs, Switzerland). Methacrylic acid (99% pure, 86.09 g/mol) was purchased from Aldrich (Schnelldorf, Germany). Methoxypolyethylene glycol 2000 ($\geq 99\%$ pure), sodium iodide (99.999% pure), methyl iodide ($\geq 99.0\%$), sodium hydroxide ($\geq 98\%$ pure), sodium chloride ($\geq 98\%$ pure), sodium dihydrogen phosphate monohydrate ($\geq 99\%$ pure), sodium bicarbonate ($\geq 99.5\%$ pure), hydrochloric acid (37% v/v), sodium deoxycholate ($\geq 98\%$ pure), sodium taurocholate ($\geq 90\%$ pure), sodium taurodeoxycholate ($\geq 97\%$ pure), orthophosphoric acid (85% w/v. 99.99% pure), tetramethylethylenediamine (99% pure, 116.20 g/mol), ammonium persulfate ($\geq 98\%$ pure, 228.20 g/mol), Pluronic F-127, *N,N'*-methylenebis(acrylamide) (99% pure, 154.17 g/mol), maleic acid (99% pure), ethylenediaminetetraacetic acid ($\geq 99.995\%$ pure) were purchased from Sigma-Aldrich (St. Louis, Missouri, USA) at reagent grade and where utilised without further purification. Dichloromethane ($\geq 99.9\%$ pure), diethyl ether ($\geq 99.0\%$ pure), acetic acid (99.99% pure), ethanol ($\geq 99.8\%$ pure) and N-

methyl-2-pyrrolidone ($\geq 99.5\%$ pure) were purchased from Merck at reagent grade and were utilised without further purification. Ac-Di-Sol[®] and Avicel[®] RC/CL type RC-591 (co-dried blend of microcrystalline cellulose and sodium carboxymethylcellulose) was purchased from FMC BioPolymer (Philadelphia, PA, USA). Egg phosphatidylcholine (97.5% pure) purchased from Lipoid GmbH (Ludwigshafen, Germany). Acetonitrile ($\geq 99.9\%$ pure) and sodium oleate ($\geq 99\%$ pure) was purchased from Sigma (St. Louis, Missouri, USA) at UPLC grade.

The pharmaceutical dosage form according to the invention typically comprises a shell, a polymeric matrix, and a swellable polymer body as described above. Optionally the pharmaceutical dosage form may comprise a coating, a cap, a spacer and a second polymeric body. Preparatory procedures for manufacturing the individual components of the dosage form and certain experimental protocols are described and/or illustrated and/or exemplified below.

Preparation of the shell

The shell is typically manufactured from a substantially non-degradable, biologically inert, non-responsive material, preferably a non-toxic biologically inert, non-responsive material. Preferably, the shell is manufactured from a U.S. Food and Drug Administration (FDA) approved material or demonstrate ISO-10993 compliant material. Such material should be safe for use in the body of a human or animal and show safe usage upon exposure to bodily fluids and bodily tissues for a time period of 30 days. The shell may be manufactured to have various shapes and/or dimensions.

Typically, the shell is manufactured to be an elongate cylindrical shell having opposing first and second end regions. The first end region defining therein outlet and the second end region defining therein an inlet. Typically, a hollow chamber or passage is located between the first and second end regions. The inlet is typically a series of apertures collaring the second end region of the shell. The outlet is typically a single aperture located at the first end. The shell is typically machined into a cylindrical structure to define a passage of about 4mm to about 4.5mm in length and having a diameter of the passage being between about 0.5mm to about 1.2cm. In a preferred embodiment of the shell a hollow chamber extends along a major portion of the length of the shell.

When the dosage form is assembled, the swellable polymer body is positioned substantially proximal the inlet, such that in use, intestinal fluid can pass from the intestinal environment into the shell via the inlet and cause the swellable polymer body to swell, which in turn urges the polymeric matrix out of the outlet of the shell to the target site. The inlet therefore allows hydration of the swellable polymer body. It is to

be understood that the inlet may be located along any portion of the shell, preferably, the inlet is located proximal the position of the swellable polymer body.

Typically, the shell's first end is open and defines the outlet, the shell's second end is closed against which the swellable polymer body urges against when it swells to facilitate displacement of the polymeric matrix. The inlet is defined as a series of apertures located at the second end region. A certain embodiment of the shell is illustrated on Figure 1 and 16 of the appended figures. In the illustrated embodiment the second end additionally includes an aperture therethrough.

In a preferred embodiment of the invention, the shell comprises polyetheretherketone.

Preparation of the polymeric matrix

The polymeric matrix is typically the main vehicle or carrier for the at least one active pharmaceutical ingredient (API). Typically, the main API of interest is dispersed and/or contained in or on the polymeric matrix. In a preferred embodiment of the invention, the polymeric matrix is mucoadhesive, such that in use, it adheres to the target site, preferably, the wall of the small intestine. Adherence to the wall of the small intestine facilitates a greater amount of API being released at the target site and hinders unwanted excretion and/or loss of API. Adherence to the wall of the small intestine also facilitates the establishment of a concentration gradient of API across the wall, therein facilitating absorption and/or transport across the wall into the systemic circulation via diffusion and/or paracellular transport means.

Typically, the polymeric matrix is a mucoadhesive polymeric matrix having at least one API, the polymeric matrix being received within, and in register with, the shell, the mucoadhesive polymeric matrix being shaped and/or dimensioned to be a tablet or pellet, typically a substantially discoid tablet.

The polymeric matrix may be manufactured from natural and/or synthetic polymers, or combinations thereof. In a preferred embodiment of the invention, the polymeric matrix comprises a chitosan derivative, typically trimethyl chitosan (TMC), further preferably trimethyl chitosan chloride (TMC:Cl). Trimethyl chitosan is a polysaccharide chitosan derivative which has demonstrated permeation enhancer, mucoadhesive, biodegradable and biocompatible properties.

Trimethyl chitosan was prepared in the same way as described by Polnok et al., 2004. The trimethyl chitosan that was prepared for this pharmaceutical dosage form consisted of two reaction steps and one ion-exchange step. Briefly, 2g of chitosan (medium molecular weight, 77.0% deacetylated), 4.8g sodium iodide was dissolved in 80mL of pre-warmed N-methyl pyrrolidone (60°C). Once the solution was homogenous, 10mL of 20% sodium hydroxide solution, also pre-warmed to 60°C, was added to the

homogenous solution. The reaction was carried out in a water bath heated to a constant 60°C for 30 minutes. The homogenous solution was then removed from the water bath and had 12mL of methyl iodide immediately added to the solution. The reaction was allowed to carry out under reflux with constant magnetic stirring of solution for 90 minutes at 50°C. The homogenous polymer solution is then removed and polymer precipitated out of solution with 250mL diethyl ether and 250mL ethanol. The entire solution is then filtered through double cellulose filters under high pressure (ensures that the filtrate is a clear yellow colour). The polymer is then collected and dried in vacuo at 60°C for 48 hours. The resulting dry polymer is then ground into a fine powder.

The ion-exchange step allows for iodide ions to be replaced by chloride ions. The finely ground powder is dissolved in 80mL of 5% (w/v) sodium chloride solution for 15 minutes under magnetic stirring. Diethyl ether (250mL) and ethanol (250mL) is added to the solution and thoroughly mixed for 2 minutes. Once the solution has been mixed (a cloudy solution is resulted), the solution is once again filtered and dried in vacuo at 60°C for 24 hours. This reaction procedure has an 87.5% yield. A pellet and/or tablet may then be manufactured through use of a tablet press. Without incorporation of an active pharmaceutical ingredient (API) the tablet will be a placebo tablet which is sometimes desired.

Loading of active pharmaceutical ingredient (API) into the polymeric matrix (Example I)

Various APIs may be loaded into the polymeric matrix. In an example embodiment of the invention a peptide and/or protein may be utilized as the API. Typically, salmon calcitonin and/or insulin was utilized, as described and/or exemplified hereunder.

The prepared trimethyl chitosan (TMC) was dried and ground into a fine powder which was placed through a 400 µm aperture sieve to ensure uniform powder. An accurate weight of 2500mg trimethyl chitosan powder was dissolved in 40 mL of Millipore water (pH 7.0) by magnetic stirring at 300 rpm for 30 minutes, at which point a viscous yellow solution was obtained. The salmon calcitonin or insulin was added in order to obtain a final concentration of 600 IU salmon calcitonin or 1 IU insulin per 3.2 mg of powder. The dispersion was frozen at 193K for 48 hours. The powder sample was lyophilised with a 2 hour condensation phase at -60°C and a 24 hour sublimation phase at 25 mm Torr in a Freezone 12 freeze drier (Lanconco, Kansas City, USA). After freeze-drying, the sample was placed in sealed glass polytops and frozen at -20°C (Silva et al., 2006; Pringels et al., 2008).

The lyophilized product was mixed with powdered EDTA-mPEG powder and sodium deoxycholate in such a way as to eliminate the potential presence of water or other solvents. This was achieved through

direct compression of these elements with the incorporation of a glidant (i.e. silica) and/or a lubricant (i.e. magnesium stearate) which have been homogenously mixed to ensure equal distribution of all elements that were present. This also ensured that the peptide and/or protein API was at an appropriate dosage without the error of dilution. Each directly compressed polymeric matrix incorporated the same mass of dry components so that there is no inter-variability between each polymeric matrix, thus releasing the required dosing amount of drug compound when hydrated by intestinal lumen fluids. The direct compression formed tablets, preferably, mini-pellet shaped structures that can easily be received into the shell.

10 Loading of insulin and/or salmon calcitonin (example APIs) into trimethyl chitosan (TMC) polymeric matrix (Example II)

In an alternative method described above, API may be loaded according to the following method described hereunder.

15

Dry granulation was utilised, which involved: salmon calcitonin loaded-lyophilised trimethyl chitosan, mPEG, Ac-Di-Sol[®] microcrystalline cellulose and dry trimethyl chitosan powder which were accurately weighted according to the optimised insulin-loaded trimethyl chitosan mini-pellet optimised Box Behnken design formulation. Once the powdered components were accurately weighted, the samples were mixed until a homogenous mixture was obtained. The homogenous mixture was compressed within a modified punch and die set to produce 4mm pellets under a compression of 3.4MPa. The pellets were immediately placed in glass polytops and frozen at -20°C.

20

Preparation of the swellable polymer body

25 The swellable polymer body may be shaped and/or dimensioned to, in use, be located inside the shell, typically in register with the shell. The body may be shaped and/or dimensioned to be a tablet and/or pellet, and typically having a generally circular shape when viewed from top or bottom so as to be operatively received within the cylindrical shell. The swellable polymer body may be located distal relative to the outlet of the shell and substantially proximal the inlet of the shell.

30

It is also to be understood that in a particular embodiment of the invention the swellable polymer body is coated on a portion of an interior surface of the shell. The portion may extend to include a minor or major portion of the interior surface.

Typically, the swellable polymer body is located proximal the second end region within the shell within, wherein the swellable polymer body may be pH responsive, such that in use, exposure of the body to a medium of increasing pH causes an increase in swelling and an increase in volume of the body, which in turn facilitates displacement of the matrix out through the outlet of the shell toward the target site for delivery of the API. The medium is typically a biological medium, more typically intestinal medium of the small intestine of a human and/or animal.

In a preferred embodiment of the invention, the swellable polymer body is a hydrogel, and is manufactured as described and/or exemplified hereunder.

Briefly, a stimuli responsive (in this case pH responsive) hydrogel swellable polymer body was synthesised using acrylamide (AAm) monomers and methacrylic acid (MAA). N,N'-Methylenebisacrylamide (MBA) is a crosslinking agent and was utilised to crosslink AAm to MAA. Pluronic F-127 was used to enhance the solubilisation of AAm, MAA and MBA in deionised water. Ammonium persulfate, a radical initiator, and tetramethylethylenediamine (TEMED), a catalyst, were used in the crosslinking reaction between AAm and MAA. The concentrations and sequential addition of chemical components that make up the swellable polymer body are presented in **Table 1**.

Table 1 The concentrations of sequentially added chemical components whilst constantly stirring, in order to form the hydrogel swellable polymer body.

Solution component	Concentration (% w/v)	Volume added to final in situ gelling solution (mL)
Acrylamide	50	3
Methacrylic acid	50	2
N,N'-Methylenebis(acrylamide)	2.5	0.7
Deionised water	-	3
Pluronic F-127	10	0.3
Ammonium persulfate	20	0.25
Tetramethylethylenediamine	20	0.25

Once all the respective solutions were prepared and added to a glass beaker under constant magnetic stirring, 100mg of sodium bicarbonate was immediately added. The sodium bicarbonate generated carbon dioxide gas within the polymerising solution, thus inducing the formation of a porous gel. Moulds were

produced that would allow the in situ curing process to take place within a substantially cylindrical shape (inner diameter of cylindrical moulds was 4.77mm). The moulds were placed in a glass beaker and incubated in a water bath at 37°C ($\pm 0.5^\circ\text{C}$) for 12 hours. Once the curing process was completed, the in situ cured rods were then removed from the cylindrical moulds and cut, transversely, into 0.5mm pieces and then longitudinally into 0.3mm pieces. These cut pieces were substantially discoid tablets have a generally circular shape when viewed from top or bottom so as to be operatively received within the cylindrical shell.

Loading the swellable polymer body

It certain embodiments of the invention, and in certain applications, it may be desired to load the swellable polymer body with at least one API. Below the loading of at least one API into the above described hydrogel swellable polymer body is described and/or exemplified.

The active pharmaceutical ingredients (APIs) (theophylline, metronidazole, zidovudine, indomethacin, sulfamethoxazole, ciprofloxacin, sulpiride, and/or naproxen) were loaded by equilibrium partitioning in a slightly modified manner as previously described (Schoener et al., 2012). The APIs/drugs were dissolved within nine solutions of 2% v/v DMSO/Millipore® water solutions (25°C, 100 rpm) which contained a final concentrations of theophylline (0.003 M), ciprofloxacin (0.17 M), indomethacin (0.18 m), metronidazole (0.007 M), sulfamethazole (0.003 M), 4-aminosalicylic acid (0.0014 M), zidovudine (0.001 M) sulpiride (0.003 M) and naproxen (0.003M), respectively. The AAm-MAA hydrogel swellable polymer body formulation (as described above), which had non-reacted monomers removed, was placed within the drug solutions and allowed to swell over a period of 24 hours. The hydrogels were dried within a vacuum oven for 24 hours at 40°C. The dried API loaded hydrogel swellable polymer body was then formed into a desired shaped and/or dimensions before being inserted into the shell. The API loaded hydrogel swellable body was placed substantially proximal the apertures defined by the second end region of the shell.

API release studies from crosslinked AAm-MAA hydrogel swellable polymer body within dissolution fluids and isolated porcine gastrointestinal fluids

The in vitro and ex vivo release studies were conducted in a previously described manner (Dünhaupt et al., 2012). Each API (drug) loaded hydrogel swellable polymer body was placed within a 20 mL glass polytop containing 10 mL biorelevant dissolution fluid, United States pharmacopeia dissolution fluid or isolated porcine gastrointestinal fluid for a time period of 24 hours. A limited volume of dissolution fluid

was utilized within this experimental protocol due to a limited amount of isolated porcine gastrointestinal fluid that was available and the volume must stay constant for competitive purposes. The polytops were placed within an Orbit Shaker Incubator (LM-530-2, MRC Laboratory Instruments Ltd, Hahistadrut, Holon, Israel) at $37\pm0.5^{\circ}\text{C}$ at 50 rpm. Sink conditions were maintained throughout the study. At
5 predetermined time points, a 1 mL sample was withdrawn and replaced with a temperature equilibrated aliquot of the respective fluid. The samples were filtered through a $0.22\text{ }\mu\text{m}$ Millipore Millex injection filter (Billerica, MA, USA) and subject to UPLC analysis. The cumulative percentage of drug release and the concentration of drug release were plotted against time. Each API (drug) release study was repeated in triplicate.

Application of EudragitTM layers or chitosan phathate layer

The pharmaceutical dosage form may further comprise a coating at least partially enveloping the dosage form. Preferably, the coating totally envelopes the dosage form. The coating is optional but is included in preferred embodiments of the invention.

The coating is typically an enteric coating. The stability and structural integrity of the enteric coating may increase with a corresponding decrease in pH such that the enteric coating is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT). Typically, an enteric coating being pH responsive to degrade at about
20 neutral pH 5 is preferred.

In a preferred embodiment of the invention, the enteric coating comprises cellulose acetate phthalate or Eudragit, or a combination thereof. Typically, the coating is applied through known spray coating techniques utilized to coat pharmaceutical dosage forms. Typically, the combination includes Eudragit[®]
25 L100 (composed of polymethacrylic acid-co-methyl methacrylate in ratio of 1:1)) and Eudragit[®] S100 (composed of polymethacrylic acid-co-methyl methacrylate in a ratio of 1:2).

Preparation of the cap

It is to be understood that the coating described above may envelop the shell to cover the outlet of the
30 shell, and in so doing, provide for a cap. However, in certain embodiments of the invention a separate cap is provided to close the outlet. The above described coat is then optionally applied to envelope the capped shell. The cap may be optional.

The cap closes the outlet of the shell.

The cap may further extend to cover an exterior surface of the shell and the inlet, in so doing, forming the coating enveloping the shell.

5

The cap may comprise a pH responsive polymer. The stability and structural integrity of the cap may increase with a corresponding decrease in pH such that the cap is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

10

The cap may further include metal chelator such that in use the metal chelator chelates divalent metal ions hindering pre-systemic degradation of peptide and/or protein API by peptidase enzymes.

15

Typically, the cap comprises Eudragit and/or chitosan phthalate, such that in use, the stability and structural integrity of the cap may increase with a corresponding decrease in pH such that the cap is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT). In another embodiment the cap comprises Eudragit® L100 (composed of polymethacrylic acid-co-methyl methacrylate in ratio of 1:1)) and Eudragit® S100 (composed of polymethacrylic acid-co-methyl methacrylate in a ratio of 1:2).

20

Preparation of the spacer

25

It is to be understood that an optional spacer may further be included into the pharmaceutical dosage form according to the invention to space apart the swellable polymer body and the polymeric matrix, the spacer located within the shell. The spacer preferably comprises methyl cellulose and is typically shaped and/or dimensioned to be a disc and/or pellet and/or tablet. It is to be understood that the shape and/or dimension may vary.

30

Methyl cellulose was accurately weighted out (20mg) and placed within the punch and die set to produce discs and/or mini-pellets having a diameter of 4mm and a length of 1mm. A methyl cellulose disc was placed between the stimuli responsive hydrogel swellable polymer body and the polymeric matrix to limit water which in use hydrates the swellable polymer body via the apertures in the shell from contacting the polymeric matrix (containing the peptide and/or protein API). Additionally, the methyl cellulose disc spacer eroded very slowly within a hydrophilic environment, and acted as a surface that the stimuli responsive hydrogel swellable polymer body could physically act against when swelling in use. The

spacer increased the ability of the hydrogel swellable polymer body to, in use, urge out the polymeric matrix through the outlet of the shell to the target site.

Preparation of the second polymeric body

- 5 The pharmaceutical dosage form may further comprise a second polymeric body located proximal the outlet of the shell, such that in use, the second polymeric body is released from the shell at a target site prior to the polymeric matrix. Preferably, the second polymeric body is located between the cap and the polymeric matrix inside the shell.
- 10 The second polymeric body typically includes a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the wall of the small intestine allowing the at least one API to pass through the wall into systemic circulation.

The second polymeric body further typically includes a metal chelator, such that in use, the metal chelator
15 chelates divalent metal ions located at the wall of the small intestine therein hindering pre-systemic degradation of peptide and/or protein API by peptidase enzymes. The metal chelator may for example be ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

- 20 In a preferred embodiment of the invention a second polymeric body comprising Avicel-EDTA-mPEG was synthesised having a ratio of 33.5% ^{w/w} mPEG, 33.5% ^{w/w} EDTA and 33% ^{w/w} Avicel[®] RC/CL type R-591. The mPEG was first melted at 60°C on a watch glass heated by a calibrated hot plate magnetic stirrer. Once the solid mass of mPEG was melted to a liquid phase, EDTA was added to the molten mPEG. The EDTA was homogenously distributed within the molten mPEG with a wooden spatula. Once
25 a uniform distribution was obtained, the EDTA-mPEG hot melt dispersion was removed from the hot plate magnetic stirrer and allowed to cool under constant stirring. Once the EDTA-mPEG hot melt dispersion had become a cool solid, the solid mass was place through a metal sieve with an aperture of 850µm to form a fine powder. Avicel[®] RC/CL type R-591 was accurately weighted out and mixed (at 250rpm) with the fine EDTA-mPEG powder until a homogenous mixture was obtained. The homogenous
30 mixture was then accurately weighted out into 30mg aliquots and placed within the punch and die set. Mini-pellets were produced under a pressure of 3.5MPa with a diameter of 4 mm and a length of 3.27 mm.

Assembly of a preferred embodiment of the pharmaceutical dosage form according to the invention

A preferred embodiment of the pharmaceutical dosage form according to the invention was assembled by placing the swellable polymer body (accurately weighted 10 mg) against the second end region (opposite the first end region) of the non-responsive non-degradable elongate shell component. The shell's first end is open and defines the outlet, the shell's second end is closed against which the swellable polymer body urges against when it swells to facilitate displacement of the polymeric matrix. The inlet is defined as a series of apertures at the second end region of the shell. The swellable polymer body was positioned to be substantially proximate the series of apertures defining the inlet located at the second end region of the shell. A methyl cellulose disc spacer was placed against the swellable polymer body inside the shell, followed by a salmon calcitonin-loaded trimethyl chitosan mini-pellet polymeric matrix, and finally an Avicel®-EDTA-mPEG mini-pellet second polymeric body. The entire shell (including the outlet) was spray coated in an enteric coating solution. The enteric coating solution contained a 4% w/w solution of Eudragit® L100 and a 4% w/w solution of Eudragit® S100 within an organic solvent composed of 33% v/v ethanol and 67% v/v acetone. Triethyl citrate was added to the solution at a concentration of 35% w/w of the Eudragit® component of the coating solution. The coated pharmaceutical dosage form was placed within glass polytops and stored at -20°C until use.

Dissolution of optimized Eudragit® coated pharmaceutical dosage form according to the invention

The optimized Eudragit® coated pharmaceutical dosage form according to the invention was prepared and placed within United States Pharmacopeia dissolution fluid, biorelevant dissolution fluid and isolated gastrointestinal dissolution fluid. The major addition to these dissolution studies is the inclusion of biorelevant media. Additionally, isolated gastrointestinal porcine fluids (fasted state) were utilized for ex vivo dissolution studies. A total of four dissolution sets (USP pH 1.2 to USP pH 6.8; FaSSGF to FaSSIF-V2; FaSSGF-FaSSIF-V2; FaSSGFc pH 1.6 to FaSSIFc pH 7.5) were utilized to generate fractional release-time profiles. Additionally, a fractional release-time profile was determined within an ex vivo set (isolated porcine gastric fluid to isolated porcine intestinal fluid). The utilization of these dissolution sets allows for the determination of which dissolution fluid facilitates the closest in vivo plasma drug concentration-time profile.

The above used abbreviations are explained below for clarity:

USP pH 1.2: United State Pharmacopeia simulated gastric fluid pH 1.2

USP pH 6.8: United States Pharmacopeia simulated small intestinal fluid pH 6.8

FaSSGF: Fasted State Simulated Gastric Fluid for human model

FaSSIF V2: Fasted State Simulated Intestinal Fluid Version 2 for human model

FeSSIF V2: Fed State Simulated Intestinal Fluid Version 2 for human model

5 FaSSGFc pH 1.6: Fasted State Simulated Gastric Fluid canine model pH 1.6

FaSSIFc pH 7.5: Fasted State Simulated Intestinal Fluid canine model pH 7.5

In vitro-in vivo correlations of the optimized Eudragit[®] coated pharmaceutical dosage form according to the invention

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The in vitro-in vivo correlation was conducted with Winnonlin (Pharsight, Version 5.0). Correlation validation utilizes convolution which is the reverse process of deconvolution. If the unit impulse response (UIR) and fractional absorption profile of an oral administered API/drug is known, convolution allows for the plasma drug concentration-time profile to be predicted. These predicted plasma drug concentration-time profiles can be compared with the observed plasma drug concentration-time profiles to determine if the UIR can accurately determine plasma concentration through non-compartmental analysis. The greater the number of non-compartmental parameters that achieve similar or identical observed vs. predicted ratios of 1:1, the better correlation that was achieved between in vitro dissolution and the in vivo plasma drug concentration-time profiles. This correlation validation was conducted for each salmon calcitonin dissolution within each dissolution fluid and isolated porcine gastrointestinal fluid to determine which dissolution fluid achieved the greatest in vitro-in vivo correlation.

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Results and Discussion

25 Polymeric matrix

Preparation and characterisation of trimethyl chitosan (TMC) and protein and/or peptide loaded EDTA-mPEG-sodium seoxycholate-trimethyl chitosan formulations was undertaken. Various ratios of EDTA-mPEG were analyzed for matrix resilience and disintegration time as shown in Figures 3 and 4 respectively.

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TMC:Cl is a synthesized derivative of chitosan that is a pale yellow, free flowing powder excipient that readily dissolves within neutral solvents to form a light yellow solution. Chitosan was not utilized in this study because chitosan does not dissolve within neutral conditions and this is a formulation issue when

the biological perspective is considered. Therefore, TMC:Cl was synthesized in order to retain the positive innate properties of chitosan and allow for these highly desirable properties to be extended into the neutral environment by increasing the solubility of the parent compound. During the synthesis of TMC:Cl the number of positive charges on the polymer chain is increased causing the polymeric molecule to expand in solution due to repelling electrostatic forces between the functional groups (Martins et al., 2011). TMC:Cl is able to increase transport of large compounds, such as protein and/or peptide APIs, because the charge density and structural features along the backbone structure of this chitosan derivative enables augmented absorption across mucosal epithelia by opening tight junctions (Martins et al., 2011).

The ATR-FTIR indicate that TMC:Cl was successfully synthesized as indicated by the presence peak 1475 cm^{-1} and 1559 cm^{-1} , whereas peak 1577 cm^{-1} is specific to chitosan (Mourya and Inamdar, 2009). The peak located at 1475 cm^{-1} is attributed to the asymmetrical angular deformation of the C-H bonds of methyl groups. The peak at 1577 cm^{-1} for chitosan and 1555 cm^{-1} for TMC:Cl is due to angular deformation of N-H bond of amino groups but the intensity of peak 1555 cm^{-1} is reduced in comparison to peak 1577 cm^{-1} due to N-methylation (Martins et al., 2011). The peak at 1555 cm^{-1} within the TMC:Cl spectra indicates the presence of N-H bending but the N-methylation reaction was partial, as the presence of mono and disubstituted amino groups are possible. The peak range $1415\text{--}1430\text{ cm}^{-1}$ is assigned to the characteristic absorption of N-CH₃. The alterations of peak 1150 cm^{-1} within chitosan indicate that the introduction of alkyl groups occurred at C-3 and C-6 within TMC:Cl (Mourya and Inamadar, 2009). (This is not shown in the Figures).

The major powder X-ray diffraction (XRD) reflections for medium molecular weight chitosan occurred at 2θ -values of 20.0° (58590), 36.7° (79700 cps), 42.9° (46670 cps), 63.3° (17888 cps), 76.4° (37853 cps) and 80.6° (31535 cps). In comparison, the major XRD reflections for TMC:Cl occurred at 2θ -values of 20.0° (11495 cps), 31.5° (31771 cps), 45.2° (17010 cps), 56.3° (7723 cps), 66° (5033 cps), 75.1° (5548 cps) and 83.8° (4918 cps). The degree of crystallinity was determined to be 31.8% for chitosan and 86% for TMC:Cl. (This is not shown in the Figures).

The major XRD reflection that occurred at 20.0° within chitosan became essentially lost within the trimethyl chitosan. Interestingly the major reflection peaks did not overlap between the parent compound and the derivative product. The major change in the powdered XRD pattern between chitosan and TMC:Cl indicates that the physical crystal structure of the derivative changed significantly during the quaterization process. The increase of the crystallinity can also be attributed to the quaterinization

process. Additionally, the intensity of the XRD reflections within TMC:Cl was reduced in comparison to chitosan. The presence of the chloride ions enhances the crystallinity of TMC. The higher degree of crystallinity within the TMC:Cl is one of the major factors that impacts the compaction of this excipient into a solid dosage form. Auxiliary excipients, EDTA-mPEG powder and Ac-Di-Sol[®], were utilized to
5 reduce the impact of the crystalline nature of TMC:Cl.

The mean dissolution time (MDT) and fractional release after 8 hours performance with respect to matrix hardness can be adjusted with the adjustment of excipient mass concentrations. The mucoadhesive performance of the peptide-loaded EDTA-mPEG-sodium deoxycholate-trimethyl chitosan mini-pellets
10 were evaluated with respect to matrix hardness as well. The ability of mini-pellet to be mucoadhesive is dependent on the excipient mass concentrations and the presence of mucin. The presence of mucin enabled the mini-pellet to adhere more affirmably than the absence of mucin. The maximum detachment force (MDF), measured as adhesion, was determined for the trimethyl chitosan mini-pellet formulation and the chitosan mini-pellet formulation. The trimethyl chitosan mini-pellet formulation achieved greater
15 maximum attachment force than chitosan. The maximum detachment force was reduced ~10 fold and the work of adhesion was reduced ~100 fold when the 0.3% mucin solution was not present.

The mucoadhesive property of TMC:Cl has been compared with many other mucoadhesive polymers, such as pectinate, and has often demonstrated significant mucoadhesive properties but sometimes failing
20 to be equivalent with known mucoadhesive polymers (Hagesaether et al., 2009). This has been attributed to overhydration of the TMC:Cl which causes a significant reduction in the mucoadhesive properties of the polymer (Atyabi et al., 2007). The Eudragit[®] spray coating that was utilized for the pharmaceutical dosage form according to the invention was incorporated to, amongst other things, reduce the overhydration of TMC:Cl and to target the mini-pellet formulation for the jejunum-ileum environment of
25 the small intestine. The jejunum-ileum environment of the small intestine is the best site for TMC:Cl mediated peptide API absorption due to the reduced integrity of tight junctions and the presence of a mucus layer (Markov et al., 2010; Kotzé et al., 1999). The increased positive charge that exists within trimethyl chitosan, with respect to chitosan, may assist in enhanced dipole-dipole interactions between these molecules. This indicates that the ability of TMC:Cl to facilitate drug delivery applications, since, if
30 mucin is present within the site of delivery, the ability of TMC:Cl to interact with tight junctions would be greatly increased and the maintained close proximal association with the intestinal wall would be positively impacted.

The dipole-dipole interactions allows trimethyl chitosan to establish stabilized interactions elements in the tight junction complex which reduces the affinity of these elements interacting with each other, thus, permitting the tight junction to reversibly open. Trimethyl chitosan does not enter the tight junction as the polymer chain is too long and the peptide therapeutic is still required to diffuse through the tight junction.

- 5 If trimethyl chitosan was not present, the tight junctions would retain integrity and a pharmaceutically achievable concentration of a peptide therapeutic would not be achievable (i.e. the protein and/or peptide API would not transverse the epidermis of the small intestine and thus trimethyl chitosan facilitates paracellular transport).

10 Stimuli responsive hydrogel swellable polymer body

- The attenuated total reflectance Fourier transform infra-red (ATR-FTIR) analysis determined that the free radical polymerization of acrylamide and methacrylic acid was successful by incorporation of MBA within the hydrogel structure. Additionally, the absorbance intensity of characteristic functional groups within the hydrogel formulations may be reduced because these functional groups are participating in the crosslinking network structure. A peak occurred at 1648 cm^{-1} . The freshly synthesised AAm-MAA hydrogel had peaks at 1655 and 1453 cm^{-1} which was similar to the dried AAm-MAA hydrogel that had peaks at 1648 and 1444 cm^{-1} . The peak located at 1648 cm^{-1} was determined to occur due to an amide-I band of the amide group of acrylamide (Nakason et al., 2010). Wavenumber peaks present in MBA (2769 cm^{-1} and 1072 cm^{-1}) were present in the AAm-MAA hydrogel swellable polymer body at 2763 cm^{-1} and 1071 cm^{-1} . The characteristic wavenumber peak of methylacrylic acid at 1425 cm^{-1} was lost within the polymerized hydrogel and a new peak occurred at 1425 cm^{-1} . Wavenumber peaks that were common between the polymerized hydrogel and acrylamide were located at 1049 cm^{-1} , respectively. This peak indicates that the AAm-MAA hydrogel may have C-O-C stretching vibrations (Dadsetan et al., 2010).
- 25 (This is not shown in the Figures).

- The ability of the hydrogel swellable polymer body to swell within a solution has been attributed to the effective crosslinking that exists between the polymerized monomers within a hydrogel matrix (Hwang et al., 2010). The concentration of pH sensitive monomers in the presence of constant crosslinking agent (i.e. MBA) concentration also has an important influence on the ability of a hydrogel to swell within a solvent. This was evident in the gel fraction percent determination whereby, even though a high concentration of methylacrylic acid was present, the ability of the crosslinker to induce polymerization was limited in comparison to acrylamide. Millipore® water was utilized to assess the swelling potential of a particular hydrogel formulation and compare this ability to that within a dissolution fluid. Millipore®
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water allows the hydrogel swellable polymer body formulation to swell unimpeded by a significant reduction in metal ion concentration and relatively neutral pH characteristics. A scanning electron microscope (SEM) image of the crosslinked AAm-MAA hydrogel swellable polymer body exposed to different media is shown in Figure 14.

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Gravimetric swelling analysis of the AAm-MAA hydrogel swellable polymer body, utilizing different mass concentrations, was conducted in United States Pharmacopeia simulated dissolution fluids, biorelevant dissolution fluids and Millipore® water. The swelling ability of the hydrogel swellable polymer body was adjustable with the inclusion of altered monomer mass concentration and could easily achieve over 2000% swelling within neutral environments but also swelled only up to 95% within acidic environments within a 24 hour period. The adjustable nature of the swelling therefore facilitated a customizable rate at which the API-loaded polymeric matrix mini-pellets could be ejected from the shell of the dosage form. A customizable ejection allows for the device to be optimized for a particular drug delivery application. The swelling ability of the hydrogel swellable polymer body to swell within different biorelevant dissolution fluids was also investigated. The swelling percent against time profile was determined using a regression fitting for the exponential to rise maximum (3 parameter model). Results from swelling experimental protocols for the hydrogel swellable polymer body are shown in Figures 6 and 7.

The area under the curve was determined using DDSolver add-in for Microsoft Excel 2007 for each swelling percent-time profile. The area under curve allows for direct comparison between the swelling profiles of the hydrogel swellable polymer body and it was noted that the biorelevant dissolution fluid did significantly impact the swelling potential of the AAm-MAA hydrogel swellable polymer body. A specific drug application that utilizes the pharmaceutical dosage form according to the invention should also characterize the selected customizable stimuli responsive hydrogel within biorelevant dissolution fluid. The swelling profiling the AAm-MAA hydrogel was highly predictable and regression curve fitting could achieve extremely good fits ($R^2_{\text{adjusted}} \geq 0.98$).

The velocity at which a hydrogel swellable polymer body formulation can swell against a constant force is an indication of the physicommechanical strength of the hydrogel macrostructure under constant strain. This assessment was conducted on the AAm-MAA hydrogel to determine the predictable physicommechanical properties of the hydrogel formulation within a multitude of dissolution fluids but also within isolated porcine gastrointestinal fluids. The distance-time profile for the stimuli responsive

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hydrogel formulation that was achieved within each dissolution fluid was plotted within a scatter plot and a regression curve was fitted to each scatter.

The experimental protocols conducted demonstrated that the stimuli responsive hydrogel swellable polymer body can respond to a near neutral pH and exert a force against a compressing load. This has important implications because the hydrogel can act as a mechanism to physically displace the API-loaded polymeric matrix mini-pellets that are located within the shell at a desired pH and rate. The swelling of the AAm-MAA hydrogel had predictable swelling velocity within a dissolution fluid (USP dissolution fluid, biorelevant dissolution fluid or isolated porcine gastrointestinal fluid) and a response could be customizable with the adjustment of monomer mass concentrations.

Analysis of the manufactured Avicel®-EDTA-mPEG second polymeric body

A particle size analysis was employed since a suggested improvement of the dissolution behaviour of poorly soluble active pharmaceutical ingredient (API) is facilitated when an API is placed within a solid dispersion which is partly attributed to a reduction in API particle size (Lloyd et al., 1997; Qi et al., 2008; Andrews et al., 2010). The Polydispersion Index (PDI) of the unfiltered EDTA, 0.22 µm injection-filtered EDTA, and the above described Avicel®-EDTA-mPEG second polymeric body compressed dispersion powder was determined in triplicate. The PDI of unfiltered EDTA, 0.22 µm injection filtered EDTA, and the Avicel®-EDTA-mPEG second polymeric body was determined to be 0.351 (SD, 0.012), 0.212 (SD, 0.037) and 0.4 (SD, 0.023) respectively. Therefore, incorporating EDTA within mPEG 2000 in the second polymeric body will enable the metal chelator the ability to infiltrate the mucus layer faster and chelate divalent ions in a shorter time frame. The faster the ionic load is reduced, the less protein and/or peptide API will be lost due to pre-systemic degradation by peptidase enzymes.

