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(71) Applicant(s)
Ferring B.V.

(72) Inventor(s)
Zurutuza, Amaia;Halliday, Janet A.;Livingston, Mark;Tuominen, Jukka

(74) Agent / Attorney
Shelston IP, L 21 60 Margaret St, Sydney, NSW, 2000

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(71) Applicant *(for all designated States except US)*: **CONTROLLED THERAPEUTICS (SCOTLAND) LIMITED** [GB/GB]; 1 Redwood Place, Peel Park Campus, East Kilbride G74 5PB (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TUOMINEN, Jukka** [FI/GB]; 30 Stobo, Calderwood, East Kilbride G74 3HL (GB). **ZURUTUZA, Amaia** [ES/GB]; Flat 32, 144 Queen Margaret Drive, Glasgow G20 8NY (GB). **LIVINGSTON, Mark** [GB/GB]; 7 Chestnut Gardens, Stanecastle, Irvine KA11 1RW (GB). **HALLIDAY, Janet, A.** [GB/GB]; 5 Dundas Street, Bo'ness, West Lothian EH52 0DF (GB).

(74) Agents: SZCZUKA, Jan et al.; MARKS & CLERK, 19 Royal Exchange Square, Glasgow G1 3AE (GB).

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(54) Title: POLYURETHANE ELASTOMERS

(57) Abstract: A linear polymer is obtained by reacting together a polyethylene glycol or polypropylene glycol; a PEG-PPG-PEG or PPG-PEG-PPG block copolymer; a difunctional amine or diol; and a diisocyanate. A controlled release composition comprises the polymer together with an active agent. Active agents of molecular weight 200 to 20,000 may be used.

POLYURETHANE ELASTOMERS

The present invention relates to hydrophilic thermoplastic polyurethane elastomer polymers, suitable for the production of controlled release compositions for release of pharmaceutically active agents over a prolonged period of time. Their elastomeric nature provides better comfort in use, for example, in pessaries, suppositories or vaginal rings.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Certain cross-linked polyurethane hydrogel polymers are known from European Patent Publications EP 0016652 and EP 0016654. These patent specifications describe cross-linked polyurethanes formed by reacting a polyethylene oxide of equivalent weight greater than 1500 with a polyfunctional isocyanate and a trifunctional compound reactive therewith, such as an alkane triol. The resultant cross-linked polyurethane polymers are water-swellable to form a hydrogel but are water-insoluble and may be loaded with water-soluble pharmaceutically active agents. One particular polyurethane polymer is the reaction product of polyethylene glycol 8000, Desmodur (DMDI i.e. dicyclohexylmethane-4,4-diisocyanate) and 1,2,6-hexane triol and which has been used commercially for vaginal delivery of prostaglandins.

However, such polyurethane polymers possess a number of practical disadvantages. Whilst the use of a triol cross-linking agent is effective in providing polymers of relatively reproducible swelling characteristics, the percent swelling is typically 200-300% (i.e. the increase in weight of the swollen polymer divided by the weight of the dry polymer). Pharmaceutically active agents are loaded by contacting the polymer with an aqueous solution of pharmaceutically active agent, such that the solution becomes absorbed into the polymer, forming a hydrogel. The swollen polymer is then dried back to the chosen water content before use. A consequence is that with the conventional cross-linked polyurethane, the degree of swelling limits the molecular weight of the pharmaceutically active agent which can be absorbed into the hydrogel structure to below about 3000 g/mol. A further disadvantage is that only water-soluble pharmaceutically active agents may be used. Finally, since the conventional cross-linked polyurethane polymer is essentially a non-thermoplastic polymer (thermoset), insoluble in both water and organic solvents, the further processing of the formed polymer into other solid forms, such as films, monolithic devices, foams, wafers, composites, sandwich structures, particles, pellets, foams or coatings, is not possible. In addition, the thermoset nature of the conventional cross-linked polyurethane polymer rules out the possibility of melt mixing drug with the polymer, in order to load the polymer with a suitable active agent without using solvents or water.

