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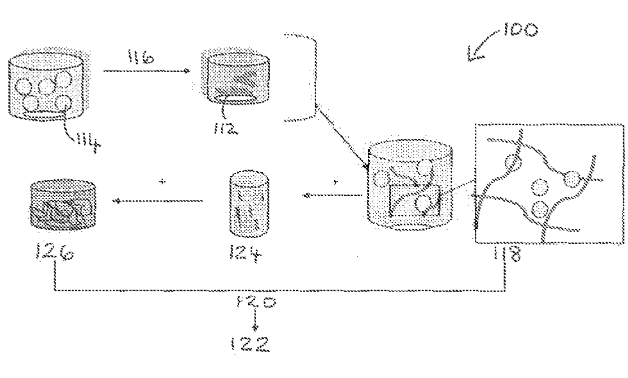

FIGURE 2

(57) **Abstract**: The invention relates to an oral pharmaceutical dosage form comprising a first layer of porous crosslinked polymers including a polysaccharide, polyethylene oxide (PEO) and/or polyethylene glycol or a derivative of polyethylene glycol, a crosslinking agent, and a first active pharmaceutical ingredient, the first layer to provide uniform release of the first (API) upon oral administration of the dosage form. The dosage form preferably further comprises a second layer, the second layer comprising a plurality of multilayered devices embedded within a carrier, the second layer to provide pulsatile release of a second pharmaceutically active ingredient (API) upon oral administration of the dosage form.

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2 LAYERS TABLET ORAL DOSAGE FORM FOR VARIOUS DRUG RELEASE

FIELD OF THE INVENTION

This invention relates to oral pharmaceutical dosage form for providing in use uniform and/or pulsatile release of active pharmaceutical ingredients (APIs) in use.

BACKGROUND OF THE INVENTION

The treatment of schizophrenia syndrome has seen vast improvement in the recent years with the discovery and introduction of second generation antipsychotic agents, which depict a clinically reduced occurrence of extrapyramidal side effects (Bravo-Mehmedbasic A., 2011). Schizophrenia is one of the major psychiatric disorders that greatly impairs the quality of life of patients and their caregivers as well creating an substantial financial burden on society (Peuskens J., et al., 1999). The high cost of second generation antipsychotics as compared to their first generation counterparts has led to a great many debates about the cost benefit ratios, however comparative studies have shown that these agents improve negative symptoms and concomitant depression better than the conventional agents (Leucht S., et al., 2009). Furthermore clinical outcomes with first generation agents have shown suboptimal results with a high degree of extrapyramidal side effects and relapse rates compared to second generation agents (Jones P.B, et al., 2006). Among the second generation antipsychotics are sulpiride, one of the many drugs used in the management and treatment of psychiatric disorders. It is an anti-psychotic neuroleptic agent that displays anti-dopminergic activity which is responsible for it efficacy to treat psychotic disorders. It has been shown to display low bioavailability (30%; Chitneni M et al., 2011) and is effective in the treatment of schizophrenia; the acute and chronic types, poor lactation, depression, anxiety, tardive dyskinesia and tension (Soares et al., 2011).

Non adherence to therapy is a common cause for relapse and hospitalization among the schizophrenic community and thereby leads to greater costs incurred in treatment programs as well as reduced prognosis; many studies have linked poor therapeutic outcomes with low patient compliance, thus researchers have suggested that the use of long-acting drug delivery systems may significantly improve compliance (Olivares et al., 2009).

In general, the hazard and intensity of side-effects related to anti-psychotic drugs increases with a corresponding increase in dosage, furthermore it has been stated that the risk of side-effects also depends on the rate of drug delivery (Barnes et al., 2006). The current challenge in the treatment of Schizophrenia with antipsychotics and sulpiride in particular is that it requires the administration of high dosages (owing in part to its low bioavailability) which has many disadvantages such as multiple dosing, thus leading to reduced patient compliance and hence treatment failure (Barnes et al, 2006).

There remains a need to address the poor bioavailability, poor patient compliance, and multiple dosage administrations of active pharmaceutical ingredients (APIs) typically associated with the treatment of mental disorders, preferably antipsychotics such as sulpiride.

SUMMARY OF THE INVENTION

In accordance with the invention there is provided an oral pharmaceutical dosage form comprising a first layer of porous crosslinked polymers including a polysaccharide, polyethylene oxide (PEO) and/or polyethylene glycol or derivatives of polyethylene glycol, and a crosslinking agent, the first layer to provide uniform release of a first active pharmaceutical ingredient (API) upon oral administration of the dosage form.

Derivatives of polyethylene glycol may include at least one of the following group: high molecular weight polyethylene derivatives such as, but not limited to, the following group: polyoxyethlene, polyoxyethlene ether, polyglycol, and hydro-omega hydroxy poly (oxy-1, 2-ethanediyl).

The oral pharmaceutical dosage form may further comprise a second layer including a plurality of multilayered devices loaded with a second API and said plurality of multilayered devices embedded within a carrier, the second layer to provide pulsatile release of the multilayered devices and in turn pulsative release of the second active pharmaceutical ingredient (API) upon oral administration of the dosage form. Further inclusion of the second layer provides a dosage form having a dual layered or bi-layered configuration.

The carrier may comprise porous crosslinked polymers including the polysaccharide, polyethylene glycol (PEO), and a crosslinking agent. Alternatively, and in a preferred embodiment of the invention, the carrier may comprise carboxymethylcellulose and gellan gum.

The first layer may further include a first lipid such that in use after oral administration of the dosage form, the first lipid and the polysaccharide form *in situ* a lipopolysaccharide increasing permeation of the first API at the blood brain barrier and in so doing improving bioavailability of the first API and further facilitating interaction of the dosage form with surface carbohydrates on mucous or epithelial cells of a stomach of a user therein increasing adhesion of the dosage form to the stomach wall to increase gastric retention.

The carrier may further comprise a second lipid such that in use after oral administration of the dosage form, the second lipid and the polysaccharide form *in situ* a lipopolysaccharide increasing permeation of the second API at the blood brain barrier and in so doing improving bioavailability of the second API, and further facilitating interaction of the dosage form with surface carbohydrates on mucous or epithelial cells of a stomach of a user therein increasing adhesion of the dosage form to the stomach wall to increase gastric retention.

The first and second API may be the same and/or different. The first and/or second API may be an anti-psychotic agent. The anti-psychotic agent may be a typical and/or atypical anti-psychotic agent. The first and/or second APIs may be sulpiride and/or valproic acid.

The first and second lipid may be the same. The first and second lipids may be lectins and/or lecithins.

The polysaccharide may be a starch based polysaccharide or a derivative thereof. The polysaccharide may be gellan gum.

The crosslinking agent may be phosphorus oxychloride ($POCl_3$), sodium trimethaphosphate, epichlorohydrin and/or a derivatives of the aforementioned. Preferably, the crosslinking agent is epichlorohydrin.

The first layer of porous crosslinked polymers and/or the carrier may further each comprise at least one inactive polymer agent selected from the group including, but not limited to: substituted or unsubstituted acrylic and methacrylic acids, alkyl celluloses, polyethylene glycol, sodium alginate, polyvinyl alcohol, carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, ethylcellulose, hydroxyethylcellulose, a sugar or sugar based group, and mixtures of the aforementioned.

The first layer of porous crosslinked polymers and/or the carrier may further each comprise N-acetyl cysteine facilitating bioadhesion of the dosage form to the stomach in use.

The first layer of porous crosslinked polymers and/or the carrier may each form a semi-interpenetrating polymer network (IPN) wherein the polysaccharide and the polyethylene oxide (PEO) semi-interpenetrate each other. In a preferred embodiment of the invention a semi-interpenetrating polymer network (IPN) forms from crosslinked PEO and gellan gum.

The first layer of porous crosslinked polymers and/or the carrier may be layered like an onion and/or a sandwich.

In a certain embodiment of the invention, the first layer of the dosage form may comprise 1 part by weight of a API in predominantly amorphous form, between 0.1-12 parts by weight of an inactive polymer that assists in the dissolution of the API in a ratio of 2 parts by weight of the crosslinked polymer and crosslinked by 0.4-0.8 part by weight of crosslinking agent.

The first layer may comprise 1 part by weight of API relative to 1-10 parts by weight of crosslinked polymer.

In another embodiment of the invention, the first layer may comprise 2 parts by weight of API in a predominantly amorphous form and between 1-12.5 part by weight of an inactive polymer that assists in controlling the dissolution of the active agent in ratio of 0.5 parts by weight of crosslinked polymer and crosslinked by 0.3-6% by weight crosslinking agent.

In another embodiment of the invention, the first layer may comprise 2 parts by weight of the API relative to 1.12.5 parts by weight of crosslinked polymer.

Each of the plurality of multilayered devices may comprise:

a mucus cleaving layer, preferably the mucous cleaving layer may comprise N-acetyl cysteine loaded alginate;

a mucoadhesive layer comprising a mucoadhesive polymer, preferably the mucoadhesive layer comprising lectin, hypromellose and chitosan;

a second API carrier layer, preferably the second API carrier layer comprising crosslinked Eudragit, sodium alginate and the second API; and

a water insoluble layer, preferably the water insoluble layer comprising a water insoluble polymer, further preferably the water insoluble polymer may comprise gellan gum.

Each of the plurality of multilayered devices may be layered like an onion and/or a sandwich.

There is further provided for an oral pharmaceutical dosage form substantially as herein described, illustrated and/or exemplified with reference to any one of the accompanying examples and/or diagrammatic drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the disclosure will be described below by way of example only and with reference to the accompanying drawings in which:

FIGURE 1 shows a cross-sectional graphical illustration of an oral dosage form according to the invention;

FIGURE 2 graphically depicts the formulation processes undertaken during synthesis of a first layer of the dosage form according to the invention;

FIGURE 3 shows a cross-sectional graphical illustration of multilayered device typically embedded into the a carrier to form a second layer of the oral dosage form according to the invention;

FIGURE 4 shows a diagrammatic representation of Brinells Hardness Number for Box Behnken Statistical Formulations F1-F15 depicting the effect of polymer concentration and crosslinking density on the hardness and mechanical strength of formulations of the first layer of the dosage form;

FIGURE 5	shows an illustration of the difference of Resilience between all statistical Box Behnken design Formulations F1-F15 of the first layer of the dosage form with variances in chemical composition;
FIGURE 6	shows SEM Micrographs of (a) Formulation F1 and (b) F7 of the first layer of the dosage form, after swelling test, showing the change in morphological structure such as porosity achieved by crosslinking reactions as compared to the compact structure of the pure polymers;
FIGURE 7	shows DSC thermogram of semi IPN-xerogel Formulations F1, F7, F9 of the first layer of the dosage form, as well as PEO and GG at a heating rate of 10°C/ min from 10- 300°C under nitrogen atmosphere – Spectra (a) and (b) correspond to PEO and GG respectively with (c), (d), and (e) representing Formulations 1, 7 and 9 respectively;
FIGURE 8	shows FTIR spectra of crosslinked semi-IPN xerogel F1, F7, F9 of the first layer of the dosage frorm, as well as pure PEO and GG depicting the change within chemical structure via the identification of specific functional groups within the spectra obtained. Spectra (a) and (b) correspond to PEO and GG respectively with (c), (d) and (e) representing Formulations 1, 7 and 9 respectively;
FIGURE 9	shows a graphical illustration of the *in vitro* fractional drug release vs. time of sustained release croslinked semi IPN-xerogel first layer Formulations F1-F15 in comparison to release profiles of PEO-GG blend formulations – (a) shows Formulations F1-F7 and (b) shows Formulations F8-F15 and PEO-GG blend;
FIGURE 10	shows a graphical illustration of mucoadhesion for prepared mucoadhesive layer samples 1-20 of the multilayered devices;
FIGURE 11	shows an illustration of % swelling over 24 hours for the mucoadhesive layer samples 1-20 of the multilayered devices; and

FIGURE 12 shows values of Young's Modulus for mucoadhesive layer samples 1-20 of the multilayered devices.