The differential scanning calorimetry (DSC) profiles of the second polymeric body formulations indicate that EDTA and mPEG formed a physical melt dispersion as the melting points for both compounds did not significantly change. The heating rate of 2°C/min generally obtained the highest heat of fusion and the slower heating rate causes the sample to undergo the process of protracted melting. Interestingly, the heat of fusion process can be adjusted by altering the mass concentration of EDTA and mPEG. The onset of melting or crystallization temperature for remained relatively constant when the EDTA and mPEG components concentrations are adjusted. Additionally, the onset of melting or crystallization temperature did not change significantly when Avicel® was included. Similarly, the peak melting or crystallization temperature remained relatively unchanged even with the addition of Avicel®.

The melting point of mPEG within these formulations was ~50°C which is above average room temperature and distribution of EDTA did not affect the heat capacity of the compound. This allows for EDTA to be released from the melt dispersion in the most potent form. In addition, Avicel® did not alter the thermal heat capacity of EDTA or mPEG. (This is not shown in the Figures).

The matrix hardness of a substance is determined at a point of indentation that stresses the local intermolecular bond strength which exists between the powdered granules of the pellet by measuring the amount of force per millimetre required to indent the surface of the pellet. The greater the force required to cause an indentation within the pellet surface, the greater the bond strength between the powder granules (Ellison et al., 2008). The greater the hardness, the greater the amount of energy that is required to break these bonds and revert a pellet back to a powder form that releases a drug (Ellison et al., 2008). The matrix resilience is the ability of a substance to deform elastically but regain form when the compressing load is removed. Within a pellet, the granules form cold welded interfacing surfaces that have voids within the matrix of the pellet structure during the compression process within the tablet press (van der Voort Maarschalk et al., 1996).

The presence of Avicel® reduced matrix resilience of the second polymeric body mini-pellets because the void space within the macrostructure of the mini-pellet was reduced and further compression resulted in higher Avicel® filling these void spaces to a higher degree. The physical increase in matrix hardness and reduction in matrix resilience is due to the reduced ability of the intermolecular bonds to stretch elastically into void space when a compression load is applied and then assume the original bond orientation because physical matter prevents this freedom of movement (Craig, 2002). The pellet structure internalizes the deformation energy by effectively distributing the absorbed energy throughout the structure and then dissipates the energy out of the pellet structure over time.

The total disintegration time is the required time for the second polymeric body pellet to lose bulk structure and the powder components which make up the pellet to become solvated within a fluid. In order for a pellet to dissolve, a solvent is needed to eliminate the strength of interfacing bonds progressively at a localized level through a mechanism of a migrating pellet surface border which moves towards the central point of the pellet. This may seem to be a purely physical process whereby reduced void volume automatically increases the time required at the localized level to dissolve a pellet but this process is also highly dependent on the chemical nature of the intermolecular bond strength that forms at interfacing powder particles. If the electrostatic energy which maintains the intermolecular bonds is weak

during the solvent attack on these bonds, even though there are a great number of these bonds present, the pellet would dissolve rapidly. This is due to more ineffective void elimination within the second polymeric body pellet structure and the increase in surface area of the pellet.

5 The primary disintegration rate is the breakdown of the second polymeric body mini-pellet into granules per minute. The primary disintegration rate was determined to be the fastest when high equal mass concentrations of EDTA and mPEG were utilized even though the bulk volume was the greatest whereas the primary disintegration rate was the slowest in lower amount of mPEG was present. This could be due to a combination of two factors: increased surface area allows for greater localized attack of the solvent
10 on the intermolecular bonds between particle surfaces that was formed during the cold welding process of pellet manufacture. The presence of EDTA within mPEG induces faster primary disintegration because once the strong intermolecular bond is broken, the macrostructure of the second polymeric body mini-pellet breaks down to granules very rapidly. Whereas Avicel® reduces the primary rate of disintegration because the compound effectively eliminated void spaces that resulted in reduced surface area which
15 solvent attack may occur at cold weld spots within the macrostructure of the in situ hot melt dispersion mini-pellet. In combination, these compounds could be used to customize the disintegration rate of in situ hot melt dispersion formulations in a predictable manner.

Results for matrix hardness studies for various ratios of EDTA-mPEG are shown in Figure 2.
20 Disintegration date of various EDTA-mPEG ratios is shown in Figure 3. Disintegration data various ratios of Avicel-EDTA-mPEG is shown in Figure 5.

Release studies from crosslinked AAm-MAA hydrogel swellable polymer body within dissolution fluids and isolated porcine gastrointestinal fluids

25 The API/drug release studies conducted in USP dissolution fluids, biorelevant dissolution fluids and isolated gastrointestinal tract fluids indicate that the API/drug release was, as expected, highly dependent on the physicochemical properties of the drug compound. The in vitro dissolution of ciprofloxacin, indomethacin, metronidazole, sulfamethazole, 4-aminosalicylic acid and zidovudine is presented within
30 the was highly predictable and increase with time. The dissolution of these small molecular drugs could be used to customize the pharmaceutical dosage form to allow for to co-administration of two drug compounds. The release of the small molecular weight drug can be adjusted with the concentration of stimuli hydrogel monomers and still achieve the physico-mechanical function of ejecting the polymer matrix mini-pellets at the target location within the gastrointestinal tract. This was seen in the ability of

the AAm-MAA hydrogel swellable polymer body to alter API/drug release in response to the physicochemical/physicomechanical properties of the dissolution fluid. The fractional release of small molecular weight drugs against time was assessed within DDSolver add-in for Microsoft Excel 2007 and the five dissolution models that achieved an R^{adjusted} value greater of 0.998 was utilized. This predictable release of small molecular weight drug from the stimuli responsive hydrogel is ideal personalized drug delivery applications whereby a patient suffers from comorbidities that are treated with a peptide and/or protein API and a small molecular weight therapeutic. Both treatments can be administered within a single entity in a fully customizable manner to achieve desired pharmacokinetic parameters for each drug compound.

The physicomechanical properties of a hydrogel drug delivery platform can be underestimated or overestimated within dissolution fluids, which can have a knock on effect on the accurate prediction of drug release. Understanding of the innate physicochemical properties of the drug compound and the physicomechanical properties of a hydrogel within a specific dissolution environment should not be underestimated. For instance, the hydrogel formulations achieved a far greater ability to gravimetrically swell within USP dissolution fluids but the velocity of the hydrogel swelling under a constant force favoured near neutral biorelevant dissolution fluids. The release of a drug compound may occur in an extremely extensive manner within FaSSGFc pH 6.5 in comparison to FaSSIFc pH 7.5 or vice versa. The pH difference between the two solutions is relatively small, but the concentration of bile salt and lipid compounds is vastly higher in FaSSIFc pH 7.5. The bile salt and lipid component within biorelevant dissolution fluids may reduce swelling, which limits the physical release of the drug compound or the bile salt and lipid component may accelerate drug solubility which increases the extent of drug release. The collective understanding of a drug dissolution profile from the perspective of the innate physicochemical and physicomechanical properties of the drug compound and the hydrogel drug delivery platform will facilitate more successful applications of these technologies in the oral gastrointestinal tract.

Results from in vitro dissolution of theophylline (an example API) from AAm-MMA hydrogel in different biological and/or simulated biological media is shown in Figure 8 and 9. Results from in vitro dissolution of Indomethacin (an example API) from AAm-MMA hydrogel in different biological and/or simulated biological media is shown in Figure 10 and 11. Results from in vitro dissolution of metronidazole (an example API) from AAm-MMA hydrogel in different biological and/or simulated biological media is shown in Figure 12 and 13.

In vitro-in vivo correlation of an orally administered peptide API from the pharmaceutical dosage form according to the invention

The in vitro dissolution of salmon calcitonin from the pharmaceutical dosage form according to the invention was conducted in USP dissolution fluid, biorelevant dissolution fluid and isolated gastrointestinal fluids of the porcine model. These results indicated that salmon calcitonin release within these fluids was altered by the physicochemical properties of the fluid. Furthermore these results indicate that the dosage form according to the invention was sensitive to the change of pH and therefore facilitates controlled and targeted release of the API/drug loaded matrix. This can be observed by the sudden increase in drug concentration once the device had been removed from the gastric environment and placed with an intestinal environment. The altered API/drug release profiles obtained within the in vitro dissolution indicates that the API/drug release may change once placed within the in vivo environment. This was examined by comparing the dissolution profiles obtained within each fluid as that obtained within the in vivo environment. It was found that the biorelevant media generally achieved a tighter in vitro-in vivo correlation than USP dissolution fluid. The isolated porcine gastrointestinal fluid achieved a reasonable performance but contrary to what was expected, did not achieve the tightest in vitro-in vivo correlation. The tightest in vitro-in vivo correlation for salmon calcitonin with the administered configuration was tightest within FaSSGF-FeSSIF V2 in vitro dissolution. This is observed in the close predicted of the AUClast and Cmax obtained within this dissolution fluid set with that observed in the plasma drug concentration-time profile of the orally administered dosage form according to the invention.

Passage through the gastro-intestinal tract (GIT)

The assembled preferred embodiment of the pharmaceutical dosage form is inserted into the oral cavity of a human or animal and swallowed. The coating protects the protein and/or peptide API from the acidic conditions of the stomach. The dosage form exits the stomach and passes through the duodenum, jejunum and ileum. During this time the increasing pH causes the coating and cap to dissolve. The biological media of the small intestine now enters the shell through the inlet causing the swellable polymer body to swell which facilitates displacement of both the second polymeric body and polymeric matrix out of the shell. The polymeric matrix is mucoadhesive and adheres to the wall of the small intestine and releases API as it degrades in the specific pH of the small intestine biological media. The permeation enhancers and metal chelators of the polymeric matrix and/or second polymer body prevent the API from being inactivated and/or denatured by enzymes. The shell continues to pass through the large intestine before

being excreted by the human or animal. Figure 20 further illustrates and/or exemplifies passage of the dosage form through the GIT.

While the invention has been described in detail with respect to specific embodiments and/or examples thereof, it will be appreciated that those skilled in the art, upon attaining an understanding of the foregoing may readily conceive of alterations to, variations of and equivalents to these embodiments. Accordingly, the scope of the present invention should be assessed as that of the appended claims and any equivalents thereto.

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CLAIMS:

1. A pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising:
 - 5 a shell defining therein an outlet;
 - a polymeric matrix having at least one API, the polymeric matrix received within the shell; and
 - a swellable polymer body located within the shell, wherein the swellable polymer body is pH responsive, such that in use, exposure of the body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn, facilitates displacement of the polymeric matrix through the outlet toward the target site for delivery of the API.
- 10 2. The pharmaceutical dosage form according to claim 1, wherein the shell comprises a substantially non-degradable, biologically inert, non-responsive material, preferably a non-toxic biologically inert, non-responsive material, such that in use, the shell does not substantially biodegrade upon passage through the gastrointestinal tract (GIT).
- 15 3. The pharmaceutical dosage form according to claim 2, wherein the shell comprises a natural and/or synthetic polymer.
- 20 4. The pharmaceutical dosage form according to claim 3, wherein the natural polymer is selected from the group of polysaccharide polymers consisting of: chitosan, pectin, gellan gum, xanthan gum, sodium alginate, celluloses such as sodium carboxymethylcellulose (CMC),
25 hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), hydroxymethylpropylmethylcellulose (HPMC), and dextrans.
5. The pharmaceutical dosage form according to claim 3, wherein the synthetic polymer is selected from the group consisting of: polyetheretherketone, high density polyethylene (HDPE), ultra high
30 molecular, weight polyethylene (UHMWPE), polytetrafluoroethylene, polymethmethacrylate, polydimethylsiloxane, and poly(sulphone).
6. The pharmaceutical dosage form according to any one of claims 1 to 5, wherein the shell defines an inlet at a region proximate the location of the swellable polymer body, such that in use, the

medium penetrates into the shell through the inlet to contact the swellable polymer body causing the swellable polymer body to swell, which in turn, facilitates the displacement of the polymeric matrix out of the shell to the target site.

- 5 7. The pharmaceutical dosage form according to any one of claims 1 to 5, wherein the polymeric matrix is a natural polymer and is biodegradable and responsive to at least one colonic enzyme selected from the group consisting of: β -glycosidases, pectinases, and polysaccharidases, the colonic enzymes, in use, causing digestion and/or chemical cleavage and/or degradation of the polymeric matrix such that the at least one API is released for delivery at the target site.
- 10 8. The pharmaceutical dosage form according to any one of claims 1 to 7, wherein the polymeric matrix is mucoadhesive, such that in use, the matrix adheres at the target site, preferably the target site is the wall of the small intestine of the human or animal body.
- 15 9. The pharmaceutical dosage form according to any one of claims 1 to 8, wherein the polymeric matrix is at least one polymer selected from the group consisting of: chitosan, trimethyl chitosan, trimethyl chitosan chloride (TMC:Cl), EDTA-g-chitosan, 2-mercaptoethylamine-g-chitosan, and polyacrylic acid-cysteine.
- 20 10. The pharmaceutical dosage form according to any one of claims 1 to 9, wherein the polymeric matrix further includes a permeation enhancer, such that in use, the permeation enhancer facilitates paracellular transport by causing disruption to the integrity of the target site, preferably the wall of the small intestine, allowing the at least one API to pass through the wall into systemic circulation.
- 25 11. The pharmaceutical dosage form according to any one of claims 1 to 10, wherein the polymeric matrix further includes a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of the API.
- 30 12. The pharmaceutical dosage form according to claim 11, wherein the metal chelator is ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl polyethylene glycol (EDTA-mPEG).

13. The pharmaceutical dosage form according to any one of claims 1 to 12, wherein the polymeric matrix further includes at least one pharmaceutical excipient, preferably wherein the excipient is a lubricant, further preferably wherein the lubricant is magnesium stearate.
- 5 14. The pharmaceutical dosage form according to any one of claims 1 to 13, wherein the polymeric matrix further includes a glidant, preferably wherein the glidant is amorphous fumed silica.
- 10 15. The pharmaceutical dosage form according to any one of claims 1 to 14, wherein the polymeric matrix is crosslinked by at least one of the following processes: microwave radiation, ultra violet radiation and chemical crosslinking, such that in use, crosslinking facilitates controlled release of the at least one API.
- 15 16. The pharmaceutical dosage form according to any one of claims 1 to 15, wherein the at least one API is a peptide and/or protein therapeutic selected from the following group: salmon calcitonin, eel calcitonin, chicken calcitonin, rat calcitonin, human calcitonin, porcine calcitonin or any gene-variant of calcitonin, parathyroid hormone, parathyroid hormone analogue PTH 1-31NH₂, parathyroid hormone analogue PTH 1-34NH₂, insulin of any gene variant, vasopressin, desmopressin, luteinizing hormone-releasing factor, erythropoietin, tissue plasminogen activators, human growth factor, adrenocorticotropin, various interleukins, and enkephalin.
- 20 17. The pharmaceutical dosage form according to any one of claims 1 to 15, wherein the at least one API is selected from the following group of classes of APIs: anti-inflammatories, immunosuppressives, antibiotics, antifungals, antivirals, antimalarials, antiretrovirals, antihypertensives, chemotherapeutics, diagnostic agents, probiotics and prebiotics.
- 25 18. The pharmaceutical dosage form according to any one of claims 1 to 17, wherein the swellable polymer body is a natural and/or synthetic polymer.
- 30 19. The pharmaceutical dosage form according to claim 18 wherein the swellable polymer body comprises a hydrogel, preferably the hydrogel comprises acrylamide (AAm), methacrylic acid (MAA), N-N'-methylenebisacrylamide (MBA) and Pluronic F-127.
20. The pharmaceutical dosage form according to claim 18 or 19, wherein the swellable polymer body further includes a permeation enhancer, such that in use, the permeation enhancer facilitates

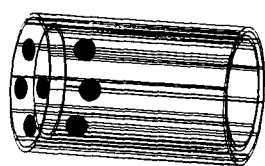
paracellular transport by causing disruption to the integrity of the wall of the target site, preferably the small intestine, allowing the at least one API to pass through the wall into systemic circulation.

- 5 21. The pharmaceutical dosage form according to any one of claims 18 to 20, wherein the swellable polymer body further includes a metal chelator, such that in use, the metal chelator chelates divalent metal ions located at the target site, preferably the wall of the small intestine, therein hindering pre-systemic enzymatic degradation of the API, preferably the metal chelator comprises ethylenediaminetetraacetic acid (EDTA) and/or ethylenediaminetetraacetic acid methyl
10 polyethylene glycol (EDTA-mPEG).
22. The pharmaceutical dosage form according to any one of claims 18 to 21, wherein the swellable polymer body further includes at least one pharmaceutical excipient.
- 15 23. The pharmaceutical dosage form according to any one of claims 18 to 22, wherein the swellable polymer body further includes at least one API.
24. The pharmaceutical dosage form according to any one of claims 18 to 23, wherein the swellable polymer body is crosslinked by at least one of the following processes: microwave radiation, ultra
20 violet radiation and chemical crosslinking.
25. The pharmaceutical dosage form according to any one of claims 1 to 24, wherein the pharmaceutical dosage form further comprises a coating which at least partially envelopes the shell, such that in use, the stability and structural integrity of the coating increases with a
25 corresponding decrease in pH such that the coating is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).
- 30 26. The pharmaceutical dosage form according to any one of claims 1 to 25, wherein the pharmaceutical dosage form further comprises a cap closing the outlet of the shell, such that in use, the stability and structural integrity of the cap increases with a corresponding decrease in pH such that the cap is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

27. The pharmaceutical dosage form according to claim 26, wherein the cap further includes a permeation enhancer and/or a metal chelator.
28. The pharmaceutical dosage form according to any one of claims 1 to 27, wherein the pharmaceutical dosage form further comprises a spacer to space apart the swellable polymer body and the polymeric matrix, the spacer being located within the shell.
29. The pharmaceutical dosage form according to any one of claims 1 to 28, wherein the pharmaceutical dosage form further comprises a second polymeric body located proximal the outlet inside the shell, such that in use, the second polymeric body is released from the shell at a target site prior to the polymeric matrix.
30. The pharmaceutical dosage form according to claim 29, wherein the second polymeric body further includes a permeation enhancer and/or a metal chelator.
31. A pharmaceutical dosage form for delivery of, at a target site in a human or animal body, an active pharmaceutical ingredient (API), said pharmaceutical dosage form comprising:
an elongate cylindrical shell defining an outlet and an inlet at opposing first and second end regions of the shell;
a mucoadhesive polymeric matrix having at least one API, the polymeric matrix received within and in register with the shell; and
a swellable polymer body located proximal the second end region received within and in register with the shell, wherein the swellable polymer body is pH responsive, such that in use, exposure of the swellable polymer body to a medium of increasing pH causes an increase in swelling and an increase in volume of the swellable polymer body, which in turn facilitates displacement of the polymeric matrix through the outlet toward the target site for delivery of the API.
32. The pharmaceutical dosage form according to claim 31, further comprising a spacer to space apart the swellable polymer body and the polymeric matrix.
33. The pharmaceutical dosage form according to claim 31 or 32, further comprising a pH responsive polymer cap closing the outlet of the shell, wherein the stability and structural integrity of the cap increases with a corresponding decrease in pH such that the cap is not degraded in the acidic

conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).

- 5 34. The pharmaceutical dosage form according to any one of claims 31 to 33, further comprising an enteric polymer coating at least partially enveloping the shell, wherein the stability and structural integrity of the enteric coating increases with a corresponding decrease in pH such that the enteric coating is not degraded in the acidic conditions of the stomach, and is degraded in the neutral and/or alkaline conditions of the small intestine of the gastrointestinal tract (GIT).
- 10 35. The pharmaceutical dosage form according to claims 33 or 34, further comprising a second polymeric body located between the cap and the polymeric matrix, such that in use, the second polymeric body is released from the shell at the target site prior to the polymeric matrix.



Shell



Swellable
Polymer
body



Polymeric
matrix



Second
polymer
body



Cap

FIG 1

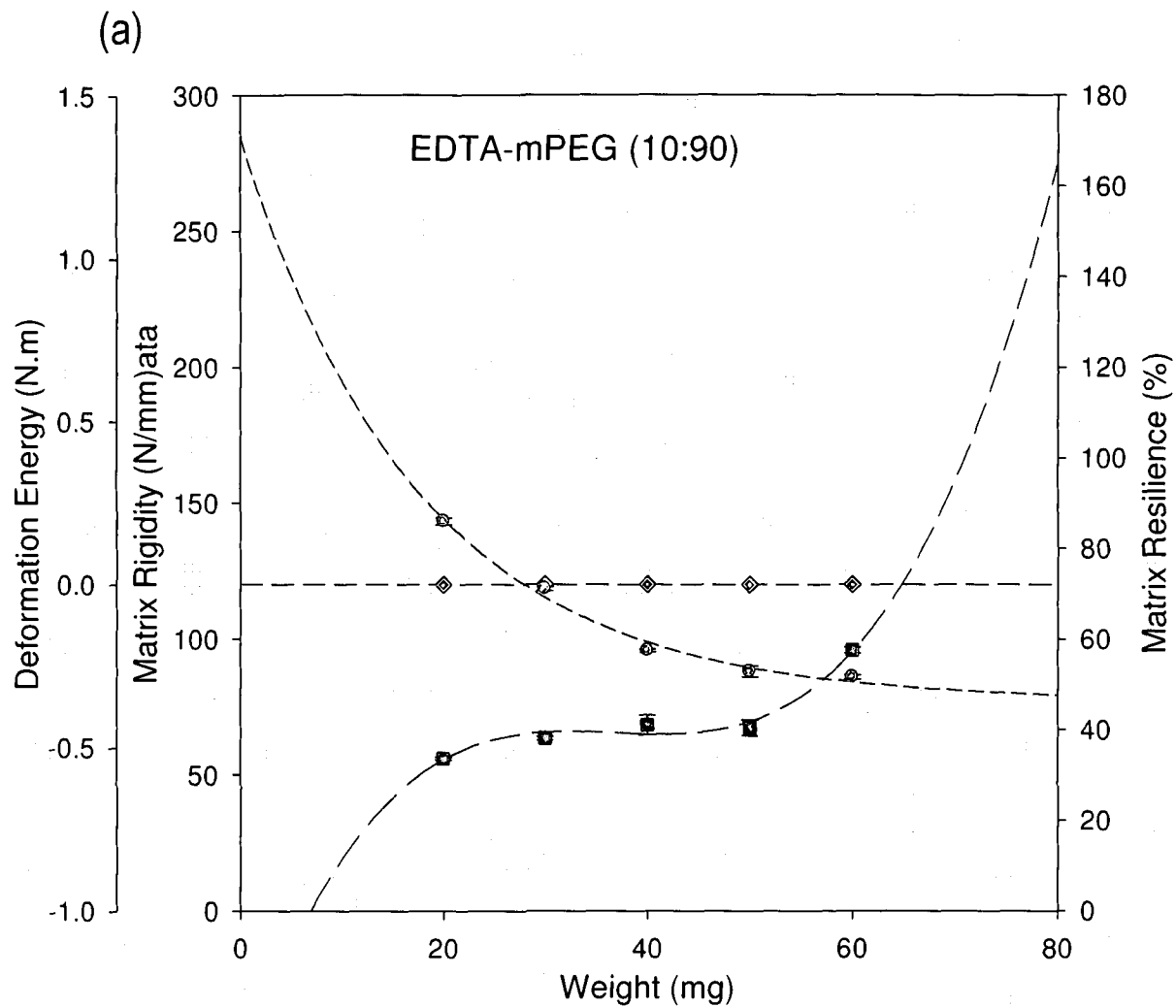


FIG 2a

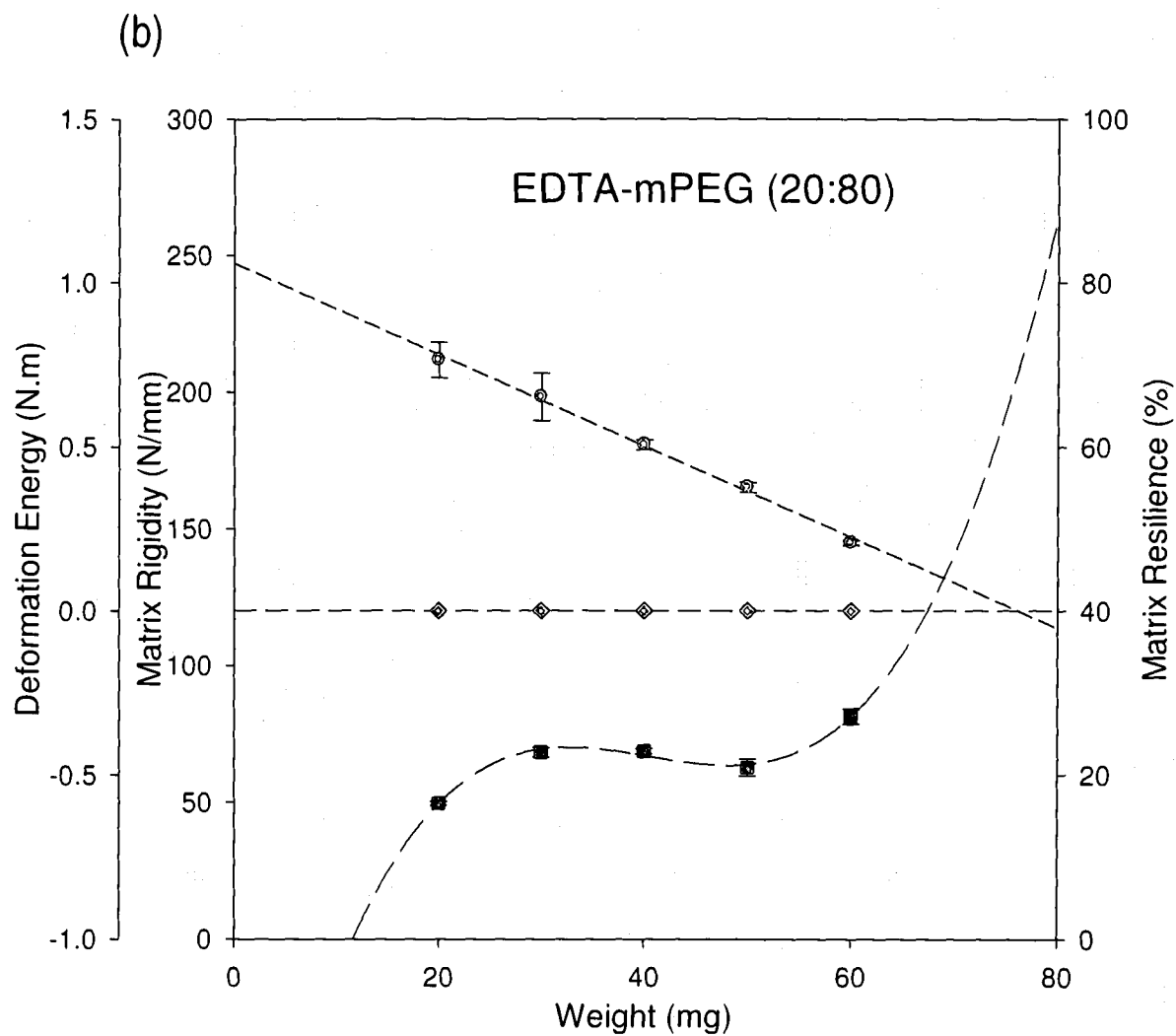


FIG 2b

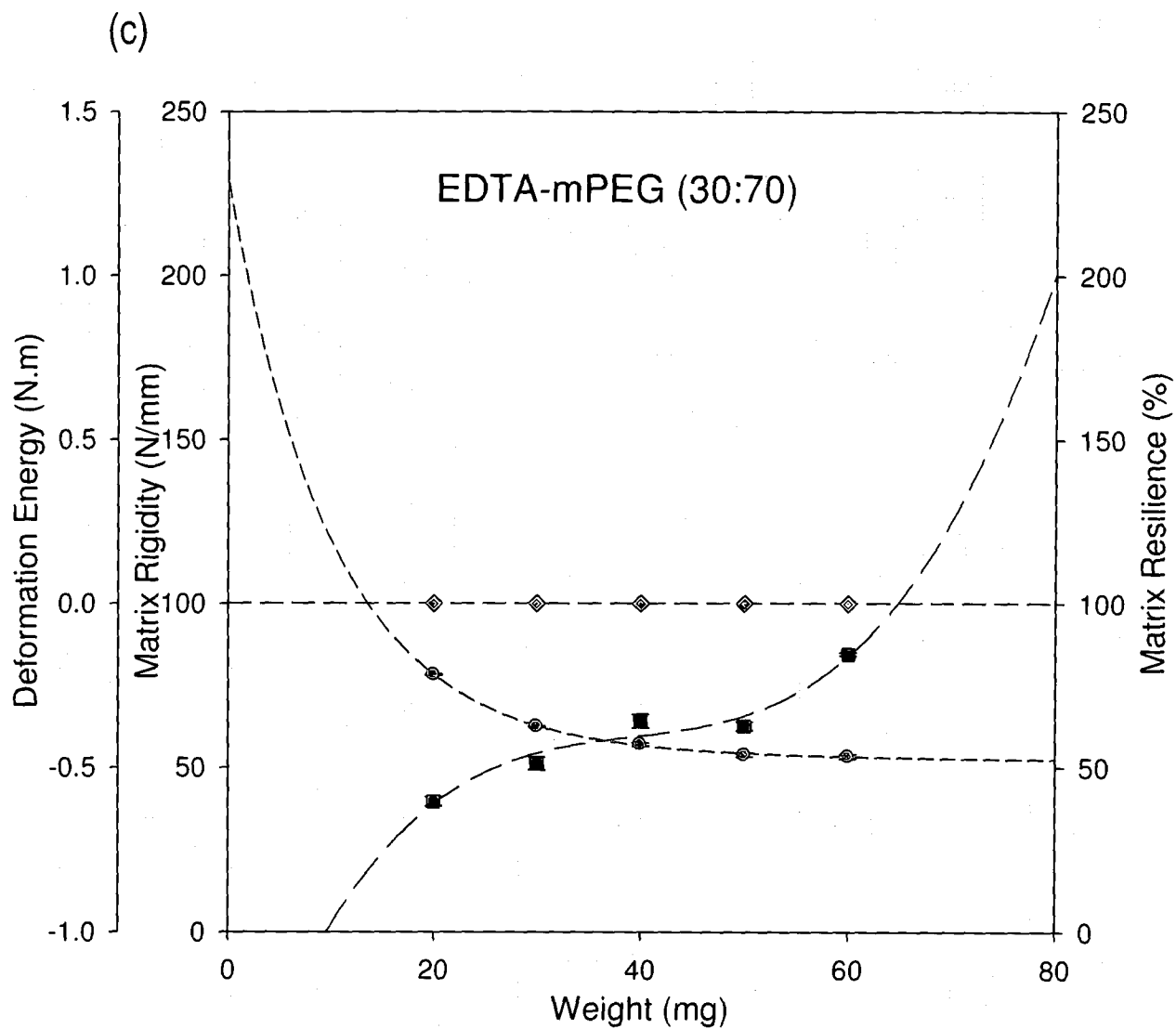


FIG 2c

(d)