Certain thermoplastic polyurethane hydrogel polymers are known from patent Publication WO2004029125. This patent specification describes linear thermoplastic polyurethanes formed by reacting a polyethylene glycol of molecular weight of greater than 4000 g/mol with a polyfunctional isocyanate and a bifunctional compound reactive therewith, such as an alkane diol or diamine. The resultant thermoplastic polyurethane polymers are water-swellable to form a hydrogel but are water-insoluble and may be loaded with water-soluble pharmaceutically active agents. One particular polyurethane polymer is the reaction product of polyethylene glycol 8000, Desmodur (DMDI i.e. dicyclohexylmethane-4,4-diisocyanate) and 1,10-decane diol, which has shown percentage-swelling from 600% up to 1700% or even above. This type of polymer has shown a suitability for diffusion loading and short-term delivery of relatively water-soluble drugs e.g. clindamycin phosphate, oxytocin, and misoprostol.

However, such a high-swelling thermoplastic polyurethane polymer possesses many practical disadvantages. Due to the high weight content and block length of PEG, the polymer is only suitable for relatively short-term release (i.e. controlled release from 10 min to only a few hours) of active agents, especially in the case of highly water-soluble drugs. In addition, the low hydrophobic content, i.e. low amount of hydrophobic compound e.g. decanediol (DD) or dodecanediol (DDD) makes the polymer inappropriate for hydrophobic drugs and thus restricts its use. Hydrophilic and hydrophobic drugs need to have interactions with both of the phases in order for their release to be controlled by the polymer structure. Further, the imbalance between hydrophobic and hydrophilic compounds hampers microphase separation, which reduces the mechanical strength of the polymer in both the dry and wet state. In addition, due to the high crystallinity of polymer and the formation of hard blocks, the final polymer is rigid and the processing temperature relatively high.

The swelling percentage of high-swelling thermoplastic polyurethanes is typically 200-1700% and is dependent on the PEG content and/or the length of PEG block. Pharmaceutically active agents can be loaded by using the same method as described above for the conventional cross-linked polyurethane, as well as melt mixing drug and polymer. The release time and profiles obtained for the high swelling and crosslinked polyurethane polymers are, however, very similar.

Patent specification WO 94/22934 discloses the production of a linear random block copolymer from polyethylene oxide (number average molecular weight 1000 to 12,000), a diamine and a diisocyanate. Yu et al. Biomaterials 12 (1991) March, No.2, page 119-120 discloses the use of polyurethane hydrogels formed of polyethylene glycol (number average molecular weight of 5830) and a low molecular weight polypropylene glycol (molecular weight 425) and a diisocyanate. Patent specification US 4,202,880 discloses the production of polyurethanes from polyethylene glycol (molecular weight 400-20,000), an alkaline glycol containing from 2-6 carbon atoms and a diisocyanate. Patent specification US 4,235,988 is a similar disclosure, although the preferred PEG range is 600-6,000.

The object of a preferred embodiment of the present invention is to provide a hydrophilic thermoplastic polyurethane elastomer, which can be processed and mixed with an active agent at the temperature below the degradation temperature of the active agent by using conventional polymer processing systems, e.g. melt mixer, extruder and injection moulding machine. An additional objective of the present invention is to enhance the melt viscosity, to increase elasticity and to lower the crystallinity of the polymer in order to apply conventional melt processing techniques e.g. extrusion and injection moulding, as well as different types of solvents to the formation of drug loaded resilient controlled release devices of any chosen shape.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

According to a first aspect, the present invention provides a pharmaceutical controlled release composition in solid dosage form which comprises:

(i) a water-swellable linear polymer obtained by reacting together;

(a) a polyethylene glycol or polypropylene glycol;

(b) a PEG-PPG-PEG or PPG-PEG-PPG block copolymer;

(c) a difunctional compound, which is a C_5 to C_{20} diol; and

(d) a difunctional isocyanate; together with

(ii) a releasable pharmaceutically active agent;

wherein the molar ratio of the components (a), (b), (c) and (d) is in the range 0.01 -1 to 0.01 – 1 to 1 to 1.02 – 3, respectively.

According to a second aspect, the present invention provides a method of producing a linear polymer used in a composition according to the first aspect, which comprises melting and drying PEG or PPG, and the block copolymer, together with the difunctional compound at a temperature of 85°C to 100°C under vacuum; and then adding the difunctional isocyanate.

Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

The present invention is based on the discovery that thermoplastic polyurethane elastomers having suitable melt processing properties for drug loading and elasticity at body temperature, as well as suitable drug release characteristics, may be obtained by reacting a polyethylene glycol or polypropylene glycol with a diol or other difunctional compound, and a PPG-PEG-PPG or PEG-PPG-PEG block copolymer and a difunctional isocyanate.

PEG stands for polyethylene glycol; and PPG stands for polypropylene glycol.

In particular, the present invention provides a hydrophilic thermoplastic polyurethane elastomer polymer obtainable by reacting together:

(a) a polyethylene glycol or polypropylene glycol;

(b) a PEG-PPG-PEG or PPG-PEG-PPG block copolymer;

(c) a difunctional compound; and

(d) a difunctional isocyanate.

The thermoplastic polyurethane elastomer produced is swellable in water to a specific degree, depending upon the ratio of the four components (a), (b), (c) and (d), for example from 1% up to 200% (e.g. 20 to 100%) thus better controlling the release of pharmaceutically active agents from the high-swelling, PEG-based linear polyurethane. The polymer of the invention is also soluble in certain organic solvents, such as dichloromethane, 1-methyl-2-pyrrolidone (NMP) and tetrahydrofuran, which allows the polymer to be dissolved and cast into films or coatings. It also allows thermally unstable active agents of poor water solubility but which are soluble in organic solvents, to be loaded into the polymer.

Due to the unique combination of starting components, these polyurethane elastomers have a composition that can control the release of active compounds from a few days up to a few months.

Polyether polyols contain the repeating ether linkage -R-O-R- and have two or more hydroxyl groups as terminal functional groups. They are manufactured by the catalysed addition of epoxides to an initiator (anionic ring-opening polymerisation). The most important of the cyclic ethers by far are ethylene oxide and propylene oxide. These oxides react with active hydrogen-containing compounds (initiators), such as water, glycols, polyols and amines. A catalyst may or may not be used. Potassium hydroxide or sodium hydroxide is the basic catalyst most often employed. After the desired degree of polymerisation has been achieved, the catalyst is neutralized, removed by filtration and additives such as antioxidants are added.

A wide variety of compositions of varying structures, chain lengths and molecular weights is possible. By selecting the oxide or oxides, initiator, and reaction conditions and catalysts, it is possible to polymerise a series of polyether polyols that range from low-molecular-weight polyglycols to high-molecular-weight polymers. Since these polymers contain repeating alkylene oxide units, they are often referred to as polyalkylene glycols or polyglycols. Most polyether polyols are produced for polyurethane applications.

Polyethylene glycols (PEG) contain the repeat unit ($-CH_2CH_2O-$) and are conveniently prepared by the addition of ethylene oxide to ethylene glycol to produce a difunctional polyethylene glycol structure $HO(CH_2CH_2O)_nH$ wherein n is an integer of varying size depending on the molecular weight of the polyethylene glycol. Polyethylene glycols used in the present invention are generally linear polyethylene glycols i.e. diols having molecular weights of 200 to 35,000 g/mol. (generally 400 to 2000).

Polypropylene glycols (PPG) are polymers of propylene oxide and thus contain the repeat unit ($-CH_2(CH_3)CH_2O-$). Polypropylene glycol has unique physical and chemical properties due to the co-occurance of both primary and secondary hydroxyl groups during polymerisation, and to the multiplicity of methyl side chains on the polymers. Conventional polymerisation of propylene glycol results in an atactic polymer. The isotactic polymers mainly exist in the laboratory. Mixtures of atactic and isotactic polymers may also occur. PPG has many properties in common with polyethylene glycol. Polypropylene glycols of all molecular weights are clear, viscous liquids with a low pour point, and which show an inverse temperature-solubility relationship, along with a rapid decrease in water solubility as the molecular weight increases. The terminal hydroxyl groups undergo the typical reactions of primary and secondary alcohols. The secondary hydroxyl group of polypropylene glycols is not as reactive as the primary hydroxyl group in polyethylene glycols. PPG is used in many formulations for polyurethanes.

Polypropylene glycols used in the present invention are generally linear having molecular weights of 200 to 4000 g/mol, (generally 400 to 2000).