PREFFERRED EMBODIMENTS OF THE INVENTION

Specific, but non-limiting embodiments of the invention will now be described. Certain advantages of the invention will also be discussed herebelow.

In accordance with the invention there is provided an oral pharmaceutical dosage form comprising a first layer of porous crosslinked polymers including a polysaccharide, polyethylene oxide (PEO) and/or polyethylene glycol (PEG) or a derivative of PEG, and a crosslinking agent, the first layer to provide uniform release of a first active pharmaceutical ingredient (API) upon oral administration of the dosage form.

Derivatives of polyethylene glycol may include at least one of, but not limited to, the following group: high molecular weight polyethylene derivatives such as but not limited to polyoxyethlene, polyoxyethlene ether, polyglycol, and hydro-omega hydroxy poly (oxy-1, 2-ethanediyl).

The oral pharmaceutical dosage form may further comprise a second layer including a plurality of multilayered devices loaded with a second API and said plurality of multilayered devices embedded within a carrier, the second layer to provide pulsatile release of the multilayered devices and in turn pulsative release of the second active pharmaceutical ingredient (API) upon oral administration of the dosage form. Further inclusion of the second layer provides a dosage form having a dual layered or bi-layered configuration.

The carrier may be porous crosslinked polymers including the polysaccharide, polyethylene glycol (PEO), and a crosslinking agent. Alternatively, and in a preferred embodiment of the invention, the carrier comprises carboxymethylcellulose and gellan gum.

The first layer may further include a first lipid such that in use after oral administration of the dosage form, the first lipid and the polysaccharide form *in situ* a lipopolysaccharide increasing permeation of the first API at the blood brain barrier and in so doing improving bioavailability of the first API and further facilitating interaction of the dosage form with surface carbohydrates on mucous or epithelial cells of a stomach of a user therein increasing adhesion of the dosage form to the stomach wall to increase gastric retention.

The Applicant believes that increasing bioavailability will allow for the prescription of lower dosages of API which will reduce the amount and/or severity of negative side effects typically associated with high dosages of API. Increased gastric retention will also facilitate more effective release of the API in use.

The carrier may further comprise a second lipid such that in use after oral administration of the dosage form, the second lipid and the polysaccharide form *in situ* a lipopolysaccharide increasing permeation of the second API at the blood brain barrier and in so doing improving bioavailability of the second API and further facilitating interaction of the dosage form with surface carbohydrates on mucous or epithelial cells of a stomach of a user therein increasing adhesion of the dosage form to the stomach wall to increase gastric retention.

The first and second API may be the same and/or different. The first and/or second API may be an anti-psychotic agent. The anti-psychotic agent may be a typical and/or atypical anti-psychotic agent. The first and/or second APIs are generally sulpiride and/or valproic acid.

The first and second lipid may be the same. The first and second lipids are generally lectins and/or lecithins.

The polysaccharide may be a starch based polysaccharide or a derivative thereof. The polysaccharide may be gellan gum.

The crosslinking agent may be phosphorus oxychloride ($POCl_3$), sodium trimethaphosphate, epichlorohydrin and/or a derivatives of the aforementioned. Preferably, the crosslinking agent is epichlorohydrin.

The first layer of porous crosslinked polymers and/or the carrier typically each further comprises at least one inactive polymer agent selected from the group including, but not limited to: substituted or unsubstituted acrylic and methacrylic acids, alkyl celluloses, polyethylene glycol, sodium alginate, polyvinyl alcohol, carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, ethylcellulose, hydroxyethylcellulose, a sugar or sugar based group, and mixtures of the aforementioned.

The first layer of porous crosslinked polymers and/or the carrier typically each further comprises N-acetyl cysteine facilitating bioadhesion of the dosage form to the stomach in use. Increased bioadhesion will facilitate more effective release of the API in use.

The first layer of porous crosslinked polymers and/or the carrier may each form a semi-interpenetrating polymer network (IPN) wherein the polysaccharide and the polyethylene oxide (PEO) semi-interpenetrate each other. In a preferred embodiment of the invention a semi-interpenetrating polymer network (IPN) forms from crosslinked PEO and gellan gum.

Gellan gum (GG) is an extracellular polysaccharide produced by the bacterium *Pseudomonas Elodea*. The naturally occurring form of gellan gum is a linear anionic heteropolysaccharide grounded on a tetrasaccharide repeat unit of glucose, rhamnose and glucuronic acid with a molar ratio of 2:1:1 (14). Gellan gum exists as a half staggered, parallel, double helix that is stabilized by hydrogen bonds linking the hydroxymethyl groups of the one chain and both the carboxylate and glyceryl groups of the other.

Polyethylene (oxide) (PEO) exists as a high viscosity non-ionic linear homopolymer of ethylene oxide, a water soluble resin which affords great biodegradable properties to pharmaceutical formulations. Polyethylene (oxide) swells when in contact with dissolution medium, API release occurs via diffusion through a gel layer and/or erosion of the swollen surface gel. The PEO also increases membrane fluidization via ATPase inhibition increasing API absorption in use.

The Applicant believes that the formation of a semi-interpenetrating network (IPN) further aids in providing uniform release of the API and/or provides mechanical stability to the dosage form.

Furthermore, in an embodiment of the invention wherein the first and/or second API is sulpiride ([N-(1-ethyl-2-pyrolidinyl) methyl]-2-methoxy-5-sulfamoylbenzamide) the gellan gum and/or the PEO may inhibit P-gp efflux transporter proteins, which P-gp efflux transporter proteins would otherwise bind to sulpiride and prevent said sulpiride from entering the bloodstream and/or crossing the blood brain barrier. Consequently, the gellan gum and/or the PEO improve bioavailability of the first and/or second API and may allow for administration of decreased dosages which will lower the negative side effects currently experienced upon administration of sulpiride, and consequently improve patient compliance.

The first layer of porous crosslinked polymers and/or the carrier may be layered like an onion and/or a sandwich.

In a certain embodiment of the invention, the first layer of the dosage form may comprise 1 part by weight of a API in predominantly amorphous form, between 0.1-12 parts by weight of an inactive polymer that assists in the dissolution of the API in a ratio of 2 parts by weight of the crosslinked polymer and crosslinked by 0.4-0.8 part by weight of crosslinking agent.

The first layer may comprise 1 part by weight of API relative to 1-10 parts by weight of crosslinked polymer.

In another embodiment of the invention, the first layer may comprise 2 parts by weight of API in a predominantly amorphous form and between 1-12.5 part by weight of an inactive polymer that assists in controlling the dissolution of the active agent in ratio of 0.5 parts by weight of crosslinked polymer and crosslinked by 0.3-6% by weight crosslinking agent.

In another embodiment of the invention, the first layer may comprise 2 parts by weight of the API relative to 1.12.5 parts by weight of crosslinked polymer.

Each of the plurality of multilayered devices typically comprises: a mucus cleaving layer, preferably the mucous cleaving layer may comprise N-acetyl cysteine loaded alginate; a mucoadhesive layer comprising a mucoadhesive polymer, preferably the mucoadhesive layer comprising lectin, hypromellose and chitosan; a second API carrier layer, preferably the second API carrier layer comprising crosslinked Eudragit, sodium alginate and the second API; and a water insoluble layer, preferably the water insoluble layer comprising a water insoluble polymer, further preferably the water insoluble polymer may comprise gellan gum.

Each of the plurality of multilayered devices may be layered like an onion and/or a sandwich.

There is further provided for an oral pharmaceutical dosage form substantially as herein described, illustrated and/or exemplified with reference to any one of the accompanying examples and/or diagrammatic drawings.

The Applicant believes that the dosage form according to the invention at least partially ameliorates some of the disadvantages known in the prior art.

Figure 1 shows a graphical illustration of a preferred embodiment of an oral dosage form 10 according to the invention. The preferred embodiment of the invention shows a dual- or bi-layered dosage form.

The dual- or bi-layered dosage form 10 shows a first layer of crosslinked polymers 12 and a first active pharmaceutical ingredient (API) 14. The first layer of crosslinked polymers 12 may include a polysaccharide, polyethylene oxide (PEO) and/or polyethylene glycol (PEG) or a derivative of PEG, and a crosslinking agent. Typically, the first layer of crosslinked polymers 12 comprises gellan gum (as the polysaccharide) and PEO which are crosslinked with epichlorohydrin (as the crosslinking agent). The first layer of crosslinked polymers 12 generally forms a semi-interpenetrating network (s-IPN).

The dual- or bi-layered dosage form 10 further comprises a second layer 16 including a plurality of multilayered devices 18 embedded within a carrier 20. Each of the multilayered devices 18 includes a second API such that in use the second layer 16 provides pulsatile release of a second pharmaceutically active ingredient (API) upon oral administration of the dosage form 10.

The carrier 20 comprises porous crosslinked polymers comprising carboxymethylcellulose and gellan gum.

As shown in Figure 3 each of the plurality of multilayered devices 18 typically comprises a mucus cleaving layer of N-acetyl cysteine loaded alginate 22; a mucoadhesive layer 24 comprising lectin hypromellose and chitosan; a second API carrier layer 26 comprising crosslinked Eudragit, sodium alginate and the second API; and a water insoluble layer 28 of gellan gum. Typically, and as shown in Figure 3 each multilayered device is layered like a sandwich. In use, the mucous cleaving layer 22 is substantially proximal a mucous layer of the stomach and/or intestinal wall, and the water insoluble layer 28 is substantially distal the mucous layer of the stomach and/or intestinal wall. The water insoluble layer 28 ensures unidirectional release of API toward the mucous layer of the stomach and/or intestinal wall in use.

EXAMPLES

Table 1: Box-Behnken design template for the statistically derived 15 semi-IPN xerogel formulations of the first layer of porous crosslinked polymers, and their respective chemical compositions.