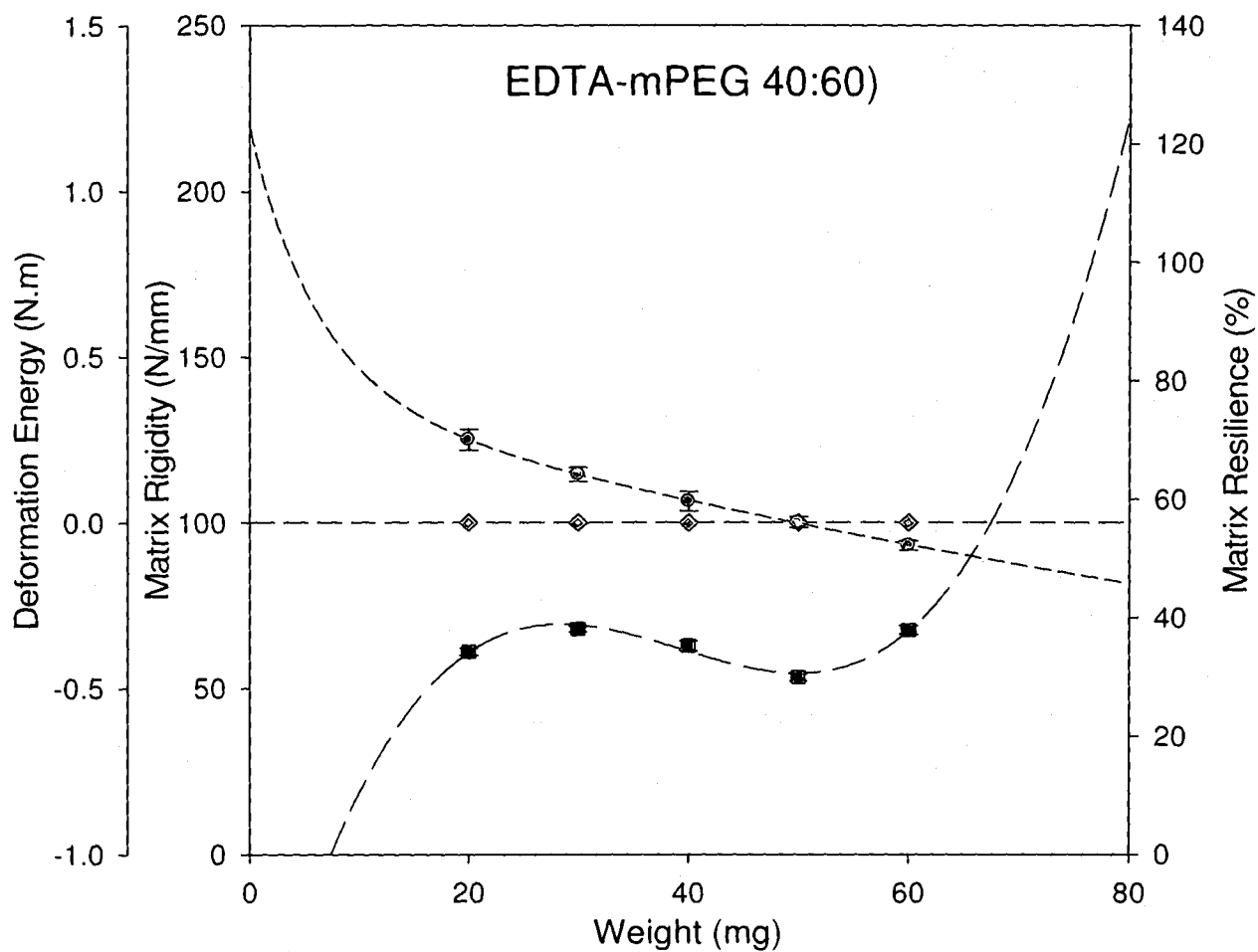


FIG 2d

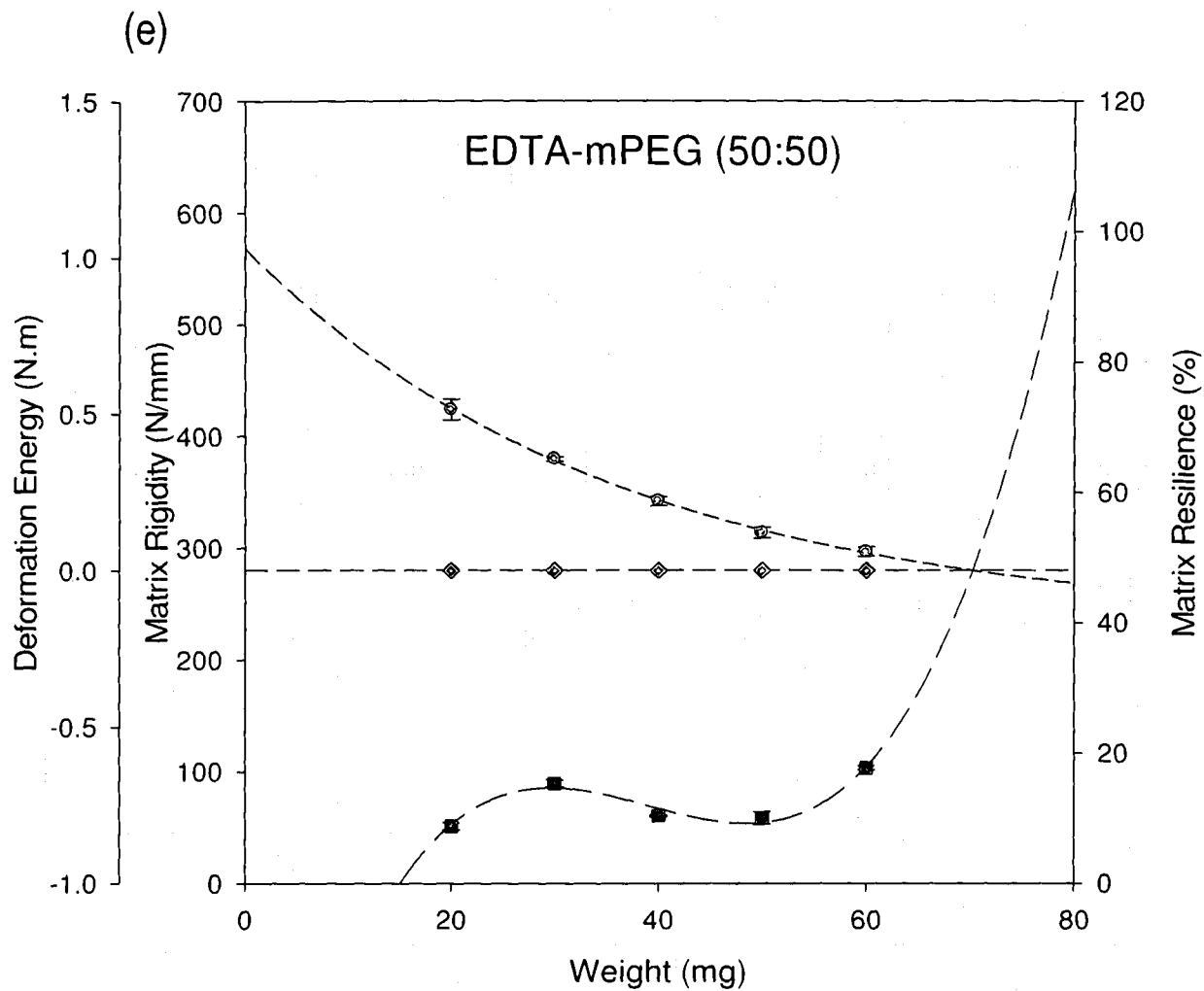


FIG 2e

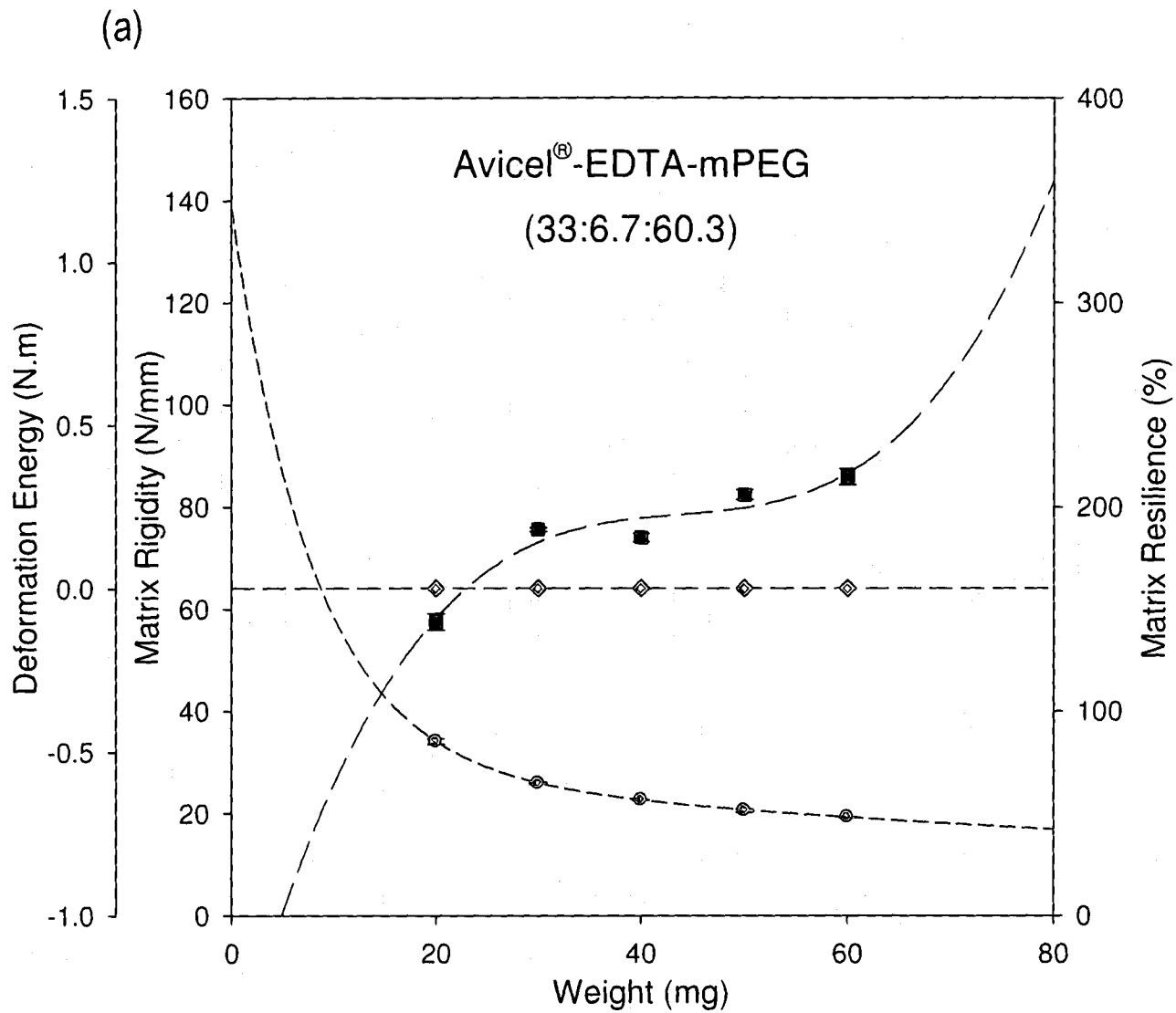


FIG 3a

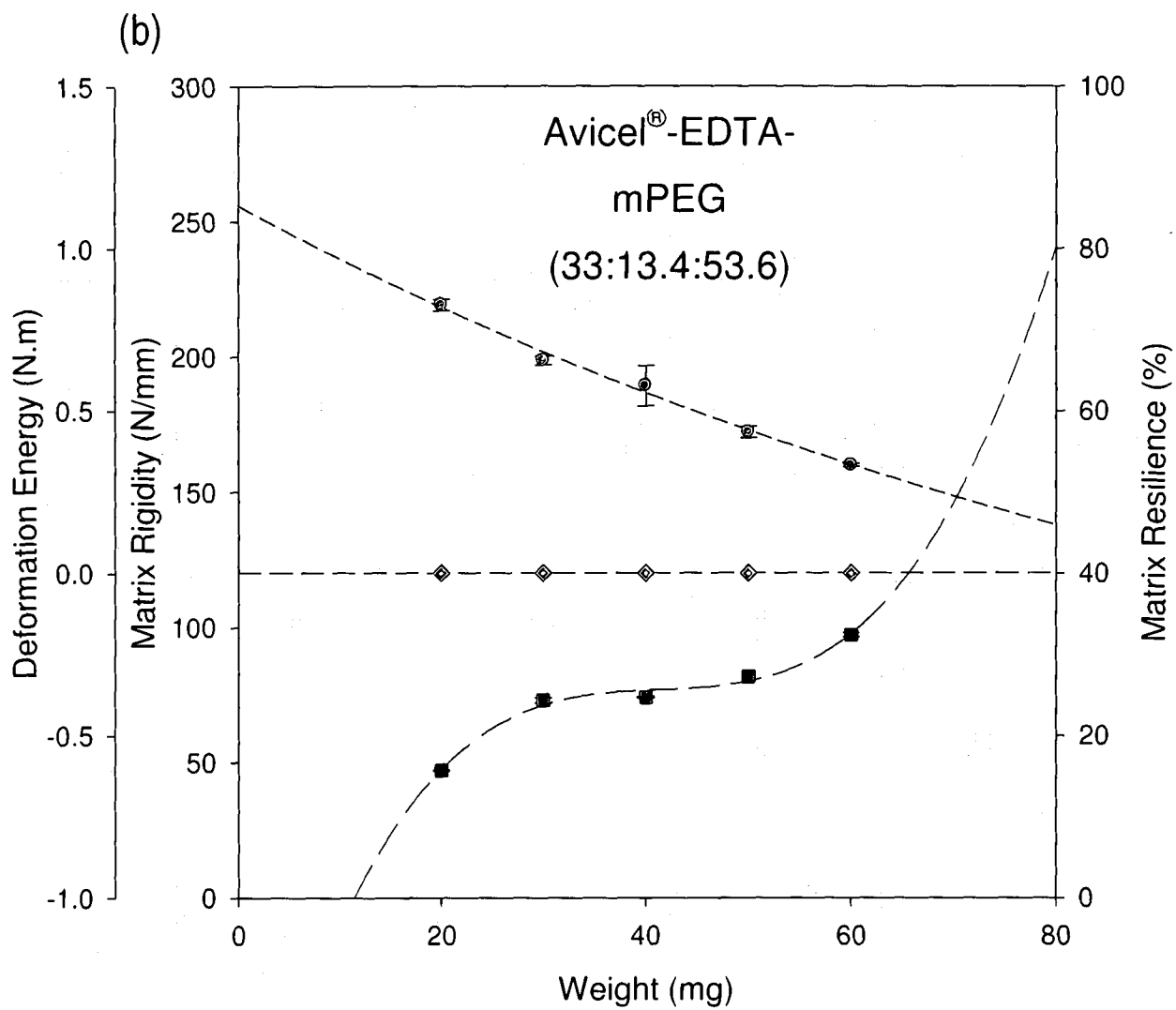


FIG 3b

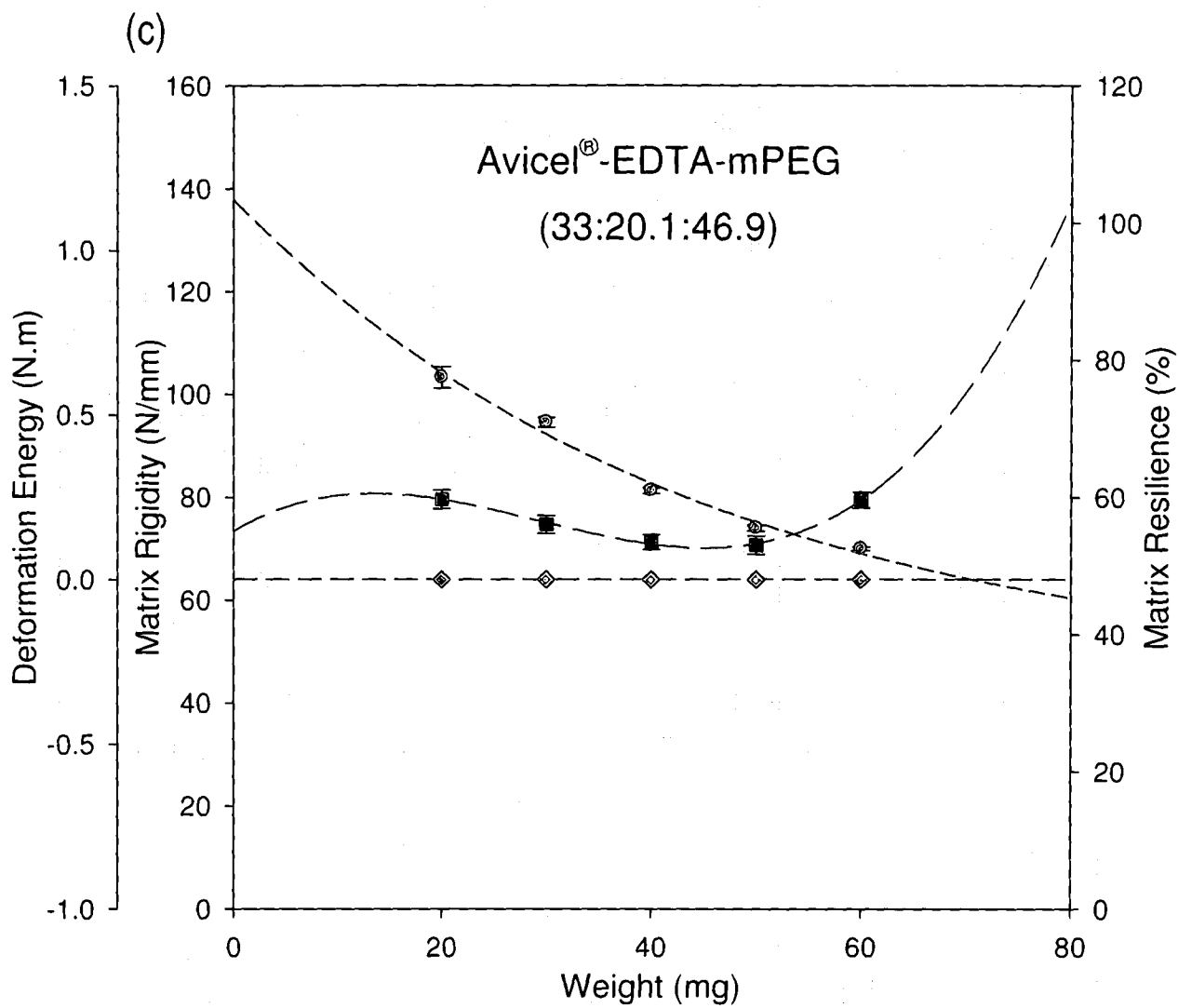


FIG 3c

(d)

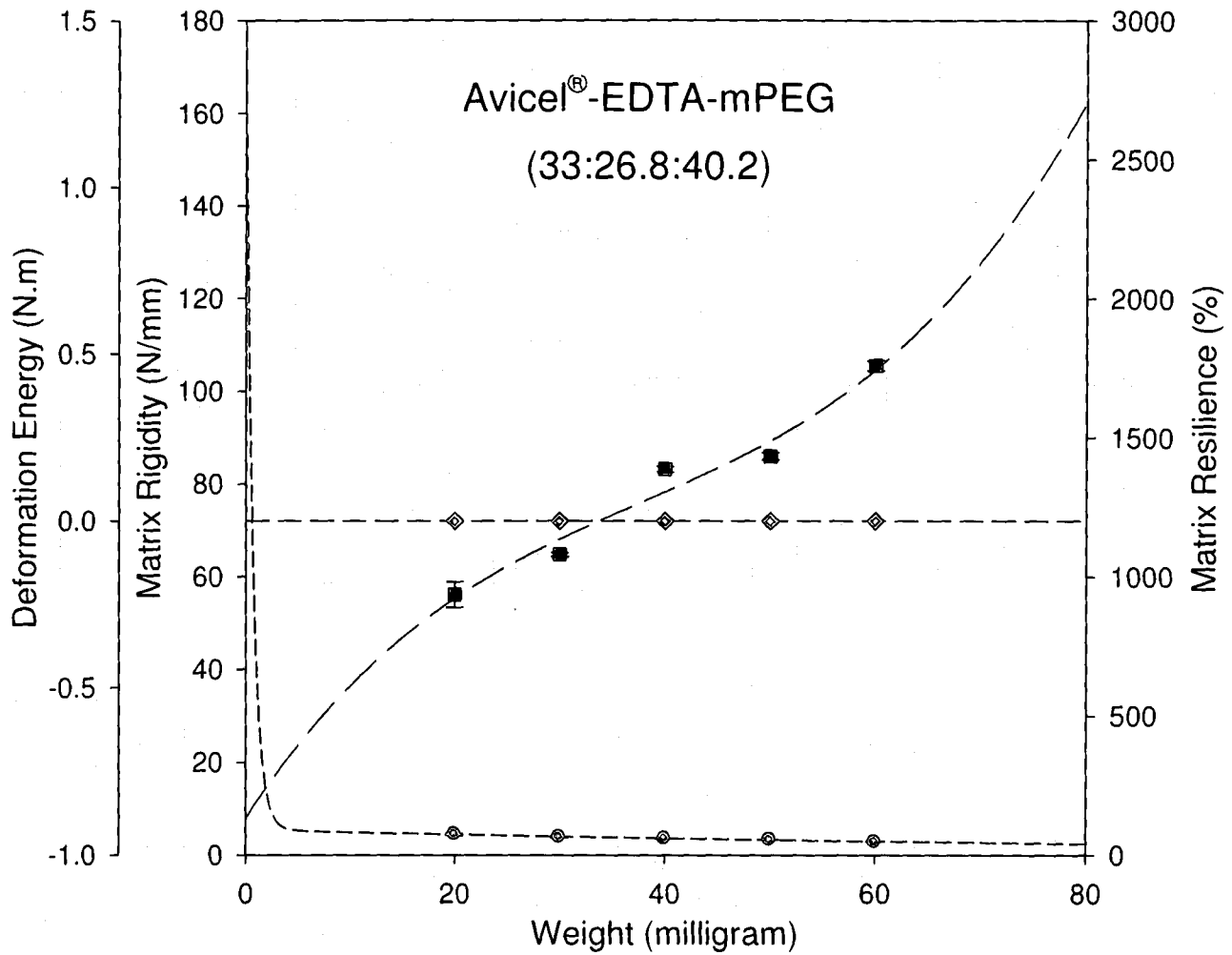


FIG 3d

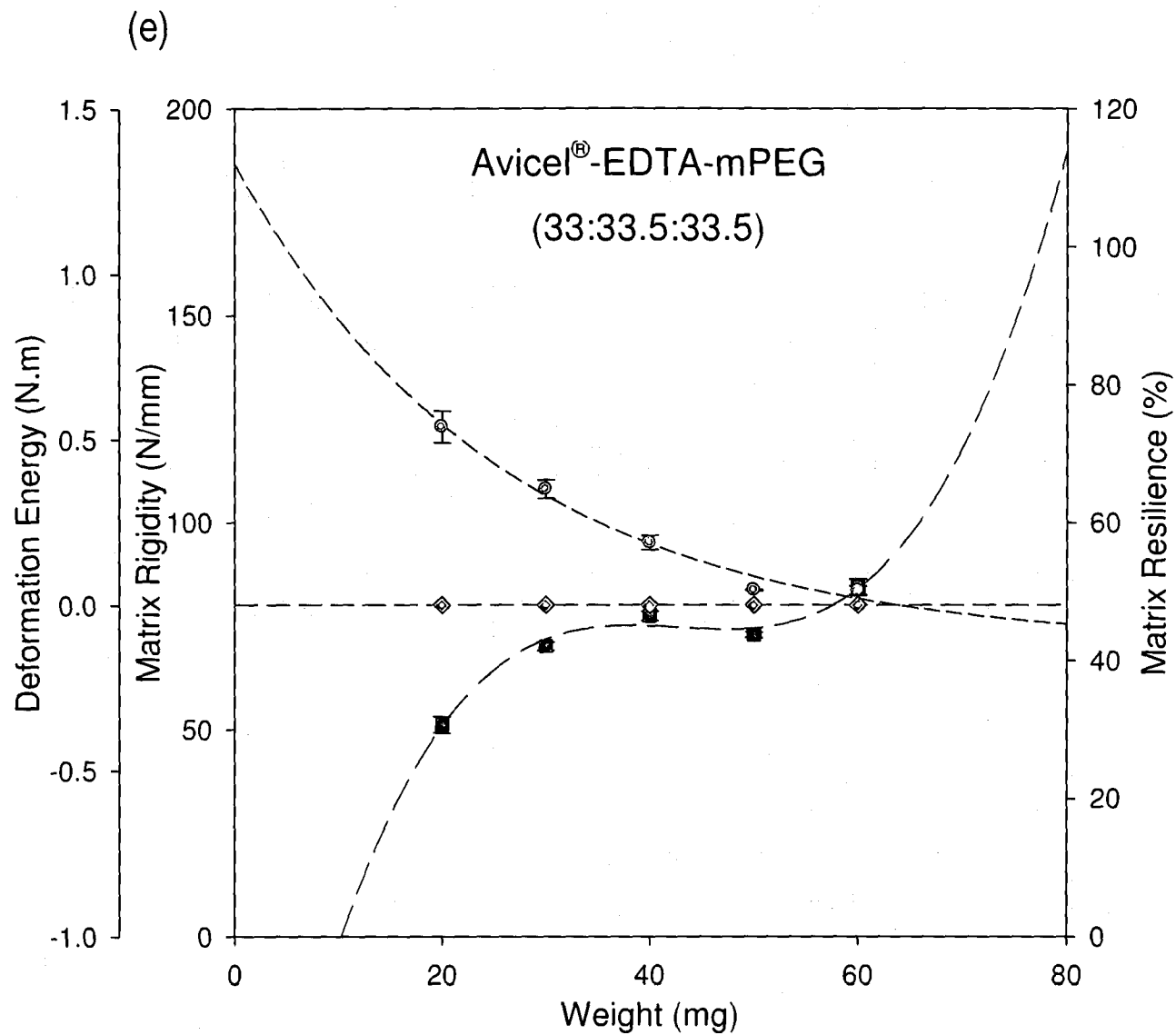


FIG 3e

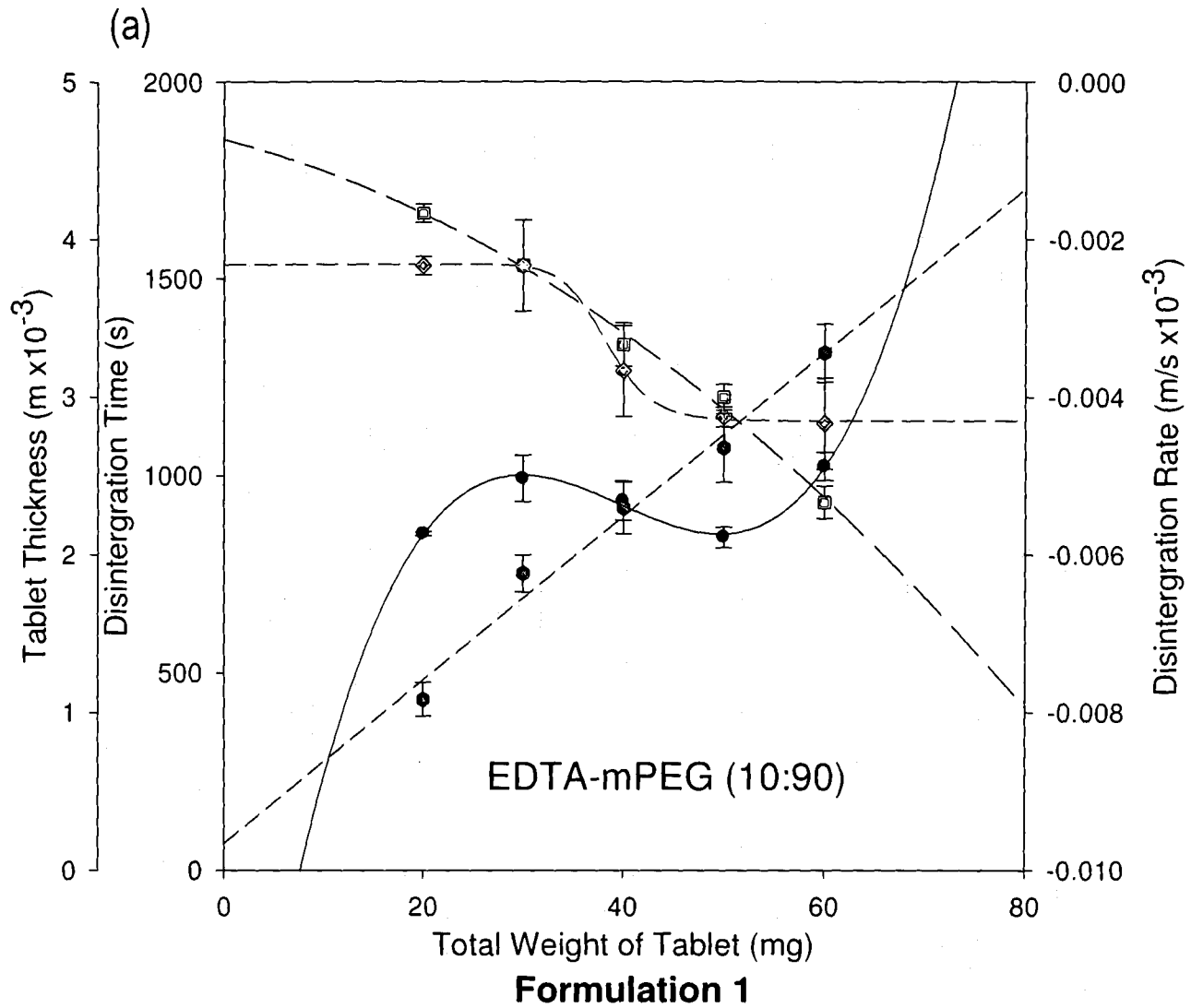


FIG 4a

(b)

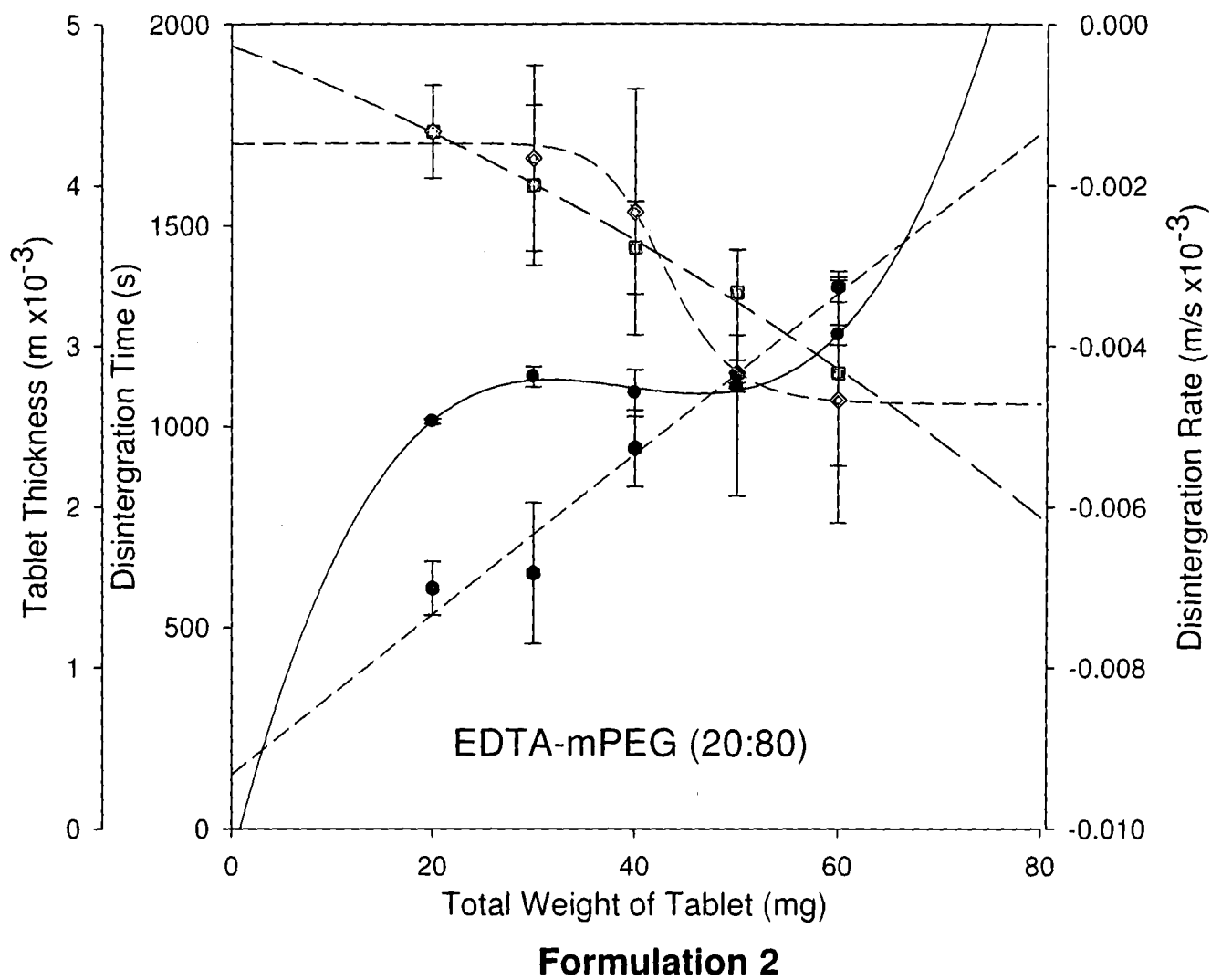


FIG 4b

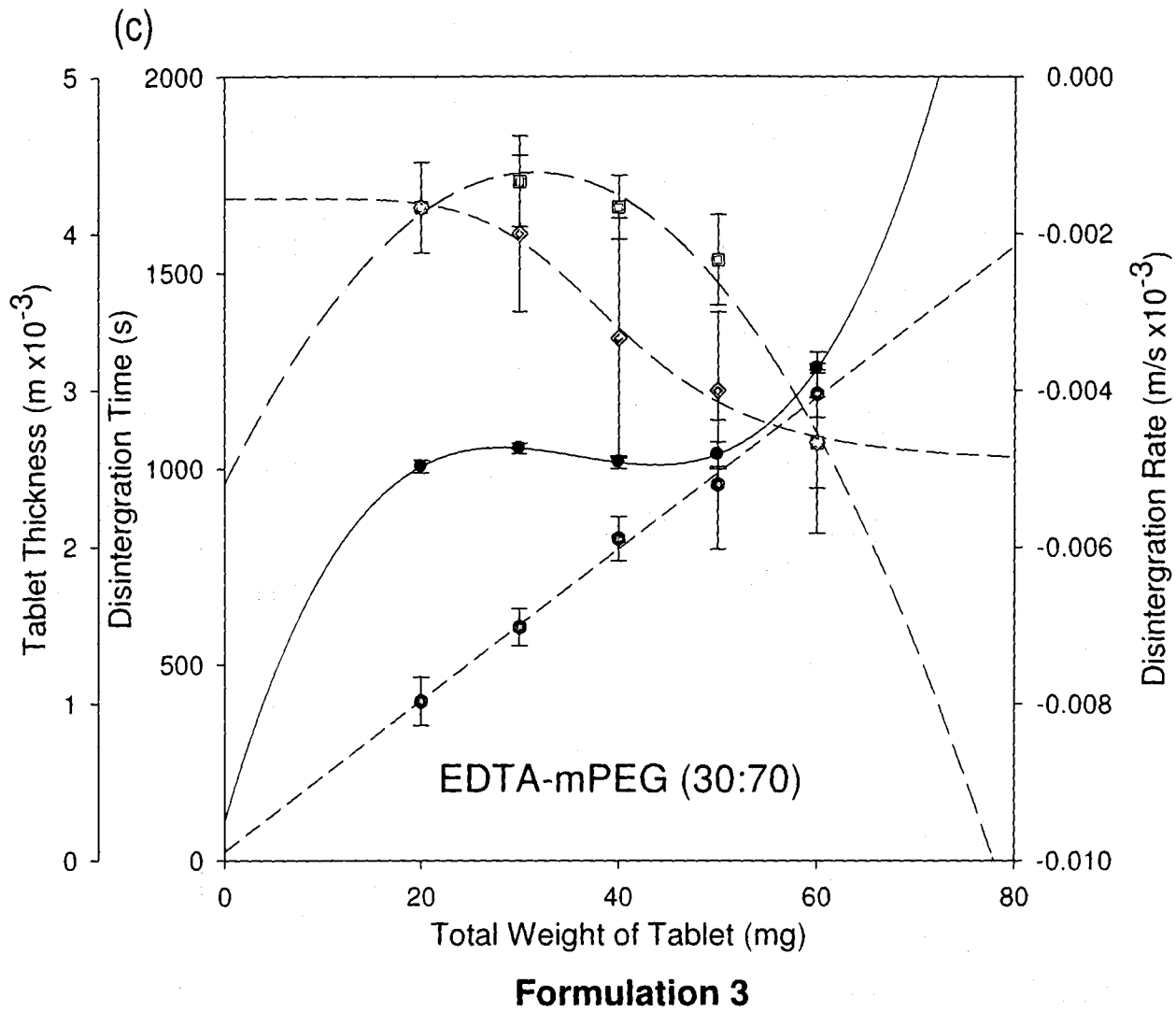


FIG 4c

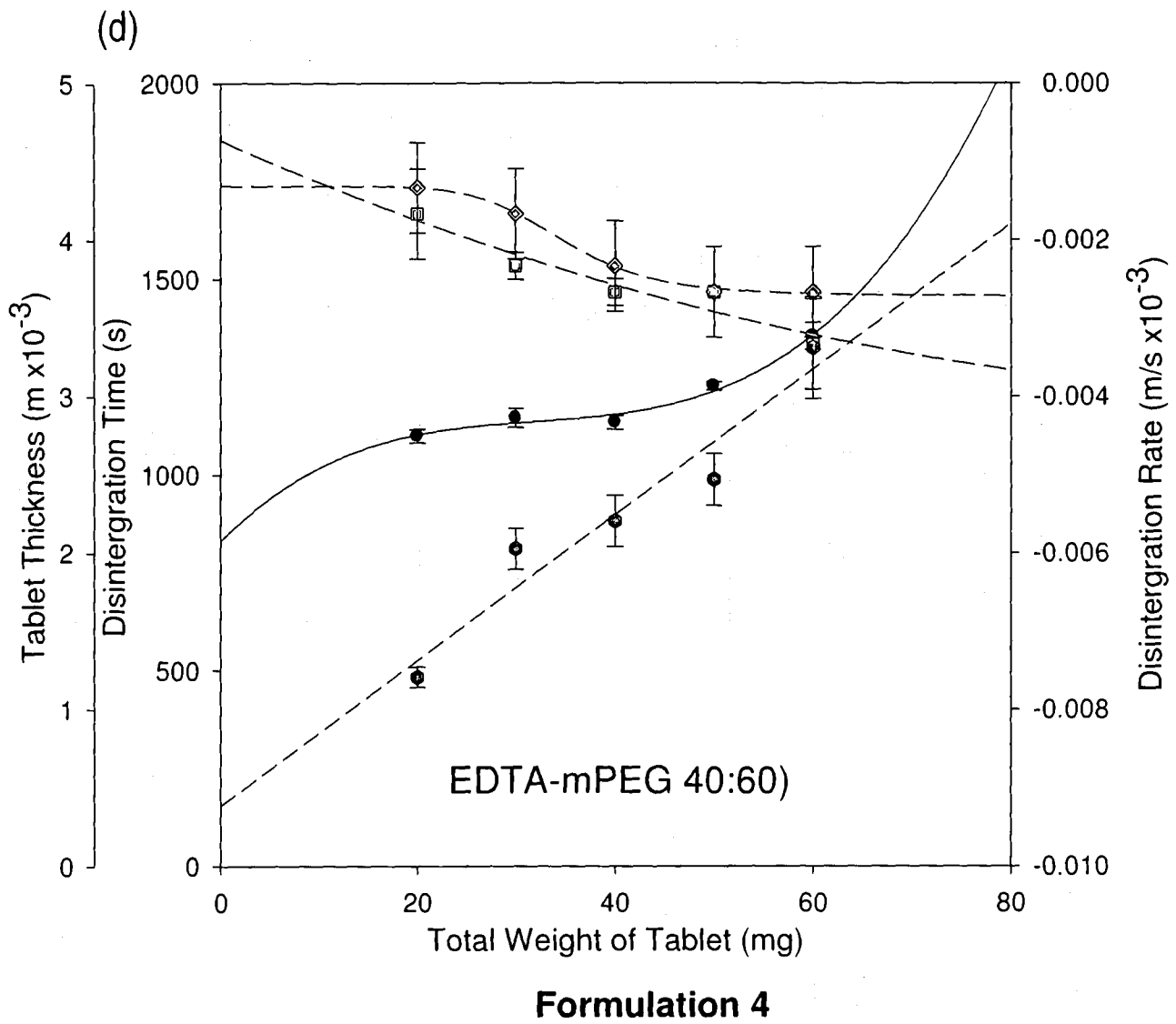


FIG 4d

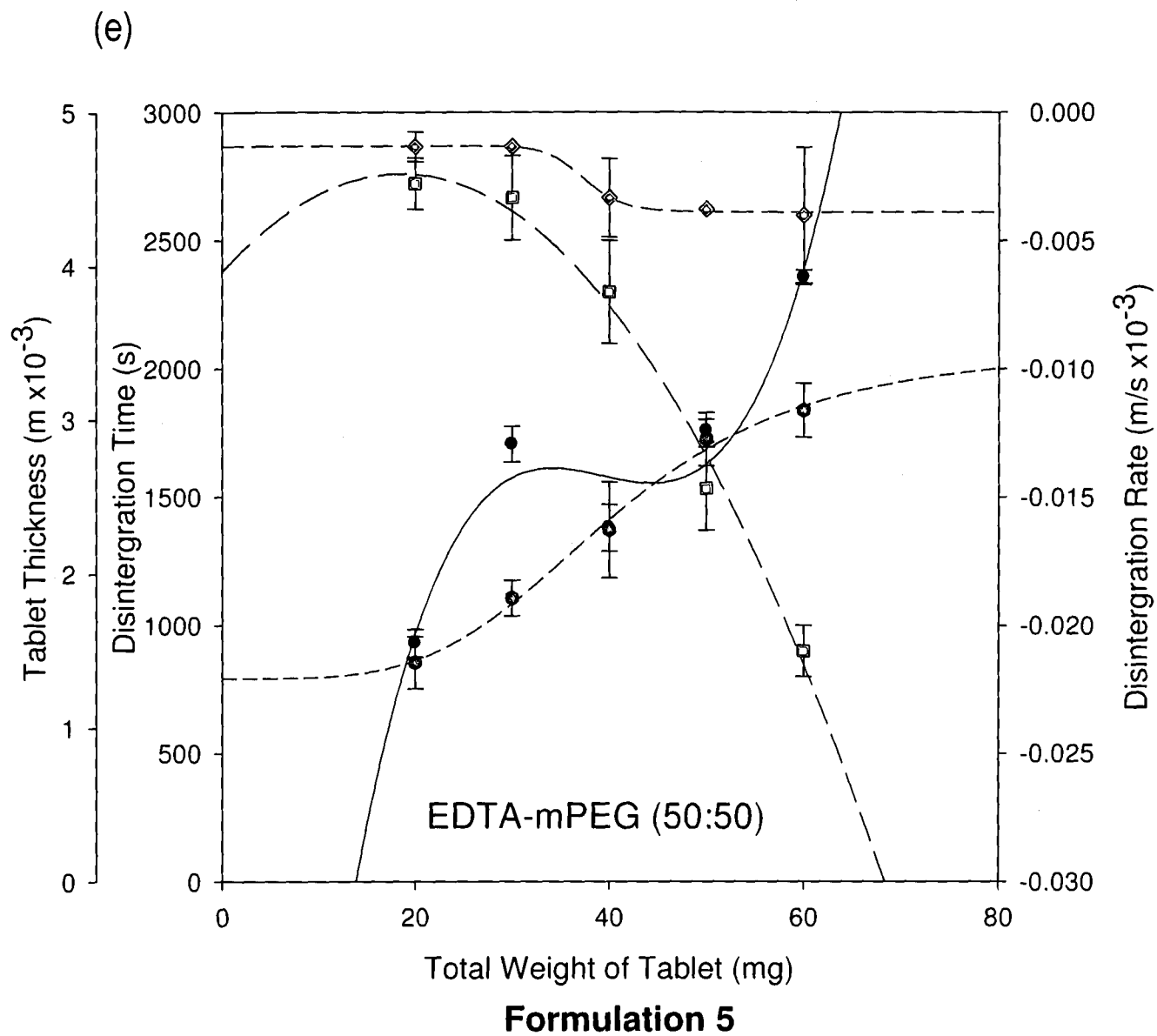


FIG 4e

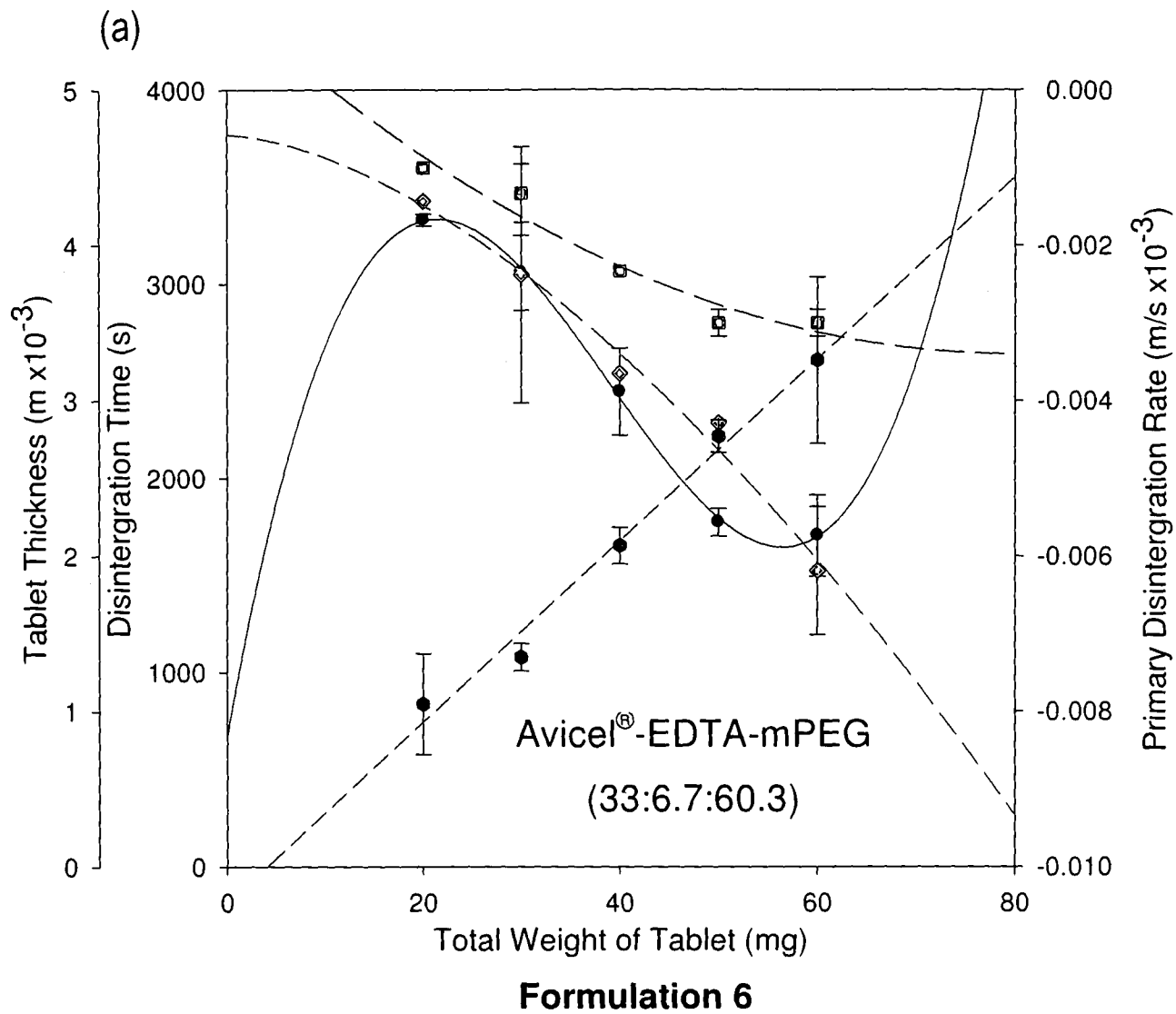


FIG 5a

(b)