The invention also provides a method of producing the linear polymer, which comprises melting and drying PEG or PPG, and the block copolymer, together with the difunctional compound at a temperature of 85°C to 100°C under vacuum; and then adding the difunctional isocyanate.

The production of block copolymers (b), based on propylene oxide and ethylene oxide, can be initiated with ethylene glycol, glycerine, trimethylolethane, trimethylolpropane, pentaerythritol, sorbitol, sucrose and several other compounds. Mixed and alternating block copolymers can also be produced. When the secondary hydroxyl groups of PPG are capped with ethylene oxides, block copolymers of PEG and PPG with terminal primary hydroxyl groups are yield. The primary hydroxyl groups are more reactive with isocyanates than secondary hydroxyl groups. PEG-PPG-PEG and PPG-PEG-PPG copolymers used in the present invention are generally linear having molecular weight of 200 to 14,000 g/mol. The block copolymer appears to contribute to the non-crystalline elastomeric nature of the polymer of the invention.

The difunctional compound (c) is reactive with the difunctional isocyanate, and is typically a difunctional amine or diol. Diols in the range C_5 to C_{20}, preferably C_8 to C_{15} are preferred. Thus, decanediol has been found to produce particularly good results. The diol may be a saturated or unsaturated diol. Branched diols may be used but straight chain diols are preferred. The two hydroxyl groups are generally on terminal carbon atoms. Preferred diols include 1,6-hexanediol, 1,10-decanediol, 1,12-dodecanediol and 1,16-hexadecanediol.

The difunctional isocyanate (d) is generally one of the conventional diisocyanates, such as dicyclohexylmethane-4,4-diisocyanate, diphenylmethane-4,4-diisocyanate, 1,6-hexamethylene diisocyanate etc.

The equivalent weight ratio of the components (a), (b), (c) and (d) is generally in the range 0.01-1 to 0.01-1 to 1 to 1.02-3 respectively. Of course, the skilled man through reasonable experimentation would determine the best ratio of ingredients to give the desired properties. The amount of component (d) is generally equal to the combined amounts of (a), (b) and (c) to provide the correct stoichiometry.

The polymers are generally produced by melting and drying PEG or PPG, and PEG-PPG-PEG or PPG-PEG-PPG block copolymer together with the difunctional compound and a typical polyurethane catalyst (if used), e.g. ferric chloride, DABCO and/or tin (II) octoate, at a temperature of 85°C to 100°C (e.g. 95°C) under vacuum to remove excess moisture; before the diisocyanate, e.g. DMDI or HMDI is added thereto. The polymerisation is carried out in a batch or alternatively a continuous reactor; or the reaction mixture is fed into moulds and reacted for a specified time. After polymerisation the polymer is cooled down, pelletised or granulated and stored in a freezer for further analysis and processing.

The elastomeric properties of the thermoplastic polyurethane elastomers of the invention are due to two factors: microphase separation of hard and soft blocks; and the semicrystalline nature of the polymer, whose amorphous phase has a low glass transition temperature. Hard blocks form from the difunctional compound and diisocyanate. Soft blocks are PEG, PPG or copolymer. The elasticity may depend on the ratio of hard to soft blocks and may be represented by Shore hardness measurements.

The linear polymers of the present invention are soluble in certain organic solvents. This allows the polymer to be dissolved and the resultant solution cast to form films. The solution may also be employed for coating granules, tablets etc., in order to modify the polymer release properties. Alternatively, the solution can be poured into a non-solvent so as to precipitate polymer/active microparticles. In addition, the polymer can be ground, chopped, pelletised and melted by using conventional techniques used for processing thermoplastic polymers.

Thus, the invention also provides a controlled release composition comprising the linear polymer together with an active agent. Any type of plastic processing equipment, e.g. extruder, injection moulding machine, compression moulding equipment and melt mixer can be used for mixing the polymer and active agent together and forming or reshape into any type of drug loaded device, e.g. a ring, pessary, patch, rod, spring or cone. The active agent may be a pharmaceutically active agent for human or animal use. It may also be any other agent where sustained release properties (e.g. algicides, fertilisers etc.) are required. The pharmaceutical solid dosage forms include suppositories, rings and pessaries for vaginal use, buccal inserts for oral administration, patches for transdermal administration etc. These dosage forms are generally administered to the patient, retained in place until delivery of active agent has occurred and the spent polymer is then removed. The polymer may also be used for implants, which remain in the body; or for coating such implants (e.g. stents).