Crosslinked Xerogel Formulation Code	PEO Concentration (%$^w/_v$)	GG Concentration (g)	EPI-Crosslinker Volume (mL)
F1	2.5	1	0.6
F2	2.5	0.75	0.8
F3	1.75	0.75	0.6
F4	1.75	0.75	0.6
F5	1	0.75	0.8
F6	1	1	0.6
F7	1.75	1	0.4
F8	1	0.5	0.6
F9	1.75	1	0.8
F10	1.75	0.5	0.8
F11	1	0.75	0.4
F12	1.75	0.75	0.6
F13	2.5	0.5	0.6
F14	1.75	0.5	0.4
F15	2.5	0.75	0.4

Table 2: Formulations of the mucoadhesive layer of the multilayered device

Mucoadhesive Film Formulation Code	Chitosan Concentration (g)	Hypromellose Concentration (g)	Citric Acid Concentration (g)
F1	0.15	0.1	0.225
F2	0.15	0.1	0.225
F3	0.15	0.05	0.225
F4	0.15	0.1	0.225
F5	0.15	0.1	0.225
F6	0.05	0.05	0.15
F7	0.05	0.05	0.3
F8	0.15	0.1	0.225
F9	0.05	0.15	0.15
F10	0.25	0.1	0.225
F11	0.25	0.15	0.15
F12	0.15	0.15	0.225
F13	0.05	0.15	0.3
F14	0.05	0.1	0.225
F15	0.25	0.05	0.3
F16	0.25	0.15	0.3
F17	0.15	0.1	0.15
F18	0.25	0.05	0.15
F19	0.15	0.1	0.3
F20	0.15	0.1	0.225

Table 3: Formulations of the Drug Loaded layer of the multilayered device

Drug Loaded Film Formulation Code	Eudragit® RS 100 Concentration (g)	Calcium Chloride Concentration (g)
F1	0.55	0.055
F2	0.55	0.1
F3	0.1	0.055
F4	1	0.1
F5	1	0.055
F6	1	0.01
F7	0.55	0.055
F8	0.55	0.01
F9	0.55	0.055
F10	0.55	0.055
F11	0.55	0.055
F12	0.1	0.1
F13	0.1	0.01

Materials and Methods

Materials

Poly (ethylene) oxide (Polyox™ WSR 303) (The Dow chemical company (Midland, MI, USA)), Gellan Gum (Gelzan™ CM), Epichlorohydrin 99%, Sulpiride, Dichloromethane, Ethyl acetate, Metronidazole, Chitosan (medium molecular weight), N-acetyl cysteine ≥ 99%, Citric acid ≥ 99.5 %, Valproic acid, Mucin, from porcine stomach were all procured from Sigma-Aldrich® (St. Louis, USA), Eglonyl ® 50mg (Sanofi Aventis) Lectins (Bio-Research products (Cherry St. North Liberty, USA)), Methacrylic acid copolymer (Eudragit RS 100) (Degussa, Röhm GMbH, Pharma polymers, Germany). Soybean Lecithin (Schuchardt (Hohenbrunn, Germany). All other reagents were of analytical grade and are used as received.

Synthesis of the first layer of porous crosslinked polymers:

In a preferred embodiment of the invention, the first layer of porous crosslinked polymers is manufactured to be a semi-interpenetrating network (IPN) xerogel formulation. Several formulations of the first layer of porous crosslinked polymeris were synthesized in accordance with the Box-Behnken statistical experimental design as shown in Table 1 and as illustrated in Figure 2. In the preferred embodiment of the invention the first layer of porous crosslinked polymers comprised gellan gum as the polysaccharide, polyethylene oxide (PEO), and epichlorohydrin as the crosslinking agent.

A process 100 for the manufacturing of the first layer is illustrated in Figure 2 wherein gellan gum 112 and poly (ethylene oxide) 114 were crosslinked 116 using epichlorohydrin as follows: % w/v solutions of poly (ethylene oxide) of varying concentrations in distilled water were prepared; thereafter a variation of weights of gellan gum ranging between 0.5-1g was mixed into the already prepared poly (ethylene oxide) solution, once gellan gum was completely dissolved, epichlorohydrin was added within a range of 0.4-0.8mL with further stirring with a magnetic stirrer for 30 minutes. These reactions conferred the formation of a tri-molecular complex 118 that pharmaceutically offers advantages to the functionality of the drug delivery system.

In a certain embodiment of the invention, the resulting gel is poured into a beaker of 200-500ml acetone, and allowed to precipitate 120 for approximately 3 hours. It is then removed from the acetone and air dried under a fumehood for a further 24 hours. The resultant xerogel is then crushed into a uniform powder for formulation with a first API.

In a certain embodiment of the process, the resulting gel was removed and air dried. The dried xerogel was then crushed employing a laboratory electric grinder to form a uniform powder. The crushed xerogel was then mixed with drug (API) and surfactant (1.5mg Magnesium Stearate) which allows for the stabilization of the polymer particles (Bassett and Hamilec, 2009) to form the porous xerogel-polymer drug loaded matrix. The porous xerogel matrix system will then be compressed 122 into the first layer using a Carver Tablet Compressor (model 3851-0). As an example API sulpiride was used. Another suitable APIs include, but are not limited to, the following group: benezenoids, benzamides, salicylamides, methoxybenzenes, benzoyl derivatives, N-alkypyrrolidines, sulfonamides, amino sulfonyl compounds, trialkylamines, secondary carboxylic acid amides, azacyclic compounds, hydrocarbon derivatives, carbonyl compounds, and drugs of poor solubility.

In another embodiment of the process 100 (and as illustrated in Figure 2), the tri-molecular complex 118 is mixed with leptin (preferably lyophilized human leptin) 124 and the first API (for example sulpiride) 126 prior to the precipitation step 120 and tableting step 122.

The second layer of the dosage form:

The carrier:

The carrier will be formulated employing an immediate release polymer in addition to tableting excipients. The carrier may include the same polymer combination as that of the first layer but without the first API (drug). Alternatively, and in a preferred embodiment of the invention, the carrier comprises carboxymethylcellulose (a fast disintegrating polymer) in combination with gellan gum.

The multilayered device:

The multilayered devices are also referred to herein as intestinal patches. Generally, the devices are multilayered films comprising four layers: (1) mucus cleaving layer, (2) a mucoadhesive layer (3) a second API (drug) carrier layer, and (4) a water insoluble layer, wherein the film is layered like a sandwich. Typically, the mucus cleaving layer adheres to a mucous layer of the stomach and/or intestinal wall and cleaves the mucus lining, the mucoadhesive layer which is layered onto the mucous cleaving layer can then more readily adhere to the intestinal wall, the second API (drug) carrier layer is layered onto the mucoadhesive layer carrying with it the second API, and the water insoluble layer is layered onto the drug carrier layer to ensure unidirectional release of the API toward the intestinal wall and subsequently into the blood stream.

(1) The mucus cleaving layer

The mucus cleaving layer is formulated with the N-acetyl cysteine loaded alginate. The incorporation of N-acetyl cysteine into the formulation enables *in vivo* interaction with surface mucous of the stomach in use, resulting in depolymerization of mucous glycoproteins, therefore hydrolyzing disulfide bonds, reducing mucous viscosity and allowing for bioadhesion of the drug delivery system to the intestinal wall. Increased bioadhesion increases gastric retention times and also increases the amount of API that can be released and that is ultimately bioavailable.

(2) Mucoadhesive layer

The mucoadhesive layer typically comprises lectin, hypromellose and chitosan.

Chitosan at 1-5% w/v will be dissolved in a citric acid 0.3-0.45% solution to aid dissolution, once dissolution is achieved hypromellose at 1-3% will be added to the above mentioned solution and allowed to become homogenous, thereafter, lectin at a concentration of 0.25mg/ml will then added and the conjugation was carried out over a 2 hour incubation period.

(3) The second API (drug) carrier layer

The drug loaded layer will be formulated via the crosslinking of Eudragit and sodium alginate with the aid of calcium chloride. Generally, the drug loaded release layer will be formulated via the crosslinking of Eudragit RS 100 at 0.2-2% with the use of calcium chloride as crosslinker at 0.02-0.2%.

(4) The water insoluble layer

The water insoluble layer, also herein referred to as the backing layer (and/or the encapsulating layer) is synthesized via the use of ethycellulose, an insoluble polymeric agent.

Preparation of the oral dosage form according to the invention:

A preferred embodiment of the invention, a dosage form, comprises a first and second layer manufactured using a direct compression method and a tableting press.

Textural analysis studies of the first layer

Textural analysis data profiles were employed to study the physiochemical properties of the crosslinked PEO-GG semi-IPN-xerogel matrix of the first layer in comparison to the PEO-gellan gum blend tablets alone when a uniaxial compression force was applied to the tablets.

The work of deformation energy which is calculated as the area under the force-distance curve points to the deformation and rigidity of the tablets. The force-distance curves obtained is a measure of the resistance force encountered by the probe infiltration as a function of the travelled distance into the tablet. A low resistance is depicted by a low slope which further illustrates that the strength of the tablet is low, while a sharp increase in force, a higher slope as the test probe penetrates deeper into the tablet corresponds to a greater strength (Pillay and Fassihi, 2000).

From the profiles of force-distance obtained there was a display of both a high and sharp curve as well as shorter and less sharp curve when viewed in comparison, thus indicating that the crosslinked PEO-GG semi IPN-xerogel matrix first layers had a greater resistance to the force applied than the comparative; namely; poly (ethylene oxide)-gellan gum blend tablets (without crosslinking). This may be further highlighted by calculating the gradients of the various force-displacement curves, whereby the gradient shows the rigidity of the tablets tested, data indicates that the crosslinked PEO-GG xerogel tablets have an greater rigidity than poly (ethylene oxide) - gellan gum blend as a consequence of the new formed polymer chain strength, with formulation F7 tablets having the highest rigidity. The same applied for deformation, the crosslinked xerogel tablet showed a lower level of deformity whereas the poly (ethylene oxide) - gellan gum blend tablet showed the highest value of deformation due to the high binding properties and loose bonds between polymer molecules. To determine the resilience of the tablets a strain of 10% was applied to the tablets whereby a textural analysis profile was generated of force (N) - time (sec) to the 1:2 and 2:3 ratios. From the results obtained it can be seen that the semi IPN-xerogel matrix tablets F1 has the greatest % resilience relative to its comparatives, which may be attributed to the greater mechanical strength of the crosslinked xerogel due to a greater concentration of crosslinker being used. Figure 4 shows Brinells Hardness numbers for Formulations F1-F15 of the first layer prepared samples, and Figure 5 shows the difference of resilience.

Theoretically, from the equation of young's modulus (*E*), (Ruvalcaba et al, 2009);

$$\tau = -E(\lambda - 1) \qquad (1)$$

Where, τ is the applied stress, and λ is the deformation.

$$E^{2/3} = \frac{KF^{2/3}}{R^{1/3}d} \qquad (2)$$

(Khalid et al, 2002).

Where *R* is the indenter radius, *d* is the displacement of the indenter, and *F* is the compression force.

Equating 1 and 2; it is found that,

$$\tau \; and \; \lambda \propto F \qquad (3)$$

And;

$$\tau \; and \; \lambda \propto 1/R \qquad (4)$$

Thus, the strain applied as well as the deformation of the xerogel is directly proportional to the compression force applied, in addition the applied stress and deformation is inversely proportional to the radius and diameter of the indenter probe.