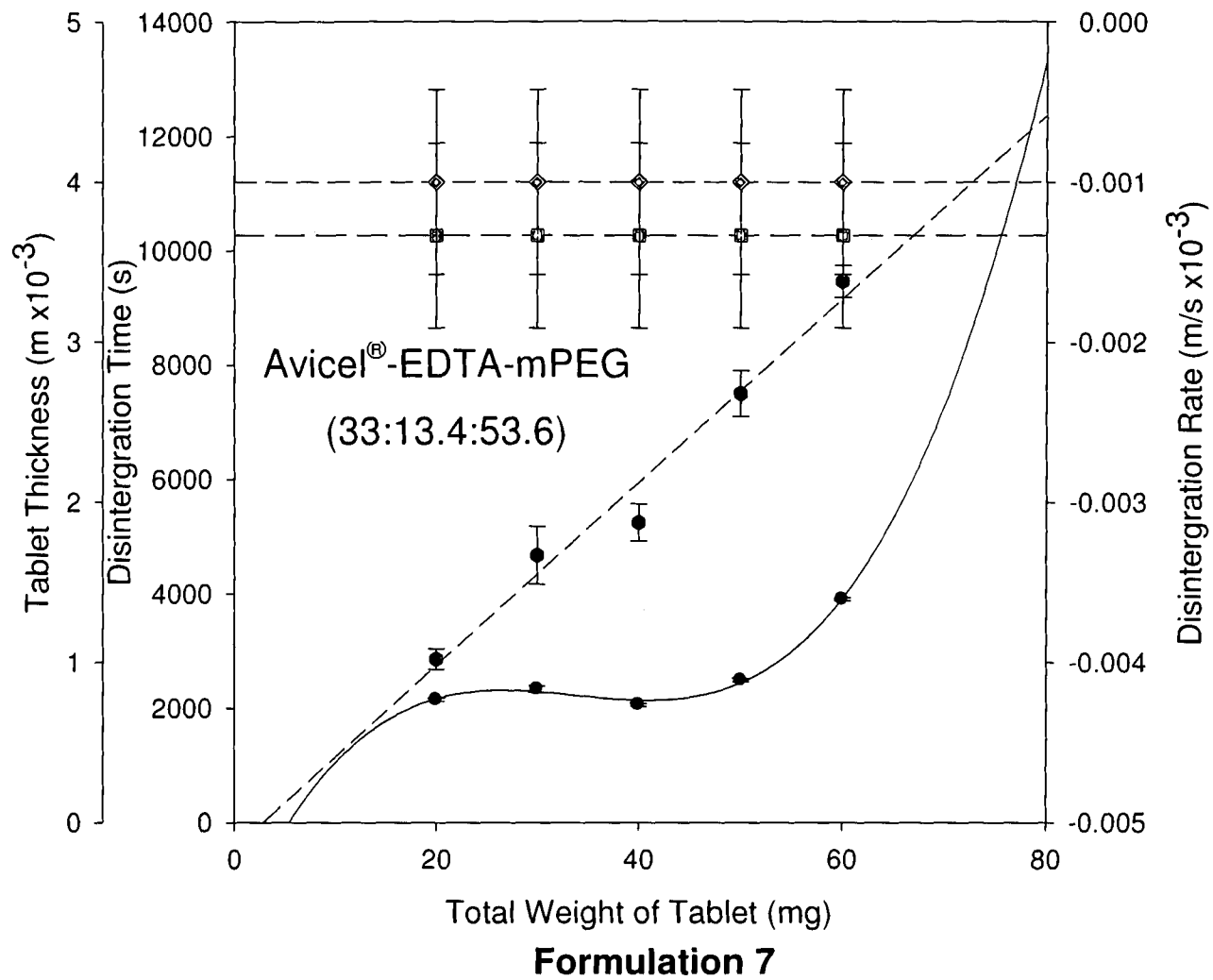
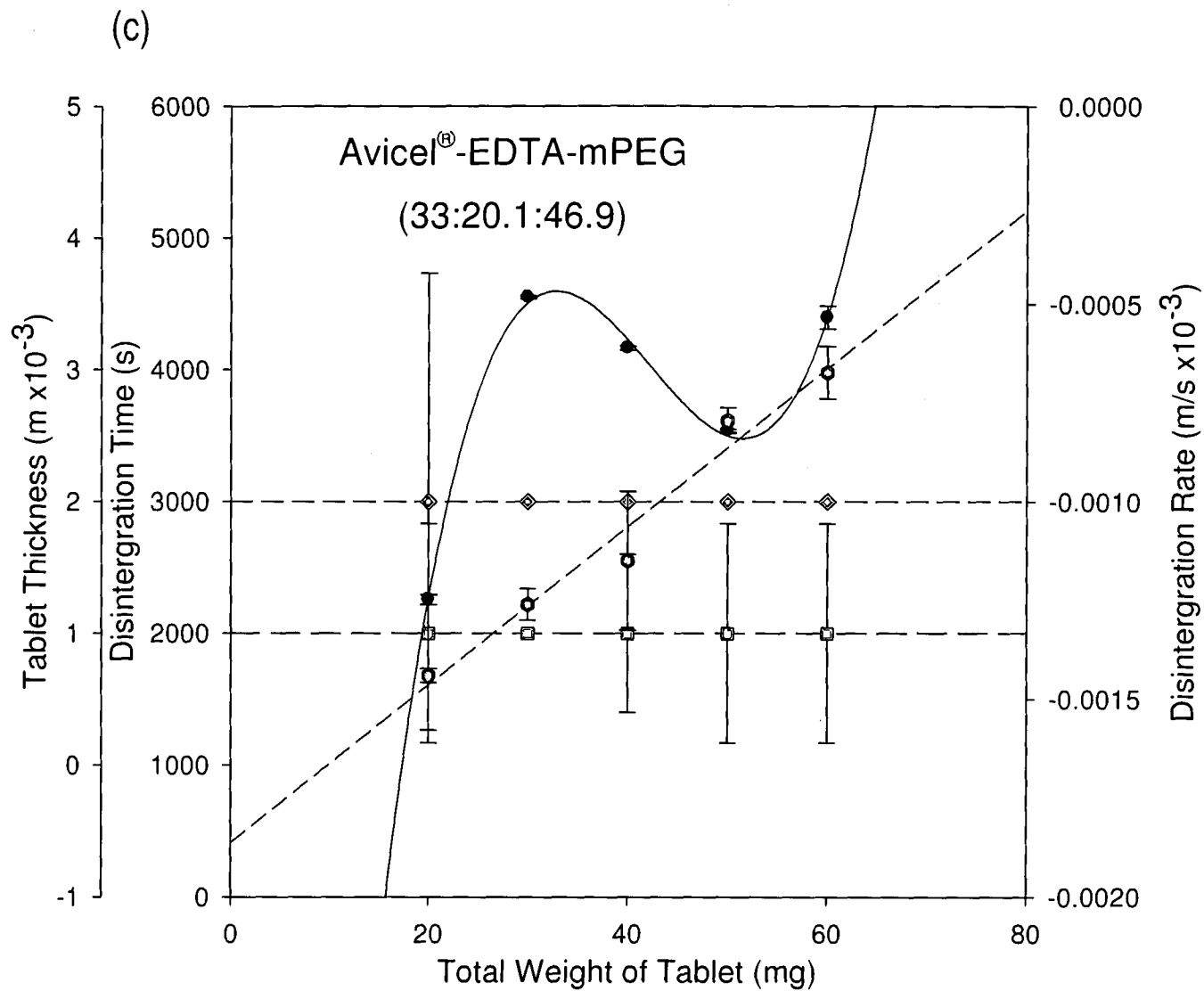


FIG 5b

**Formulation 8****FIG 5c**

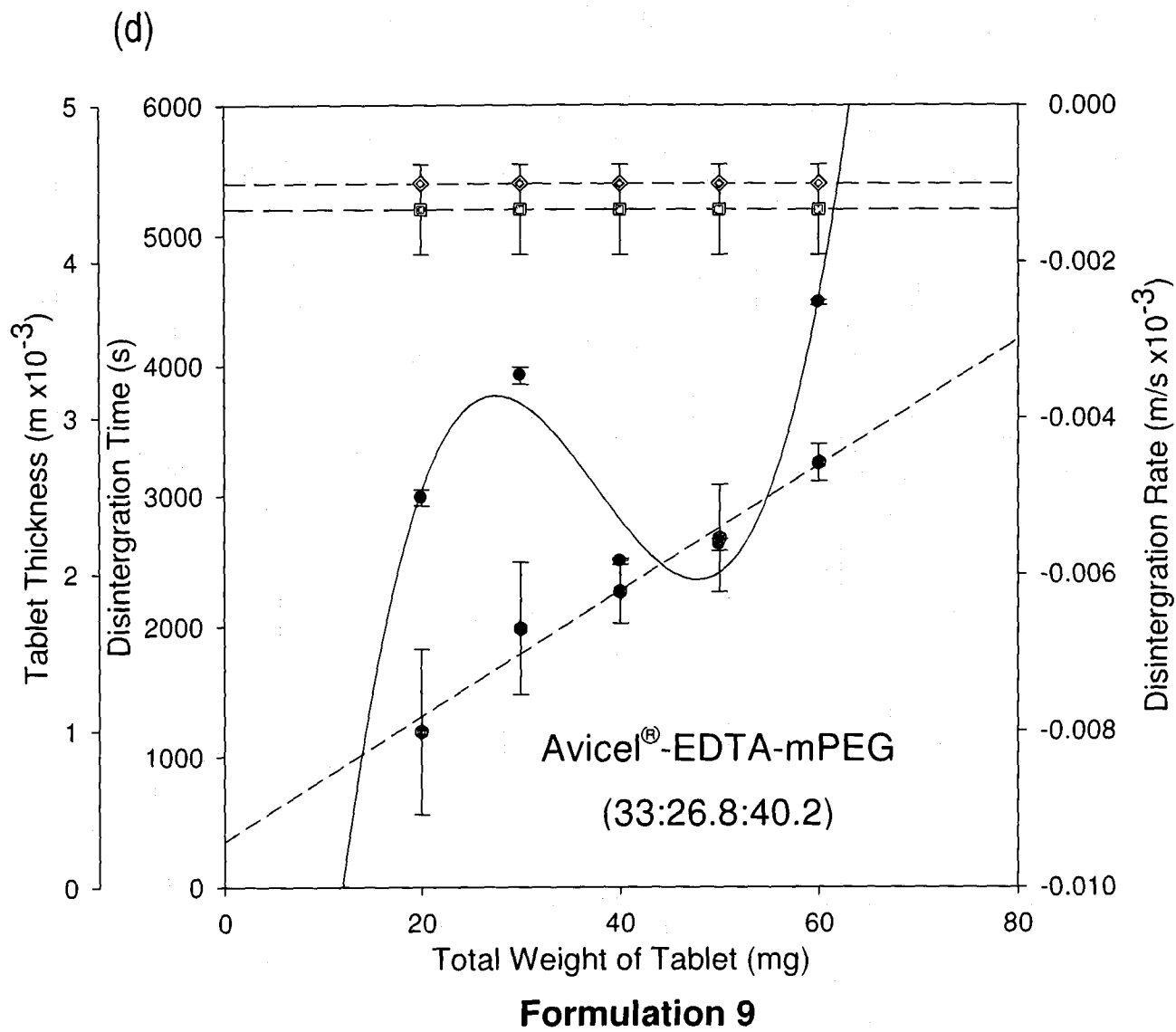


FIG 5d

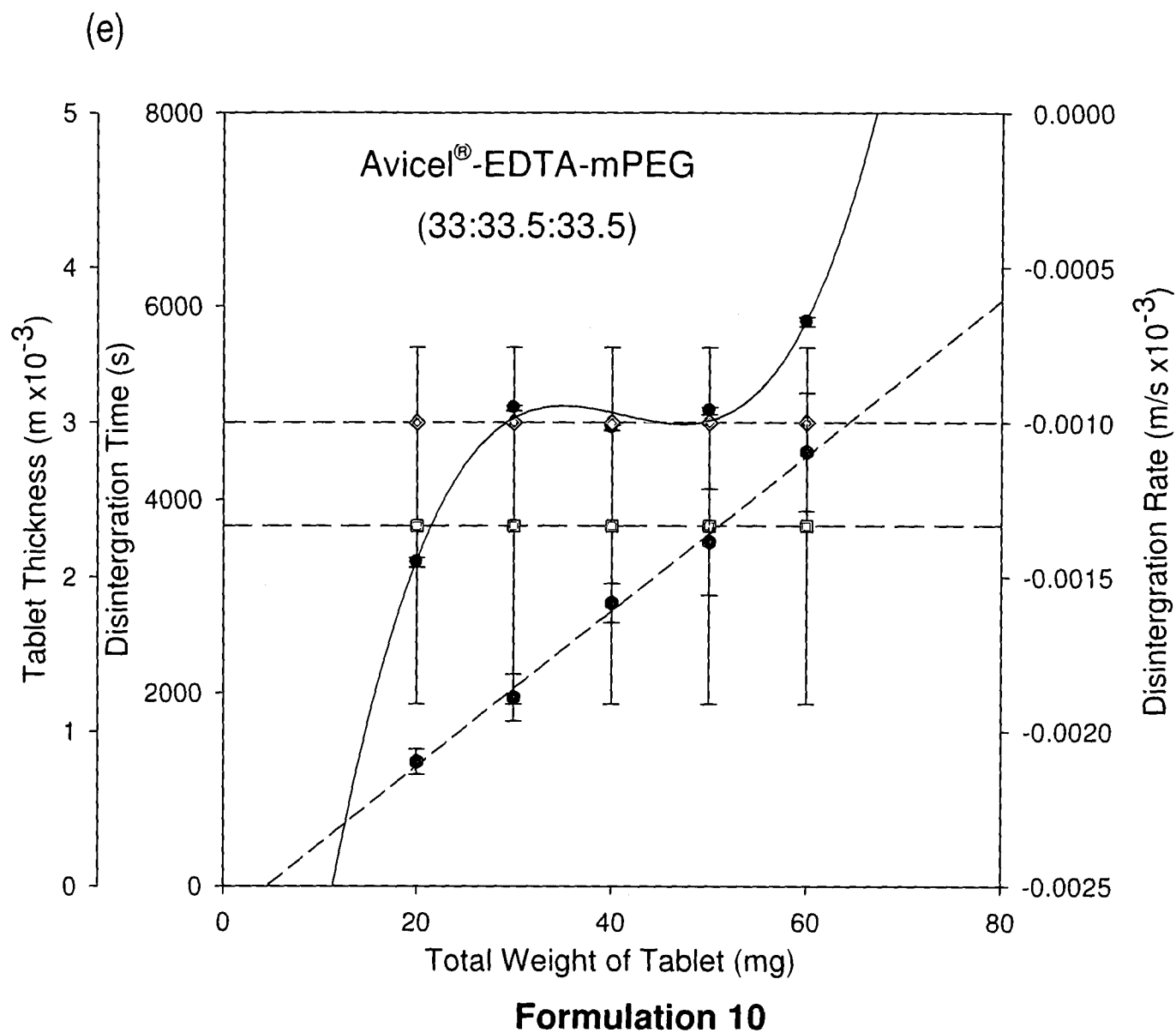


FIG 5e

AAm-MAA stimuli responsive hydrogel (10:80)

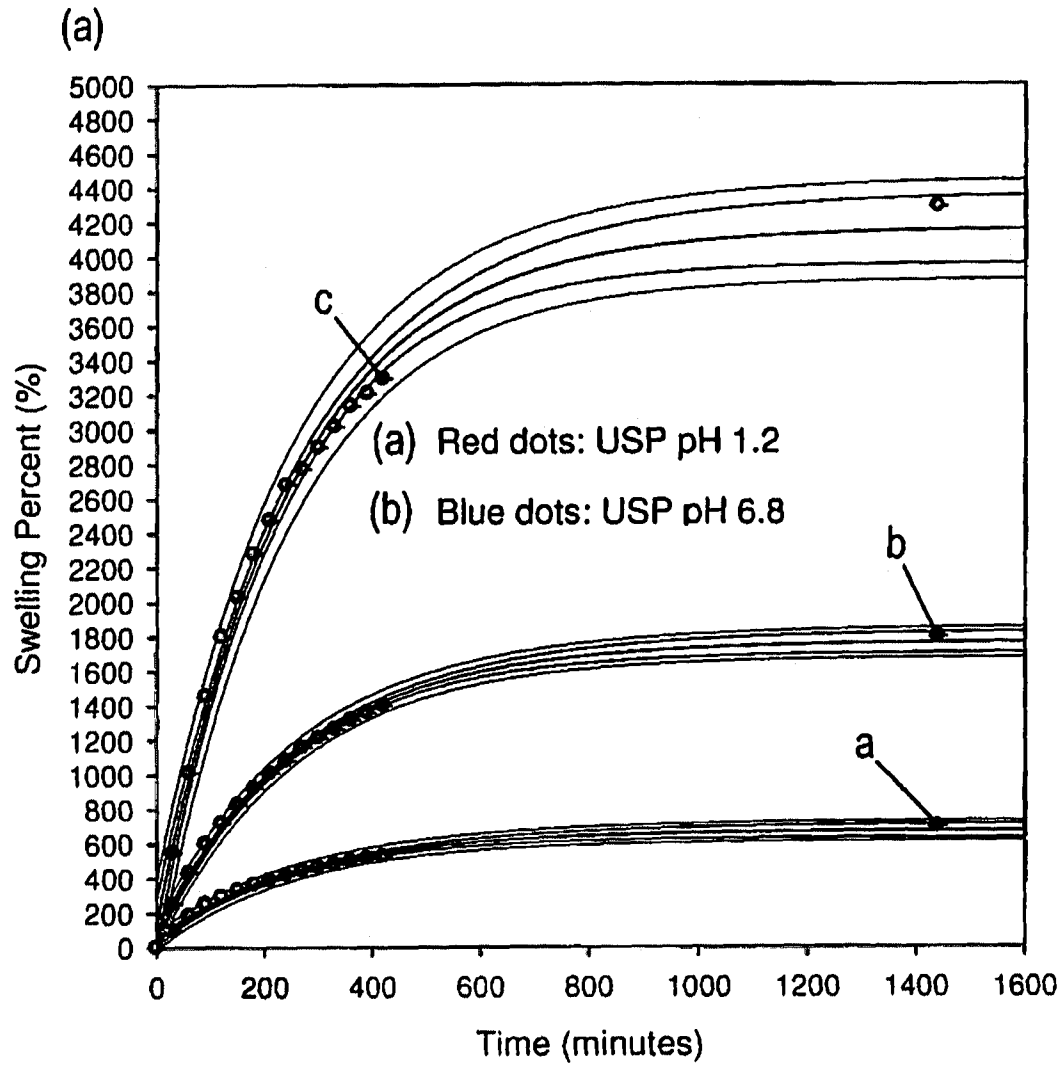


FIG 6a

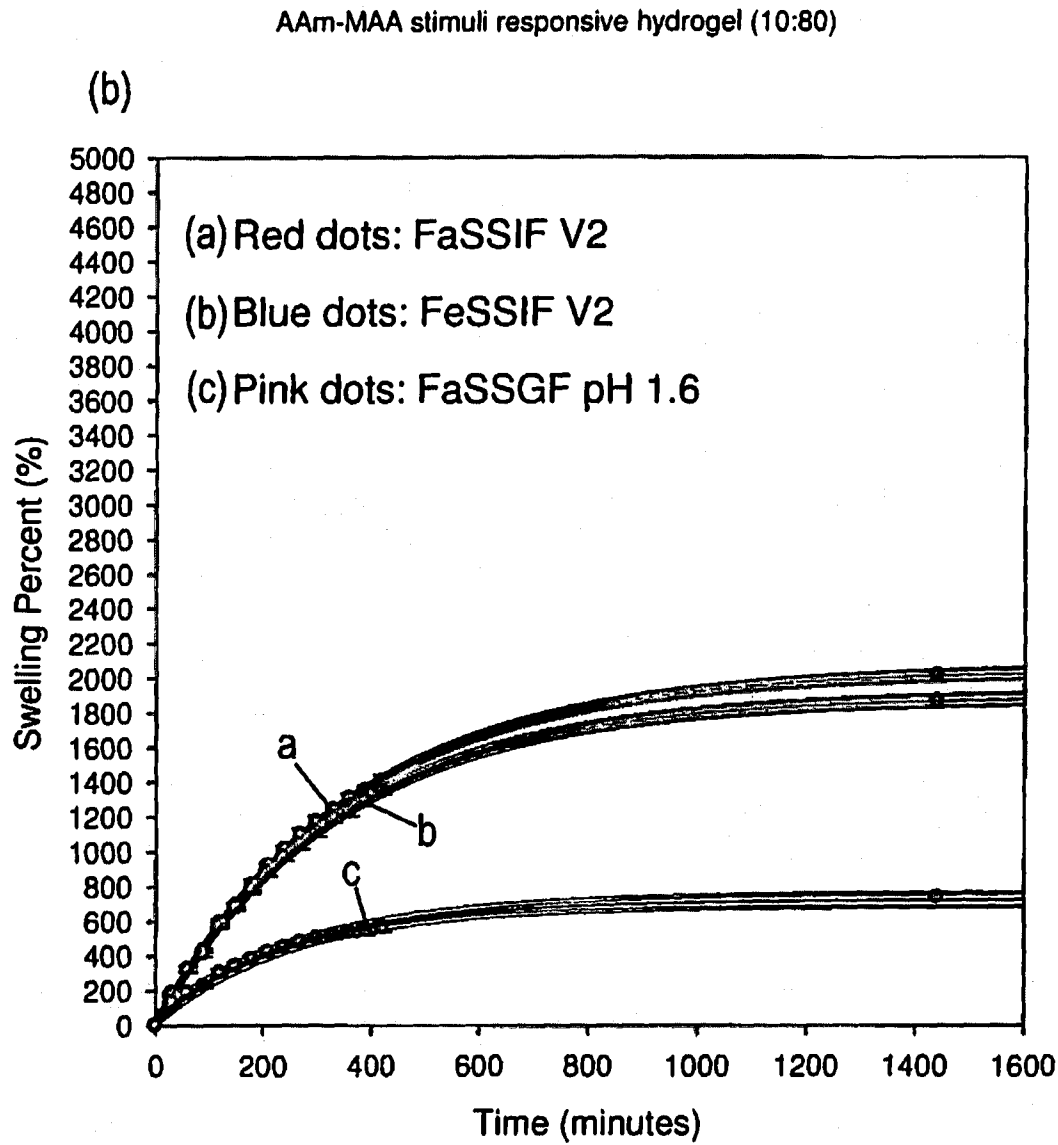


FIG 6b

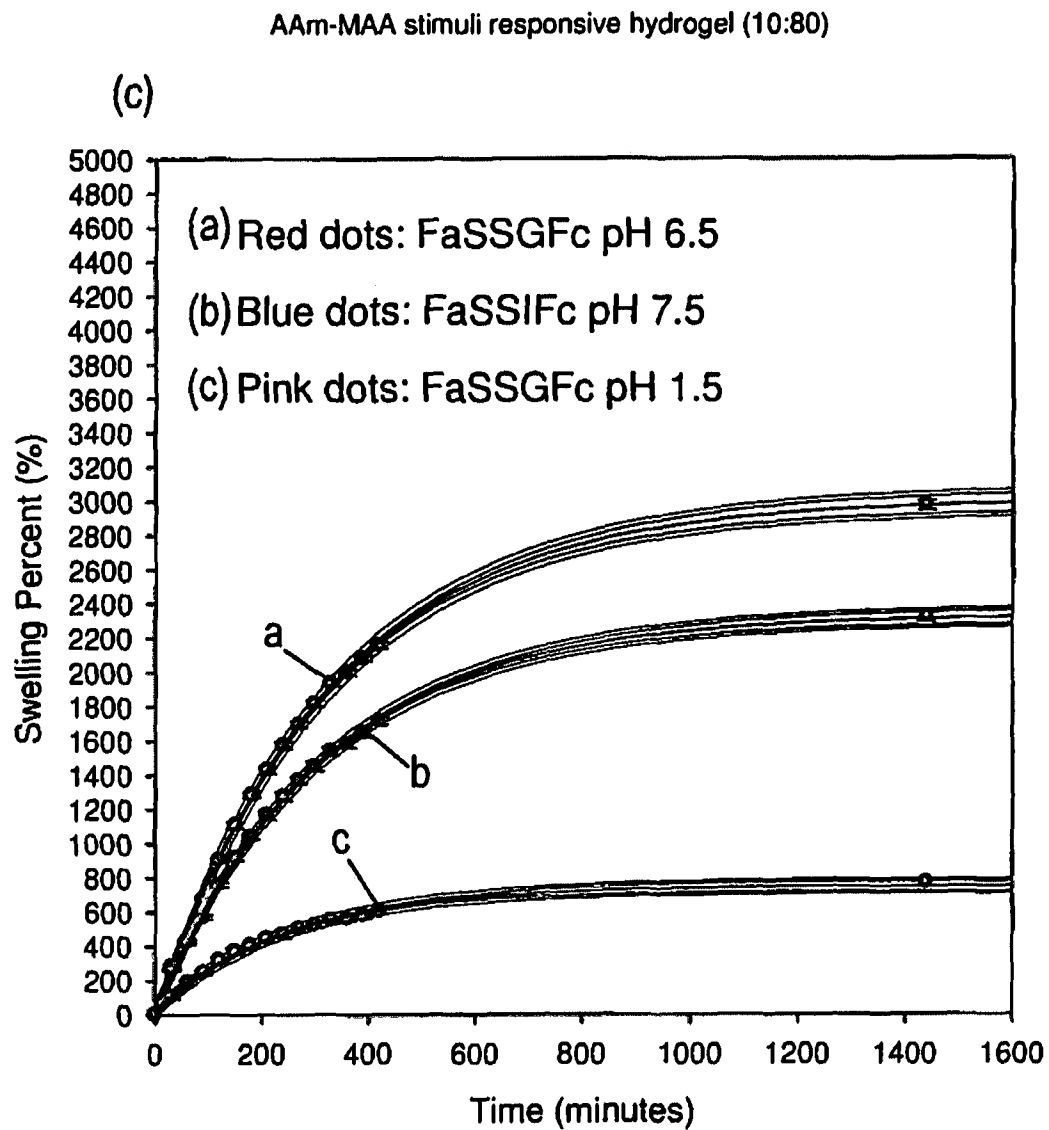


FIG 6c

AAm-MAA stimuli responsive hydrogel (50:50)

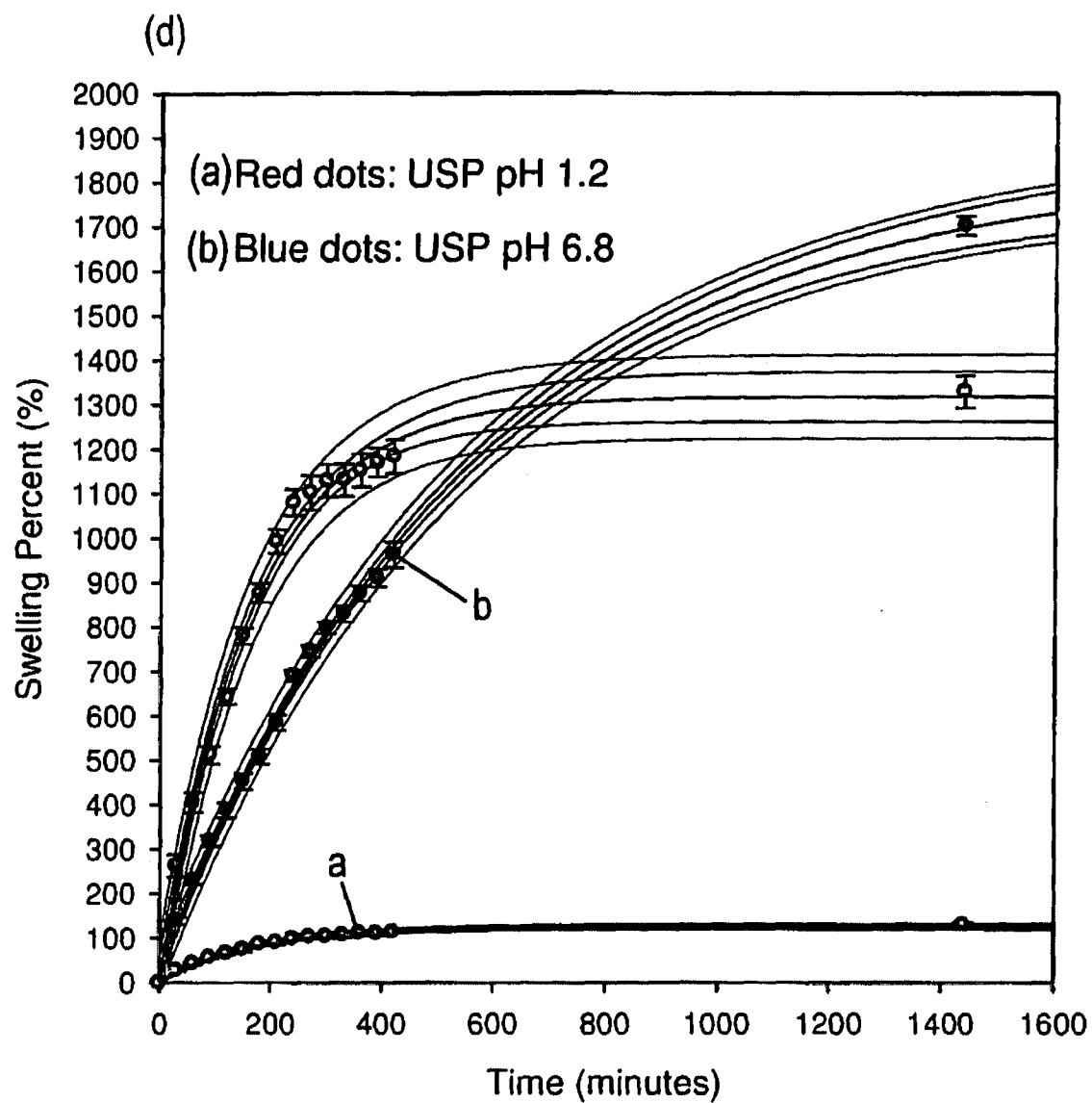


FIG 6d

AAm-MAA stimuli responsive hydrogel (50:50)

(e)