The polymer of the present invention is an amphiphilic thermoplastic polymer and is thus suitable for the uptake of hydrophilic and hydrophobic, low and high molecular weight pharmaceutically active agents (up to and exceeding a molecular weight of 3000 e.g. up to 10,000, up to 50,000, up to 100,000 or even up to 200,000).

Generally, the molecular weight of the active agent is in the range 200 to 20,000. A wide variety of water-soluble pharmaceutically active substances such as those listed in EP0016652 may thus be incorporated. Furthermore, the linear polymers of the present invention may be loaded with pharmaceutically active hydrophilic and hydrophobic agents, which are poorly water-soluble, provided that these can be dissolved in a common solvent with the polymer. The resultant solution can then be cast into any desired solid form. In addition, the linear polymers of the present invention may be extrusion loaded or melt mixed with pharmaceutically active agents, which are thermally stable at the polymer processing temperature.

The release time of the present polymers may exceed 12 hrs, 24 hrs, 5 days, 10 days, 20 days or even 80 days for substantially complete release of available active agent.

The polyether polyol blends and copolymers used in the present invention are internal and melt rheology, softness and release rate modifiers. These types of low melting amphiphilic thermoplastic polyurethane polymers are particularly suitable for the melt loading of pharmaceutically active agent and melt processing of loaded polymer to pharmaceutical devices.

Pharmaceutically active agents of particular interest include:

Proteins e.g. interferon alpha, beta and gamma, insulin, human growth hormone, leuprolide; benzodiazepines e.g. midazolam; anti-migraine agents e.g. triptophans, ergotamine and its derivatives; anti-infective agents e.g. azoles, bacterial vaginosis, candida; and ophthalmic agents e.g. latanoprost.

A detailed list of active agent includes H_2 receptor antagonist, antimuscaririe, prostaglandin analogue, proton pump inhibitor, aminosalycilate, corticosteroid, chelating agent, cardiac glycoside, phosphodiesterase inhibitor, thiazide, diuretic, carbonic anhydrase inhibitor, antihypertensive, anti-cancer, anti-depressant, calcium channel blocker, analgesic, opioid antagonist, antiplatel, anticoagulant, fibrinolytic, statin, adrenoceptor agonist, beta blocker, antihistamine, respiratory stimulant, micolytic, expertorant, benzodiazepine, barbiturate, anxiolytic, antipsychotic, tricyclic anti depressant, $5HT_1$ antagonist, opiate, 5HT, agonist, antiemetic, antiepileptic, dopaminergic, antibiotic, antifungal, anthelmintic, antiviral, antiprotozoal, antidiabetic, insulin, thyrotoxin, femal sex hormone, male sex hormone, antioestrogen, hypothalamic, pituitary hormone, posterior pituitary hormone antagonist, antidiuretic hormone antagonist, bisphosphonate, dopamine receptor stimulant, androgen, non-steroidal anti-inflammatory, immuno suppressant local anaesthetic, sedative, antipsioriatic, silver salt, topical antibacterial vaccine.

Embodiments of the present invention will now be described by way of examples below. The effects of type and ratios of PEG or PPG, PEG-PPG-PEG or PPG-PEG-PPG copolymer, diols and diisocyanates on the properties of polymers can be seen in the following Tables, Examples and Figures.

Figure 1 shows molecular weight as a function of polymerisation time for certain polymers; and

Figure 2 to 5 show various active agent release profiles.

EXAMPLE 1. Polymer manufacture

Various types of polyethylene glycols, polypropylene glycols, PEG-PPG-PEGs, PPG-PEG-PPGs, diols and diisocyanates, in a range of stoichiometric ratios were used to demonstrate their effect on the properties of the hydrophilic linear polyurethane elastomer polymers. PEG400, PEG900, PEG1000 and PEG2000 are polyethylene glycols having a molecular weight of 400, 900, 1000 and 2000 g/mol, respectively; PPG1000 and PPG2000 are polypropylene glycols having a molecular weight of 1000 and 2000g/mol; PEG-PPG-PEG1100 and PEG-PPG-PEG4400 are block copolymers having a molecular weight of 1100 and 4400 g/mol; PPG-PEG-PEG2000 is a block copolymer having a molecular weight of 2000 g/mol; DD is 1,10-decanediol and DDD is 1,12-dodecanediol; DMDI is dicyclohexylmethane-4,4-diisocyanate and HMDI is 1,6-hexamethylene diisocyanate; $FeCl_3$ is Ferric chloride, DABCO is triethylene diamine and $SnOct_2$ is Stannous octoate.