Swelling and Erosion studies of the first layer

In this study the dynamic swelling, in terms of water uptake and erosion of the crosslinked semi IPN-xerogel and poly (ethylene oxide)-gellan gum tablets were analyzed by monitoring the change in weight over a pre-determined period of time. Data indicates the percentage of water uptake and thus swelling over a period of time for the varying crosslinked semi IPN-xerogel formulations as well as the poly (ethylene oxide)-gellan gum blend tablets. The porosity of the polymeric material in question such as gellan gum is a predominant feature that determines its swelling ability. An increase in polymer porosity leads to greater initial rates of water uptake and a greater level of equilibrium swelling (Ferrero et al, 2010); swelling also depends largely on the extent of crosslinking. As seen from the obtained data xerogel formulations F1, F7 and F9 have similar swelling characteristics with a uniform delayed swelling behavior ranging between 450-500 %. Whereas poly (ethylene oxide) -gellan gum blend shows a constant exponential increase in water uptake and swelling up to and beyond the 24 hour test period. Thus the following observation was made based on swelling test results, the greater the amount of water uptake the greater the degree of erosion due mostly to gellan gum as seen from observed results.

Furthermore PEO allows for greater water retention and thus its mechanism of release is via swelling and erosion, whereas GG (gellan gum) (a gelling agent) forms a more structured gel system allowing for slightly greater water penetration than PEO, therefore both these agents offer controlled release. The crosslinking reaction employed allows the formation of polymer networks between the GG and PEO chains thus creating an interpenetrating structural configuration allowing for controlled water penetration and thereby controlled, uniform drug release.

Therefore tablets having a high degree of water uptake were found to erode at a faster rate and thus undergo complete disintegration at an accelerated rate. Although water uptake also encouraged the degree of swelling which mostly relied on the properties of poly (ethylene oxide) and related to a delayed dissolution and disintegration process. It was also noted within the study that the swelling of the semi IPN–xerogel was reduced with a corresponding increase in crosslinker concentration, due to the formation of stronger networks. Therefore the following equation substantiates this theory;

$$C_c = \frac{1}{Sw} \qquad (5)$$

Where *Sw* is the percentage swelling and *Cc* is the concentration of crosslinker.

Hence by extension a reduction in crosslink density or crosslinker concentration leads to the formation of looser polymer network or IPN which thus entails the existence of greater hydrodynamic free volume allowing for the absorption of a greater amount of solvent in turn creating a greater swelling capacity (Kulkarni et al., 2011).

In theory, from the equation of Fick's law of diffusion and the equation for dynamic swelling we can deduce the following (Kulkarni et al, 2011);

$$\frac{Mt}{M\infty} = Kt^{n} \qquad (6)$$

Where $\frac{Mt}{M\infty}$ is the fraction of drug released per unit time, *k* is the release constant and *n* is the release index.

$$\frac{Dt}{D\infty} = Kt^{n} \qquad (7)$$

Where $\frac{Dt}{D\infty}$the Dynamic swelling, k is the release constant and *n* is the release index (Rokhade et al, 2006);

Equating equations 6 and 7; we find that,

$$\frac{Mt}{M\infty} \propto \frac{Dt}{D\infty} \qquad (8)$$

Therefore, it can be further deduced that the amount of drug released is directly proportional to the extent of swelling. Furthermore the amount of drug released at time t is inversely proportional to the overall swelling; hence with an increase in swelling the drug release at time, t will be reduced.

Scanning electron microscopy of the first layer

Figures 6 a and b display the scanning electron micrographs of the surface morphology of pure poly (ethylene oxide), gellan gum (GG), and crosslinked semi-IPN Xerogel formulations F1 and F7 after swelling tests. The SEM micrographs show that the semi IPN-Xerogel formulations are highly porous as compared to the pure PEO and GG. The drastic change in surface morphology between the pure polymers and crosslinked semi IPN-xerogels shows that the modification of these polymers was successful.

The porous nature of the semi IPN-xerogel furthermore allows for the sustained release of the active from within the interpenetrating network formed. There is also shrinkage of the semi IPN molecules within certain xerogel formulations due to the greater crosslink density and concentration (Kulkarni, 2011).

Differential scanning calorimetry of the first layer

As depicted in Figure 7 the DSC Thermogram of pure poly (ethylene oxide) WSR 303; the graph shows an endothermic peak at 65.72°C which corresponds to the glass transition temperature, a second endothermic peak at 73.86°C, a broad asymmetric melting point as well as absorption of moisture, as well as an exothermic peak at 190.51°C which depicts crystallization of stable modification. Figure 7 also depicts the Thermogram of gellan gum (Gelzan™ CM), shows a glass transition peak at 55.33°C and an endothermic peak at 62.98°C. Glass transition temperature (Tg) if defined as the process by which an amorphous material undergoes melting. This is depicted by a transition in the baseline of the DSC graph. Usually the samples become physically soft or form a liquid, thus the amorphous state of the material is distorted. Tg is directly proportional to the crosslinking density, thus as seen in the DSC curves for design formulations it is clearly visible that there is an increase in the Tg with a corresponding increase in the crosslinker concentration ranging between 26.30- 68.41°C. Melting peaks for all design formulations remained within a stable, constant range between 106-107°C; however there was a slight reduction noted in the melting temperature when the ratio of polymers was reduced. The melting peaks observed were broad due to the partial crystalline nature of the polymers, this occurs due to the size distribution of crystallites. Melting is then followed by an exothermic crystallization peak, because of the presence of an oxide layer on the surface of the xerogel which after melting forms a rigid envelope thereby leading to crystallization. This crystallization peak is also present within the DSC graph of pure PEO and thus is also characteristic of the presence of PEO within the crosslinked semi IPN-xerogel. Crystallization involves the transition of the polymeric material from a liquid to a crystalline solid, with repeated units forming a rigid structure. It was found that the temperature of crystallization was shifted to higher temperatures with a corresponding increase in crosslinker and polymer concentrations. A prominent crosslinking peak is also noted within the crosslinked semi IPN-xerogel formulations, thus proving the crosslinking reaction of Gellan Gum-PEO employing epichlorohydrin. This peak is representative of the crosslinking reaction that occurs upon heating of the sample called Curing. These crosslinking peaks are observed with formulations with a higher degree of crosslinking density, but absent from those with a reduced crosslinking density, most prominent around the temperature of 215°C.

Figure 8 shows FTIR results. IR Spectroscopy shows the structure of a new compound by identifying which molecular groups are present or absent from the sample being tested. A specific group of atoms, called functional groups creates characteristic absorption bands within the spectra (Coates, 2000). The FTIR Spectra of poly (ethylene oxide) above depicts the functional groups present within the chemical compound by determining characteristic bands. Modifications in chemical structure of the semi-IPN-xerogel formulations were analyzed employing FTIR spectroscopy, which assists in identifying interactions of parent polymers upon chemical reactions such as crosslinking. The current observation of crosslinking was optically detected by noted change in solution viscosity as well as opacity on completion of the crosslinking reaction. On experimental evaluation of the FTIR data set it has been inferred that changes in the polymer ratios and crosslinking density have an effect on the vibrational frequencies observed. A broad band in the range of 2850-2960 cm^{-1} relating to C-H stretching in alkane functional groups is observed in all semi IPN-xerogel formulations, characteristic of gellan gum. Due to the presence of NaOH within the crosslinking reaction, it leads to the breakdown of O-H bonds, thus causing these hydrogen and oxygen molecules to interact with other molecules, forming new functional groups. This chemical phenomenon leads to the addition of alkene groups with C-H stretching at higher wavelengths of 3276.25 cm$^{-1,}$ as well as hydrogen hybridization of the carbon at a wavelength of 2877.94 cm^{-1} depicted by the peak highlighted in a block in Formulation 7, this confers a greater degree of conjugation thereby improving stability and as an extension the physiomechanical properties of the polymer network synthesized. In addition a strong band relating to the O-H bonding groups within the range of 3200-3600 cm^{-1} is observed in semi IPN-Xerogels that had an intermediate ratio of polymers relating to the presence of alcohols or phenols. There also exist shifts in the spectrum with the varying crosslinking density.

The introduction of N-H amine groups found in Formulations 1, 2, 3, 5, and 10 highlighted by the box within Formulation 1, this is due to the increase in crosslinker density, therefore promoting bond formation, the absence of the amino groups within the remaining formulations indicates the absence of amino groups for bonding reactions, this occurrence could be due to the reduced concentration of gellan gum and increased density of epichlorohydrin within these formulations which thereby creates steric hindrance. Formulation 9 shows C=C stretch at a wavelength of 1500 cm^{-1} highlighted by a box in the spectra , which corresponds to a conjugational asymmetrical stretch, occurring when the ratio of polymers is 1:2.5 and crosslinker is at an intermediate density. C-H stretching within the aromatic ring structure was observed with all formulations with the resulting incorporation of a C-O functional group within the aromatic structure at a wavelength of 1080 cm^{-1}. Furthermore methyl and methylene functional groups were introduced within formulations with a higher concentration of crosslinker due to the introduction of $RCH=CH_2$ bridges extending from the aromatic ring backbone. Aliphatic ethers represented by wavelengths occurring at 1060- 1150 cm^{-1} were observed in semi IPN-Xerogels that consisted of Poly(ethylene) oxide at a concentration of 1.75 % w/v. C-N stretching occurred between 1560-1650 cm^{-1} in formulations that had crosslinking density of 0.6mL, these peaks tend to occur at higher vibrational frequencies and are known to be associated with the degree of crosslinking and polymer network formation resulting in a change within the structural configuration of the molecules, thus formulations with higher degrees of crosslinking was found to have wavelengths shifting to the greater end of the spectrum.

From the data obtained from the FTIR spectra of all Formulations of the first layer that were tested it can be seen that there are distinct changes within the chemical structure with the addition and removal of certain functional groups, removal of the aromatic ether from xerogel Formulations such as 1,3,4,8,11, those with a crosslinking concentration of 0.6mL disappearance of the C-H in plane bending from xerogel formulations with a polymer ratio of 0.75:1.75, also found in spectra of PEO and GG, with the further addition of an alkyne and amine group in Formulation F1, alkane functional group in formulations F1, F7 and F9, addition of nitro compounds in F1, and methyl groups in formulations F7 and F9. Crosslinked networks of both synthetic and natural polymers have been researched to a great degree. Chemical crosslinking is one method employed among many. Modifications such as crosslinking enhance the mechanical and pharmacokinetic properties of the crosslinked agents, with many uses in the pharmaceutical industry (Syed et al, 2011). Chemical crosslinking entails the use of a crosslinking agent to allow a linkage between two polymer chains. The actual crosslinking reaction of both synthetic and natural polymers is accomplished via the reaction between their functional groups with crosslinkers such as epichlorohydrin. Chemical crosslinking largely implicates the introduction of new functional groups and molecules between the polymeric chains to thereby produce crosslinked chains (Syed et al, 2011). This theoretical explanation thus accounts for the additional functional groups and chemical orientation seen in the FTIR spectra of the crosslinked semi IPN-xerogel Formulations as compared to the spectra of poly (ethylene oxide) and gellan gum. All of the observations help to conclude that polymer concentration as well as crosslinking density has an effect on the formation of semi interpenetrating networks as observed by peaks within the FTIR spectra.

***In vitro* drug release of the first layer**

In order to determine the release profiles of the drug from samples the first layer, dissolution experiments were performed in accordance with simulated intestinal parameters.

The plot of fractional drug release vs. time for the crosslinked semi IPN-xerogel matrix tablet formulations F1 to F15 (as per Table 1) as well as the PEO-GG blend (non-crosslinked for comparison purposes) are depicted in Figure 9 a, b and c respectively.