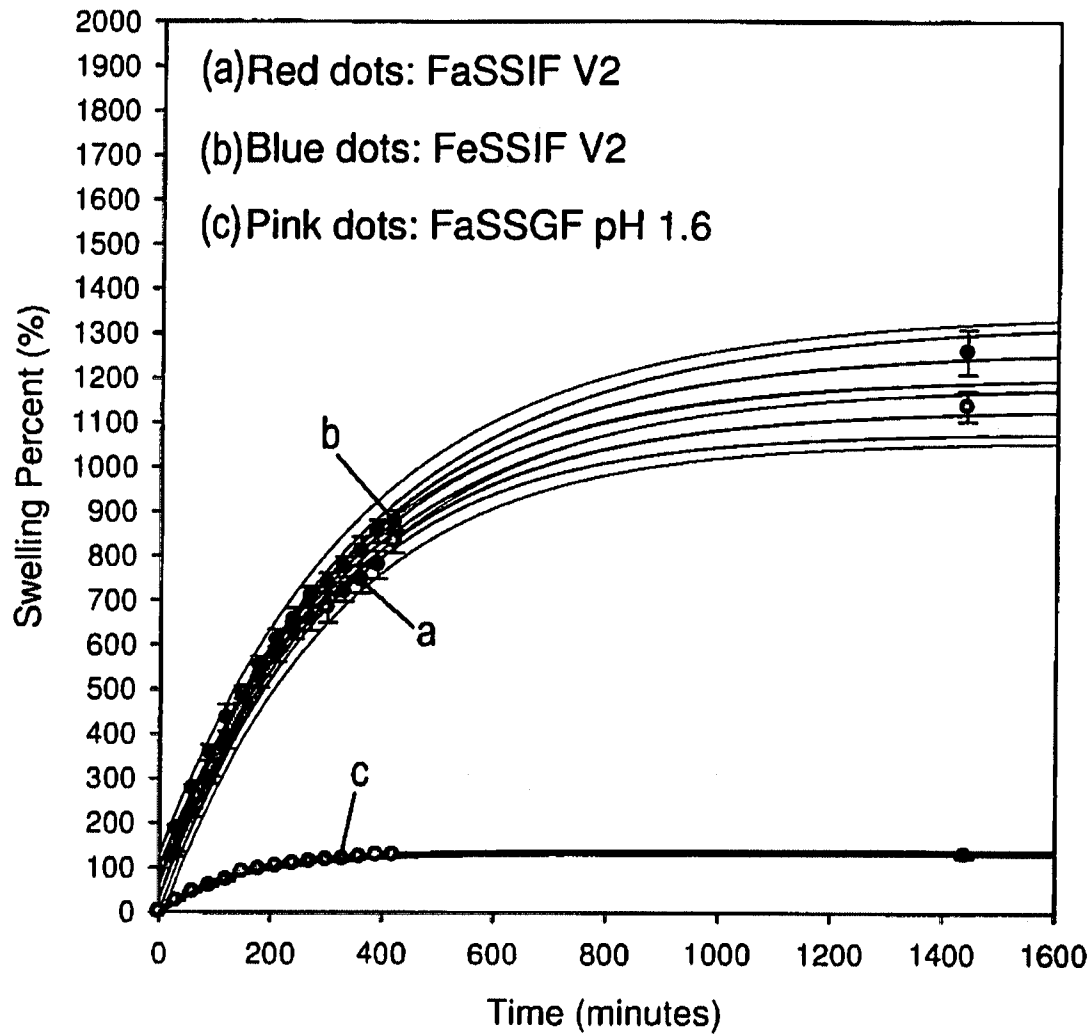


FIG 6e

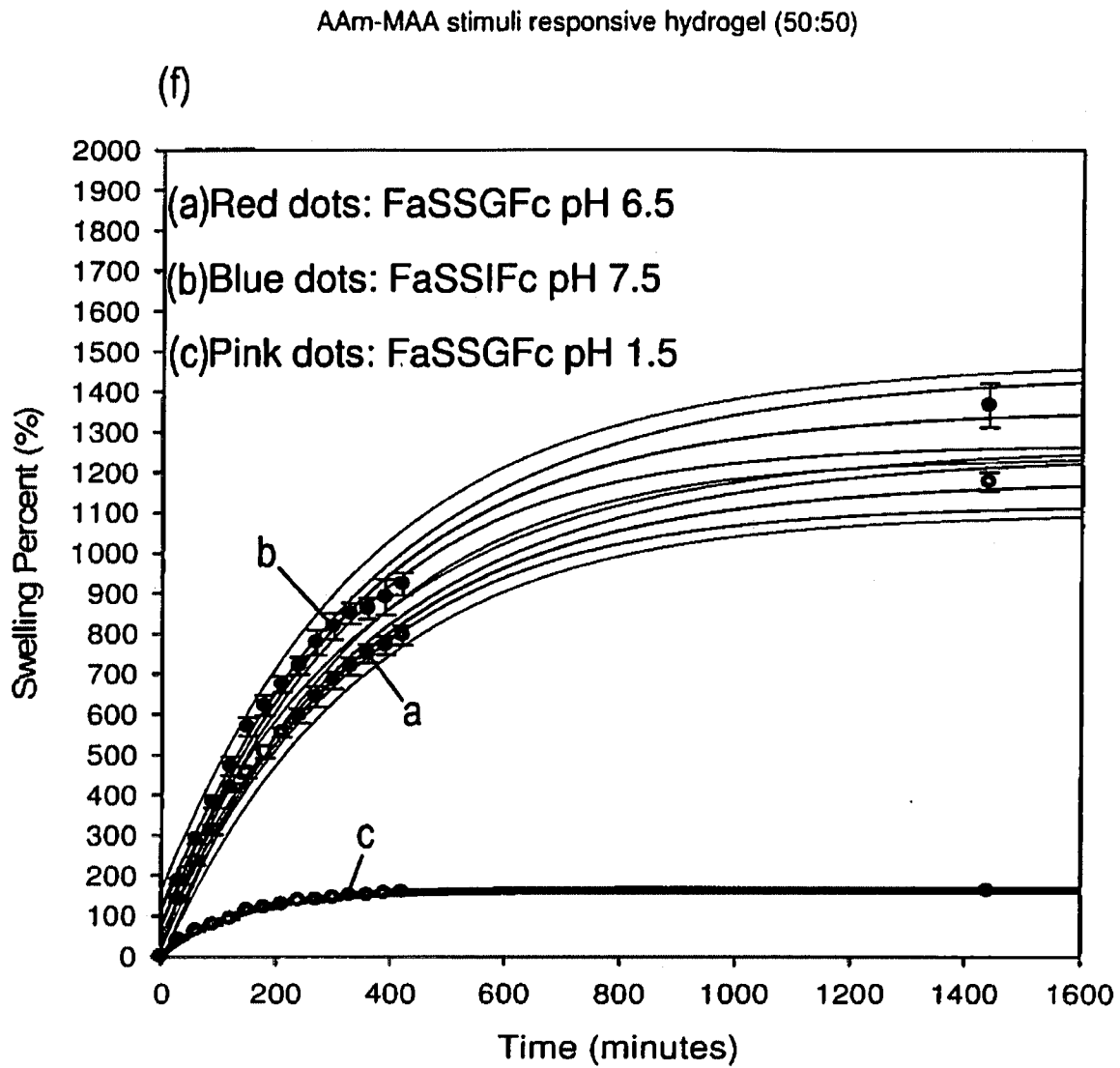


FIG 6f

AAm-MAA stimuli responsive hydrogel (70:30)

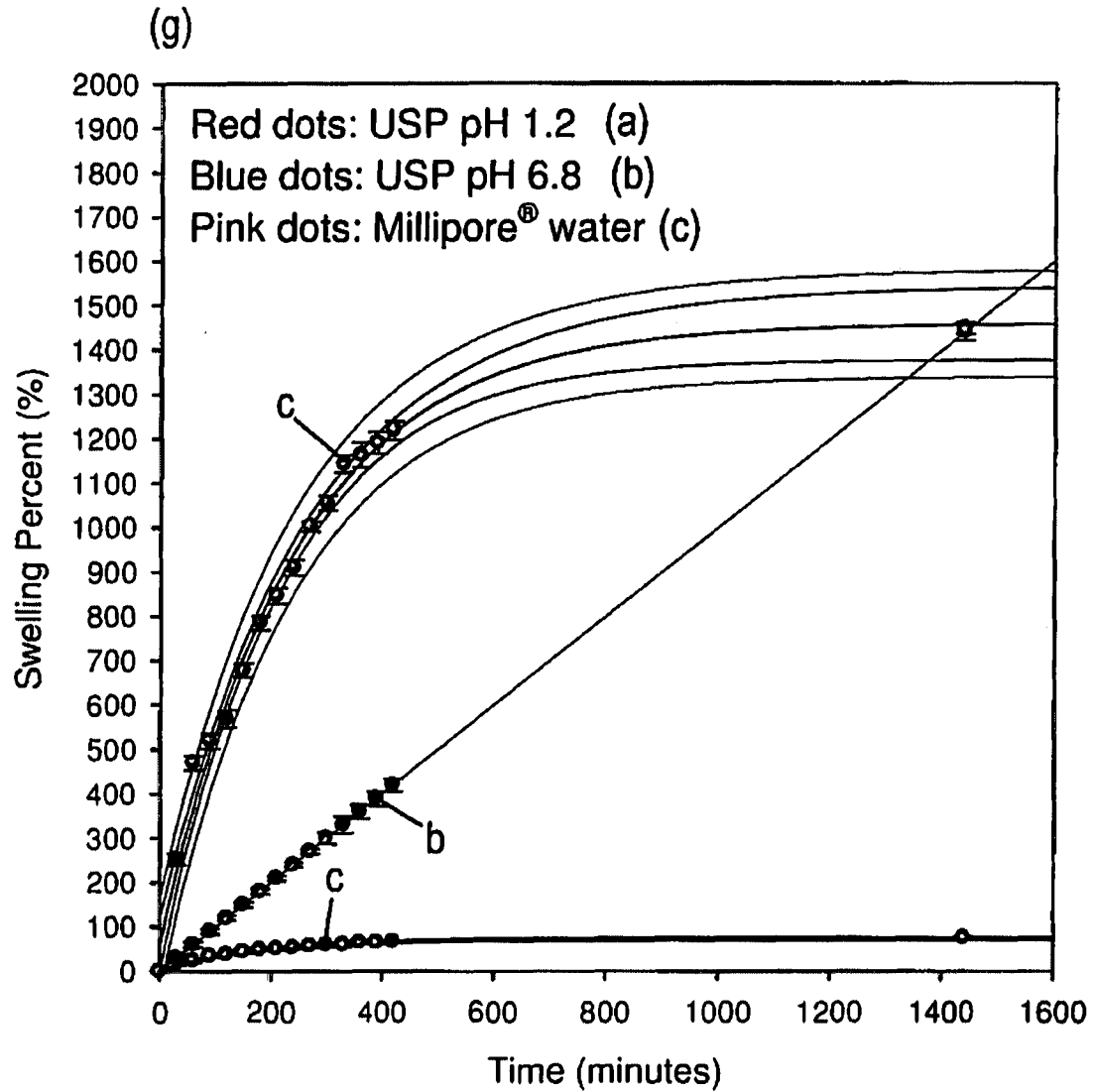


FIG 6g

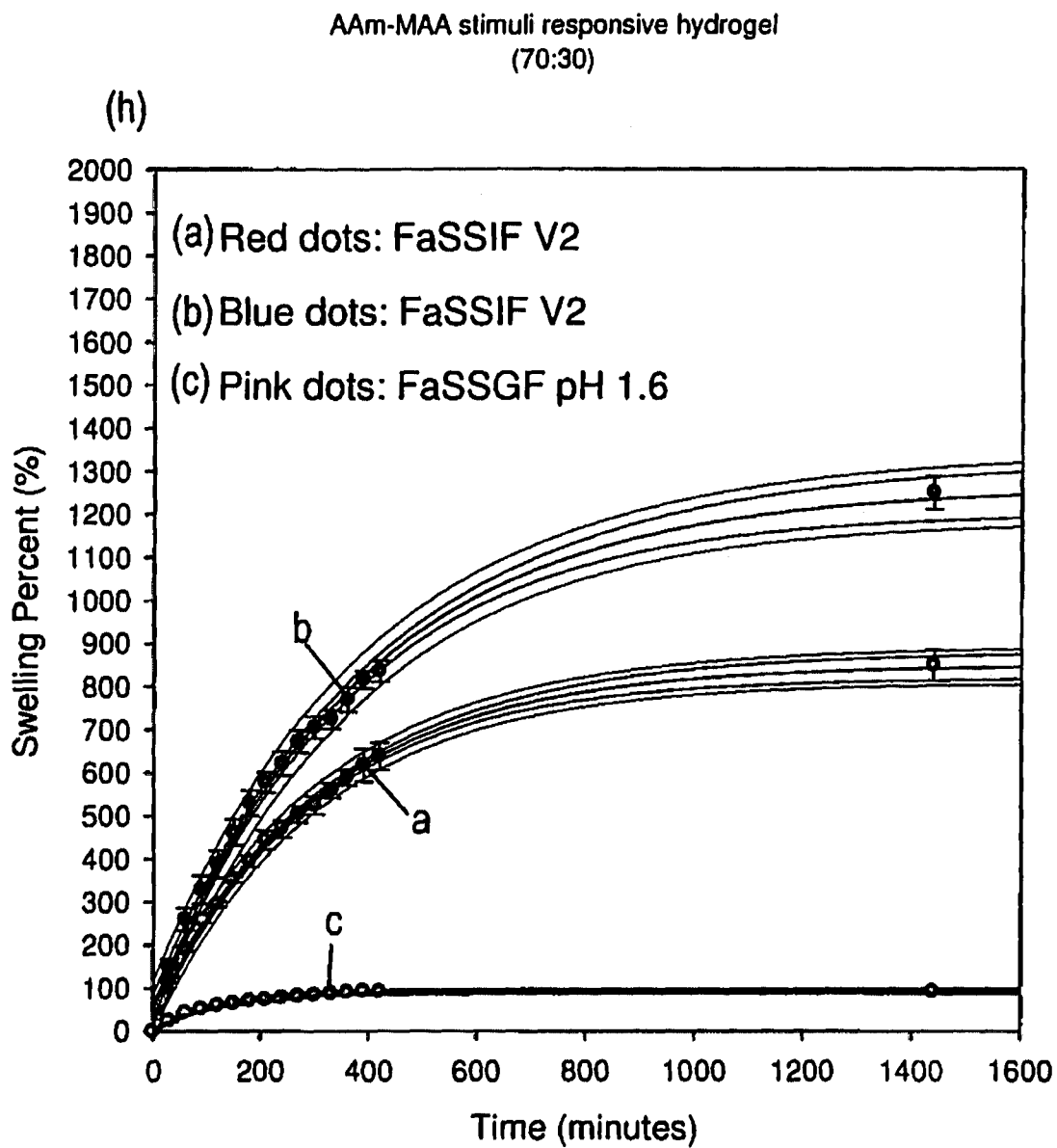


FIG 6h

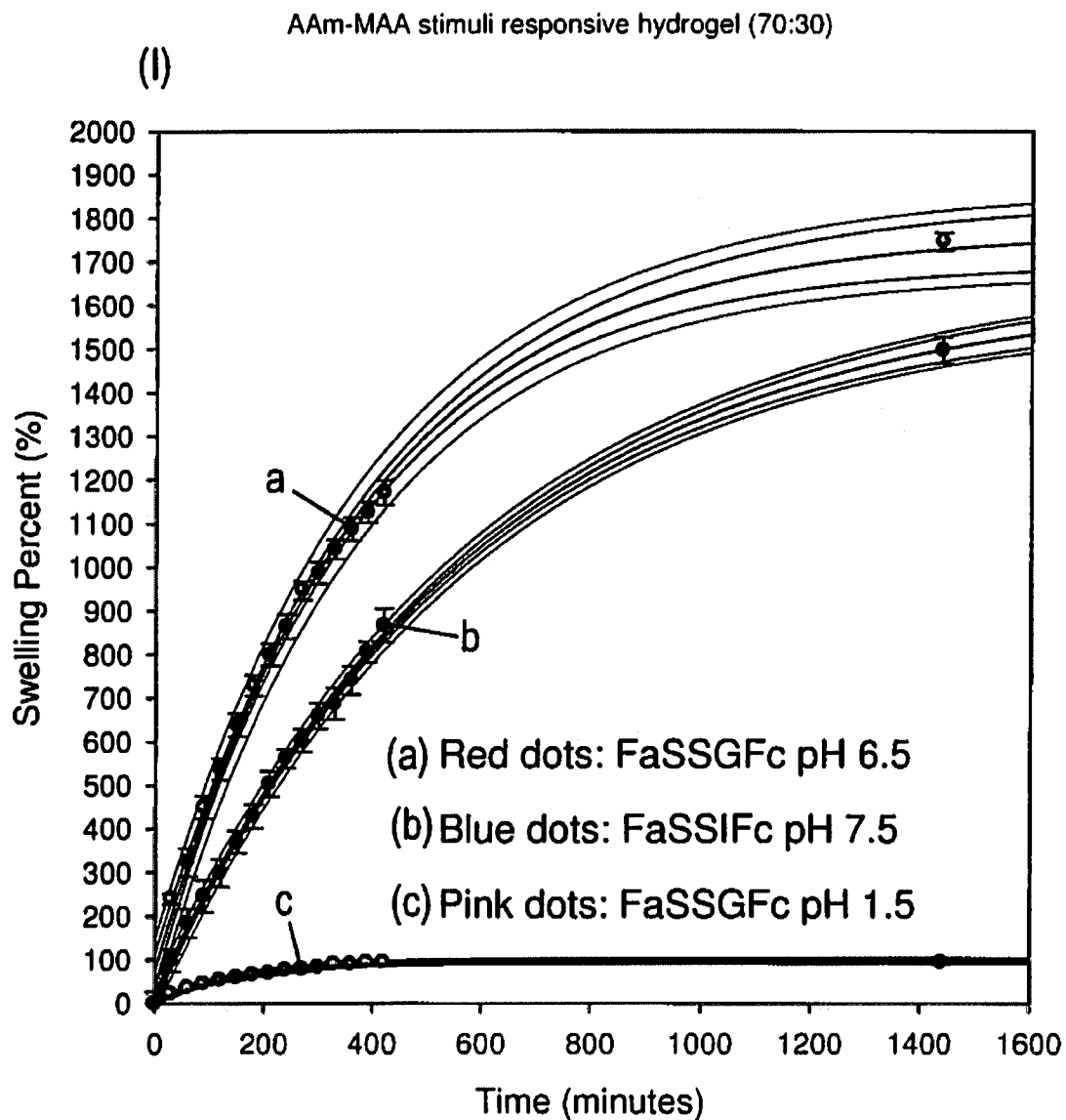


FIG 6 i

(A) AAm-MAA hydrogel (10:90)

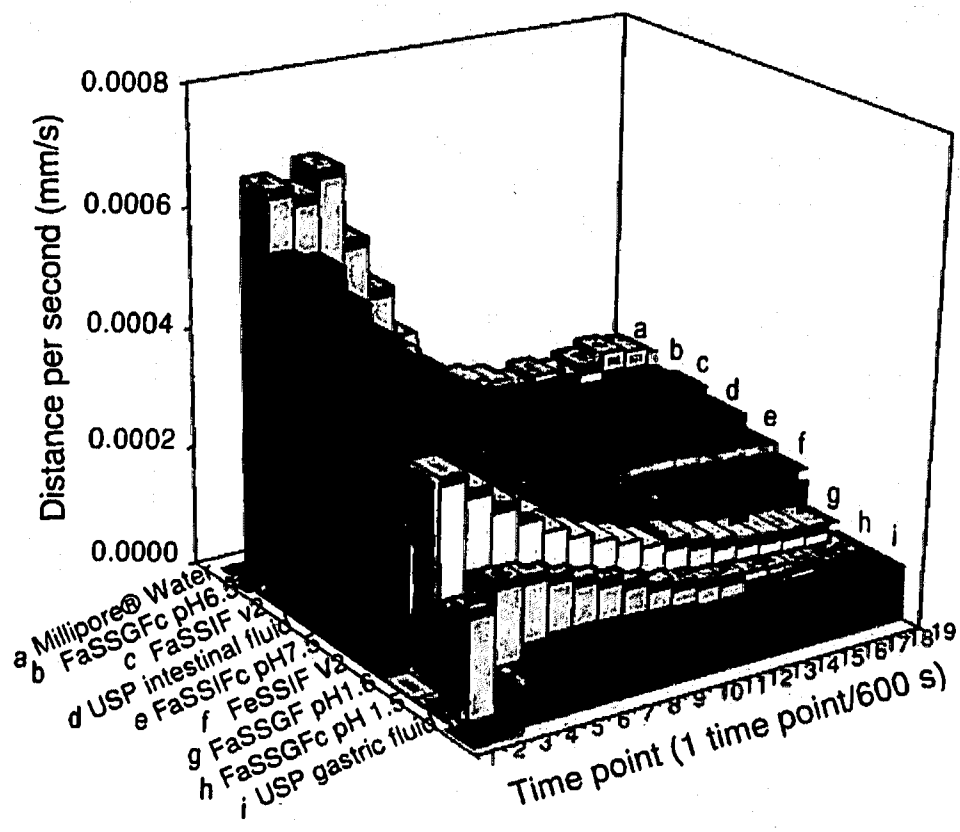


FIG 7a

(B) AAm-MAA hydrogel (50:50)

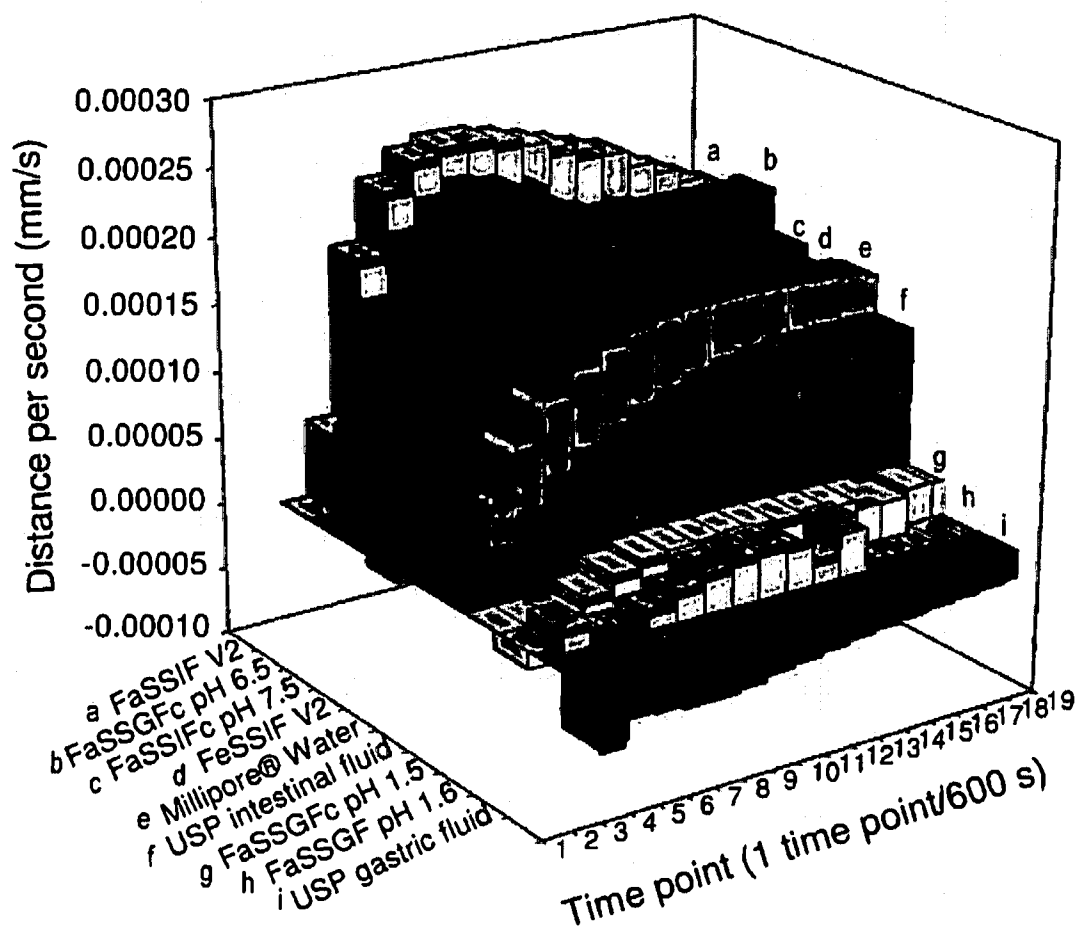


FIG 7b

(C) AAm-MAA hydrogel (70:30)

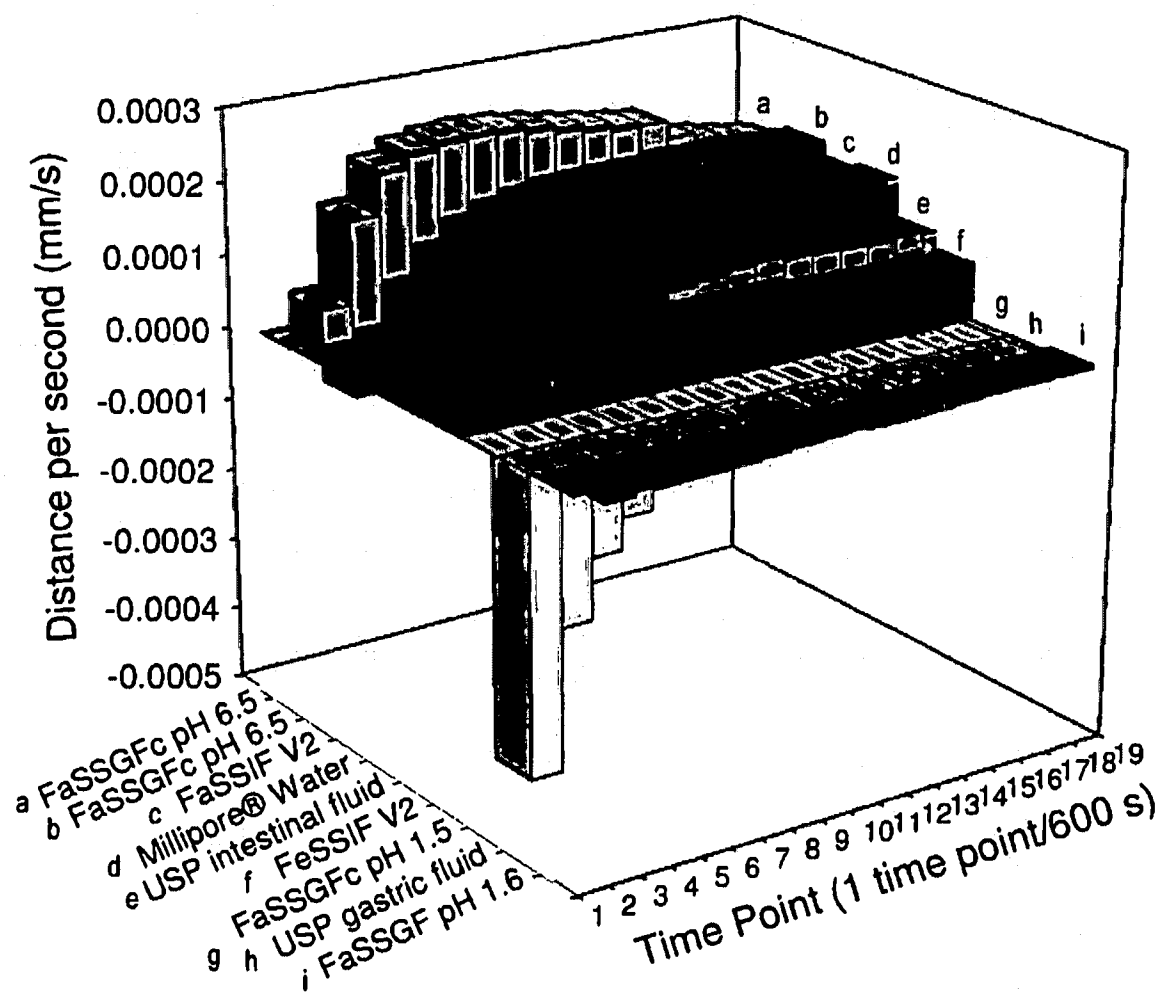


FIG 7c

(D) Isolated Porcine Fluids

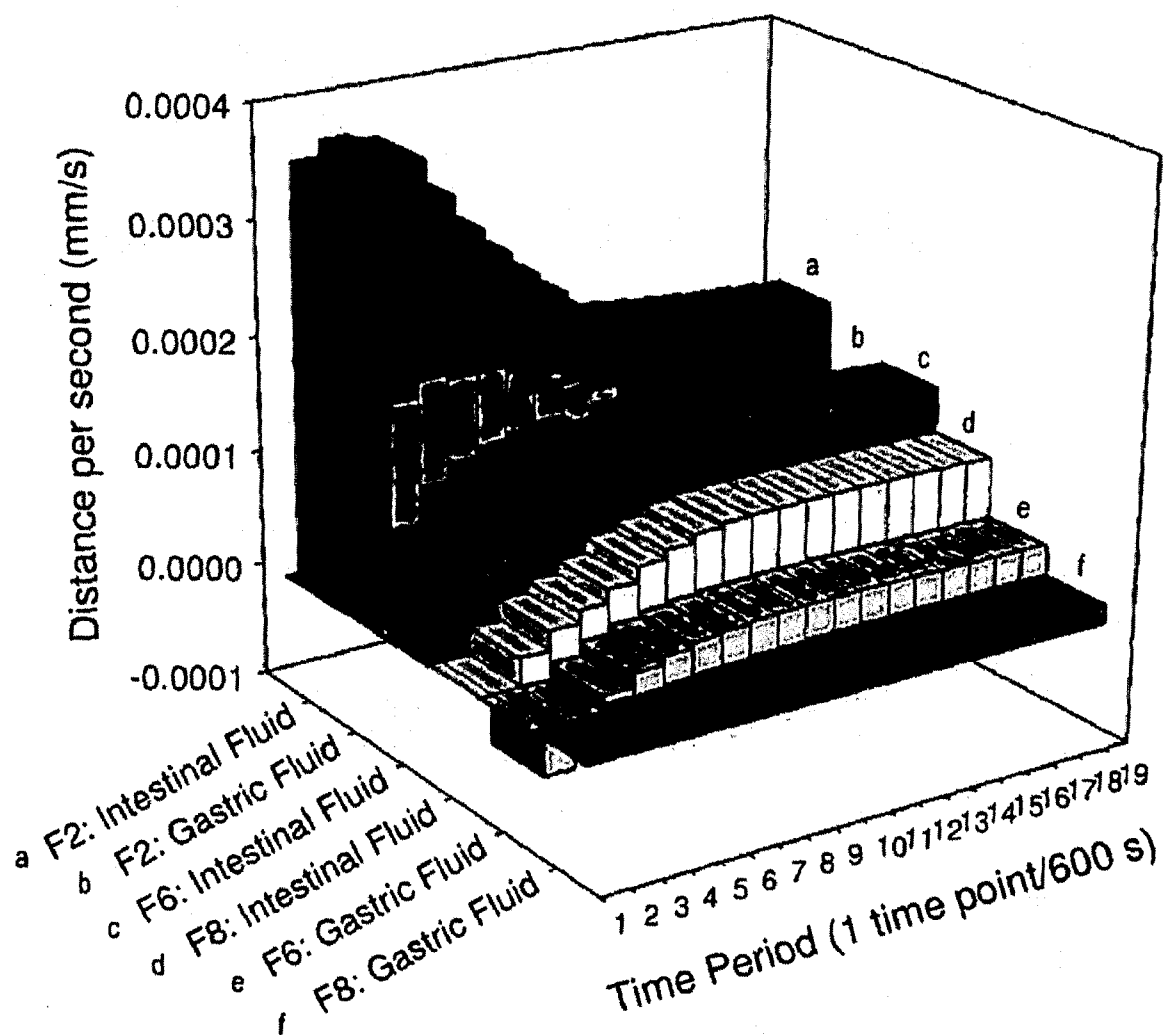


FIG 7d

Theophylline

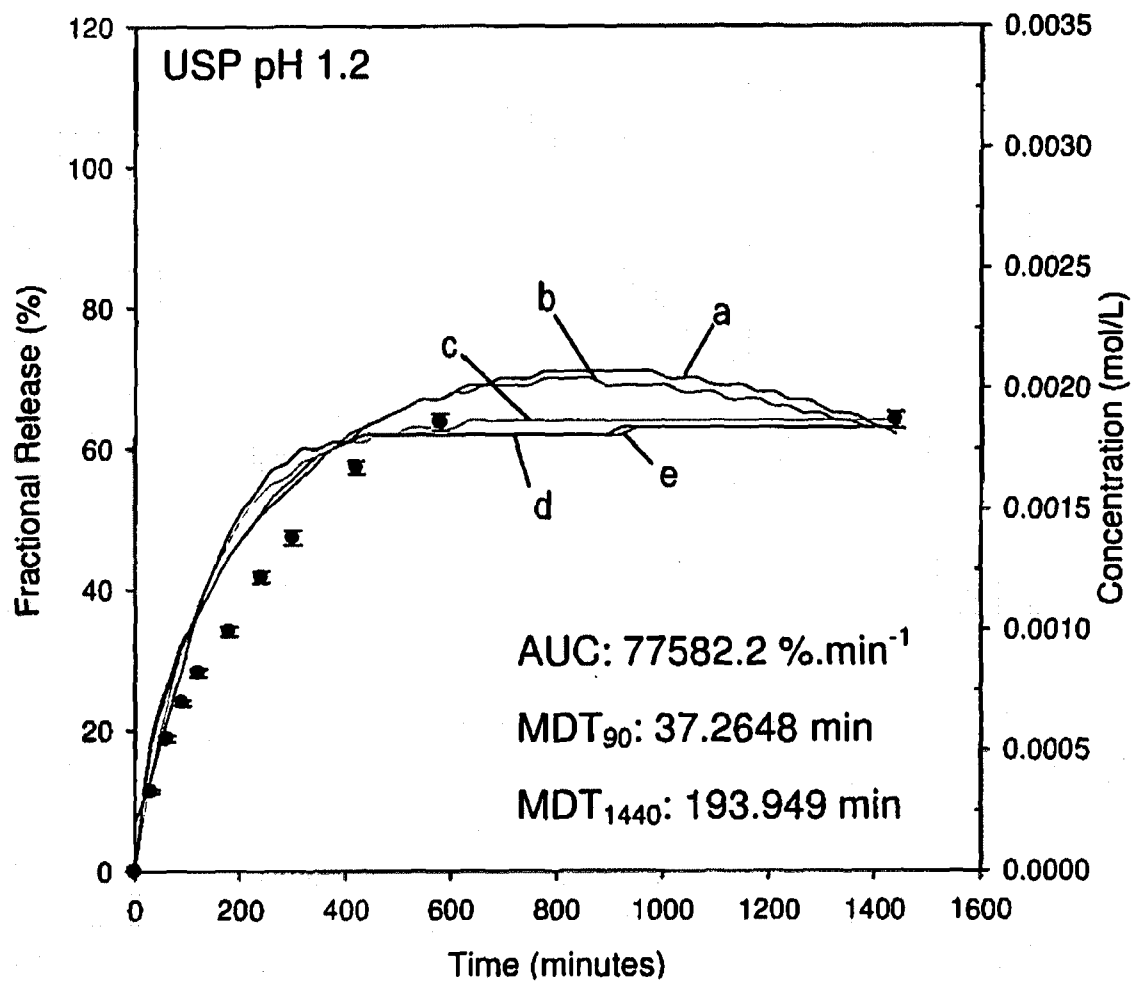


FIG 8a

Theophylline

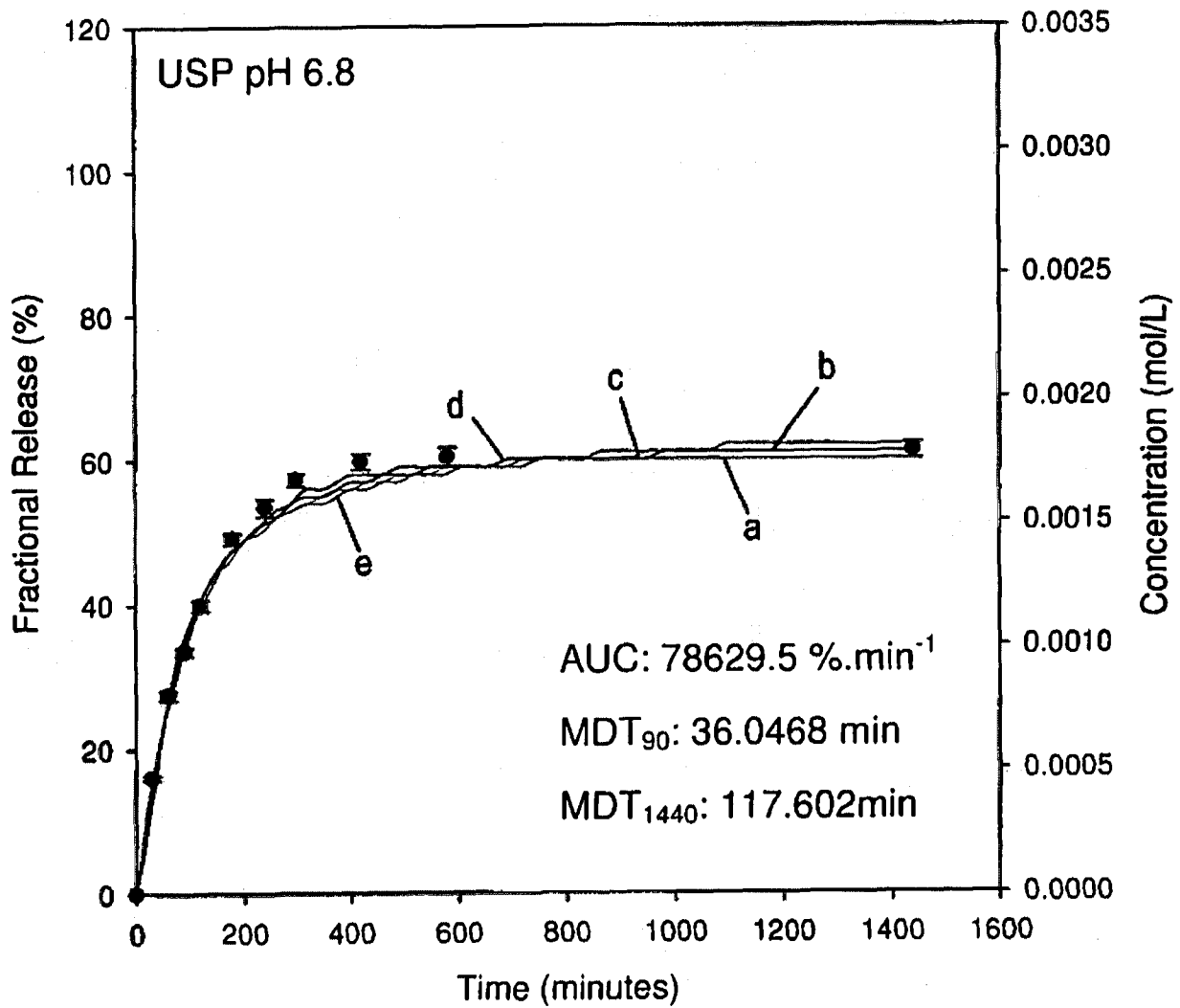


FIG 8b

Theophylline

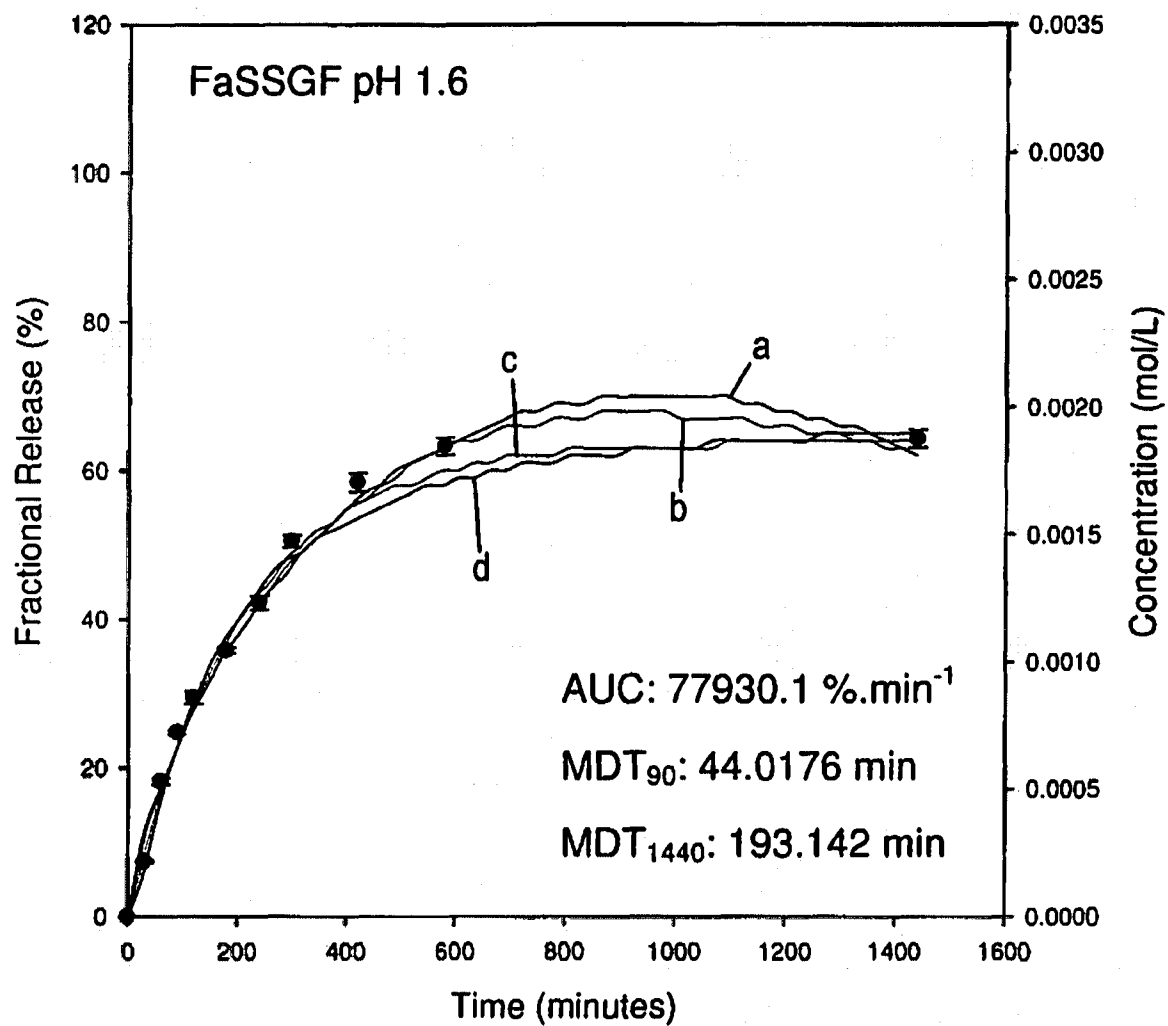


FIG 8c

Theophylline

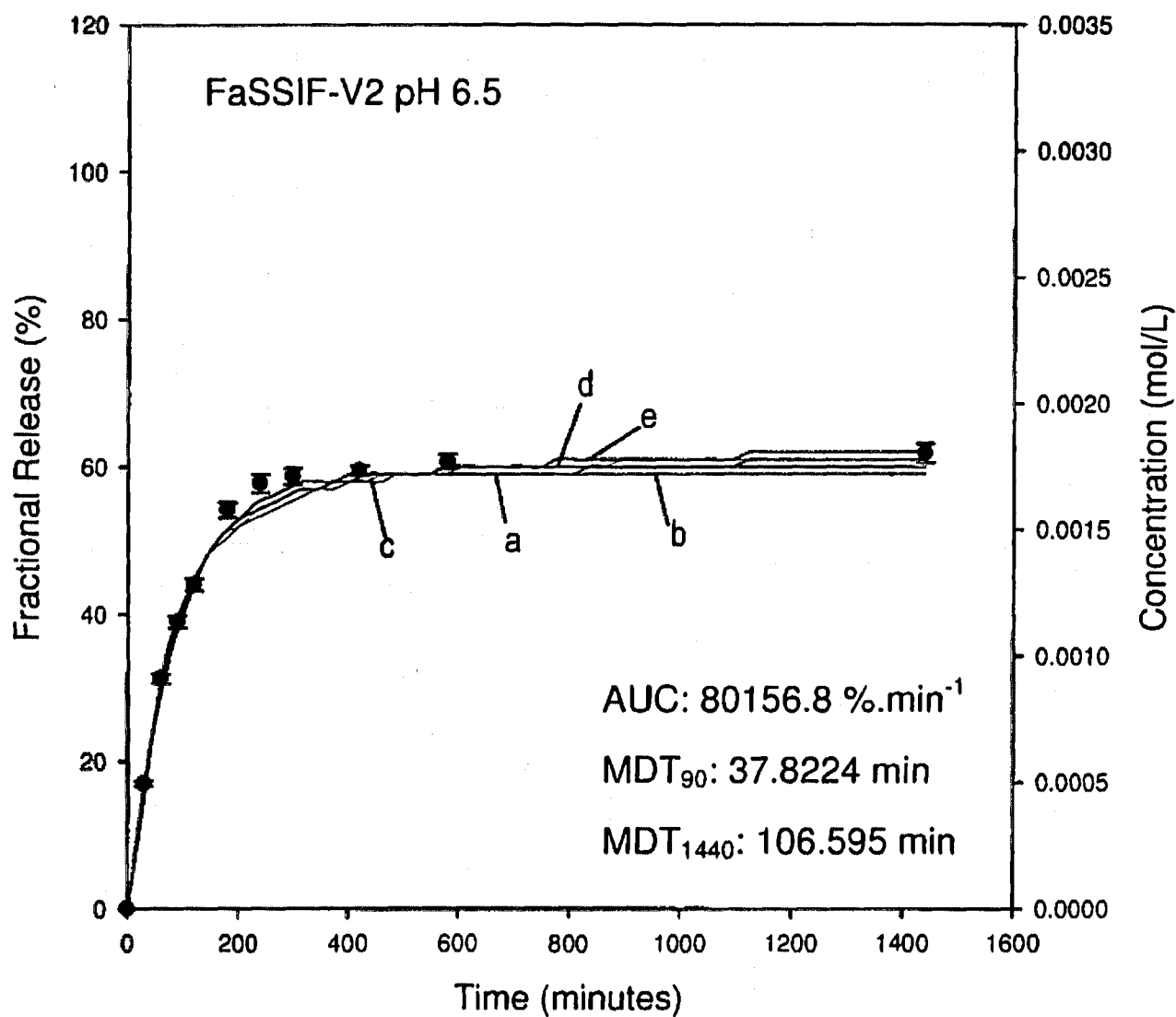


FIG 8d

Theophylline

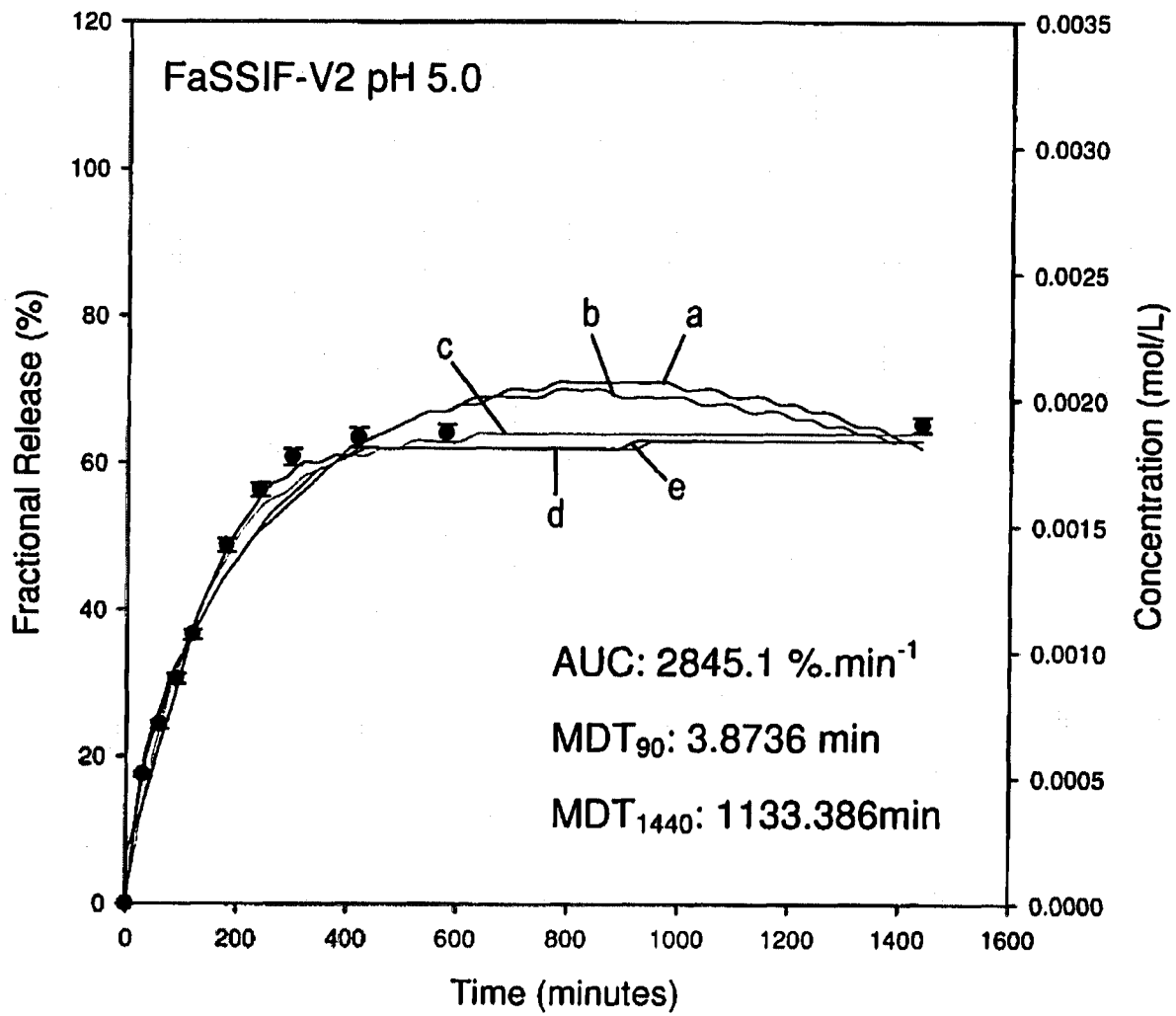


FIG 9a

Theophylline

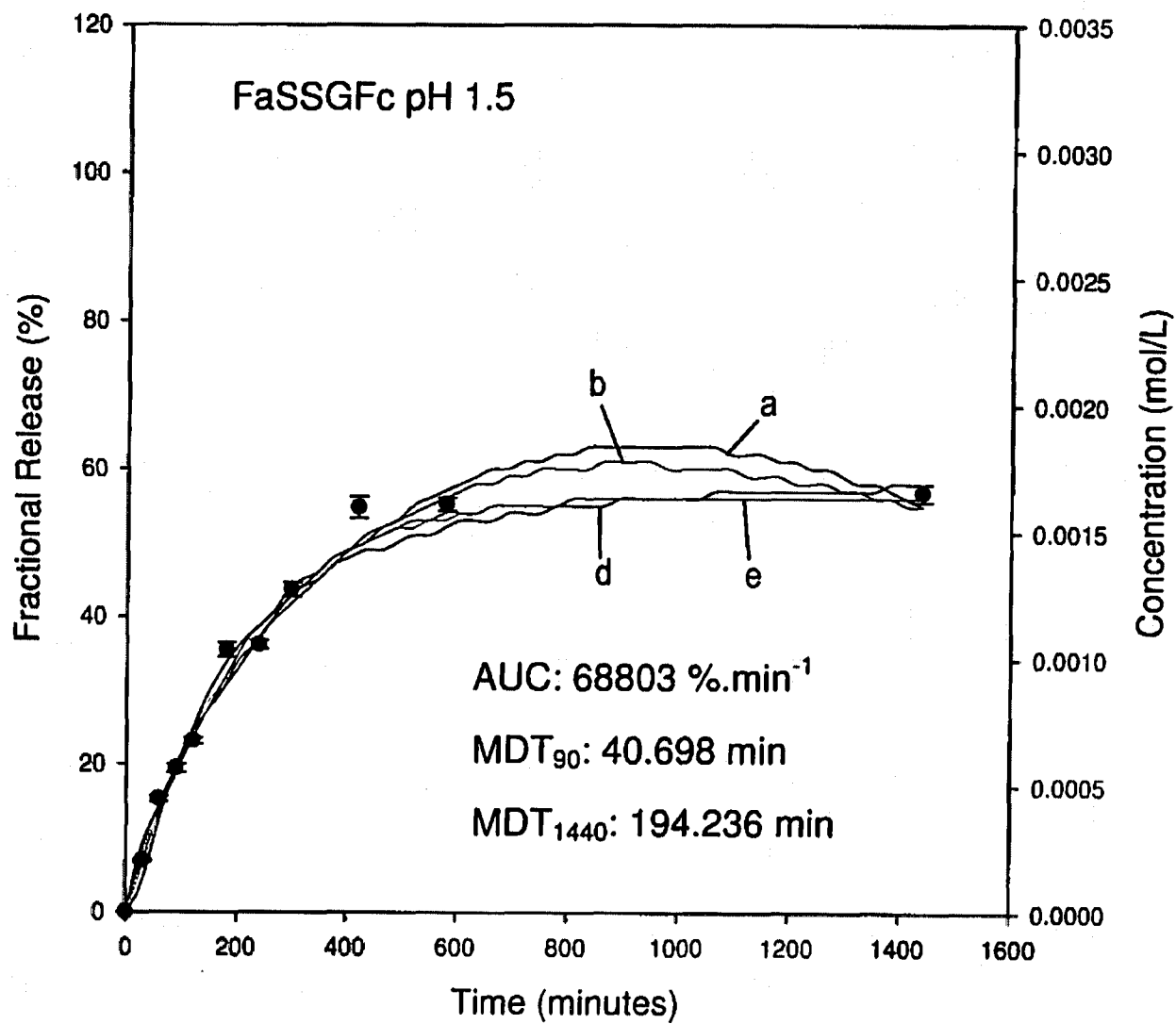


FIG 9b

Theophylline

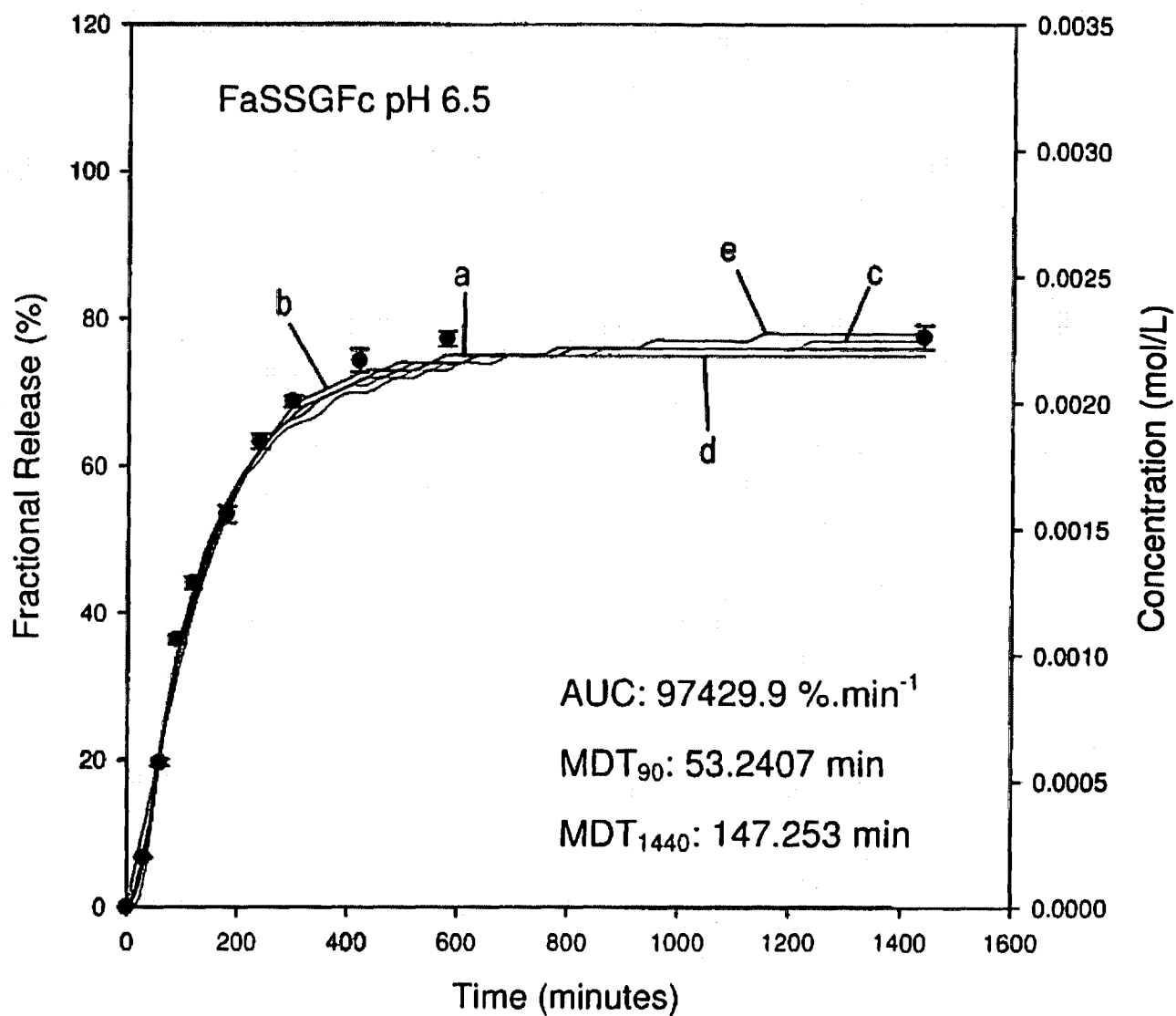


FIG 9c

Theophylline

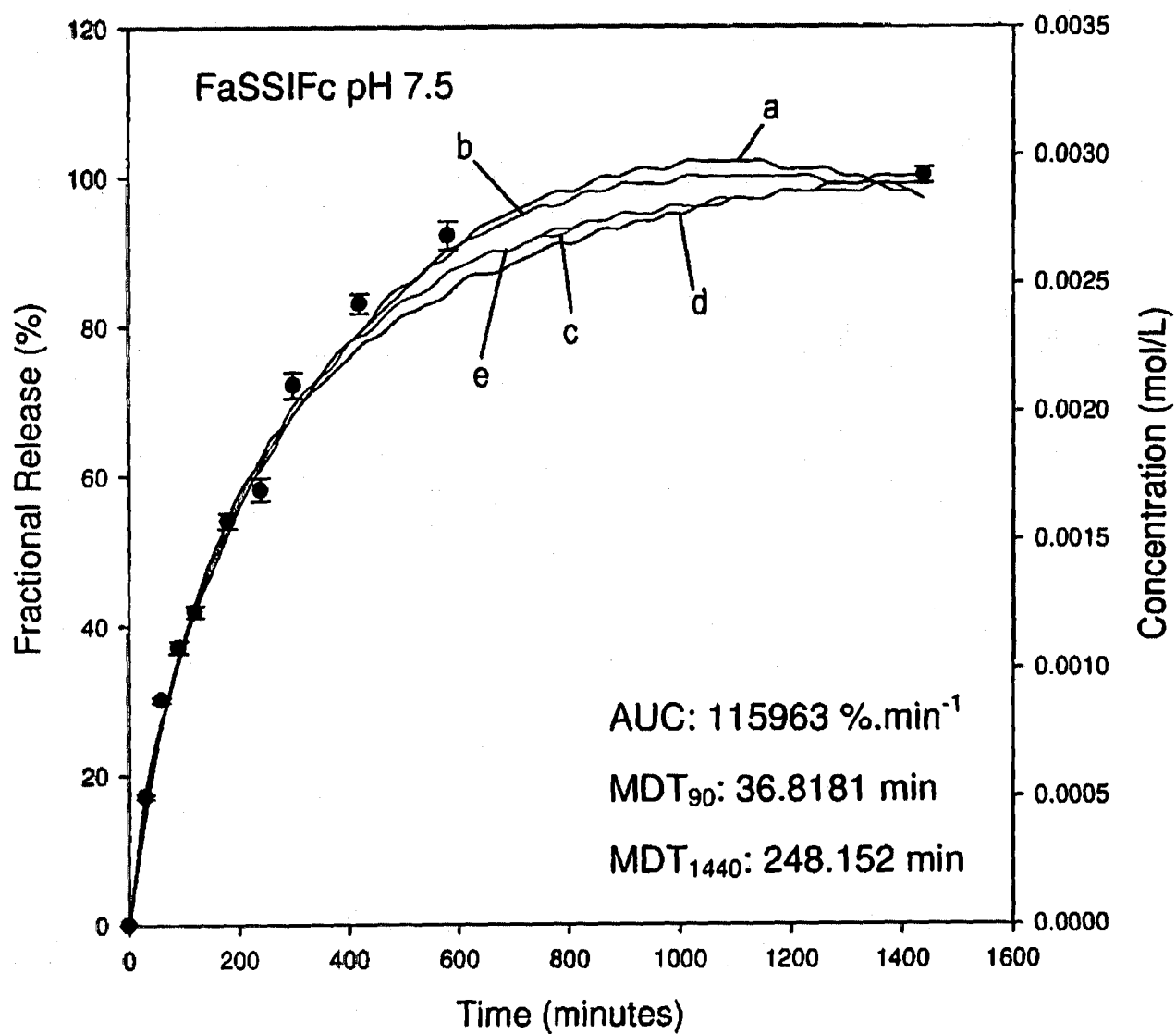


FIG 9d

Indomethacin

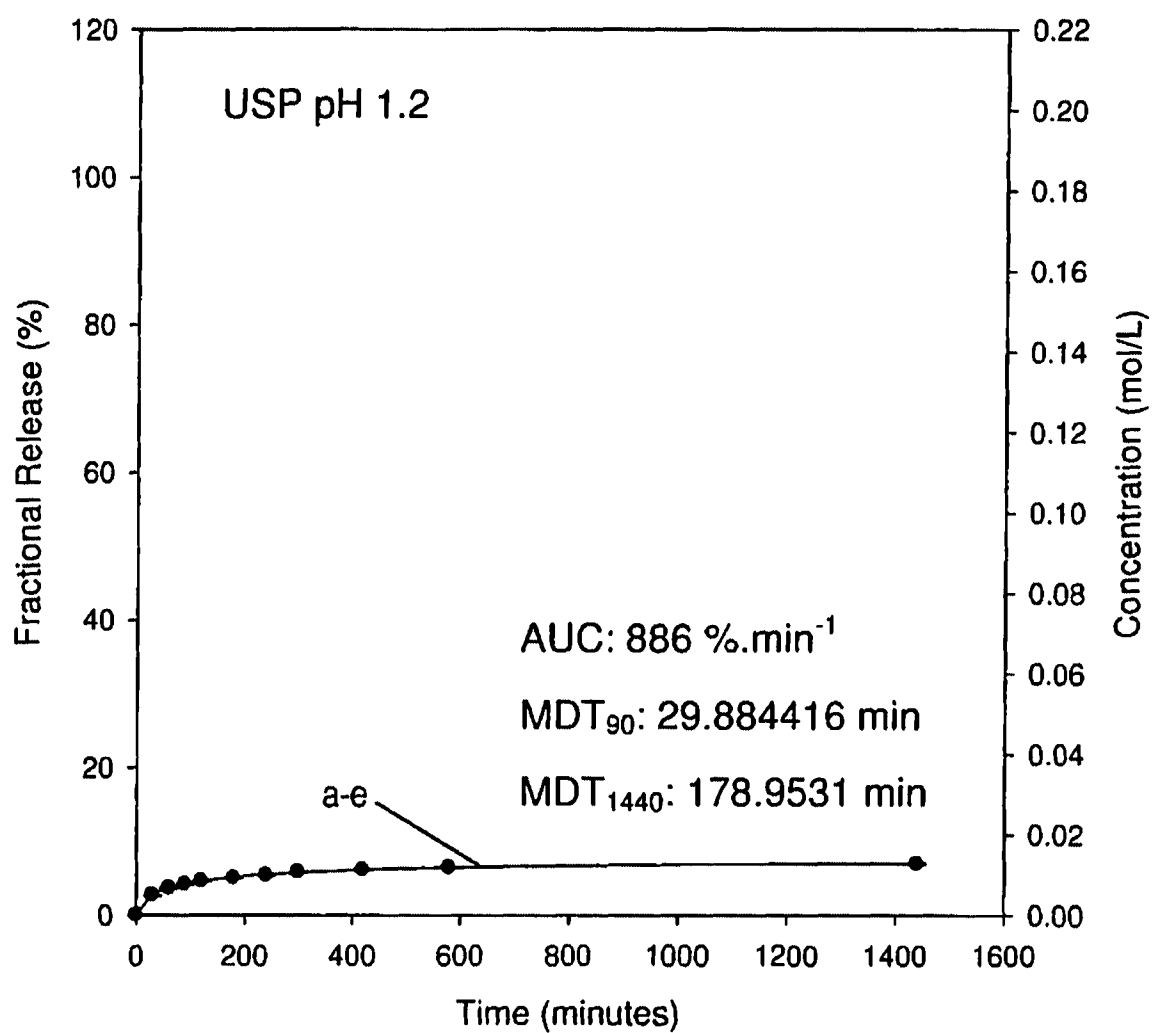


FIG 10a

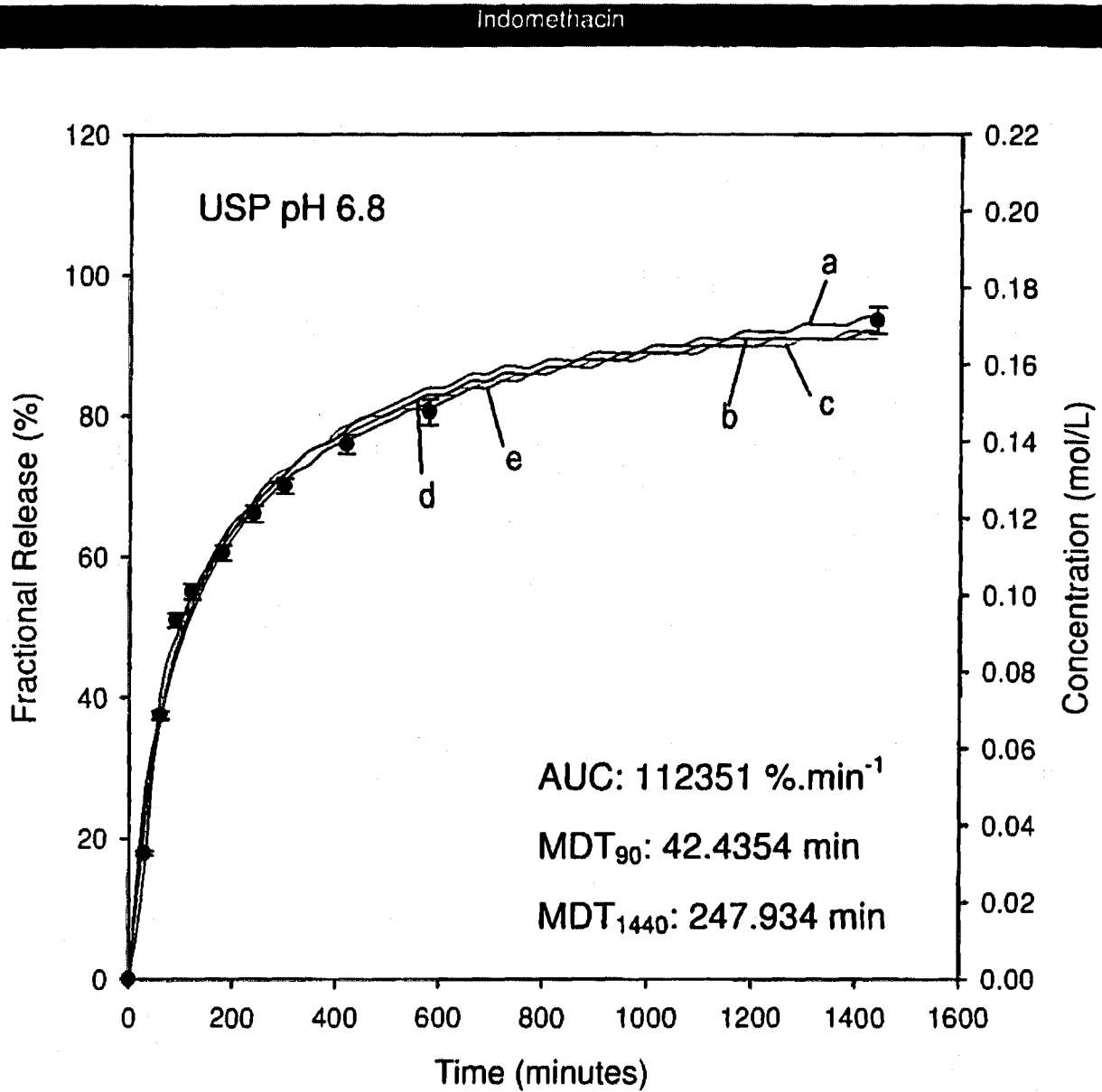


FIG 10b

Indomethacin

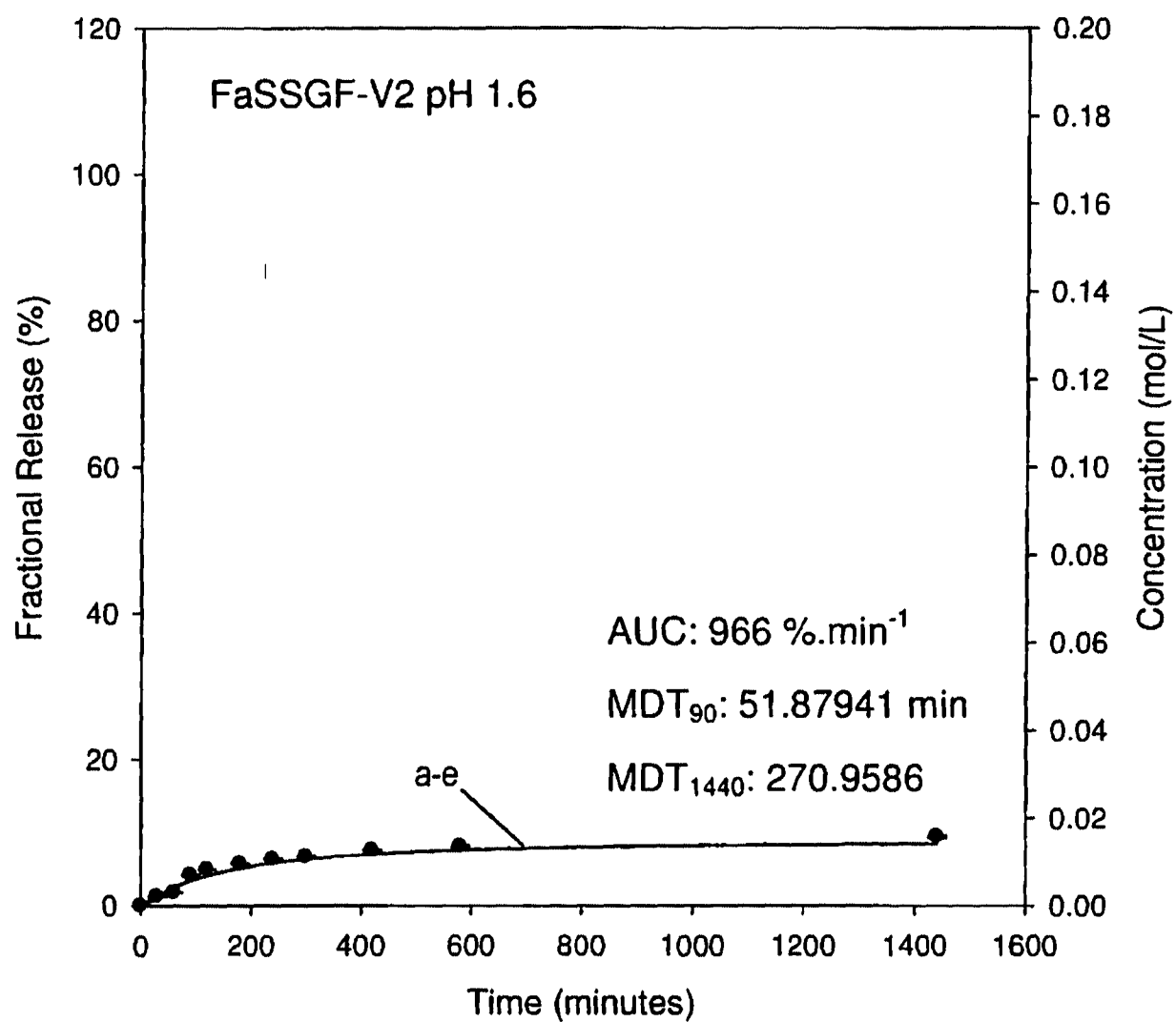


FIG 10c

Indomethacin

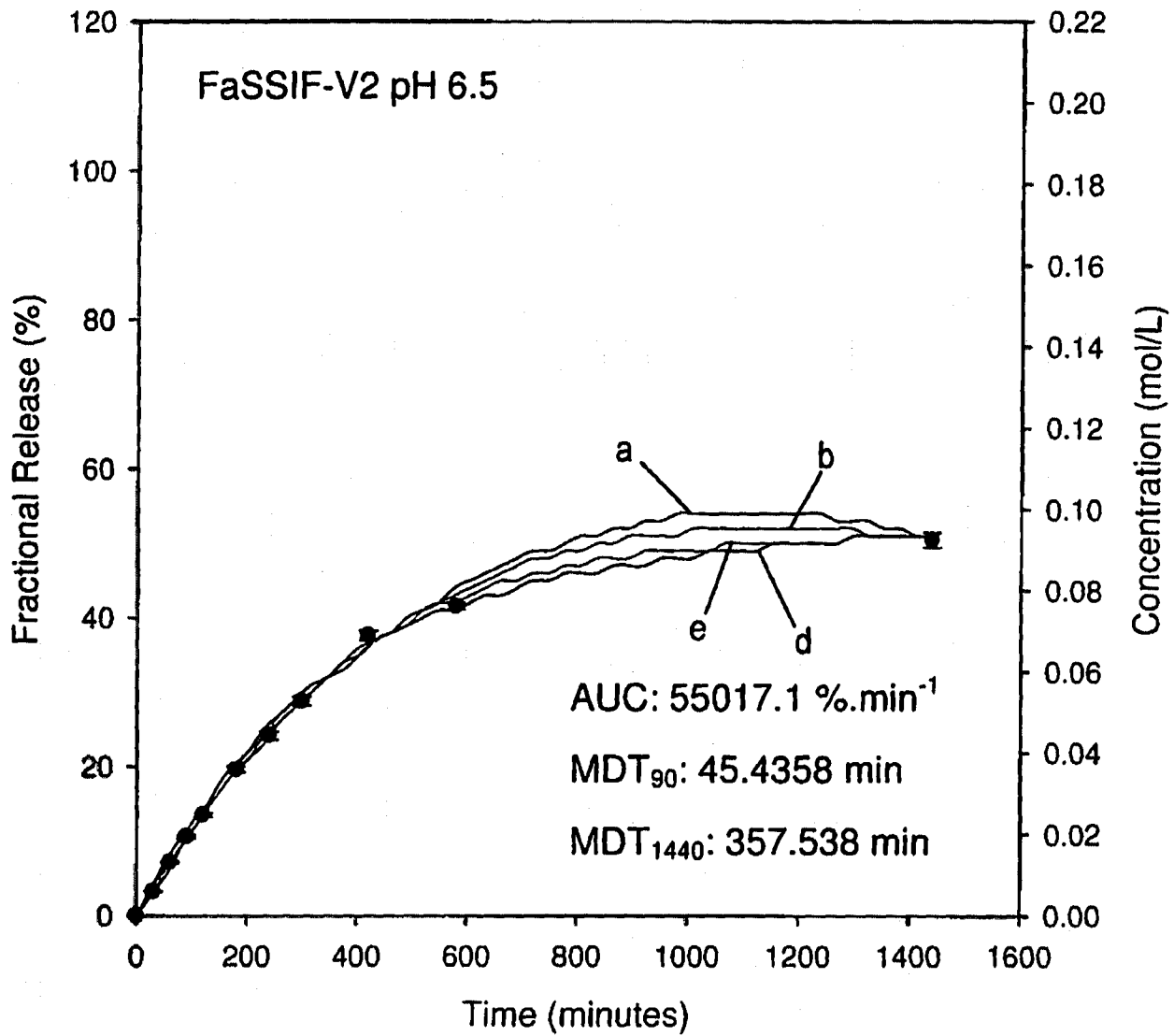


FIG 10d

Indomethacin

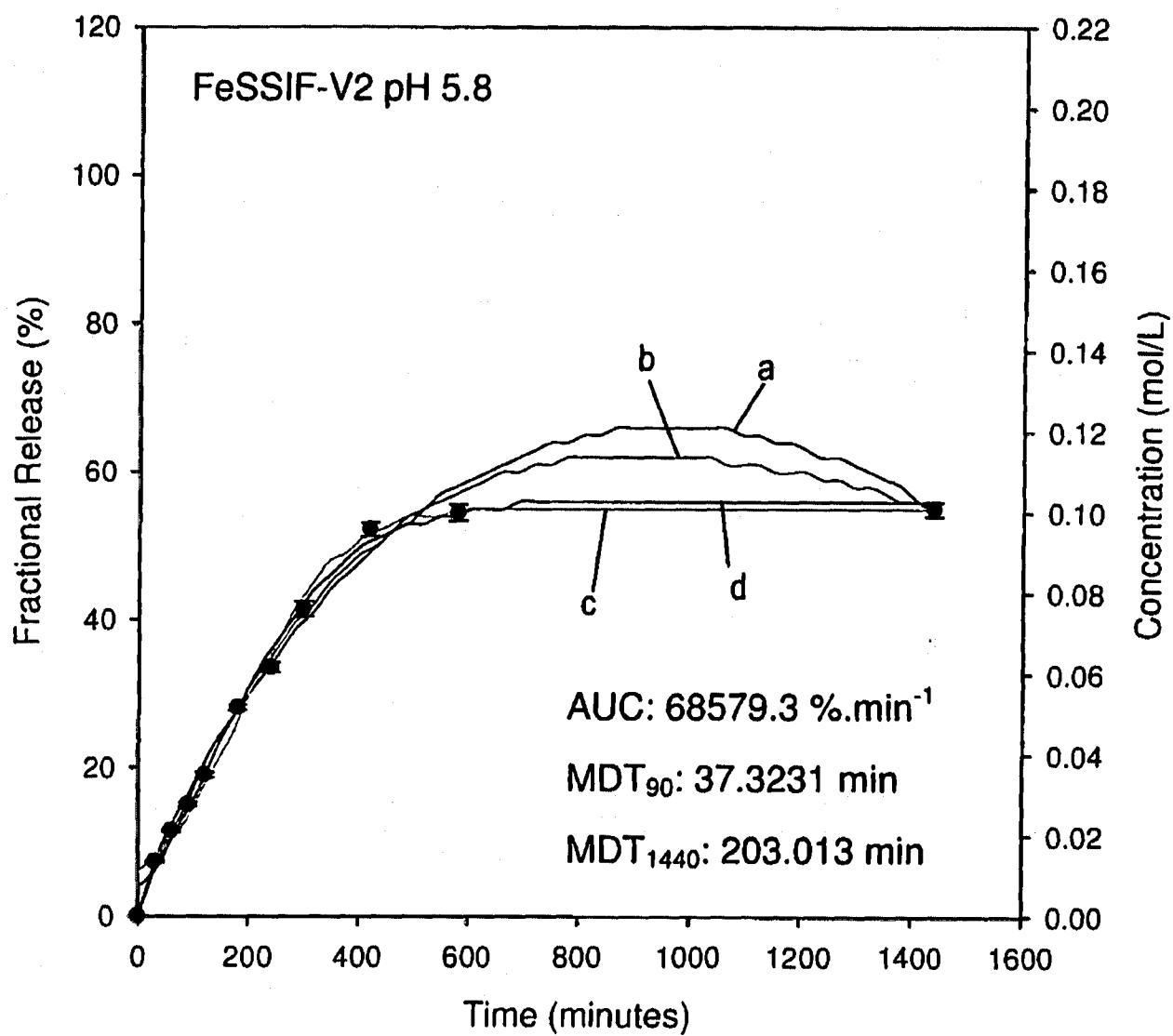


FIG 11a

Indomethacin

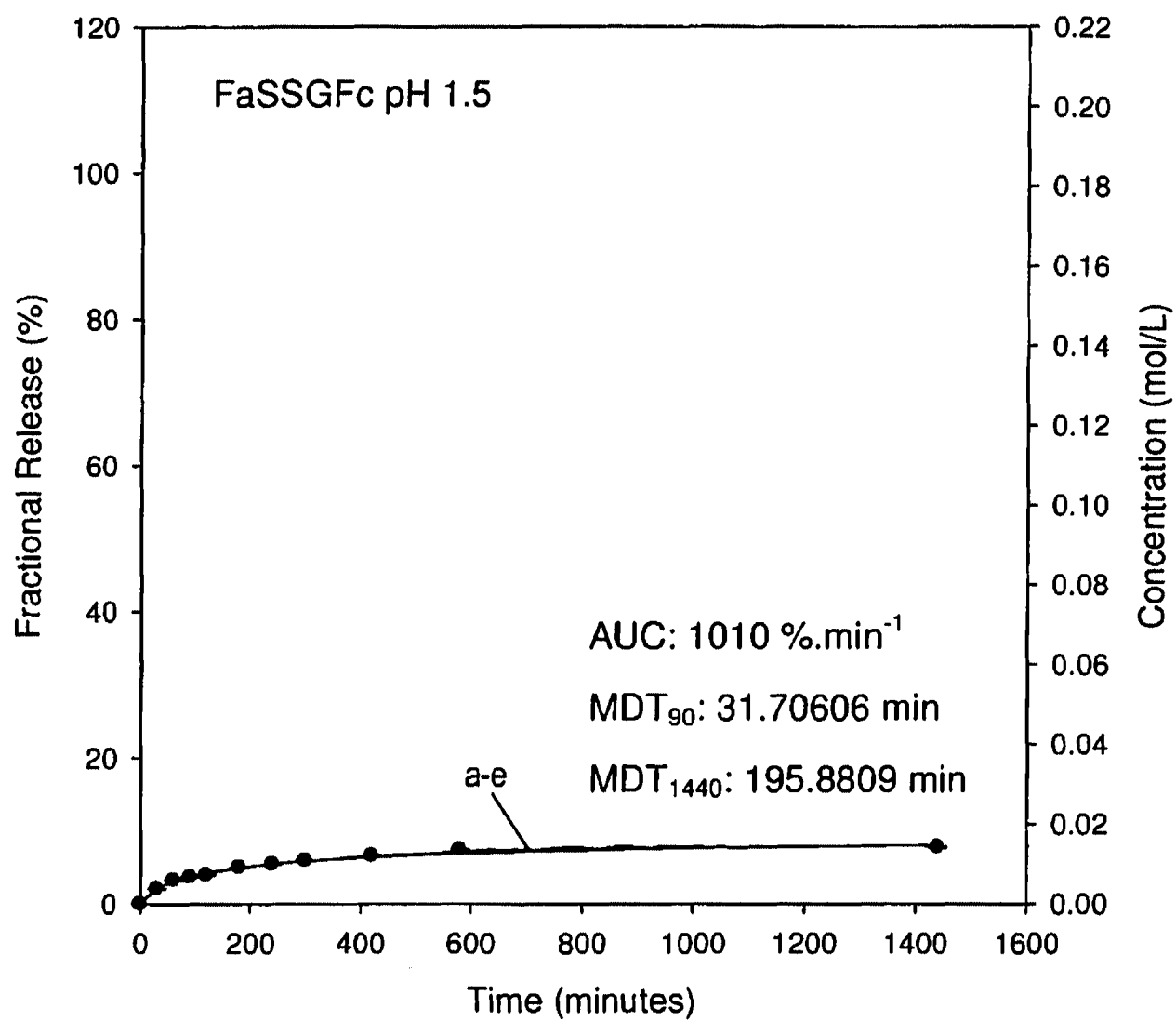


FIG 11b

Indomethacin

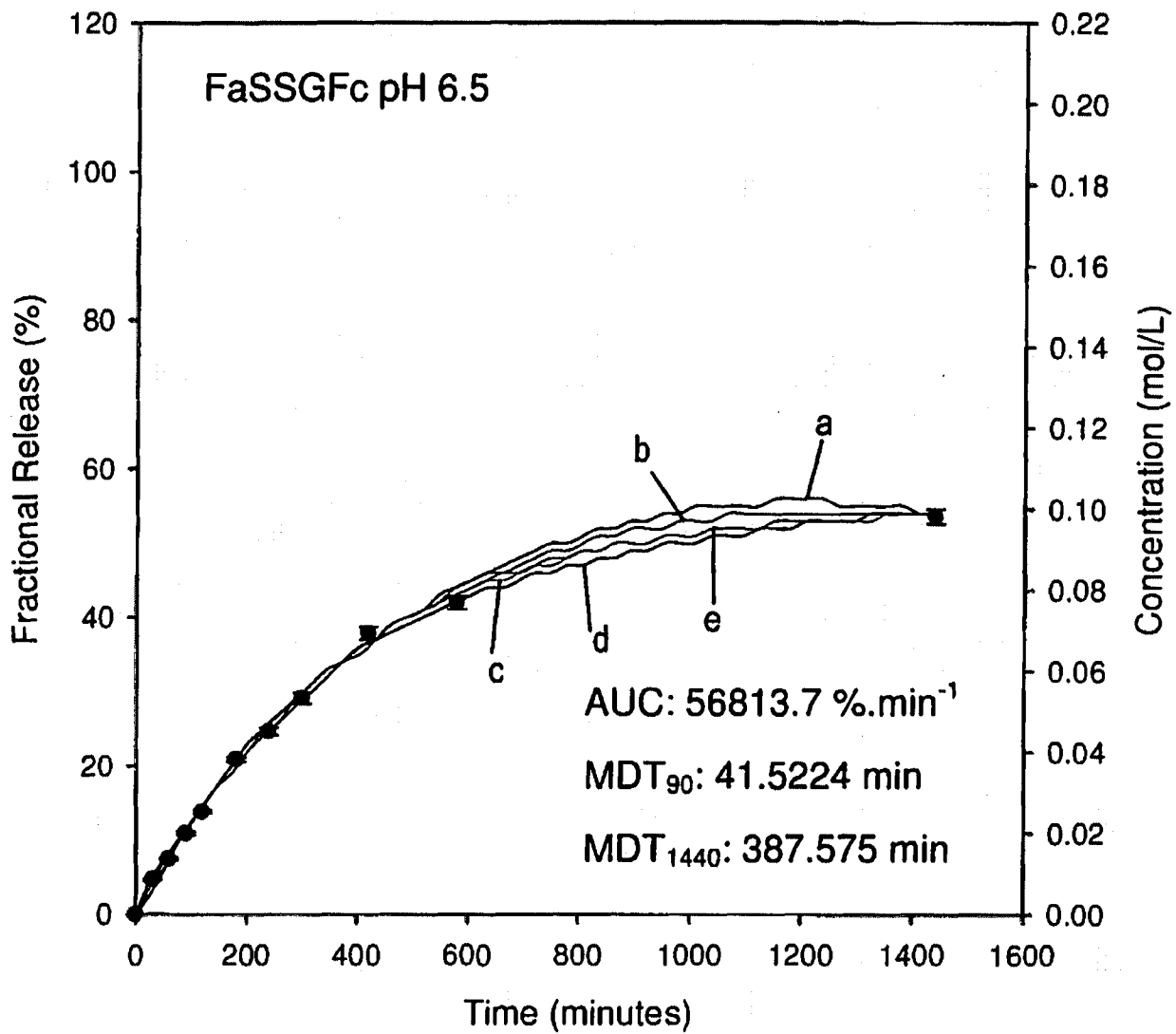


FIG 11c

Indomethacin

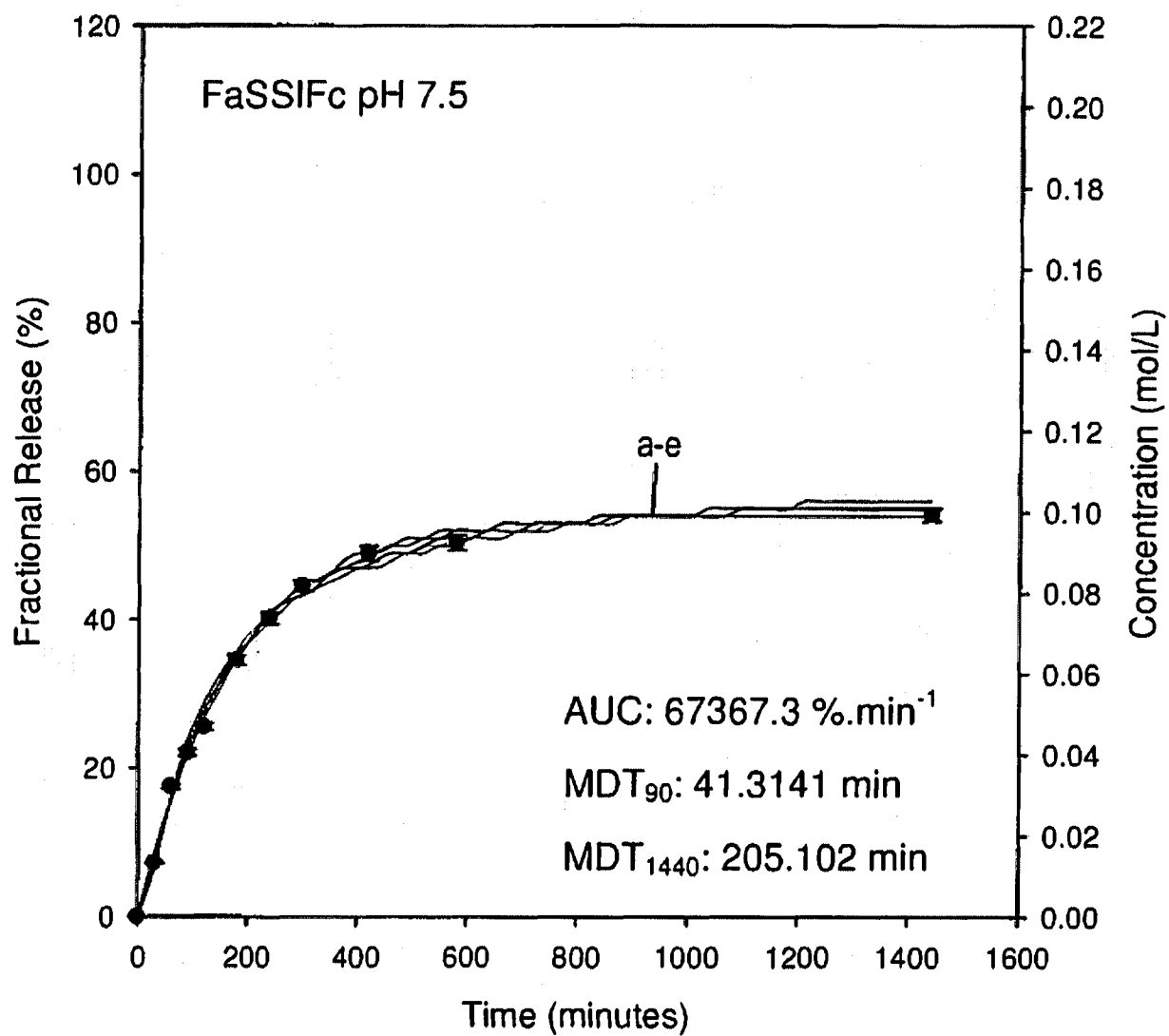


FIG 11d

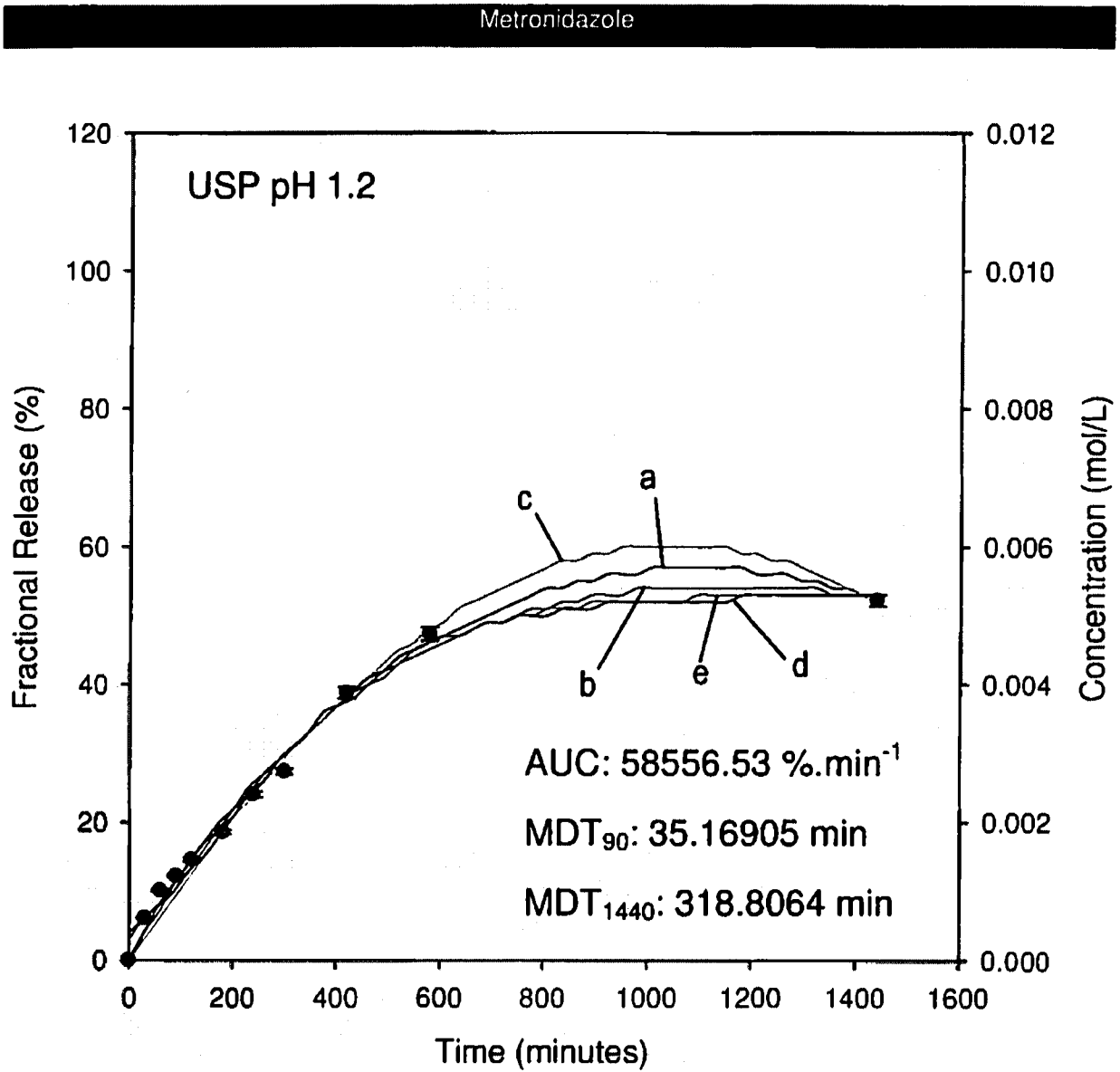


FIG 12a

Metronidazole

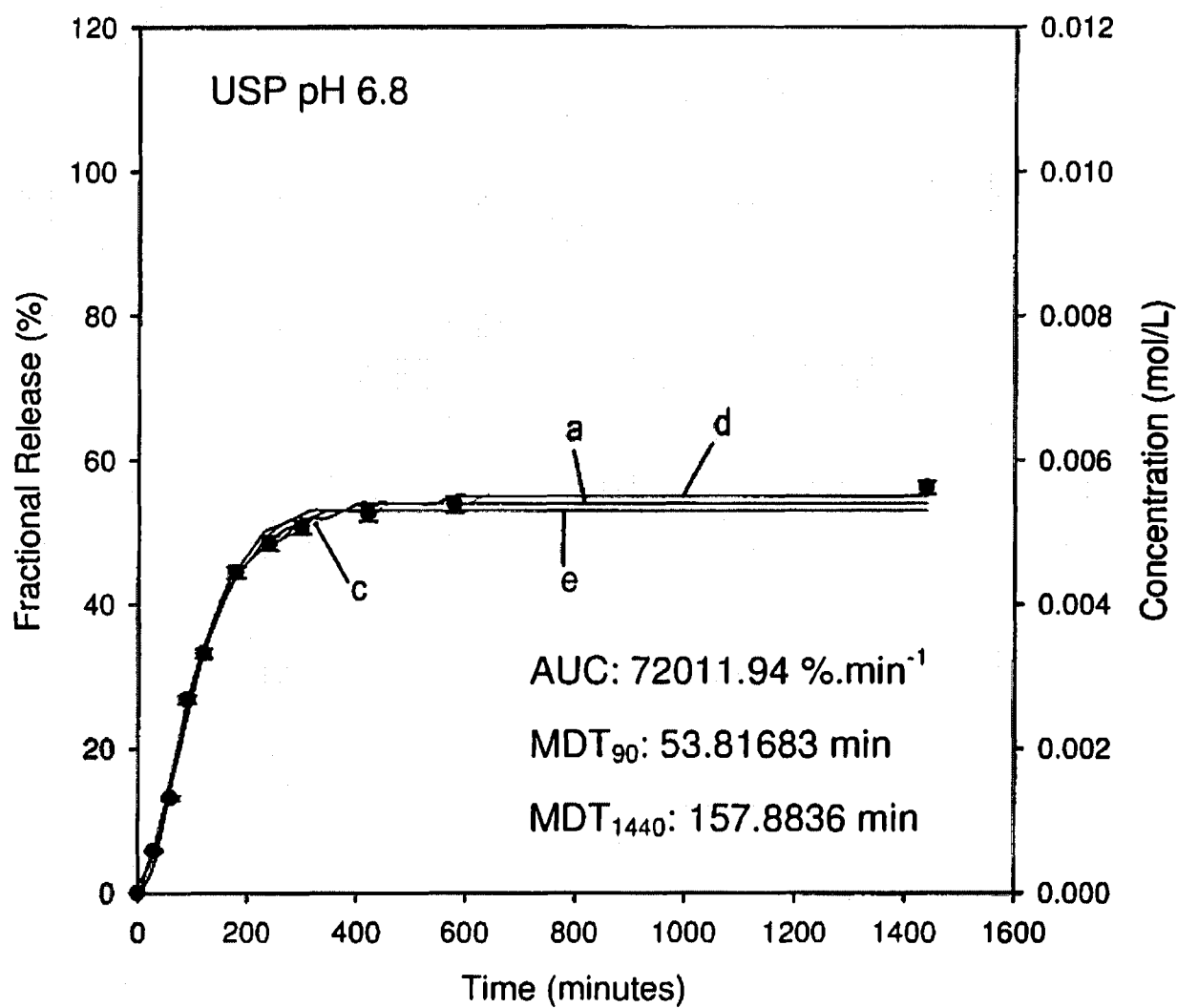


FIG 12b

Metronidazole

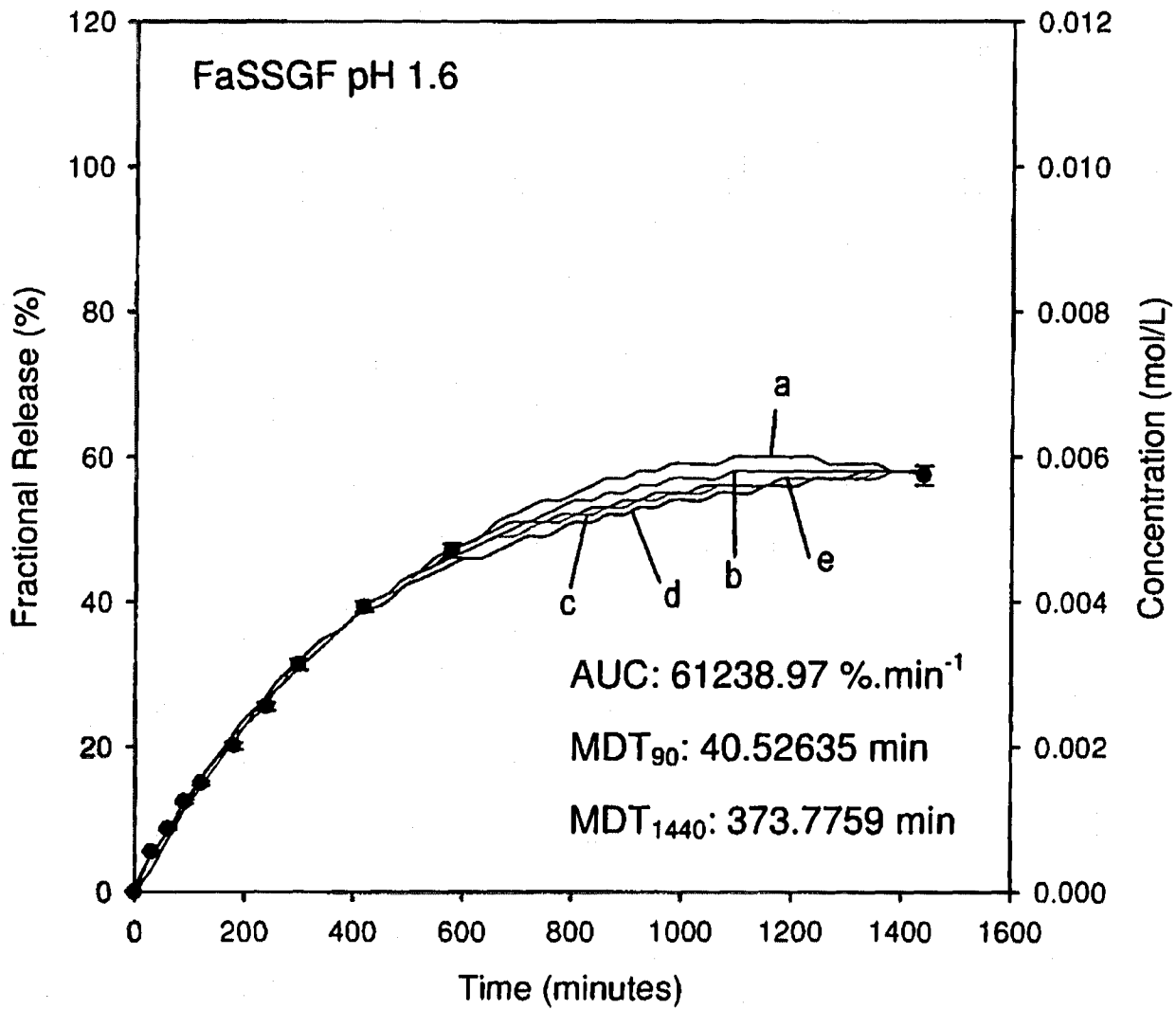


FIG 12c

Metronidazole

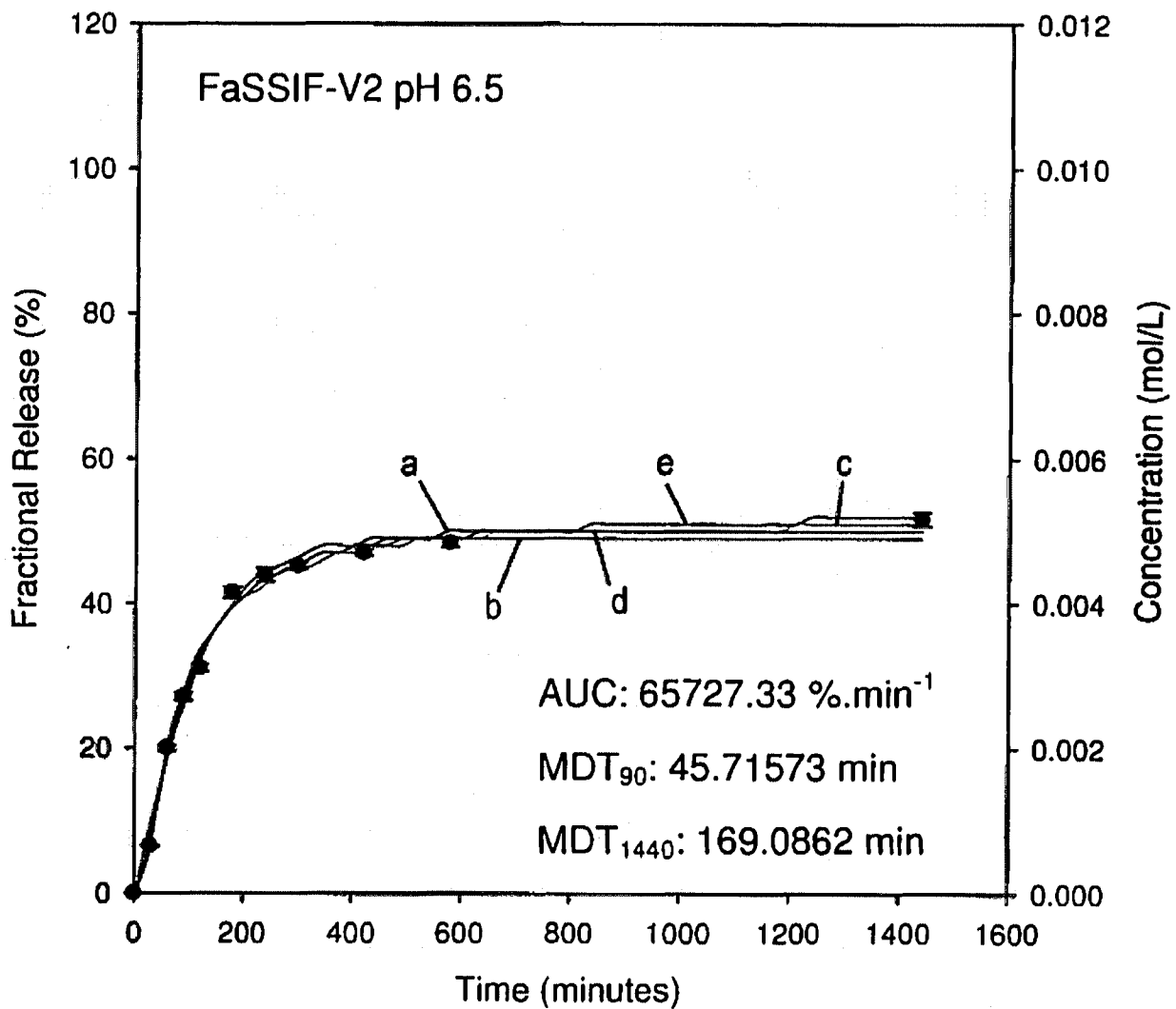


FIG 12d

Metronidazole

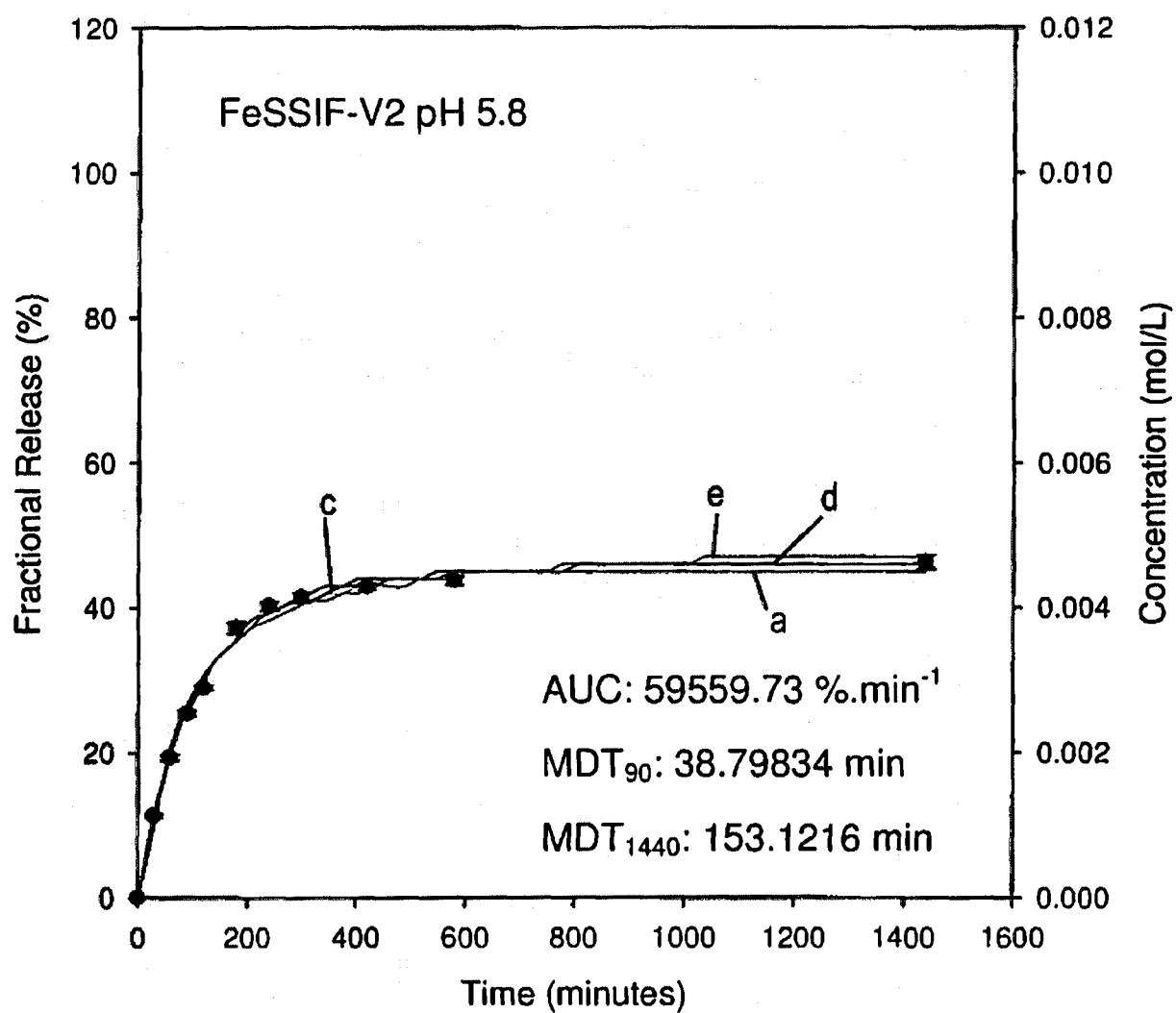


FIG 13a

Metronidazole

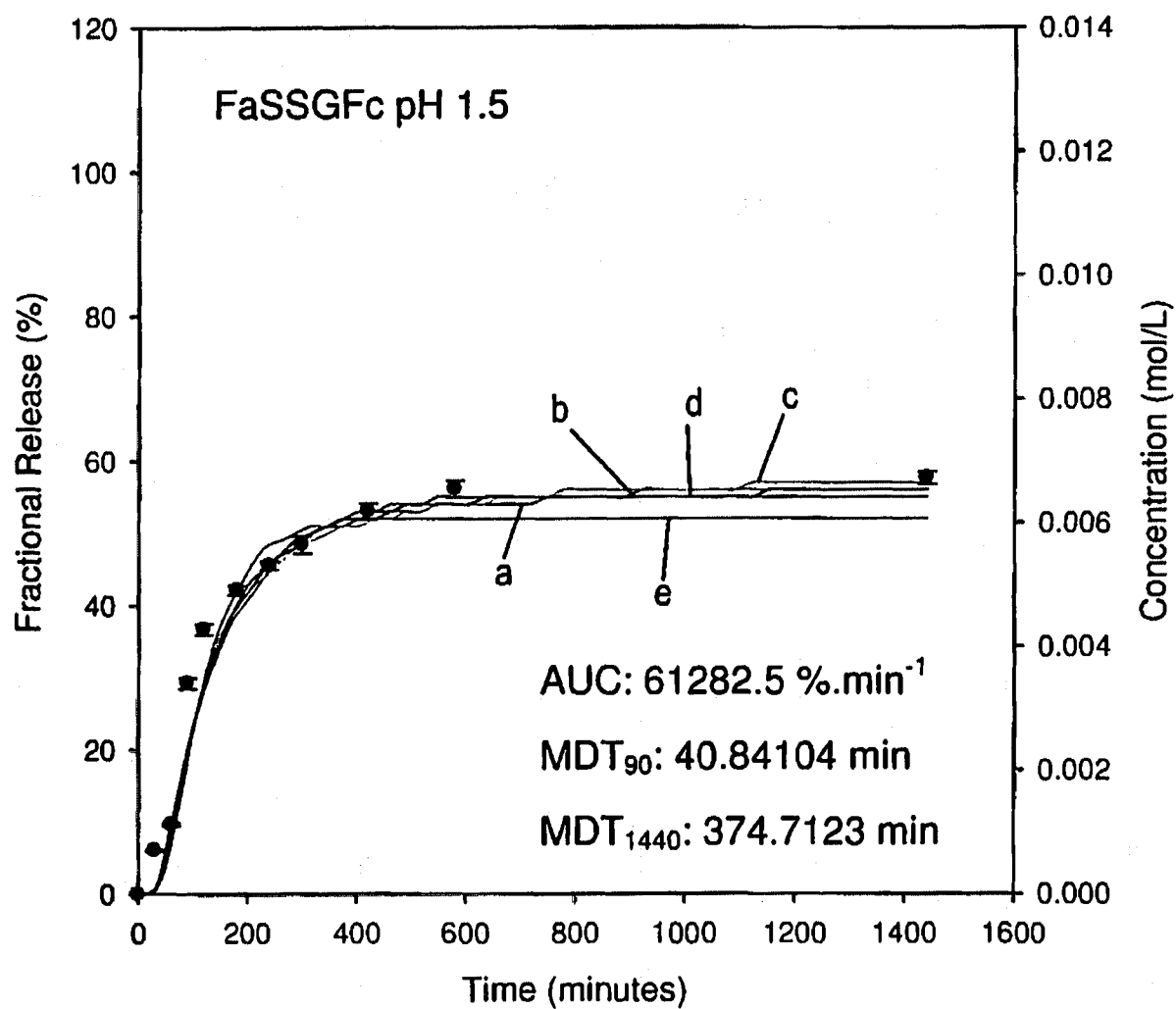


FIG 13b

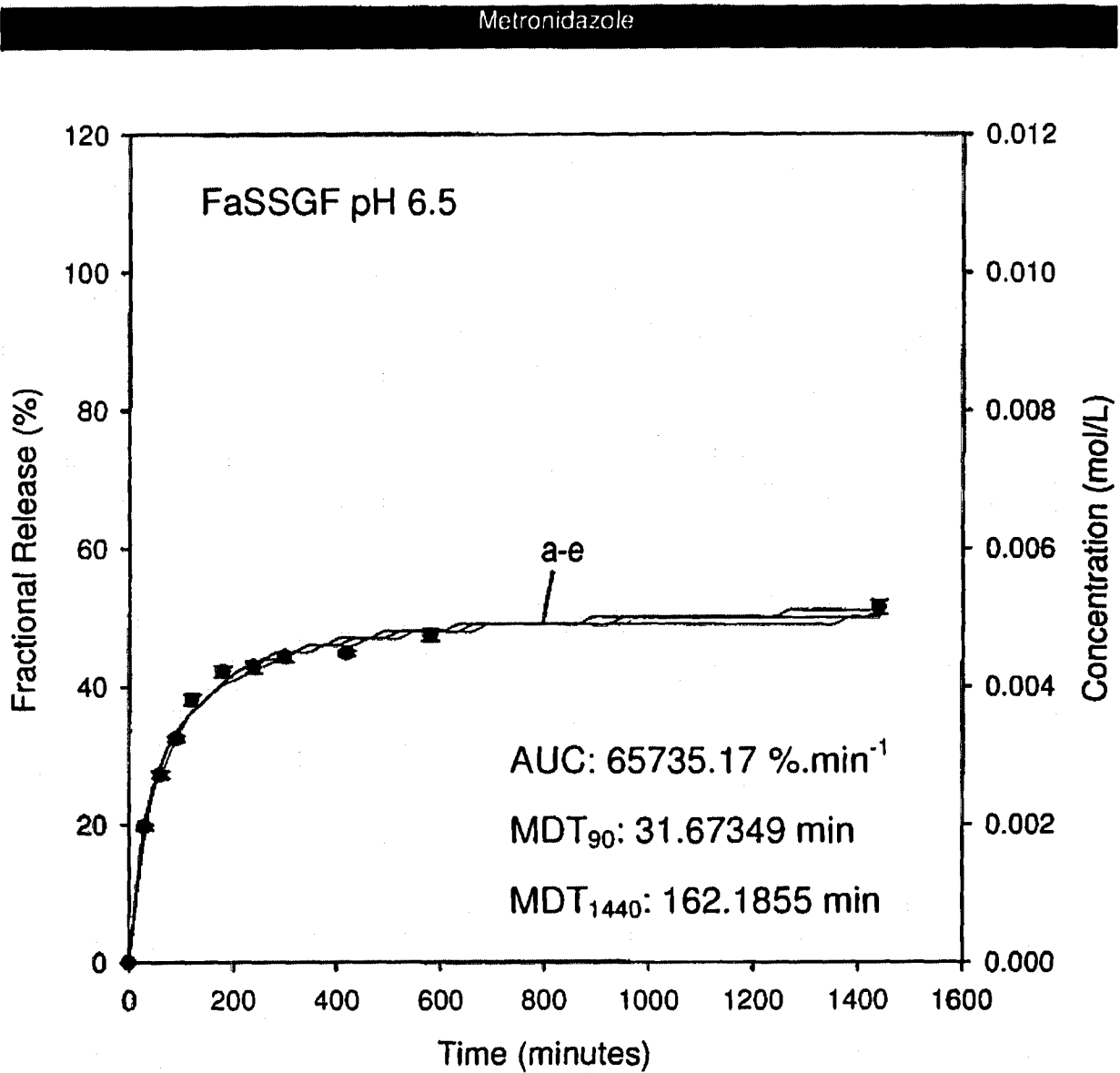


FIG 13c

Metronidazole

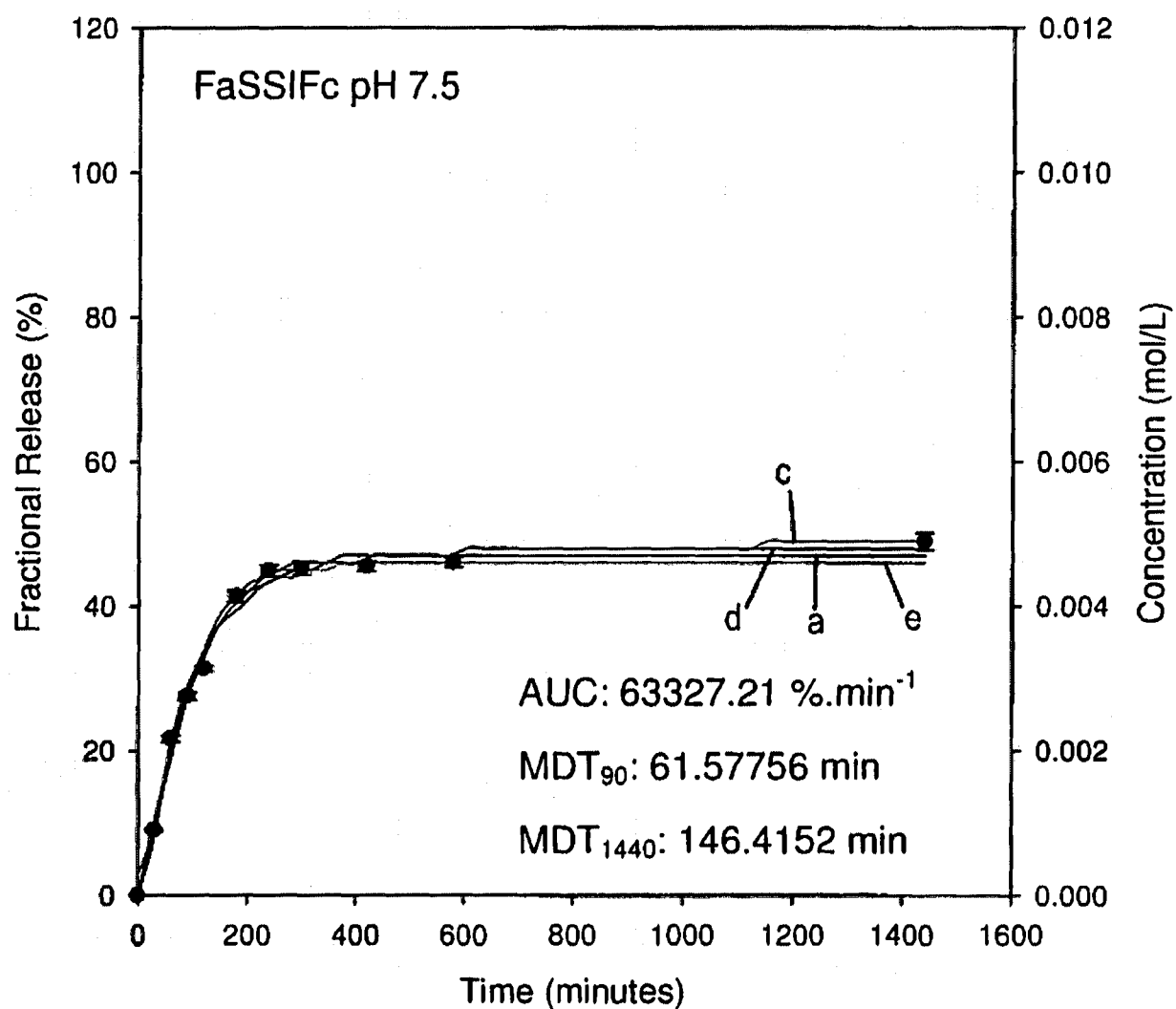


FIG 13d

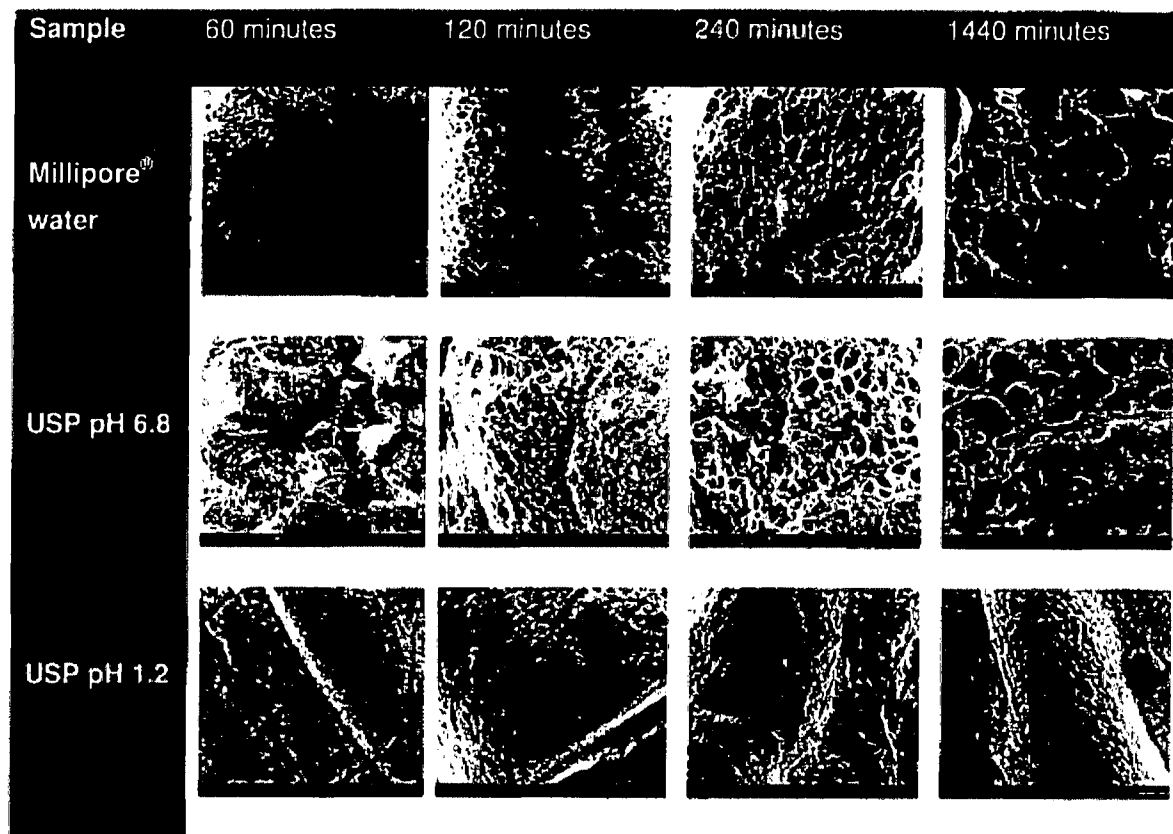


FIG 14

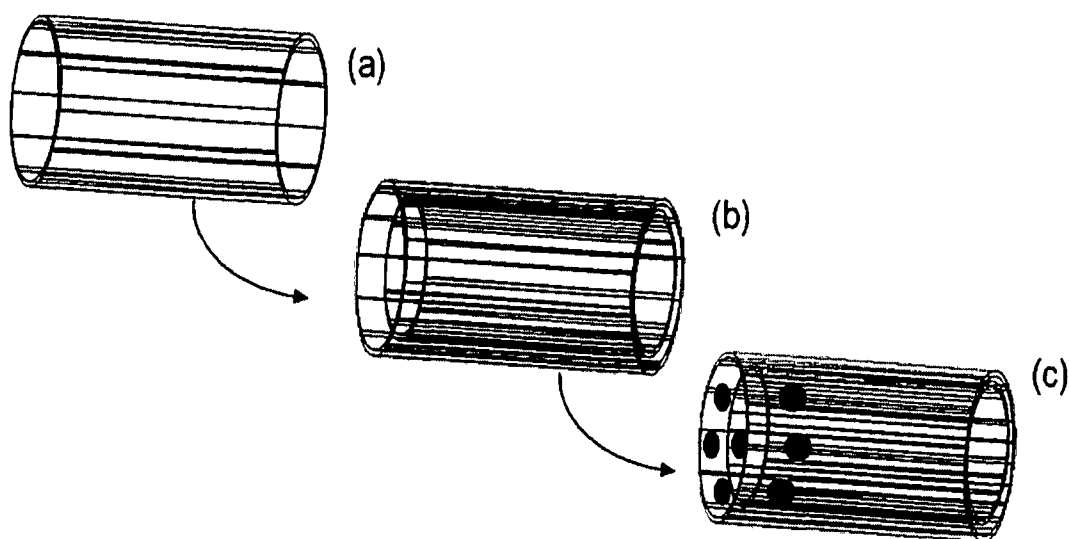


FIG 15

Noncompartmental Parameters			
Parameter	Units	IV bolus Average (SD)	Oral Average (SD)
R ²		0.991	0.9919
R ² adjusted		0.9819	0.9835
Correlation XY		-0.9983 (±0.0016)	-0.9979 (±0.0029)
Number of points for Lambda Z		3	3
Lambda Z	1/min	0.0648 (±0.0038)	0.0153 (±0.003)
Lambda Z (lower)	min	15 (±0)	126 (±13.4164)
Lambda Z (upper)	min	45 (±0)	180 (±0)
HL Lambda Z	min	10.7225 (±0.6151)	46.7703 (±8.9668)
Tlag	min		39 (±8.2158)
Tmax	Min	0 (±0)	69 (±8.2158)
Cmax	pg/mL	245.2418 (±8.5873)	92.0276 (±5.4563)