In the case of the crosslinked PEO-GG semi IPN-xerogel formulations drug release was sustained over a period of 24 hours, the variation in concentration of polymers and crosslinker did generate a noticeable deviation in drug release, however all crosslinked xerogel formulations showed a sustained release over the 24 hour study period. Drug delivery from hydrophilic matrix based systems is controlled by surface erosion of the polymers as well as diffusion of the drug out of the matrix network. Furthermore erosion is based on factors such as water uptake and polymer chain lengths. (Toti et al, 2004).

Polymers forming hydrophilic matrices that come into contact with water are known to undergo prompt 'gelification' which is due to the increased size of polymer molecules. There are mainly two mechanism by which drug release occurs within hydrophilic matrix systems; namely, release by 'controlled swelling', whereby drug undergoes the process of diffusion through the gel layer which is formed as stated above by the swelling or increase in size if polymer chains owing to entry of water, and secondly release by 'controlled dissolution' in which the water gains entry into the system thereby causing 'gelification' of the polymer chains that it comes into contact with, on the other hand, in addition to the conversion of polymer chains to a gel it also causes the polymer to be dissolved, this therefore involves dissolution or erosion of the polymer.

PEO-GG blends showed drug release behavior with characteristics of both the above mentioned mechanisms, gellan gum was subject to controlled dissolution and thus together with swelling it showed an increase tendency to disintegrate and dissolve thus leading to the initial burst effect in drug release, whereas the following controlled release behavior was mainly based on the properties of poly (ethylene) oxide which follows controlled swelling mechanisms of drug release, in that polymer chains undergo swelling on contact with aqueous phase due to the vitreous-elastic transition of the polymer been activated, thus the gel layer becomes thicker therefore making the drug release slower, because the drug molecule has to now pass through the thickened gel layer formed by swelling of polymer chains, which is at a greater distance from the surface of the dosage form, which creates a greater resistance to the diffusion of drug out of the gel layer (Maderuelo et al, 2011). Thus drug release from the PEO-GG blend indicated an initial burst effect followed by a rhythmic sustained release above the desired study period of 24 hours.

Crosslinked PEO-GG semi IPN- xerogel formulations F1-F15 displayed constant sustained release during the 24 hour period with 100% drug being released by the end of 24 hours, with slight variations in release rate due to the fact that the swelling and erosion properties of both polyethylene oxide and gellan gum where modified via the crosslinking reaction, thus these formulations showed a combined mechanism of drug release in terms of ‘controlled erosion’ and ‘controlled dissolution’. From these results it can be deduced that the higher the crosslinker concentration the greater the modification in drug release, as can be seen in formulations F1 and F9 where a concentration of crosslinker between 0.6-0.8 ml is correlated to a greater extent of sustained release, whereas formulation F7 which has a lower concentration of crosslinker depicts irregular drug release kinetics.

In theory, according to the Levenberg Marquardt method (Siepmann et al, 1999);

$$G = \frac{L \times h}{D} \qquad (9)$$

Where *G* is the 'Sherwood number', *D* is the diffusion coefficient of the drug, *h* is the coefficient of the boundary layer and *L* thickness of delivery system.

$$D' = \left(\frac{D}{\tau}\right) \qquad (10)$$

Where *D* is the diffusion coefficient of the drug, τ is the tortuosity of the diffusion matrix and *D'* is the effective diffusion coefficient (Siepmann and Peppas, 2012).

Equating equations 9 and 10;

$$h \propto \frac{1}{D'} \qquad (11)$$

And;

$$\frac{1}{\tau} \propto h \qquad (12)$$

From the above equations it can be shown that the boundary layer thickness is directly proportional to the diffusion of the drug, in addition the tortuosity of the matrix is inversely proportional to the boundary layer thickness.

Mucoadhesive analysis on mucoadhesive layer of the multilayered device

Bio-adhesion can be defined as the process by which a natural or synthetic polymer is able to adhere to a biological tissue. When the biological tissue in question is a mucosal layer then it is referred to as mucoadhesion. The material having bioadhesive properties can assist in allowing a delivery system (such as the dosage form according to the invention) to deliver a bioactive over a prolonged period of time site specifically. The current drug delivery system allows for intial mucoadhesion of the multilayered device via the mucoadhesive layer (lectin fused hypromellose-chitosan blend), then followed by bioadhesion of the mucus cleaving layer once the N-acetyl cysteine cleaves the mucous. Once the mucus cleaving layer attaches to the intestinal wall it cleaves off the excess mucus lining, thereby allowing for the following mucoadhesive layer to attach directly to the intestinal wall with minimal mucus interference. Since it is attached to the intestinal wall itself it is considered bioadhesion as it is attached to biological tissue.

Mucoadhesion studies were performed on all Box-Behnken design formulations of the mucoadhesive layer to evaluate the effect of the change in concentration of the respective polymers on the degree of mucoadhesion. The mucoadhesive layer samples were prepared according to Table 2 above.

For this study a 1% (w/v) mucin solution was prepared in USP intestinal fluid (pH 6.8). The formulated mucoadhesive layers were incubated in USP intestinal fluid in an orbital shaker maintained at 37°C and 50rpm. Concentration of free mucin in solution, after a 6 hour test period, was determined via a UV spectrophotometer, at an absorption wavelength of 201nm (IMPLEN NanophotometerTM, Implen GmbH, München Germany), using a 10 times dilution factor and a pathlenght of 0.1mm. The difference in mucin concentration in solution before and after incubation, provided an indication to the amount crosslinked with the lectin fused hypromellose-chitosan layer as seen in equation 13, showing the interaction between the mucoadhesive layer and the mucin;

$$\text{Mucoadhesion (\%)} = \frac{[\text{Mucin before}] - [\text{Mucin after}]}{[\text{Mucin before}]} \qquad (13)$$

Mucoadhesive properties of the formulation designs evaluated to determine their respective abilities to adhere to the intestinal mucosa to allow for increased retention time as well as to enhance the absorption of the bioactive through the mucosal lining of the intestine. Figure 10 summarizes the mucoadhesion results of all 20 formulations, depicting the average percentage crosslinking values of the formulation to the mucin solution.

All formulations showed desirable mucoadhesion, with all formulations in the range of 24-64%. However, it can be deduced that formulations with an increased concentration of chitosan and hypromellose showed higher values of mucoadhesion, in comparison formulations comprising of a reduced concentration of the previously mentioned polymers resulted in a proportional decrease in mucoadhesive capacity. These results depict the strong mucoadhesive properties of hypromellose and chitosan respectively, thus leading to the proportional relation between polymer concentration and the observed degree of mucoadhesion.

Swelling studies on the mucoadhesive layer of the multilayered device

The dynamic swelling of the mucoadhesive layer of the multilayered device was evaluated in simulated intestinal fluid (pH 6.8), 1×1.5mm strips of the formulated films were cut, weighed and placed in 50ml simulated intestinal fluid, and incubated in an orbital shaker maintained at 37°C and 50rpm, film samples were removed from the intestinal fluid and predetermined time intervals, dried on blotting paper and weighed to evaluate the change in weight via fluid uptake and hence swelling.

If the polymers are hydrated and expand, a greater surface area of the adhesive site is exposed and thus improves mucoadhesion. In addition, swelling promotes polymer chain entanglement amid the mucoadhesive layer of the delivery system and the mucin on the intestinal wall. Figure 11 depicts graphically the % swelling of all design formulations over a 24 hour test period.

Via gravimetric analysis it was revealed that with exposure to simulated intestinal conditions, the design formulations tend to swell, thus resulting in an increase in the weight of the mucoadhesive layer. With continuous exposure the films eventually disintegrates and erodes, thereby resulting in a decrease in weight. The underlying polymeric chains would then be exposed to the intestinal medium, and result in further swelling. As a result, fluctuations in swelling were observed at different time intervals (Salamat et al, 2005).

As seen from the swelling study, % swelling was relatively high, this may be attributed to the presence of chitosan and hypromellose which are both hydrophilic polymers and tend to swell in aqueous medium. Formulations 6, 7, 13, 14, 19 and 20 did not undergo swelling, they disintegrated on contact with the intestinal medium, and these formulations consisted of a reduced concentration of polymer and thus underwent dissolution faster. Formulations with a higher concentration of polymer were shown to swell greatly and maintain their shape over the 24 hour test period, as compare to those with an intermediate ratio of polymer, which did undergo swelling with an alteration in their shape.

Textural Analysis of the mucoadhesive layer of the multilayered device

The tensile properties of the mucoadhesive layer of the multilayered device were determined employing the (TA.XT.plus Texture Analyser, Stable Microsystems®, Surrey, UK). The texture analyzer was calibrated before samples were tested to ensure accuracy. Samples of approximately 2×15mm strips, were mounted on the specially designed tensile testing brackets. Samples were fastened on to either end of the bracket, accurate measurements of the sample widths, thickness and length were recorded using a digital caliper. The parameters employed were tension, a pre-test and test speed of 0.5 and a post test speed of 5mm/s, and a force of 0.05N. Young's Modulus (E) of all 20 design formulations were determined by equation 14;

$$E = FL_0/\ A_0\Delta L \qquad (14)$$

Where F is the force from the force vs. distance graph,

L_0 is the length before tensile testing,

A_0 is the area of the sample before testing,

And ΔL is the change length after tensile testing.

When a minor amount of stress is required to produce a large amount of strain, the material being tested is considered to be flexible and the Young's Modulus will be relatively small. The average experimental values for Young's Modulus is depicted in Figure 12. The various formulations were prepared as per Table 2 above.

The Young's Modulus values were low indicating that the mucoadhesive films demonstrated good elasticity. Formulations with a higher concentration of chitosan showed greater elasticity (lower Young's modulus) thus showing that the mucoadhesive films are flexible yet possess good mechanical characteristics as well and will therefore be able to withstand the intestinal peristalsis.

<u>Method of Textural characterization of the mucus cleaving layer</u>:

Mechanical properties of the mucous cleaving layer were evaluated via textural analysis using the TX.XT plus Texture Analyzer. Films were cut into approximately 0.55× 2.55 mm2 strips and secured within the grips, textural analysis was conducted with a pre-test and test speed of 0.5, post-test speed of 5, with the target mode being distance, and the force applied being 5N. The

Young's Modulus or ratio of stress over strain of the film was determined by the equation 15 via utilization of data obtained from textural analysis;

$$E=\frac{\text{Tensile stress}}{\text{Extensional strain}}=\frac{FL_0}{A_0\Delta L} \qquad (15)$$

Where;

E is the Young's modulus

F is the force exerted on an object under tension;

A0 is the original cross-sectional area through which the force is applied;

ΔL is the amount by which the length of the object changes;

L0 is the original length of the object.