Cmax Dose	pg/mL/mg	7357.328 (257.6216)	92.0276 (±5.4563)
C0	pg/mL	245.2418 (±8.5873)	
Tlast	min	45 (±0)	180 (±0)
Clast	pg/mL	16.8164 (±0.9357)	23.0898 (±5.0967)
AUClast	min.pg/mL	4133.328 (±188.3854)	7145.957 (±492.2036)
AUCall	min.pg/mL	4259.451 (±192.0297)	7838.652 (±415.0113)
AUCINF Observed	min.pg/mL	4393.699 (±188.4762)	8755.055 (±533.1354)
AUCINF Dose Observed	min.pg/mL/mg	131812.3 (5654.342)	8755.055 (±533.1354)
AUC % Extrapolated Observed	%	5.9339 (±0.5829)	18.21418 (±6.4542)
AUC % Back Extrapolated Observed	%	0 (±0)	
Vz Observed	L	117.6464 (±10.391)	
Cl Observed	mL/min	7597.63 (323.1484)	
	L		7683.581 (±1224.886)
Vz F Observed			
Cl F Observed	mL/min		114551.6 (±6819.484)
AUCINF predicted	min.pg/mL	4387.619 (±185.758)	8735.278 (±541.1318)
AUCINF dose predicted	min.pg/mL/mg	131629.9 (5572.796)	8735.278 (±541.1318)
AUC % Extrapolated predicted	%	5.8049 (0.6852)	18.03258 (6.3385)
AUC % Back Extrapolated predicted	%	0 (±0)	
Vz predicted	L	117.7985 (±10.2773)	
Cl predicted	mL/min	7607.853 (318.8629)	
Vz F predicted	L		7702.965 (±1238.49)

FIG 16a

Vz F predicted	mL/min	114823.5 (±6973.627)
AUMClast	min ² .pg/mL	55465.59 (±2592.511) 757968.9 (±35626.86)
AUMCINF Observed	min ² .pg/mL	71223.68 (±3148.244) 1162597 (±194881.6)
AUMC % Extrapolated Observed	%	22.1132 (±1.9221) 33.5556 (±9.7667)
AUMCINF predicted	min ² .pg/mL	70859.53 (3156.683) 1157618 (±193098.2)
AUMC % Extrapolated predicted	%	21.7047 (±2.2635) 33.3009 (±9.6122)
MRTIast	min	13.4192 (0.1439) 106.3517 (±6.7386)
MRTINF Observed	min	16.2146 (±0.4421) 132.364 (±16.815)
MRTINF pred	min	16.1546 (±0.4867) 132.1086 (±16.6435)
Vss Observation	L	123.2271 (7.0845)
Vss predicted	L	122.9402 (7.2823)

FIG 16b

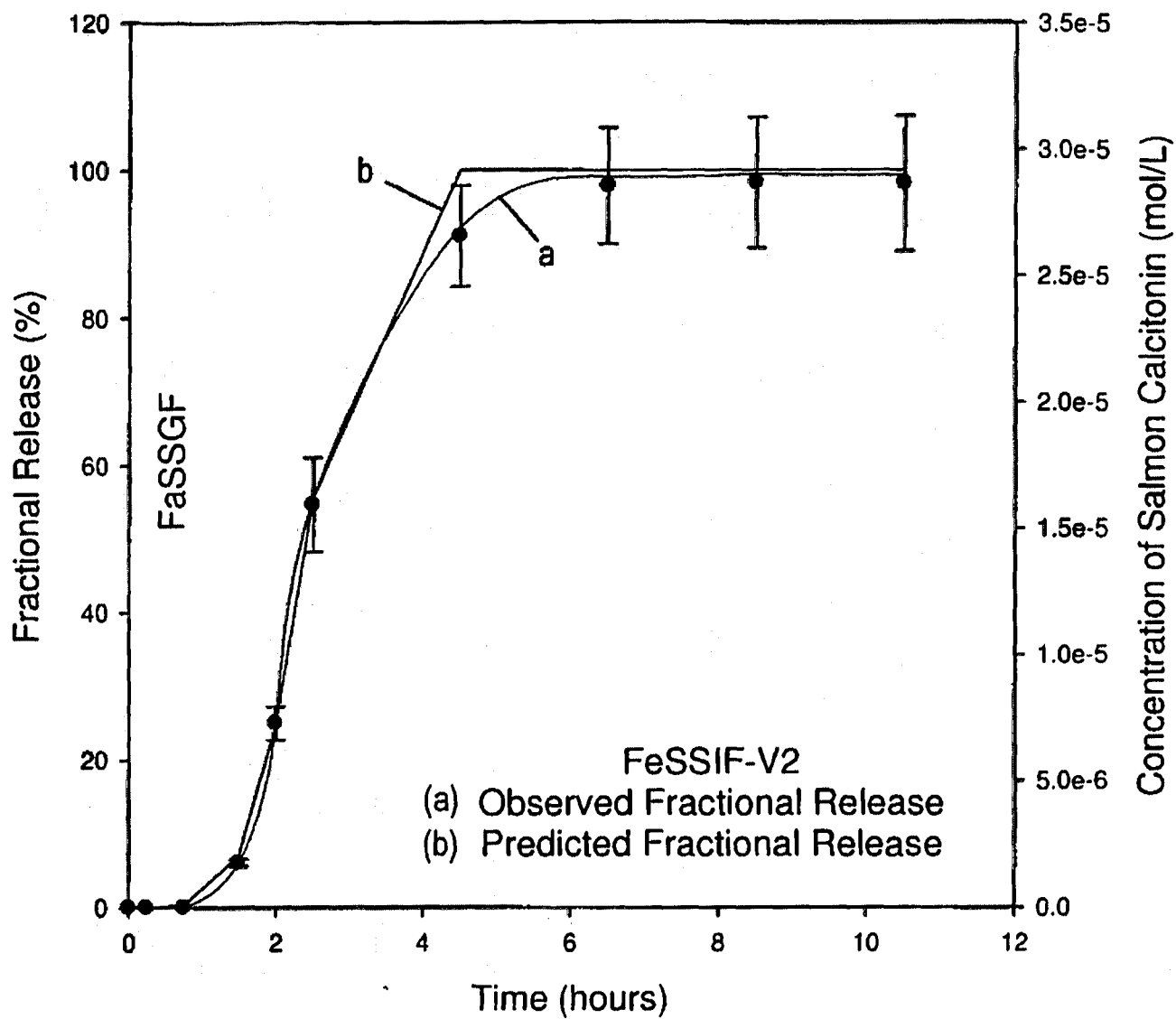


FIG 17a

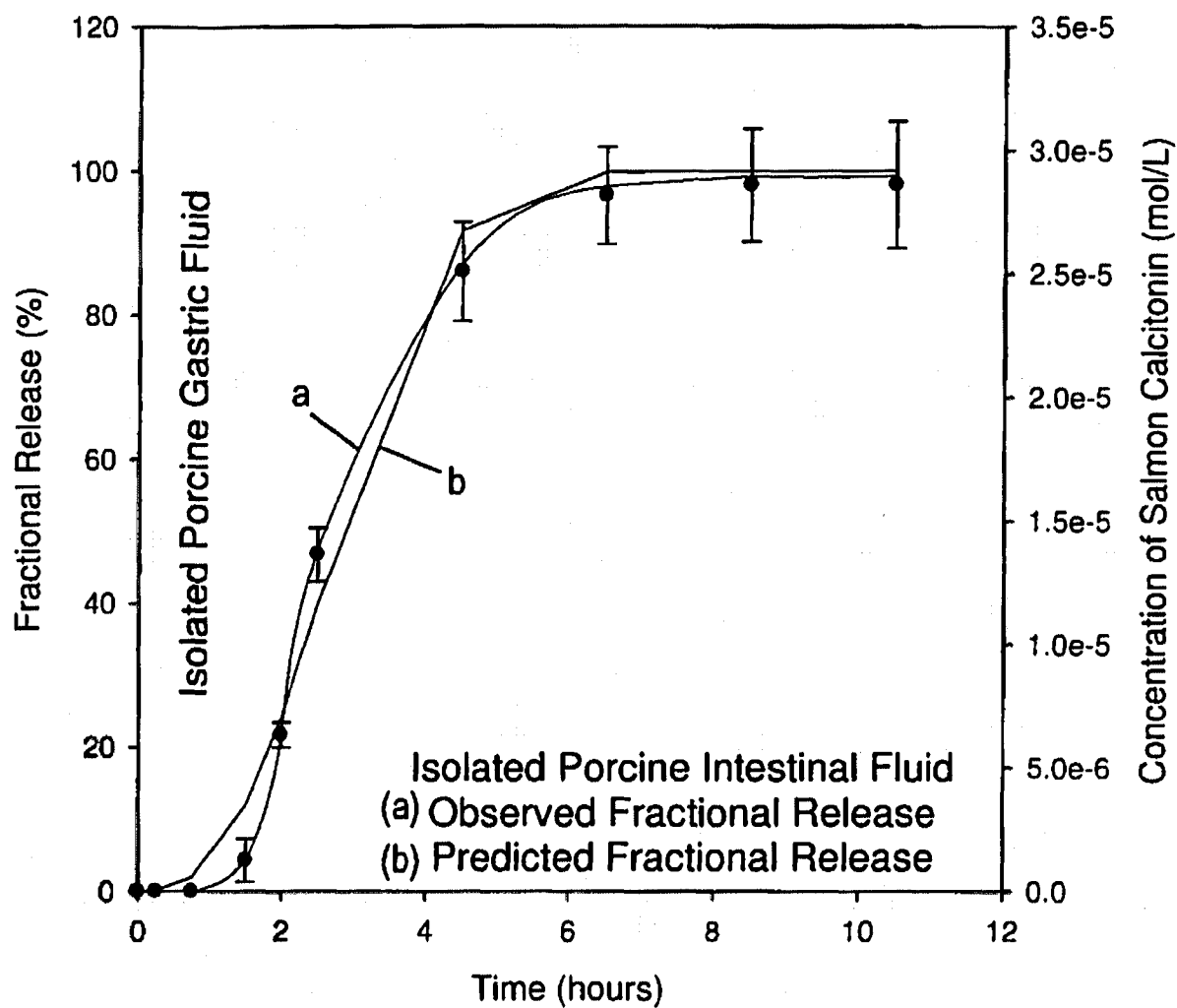


FIG 17b

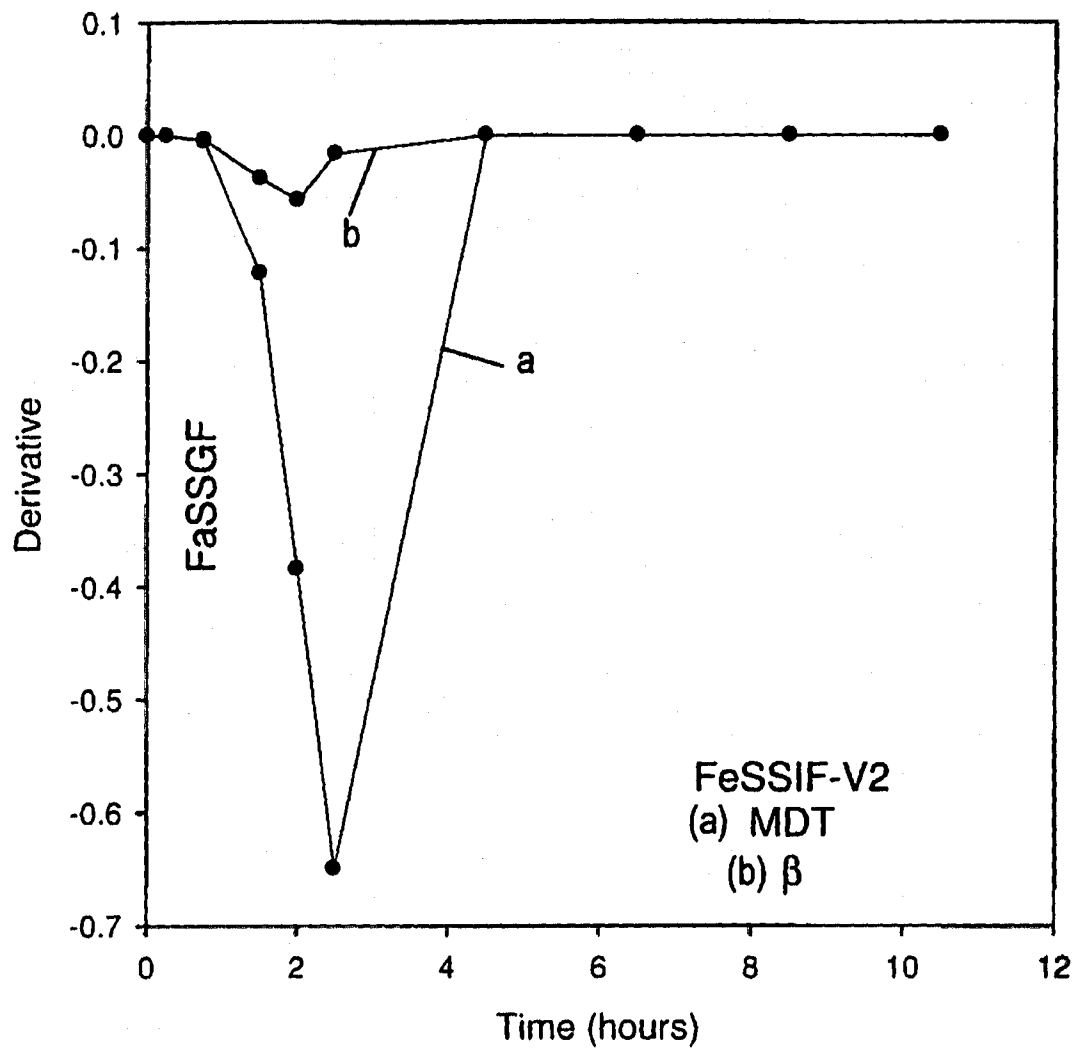


FIG 17c

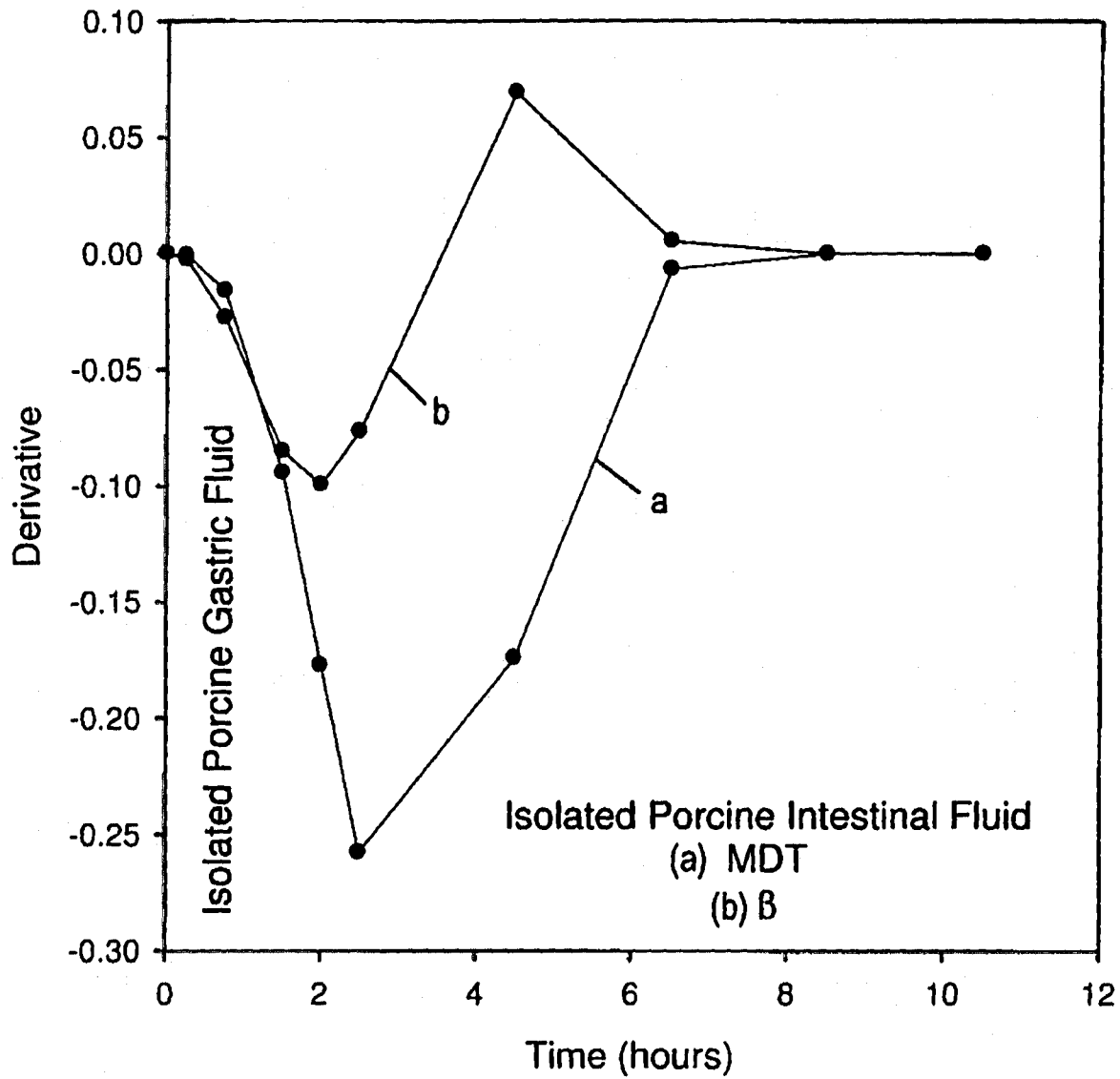


FIG 17d

Noncompartmental Analysis of Fasted State Gastric Fluids to Fasted State Small Intestinal Fluid from the Porcine Model			
Parameter	Units	In Vitro Dissolution	Predicted
R^2		0.9919	0.9947
R^2 adjusted		0.9838	0.9895
Correlation (X,Y)		-0.9959	-0.9974
Number points lambda Z		3	3
Lambda Z	1/min	0.0123	0.0307
Lambda Z lower	min	135	150
Lambda Z upper	min	180	240
Half Life Lambda z	min	56.1973	22.6133
Tlag	min	45	0
Tmax	min	75	105