Method for determination of the tensile properties and Young's modulus of the mucus cleaving layer:

The tensile characteristics and young's modulus was determined employing the NanoTensile® 5000 (Hysitron Inc. Nanomechanical Test Instrument, Minneapolis, MN). NanoTensile (NT) system was calibrated prior to sample testing to ensure accurate analysis. Samples cut into approximately 0.55× 2.55 mm2 strips were mounted on the specially designed mounting brackets. Brackets were held together with a rigid cardboard frame, enabling ease of sample alignment, samples were attached to the brackets using double sided adhesive tape, thus keeping the sample in place during evaluation. Accurate measurements of the sample width, thickness and length were recorded utilizing a digital caliper. Thereafter, the upper sample bracket was attached to the upper sample holder of the NT head and the mass recorded. The NT head was then lowered and aligned to the lower NT stage; the lower sample bracket was then secured to the lower sample holder on the NT stage. Sample mounting brackets were pulled apart at a constant rate of displacement; 100μm s-1 whereby tensile characteristics of the formulation sample was measured and recorded.

<u>Method of *in vitro* mucoadhesion studies conducted on the mucous cleaving layer:</u>

Mucoadhesion studies were performed on all Box–Behnken design formulations to deduce the effect of the change in variable concentration on the amount of mucoadhesion of the polymer. For this study a 0.1% (w/v) mucin solution prepared in USP intestinal fluid (pH 6.8) was incubated mucoadhesive films in an orbital shaker maintained at 37°C and 50 rpm. Concentration of free mucin in the solution, after 6 h duration, was determined by a UV spectrophotometer, at wavelength 201 nm(IMPLEN NanophotometerTM, Implen GmbH, München Germany),using a 10 times dilution factor of path-length 0.1 mm. The difference in the concentration of the mucin solution before and after incubation was the indication of the amount crosslinked with the mucoadhesive films as seen in equation 16, indicating the interaction between particles and mucin (He et al., 1998).

$$Mucoadhsion\ \% = \frac{[Mucin\ before] - [Mucin\ after]}{[Mucin\ before]} \times 100 \qquad (16)$$

<u>Results for experiments conducted on the mucous cleaving layer</u>:

Textural analysis

The average experimental values of Young's Modulus (E), yield stress (Q_Y) (extent of stress on the stress-strain curve at which considerable deformation occurs without any considerable increase in stress), ultimate strength (Q_U) (the maximum stress a material can withstand), ultimate strain (ε_u) and toughness (U_f) are outlined in Table 4 .

Table 4: Experimental values obtained from Textural analysis (TA) of mucus cleaving layer:

	E(MPa) NT	E(MPa) TA	Q_Y (MPa)	Q_U(MPa)	ε_u	U_f(J/cm^{-3})
Mucus Cleaving Layer	0.41	0.11	0.07	0.1	0.51	0.001

The observed Young's Modulus values were relatively low indicating that the film demonstrated good elasticity. The Youngs Modulus values for the mucus cleaving layer were low and thus indicate higher elasticity. This ideal characteristics for the multilayered device and thus is satisfactory.

Mucoadhesion analysis of the mucous cleaving layer:

Mucoadhesive properties of the mucus cleaving layer were evaluated to determine the ability to adhere to the intestinal lining, to allow for sufficient retention for mucus cleaving to occur. Mucoadhesion results for the mucus cleaving layer via mucin cleavage, yielding the average percentage crosslinking values over 6 hours of the mucus solution was 98%. This shows that the mucus cleaving layer possesses sufficient mucoadhesive strength so as to adhere to the intestinal wall for an appropriate period to allow for satisfactory mucus cleaving to occur. The incorporation of N-acetyl-cysteine displays a significant increase in mucoadhesion.

Conclusions

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 claims and any equivalents thereto, which claims are appended hereto.

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CLAIMS

1. An oral pharmaceutical dosage form comprising a first layer of porous crosslinked polymers including a polysaccharide, polyethylene oxide (PEO) and/or polyethylene glycol or a derivative of polyethylene glycol, a crosslinking agent, and a first active pharmaceutical ingredient, the first layer to provide uniform release of the first (API) upon oral administration of the dosage form.

2. The oral pharmaceutical dosage form according to Claim 1, wherein the derivative of polyethylene glycol is at least one derivative selected from the following group: polyoxyethlene, polyoxyethlene ether, polyglycol, and hydro-omega hydroxy poly (oxy-1, 2-ethanediyl).

3. The oral pharmaceutical dosage form according to Claim 1, wherein the first layer of porous crosslinked polymers comprises the polysaccharide, polyethylene oxide (PEO), the crosslinking agent and the first API.

4. The oral pharmaceutical dosage form according to any one of Claims 1 to 3, further comprising a second layer including a plurality of multilayered devices loaded with a second API and said plurality of multilayered devices embedded within a carrier, the second layer to provide pulsatile release of the multilayered devices and in turn pulsative release of the second active pharmaceutical ingredient (API) upon oral administration of the dosage form.

5. The oral pharmaceutical dosage form according to Claim 4, wherein the carrier comprises carboxymethylcellulose and gellan gum.

6. The oral pharmaceutical dosage form according to any one of Claims 1 to 5, wherein the first layer further includes a first lipid such that in use after oral administration of the dosage form, the first lipid and the polysaccharide form *in situ* a lipopolysaccharide increasing permeation of the first API at the blood brain barrier and in so doing improving bioavailability of the first API and further facilitating interaction of the dosage form with surface carbohydrates on mucous or epithelial cells of a stomach of a user

therein increasing adhesion of the dosage form to the stomach wall to increase gastric retention, preferably the first lipid being selected from lectins and/or lecithins.

7. The oral pharmaceutical dosage form according to Claim 5, wherein the carrier further comprises a second lipid such that in use after oral administration of the dosage form, the second lipid and the gellan gum form *in situ* a lipopolysaccharide increasing permeation of the second API at the blood brain barrier and in so doing improving bioavailability of the second API and further facilitating interaction of the dosage form with surface carbohydrates on mucous or epithelial cells of a stomach of a user therein increasing adhesion of the dosage form to the stomach wall to increase gastric retention, preferably the second lipid being selected from lectins and/or lecithins.

8. The oral pharmaceutical dosage form according to Claim 4, wherein the first and second API are the same or different.

9. The oral pharmaceutical dosage form according to Claim 8, wherein the first and/or second API is an anti-psychotic agent, preferably the anti-psychotic agent is sulpiride and/or valproic acid.

10. The oral pharmaceutical dosage form according to any one of Claims 1 to 9, wherein the polysaccharide of the first layer of porous crosslinked polymers is gellan gum.

11. The oral pharmaceutical dosage form according to any one of Claims 1 to 10, wherein the crosslinking agent is epichlorohydrin and/or a derivative thereof.

12. The oral pharmaceutical dosage form according to any one of Claims 4 to 11, wherein the first layer of porous crosslinked polymers and/or the carrier further each comprises at least one inactive polymer agent selected from the group: substituted or unsubstituted acrylic and methacrylic acids, alkyl celluloses, polyethylene glycol, sodium alginate, polyvinyl alcohol, carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, ethylcellulose, hydroxyethylcellulose, a sugar or sugar based group, and mixtures of the aforementioned.

13. The oral pharmaceutical dosage form according to any one of Claims 4 to 12, wherein the first layer of porous crosslinked polymers and/or the carrier further each comprises N-acetyl cysteine facilitating bioadhesion of the dosage form to the stomach in use.

14. The oral pharmaceutical dosage form according to Claim 4 or Claim 5, wherein the each of the plurality of multilayered devices comprises:

a mucus cleaving layer, preferably the mucous clearing layer comprising N-acetyl cysteine loaded alginate;

a mucoadhesive layer, preferably the mucoadhesive layer comprises lectin, hypromellose and chitosan;

a second API carrier layer, preferably the second API carrier layer comprising crosslinked Eudragit, sodium alginate and the second API; and

a water insoluble layer, preferably the water insoluble layer comprising gellan gum.

15. The oral pharmaceutical dosage form according to any one of Claim 1 to 14, wherein the first layer of crosslinked polymers forms a semi-interpenetrating network (s-IPN) further facilitating the uniform release of API from the dosage form.