Cmax	pg/mL	93.8674	74.3135
Cmax D	pg/mL/mg	93.8674	74.3135
Tlast	min	180	240
Clast	pg/mL	28.3373	3.2087
AUClast	min*pg/mL	7281.047	8300.917
AUCall	min*pg/mL	8131.166	8300.917
AUCINF observed	min*pg/mL	9578.508	8405.597
AUCINF D observed	min*pg/mL/mg	9578.508	8405.597
AUC %Extrap observed	%	23.9856	1.2454
Vz F observed	mL	8464317	3881231
CL F observed	mL/min	104400.4	118968.4
AUCINF predicted	min*pg/mL	9556.405	8409.718
AUCINF D predicted	min*pg/mL/mg	9556.405	8409.718
AUC %Extrap predicted	%	23.8098	1.2938
Vz F predicted	mL	8483894	3879329
CL F predicted	mL/min	104641.9	118910.1
AUMClast	min*min*pg/mL	808258.7	958581
AUMCINF observed	min*min*pg/mL	1408070	987119.4
AUMC %Extrap observed	%	42.5981	2.8911
AUMCINF predicted	min*min*pg/mL	1402299	988242.9
AUMC %Extrap predicted	%	42.3619	3.0015
MRTlast	min	111.0086	115.4789
MRTINF observed	min	147.003	117.436
MRTINF predicted	min	146.7392	117.512

FIG 18

Noncompartmental Analysis of Fasted State Simulated Gastric Fluid to Fed State Simulated Intestinal Fluid
Version 2 human model

Parameter	Units	In Vitro Dissolution	Predicted
R^2		0.9919	1
R^2 adjusted		0.9838	1
Correlation (X,Y)		-0.9959	-1
Number points lambda Z		3	4
Lambda Z	1/min	0.0123	0.0356
Lambda Z lower	min	135	135
Lambda Z upper	min	180	240
Half Life Lambda z	min	56.1973	19.4602
Tlag	min	45	0
Tmax	min	75	105
Cmax	pg/mL	93.8674	107.2579
Cmax D	pg/mL/mg	93.8674	107.2579
Tlast	min	180	240
Clast	pg/mL	28.3373	1.4398
AUClast	min*pg/mL	7281.047	7926.316
AUCall	min*pg/mL	8131.166	7926.316
AUCINF observed	min*pg/mL	9578.508	7966.737
AUCINF D observed	min*pg/mL/mg	9578.508	7966.737
AUC %Extrap observed	%	23.9856	0.5074
Vz F observed	mL	8464317	3524039
CL F observed	mL/min	104400.4	125521.9
AUCINF predicted	min*pg/mL	9556.405	7966.856
AUCINF D predicted	min*pg/mL/mg	9556.405	7966.856
AUC %Extrap predicted	%	23.8098	0.5089
Vz F predicted	mL	8483894	3523986
CL F predicted	mL/min	104641.9	125520
AUMClast	min*min*pg/mL	808258.7	895149
AUMCINF observed	min*min*pg/mL	1408070	905985
AUMC %Extrap observed	%	42.5981	1.196
AUMCINF predicted	min*min*pg/mL	1402299	906016.8
AUMC %Extrap predicted	%	42.3619	1.1995
MRTlast	min	111.0086	112.9338
MRTINF observed	min	147.003	113.721
MRTINF predicted	min	146.7392	113.7233

FIG 19

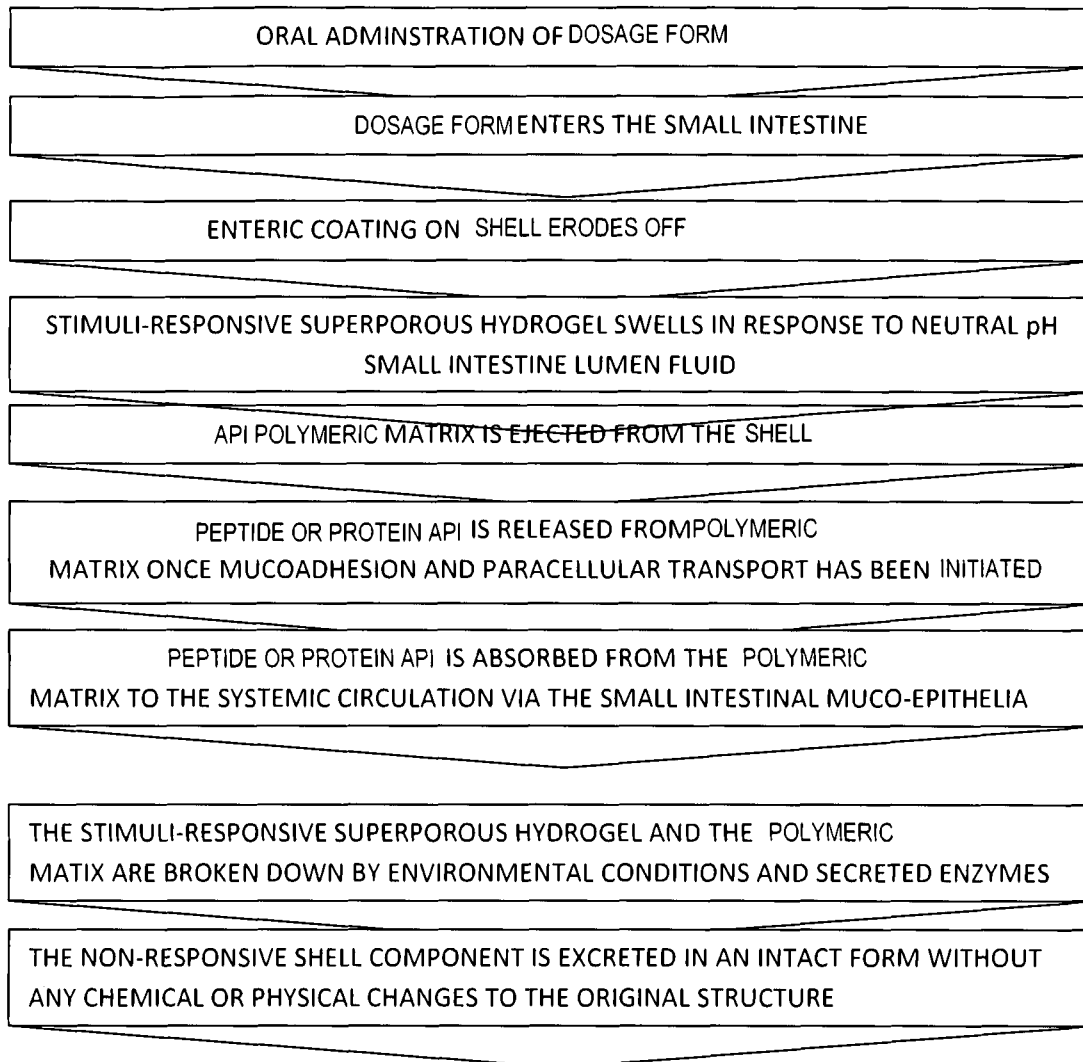


FIG 20