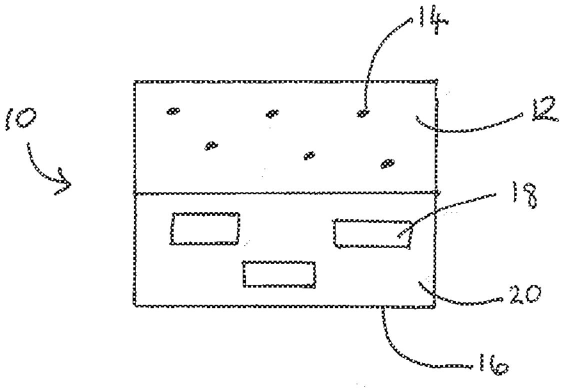


FIGURE 1

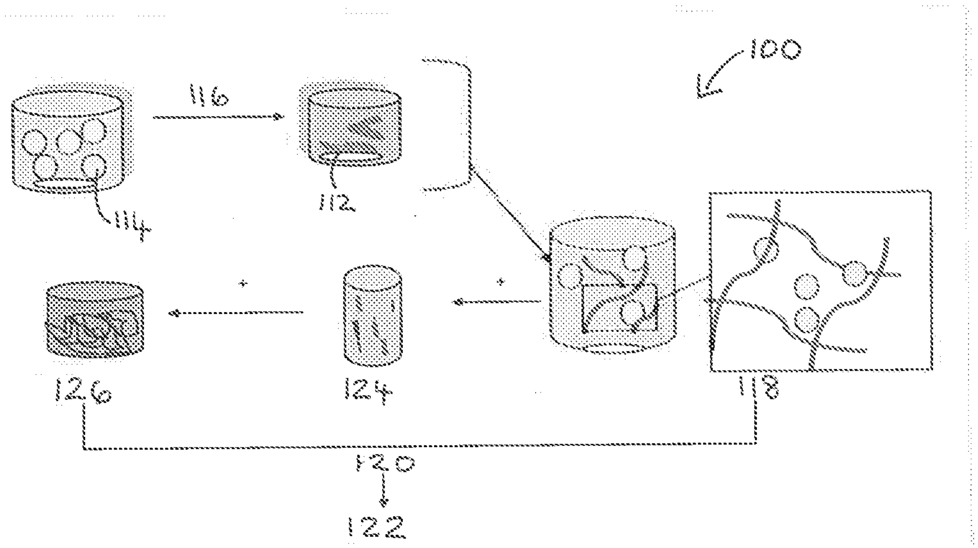


FIGURE 2

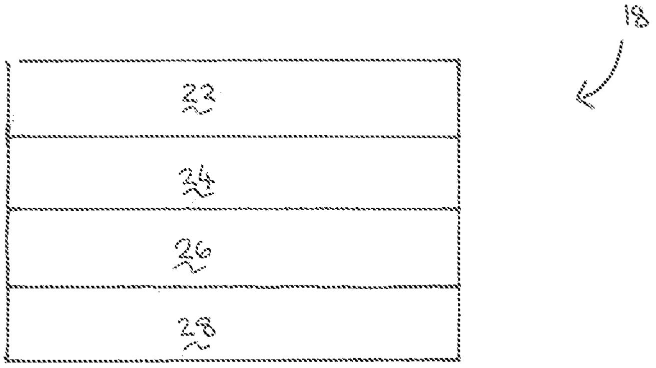


FIGURE 3

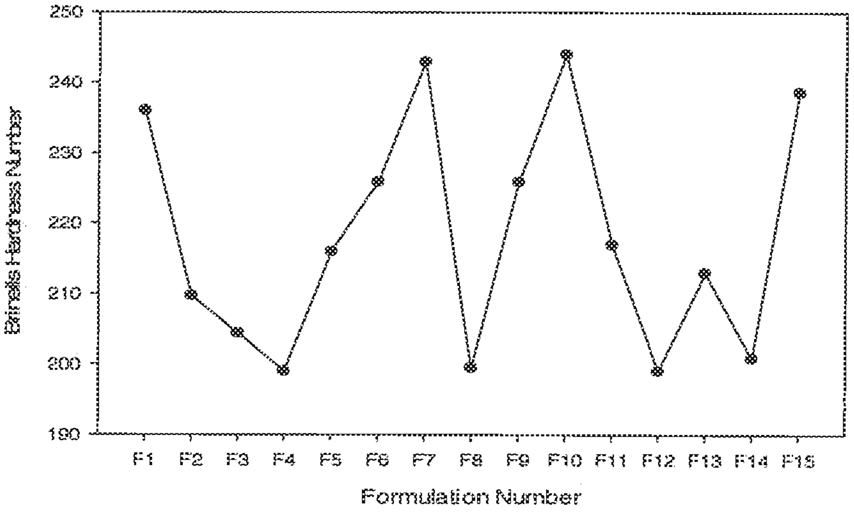


FIGURE 4

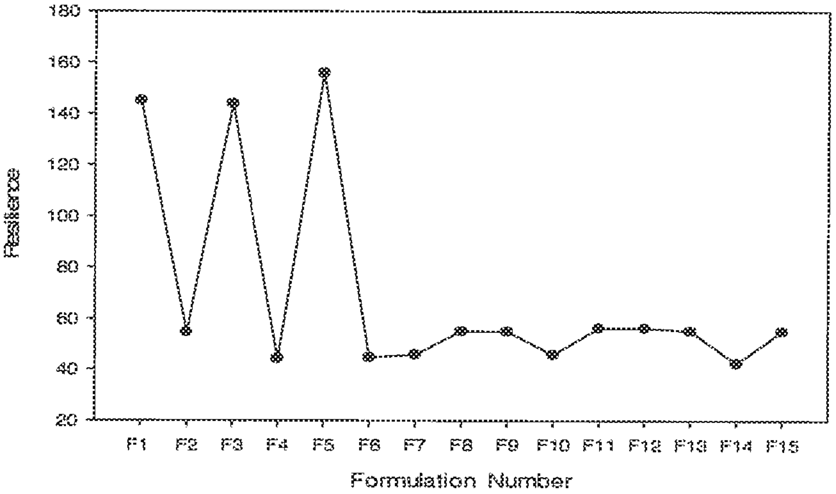
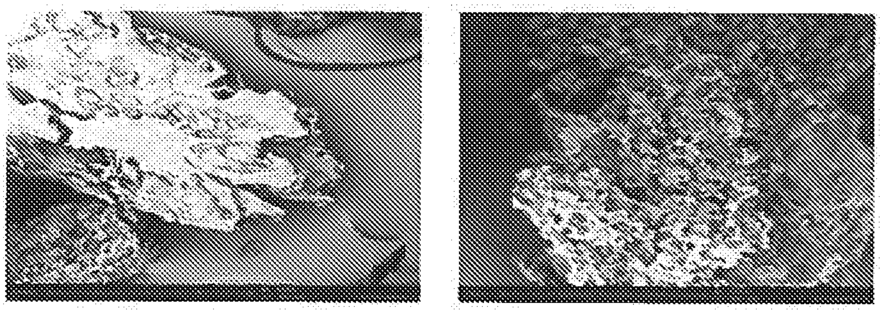


FIGURE 5



(a) (b)

FIGURE 6

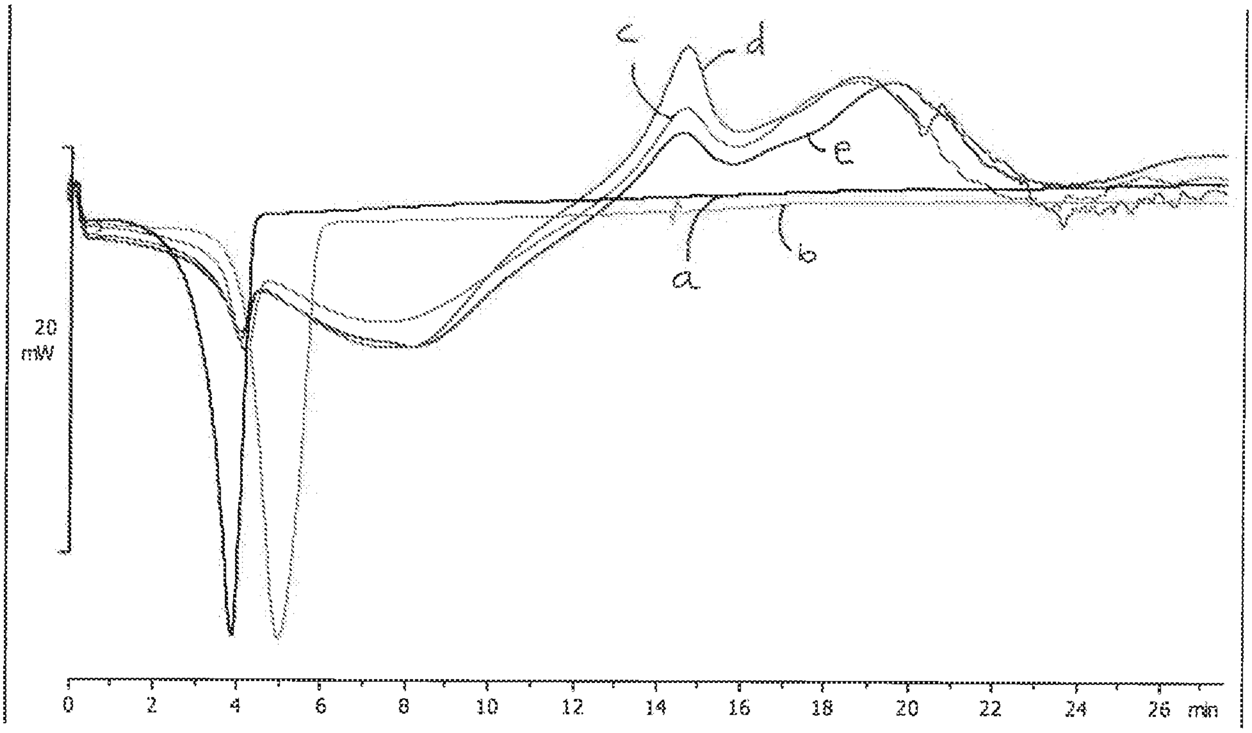


FIGURE 7

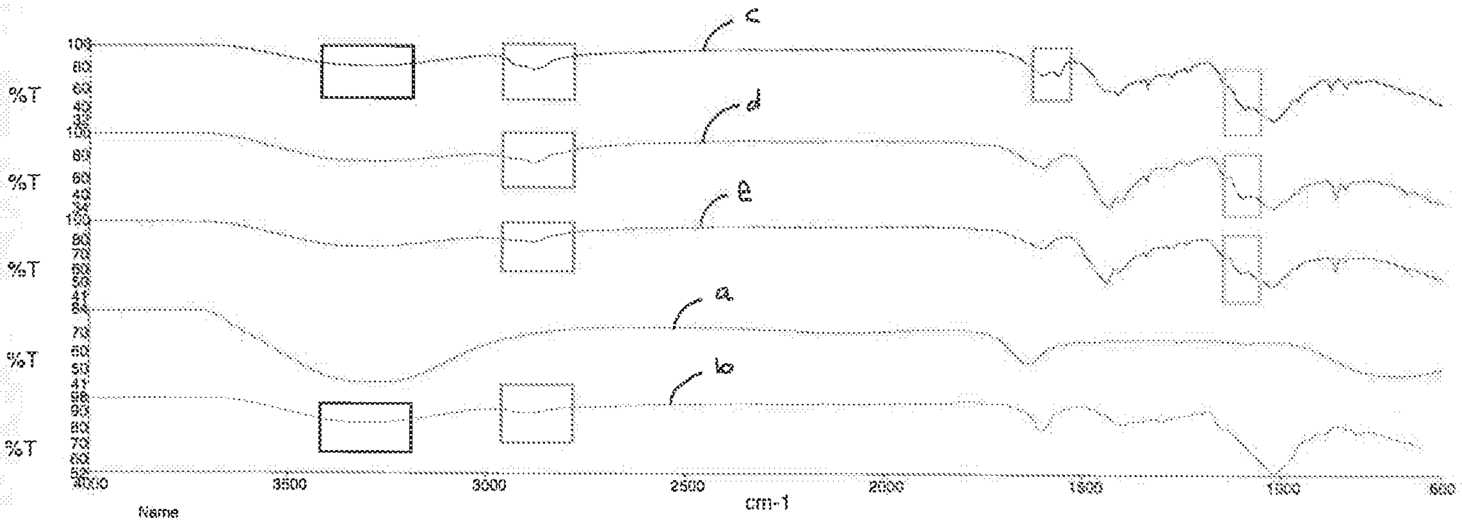


FIGURE 8

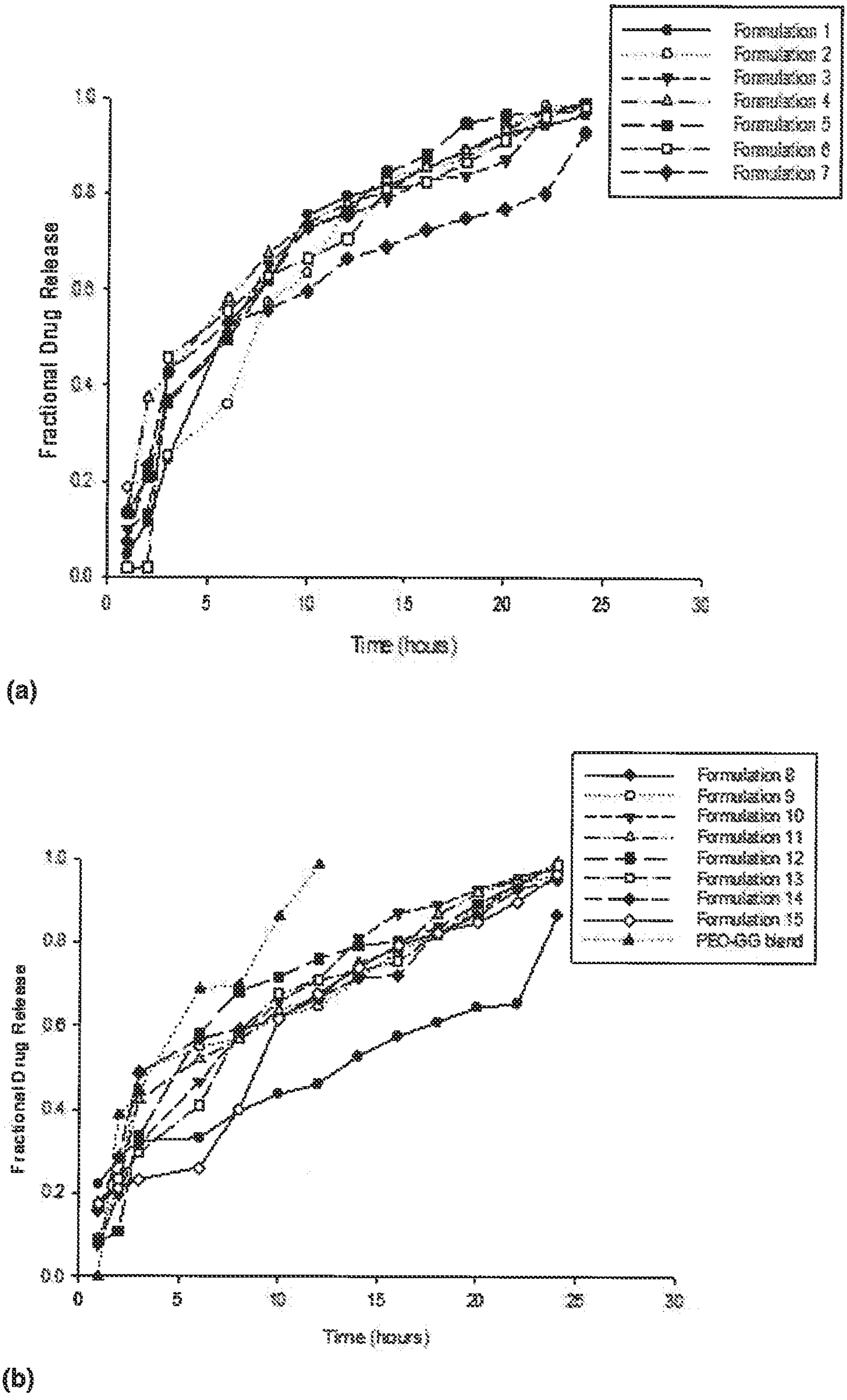

Formulation 1
Formulation 2
Formulation 3
Formulation 4
Formulation 5
Formulation 6
Formulation 7
Fractional Drug Release
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Time (hours)
(a)
Formulation 8
Formulation 9
Formulation 10
Formulation 11
Formulation 12
Formulation 13
Formulation 14
Formulation 15
PEO-GG blend
Fractional Drug Release
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Time (hours)
(b)

FIGURE 9

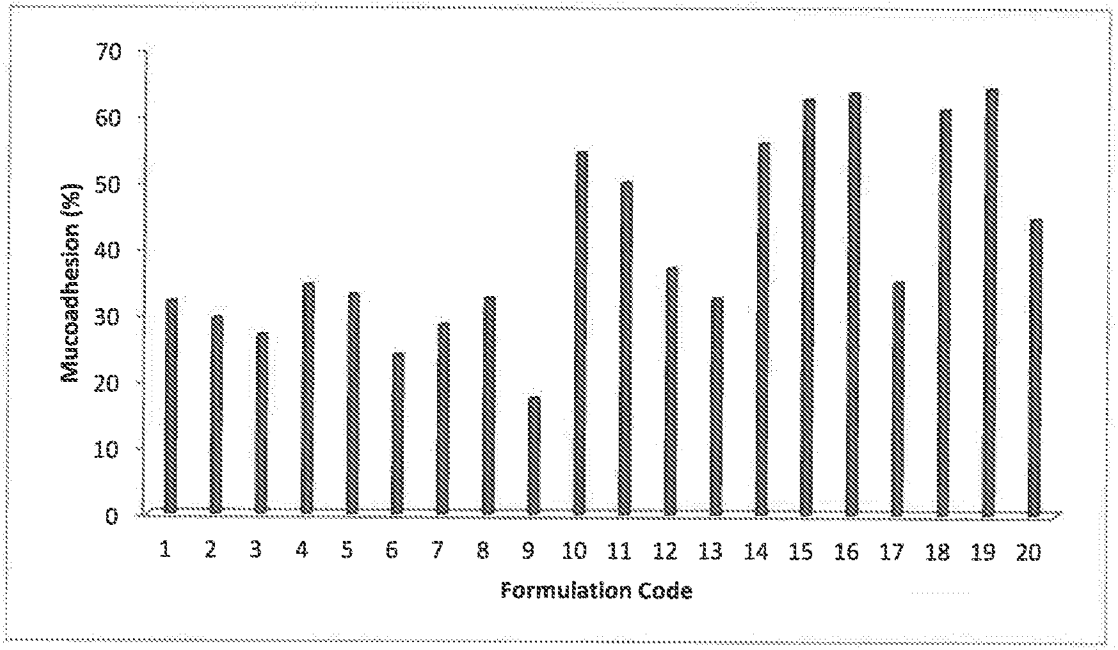


FIGURE 10

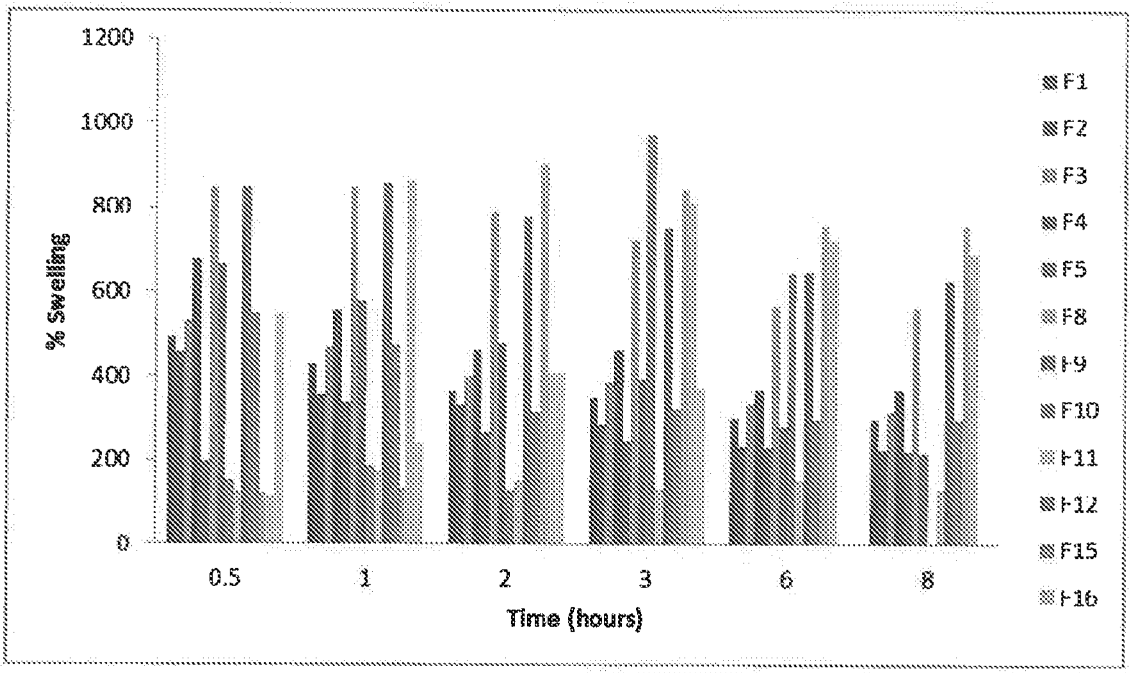
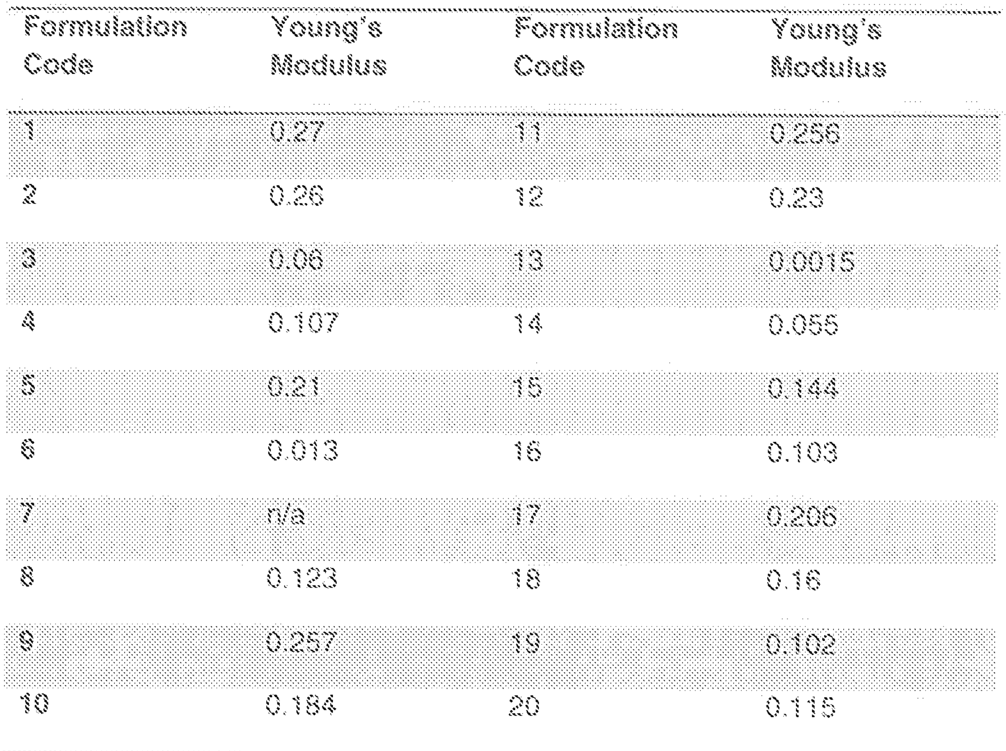


FIGURE 11



Formulation Code	Young's Modulus	Formulation Code	Young's Modulus
1	0.27	11	0.256
2	0.26	12	0.23
3	0.06	13	0.0015
4	0.107	14	0.055
5	0.21	15	0.144
6	0.013	16	0.103
7	n/a	17	0.206
8	0.123	18	0.16
9	0.257	19	0.102
10	0.184	20	0.115

FIGURE 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/054270

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/24 A61K31/00
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/182987 A1 (BAWA PRIYA [ZA] ET AL) 28 July 2011 (2011-07-28) paragraphs [0012] - [0047] figure 16 claims; examples -----	1-15
X	US 2013/337022 A1 (PILLAY VINESS [ZA] ET AL) 19 December 2013 (2013-12-19) paragraphs [0047] - [0061]; claims; examples -----	1-15
X	US 2011/052700 A1 (HAN CHIEN-HSUAN [US] ET AL) 3 March 2011 (2011-03-03) paragraphs [0075] - [0088], [0094], [0101] - [0117] ----- -/--	1,3,4,8, 9,12,15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 9 September 2015	Date of mailing of the international search report 16/09/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Ceyte, Mathilde

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/054270

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/311191 A1 (NANGIA AVINASH [US] ET AL) 18 December 2008 (2008-12-18) paragraphs [0027] - [0050], [0133] - [0136], [0156] - [0158] claims; examples -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/054270

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2013544259 A	12-12-2013
		US 2013337022 A1	19-12-2013
		WO 2012070028 A1	31-05-2012
US 2011052700 A1	03-03-2011	NONE	
US 2008311191 A1	18-12-2008	NONE	