Polymers were produced by applying the polymerisation method described in WO patent Publication WO2004029125. The PEG, PPG, PEG-PPG-PEG and/or PPG-PEG-PPG were melted and vacuum dried at 95°C along with the diol and the catalyst (if used) in a rotary-evaporator for an hour at a pressure below 1 mbar. At this point the dried mixture was fed into a reactor prior to the diisocyanate addition. The manufactured polymers are shown in Table 1.

Table 1. Manufactured hydrophilic thermoplastic polyurethane elastomers.

Polymer	PEG		PPG		PEG-PPG-PEG		PPG-PEG-PPG		DD		DDD		DMDI		HMDI	
Name	Mw	mol ratio	Mw	mol ratio	Mw	mol ratio	Mw	mol ratio	Mw	mol ratio	Mw	mol ratio	Mw	mol ratio	Mw	mol ratio
Polymer A	-	-	1000	0.054	4400	0.046	-	-	174	1	-	-	262	1.1	-	-
Polymer B	-	-	1000	0.054	-	-	2000	0.046	174	1	-	-	262	1.1	-	-
Polymer C	400	0.216	-	-	-	-	2000	0.184	174	1	-	-	262	1.4	-	-
Polymer D	900	0.3	1000	0.3	-	-	-	-	-	-	202	0.3	262	0.9	-	-
Polymer E	2000	0.3	2000	0.3	-	-	-	-	-	-	202	0.3	262	0.9	-	-
Polymer F	-	-	1000	0.054	4400	0.046	-	-	174	1	-	-	-	-	168	1.1
Polymer G	-	-	1000	0.054	-	-	2000	0.046	174	1	-	-	-	-	168	1.1
Polymer H*1	-	-	1000	0.054	-	-	2000	0.046	174	1	-	-	-	-	168	1.1
Polymer I	-	-	1000	0.054	-	-	2000	0.046	-	-	202	1	-	-	168	1.1
Polymer J	400	0.216	-	-	4400	0.184	-	-	174	1	-	-	262	1.4	-	-
Polymer K	400	0.216	-	-	4400	0.184	-	-	-	-	202	1	-	-	168	1.4
Polymer L	400	0.216	-	-	1100	0.184	-	-	174	1	-	-	-	-	168	1.4
Polymer M*2	1000	0.2	-	-	1100	0.2	-	-	174	1	-	-	-	-	168	1.4
Polymer N*3	1000	0.2	-	-	1100	0.2	-	-	174	1	-	-	-	-	168	1.4
Polymer O	-	-	2000	0.1	-	-	2000	0.1	174	1	-	-	-	-	168	1.2
Polymer P	-	-	2000	0.25	-	-	2000	0.25	174	1	-	-	-	-	168	1.2
Polymer Q	-	-	2000	1	-	-	2000	1	174	1	-	-	-	-	168	3
Polymer R	2000	0.25	-	-	2000	0.25	-	-	174	1	-	-	-	-	168	1.5

*1 No catalyst
*2 DABCO
*3 DABCO + SnOct

EXAMPLE 2. Polymerisation reaction as a function of time

The effect of polymerisation time on the polymer produced was investigated using triple detection Size Exclusion Chromatography (SEC). Molecular weight determination as a function of polymerisation time was carried out for Polymers B and C, see Figure 1 below. The molecular weight of the polymer will determine the rheology, melt flow and mechanical properties of the polymer. Therefore the importance of determining molecular weight values is evident.

EXAMPLE 3. The effect of the catalyst on the polymerisation reactions

The polymerisations were performed as in Example 1 but the ferric chloride was replaced by DABCO and $SnOct_2$ for Polymer N (Table 1); while DABCO alone was used for Polymer M (Table 1). Polymer H (Table 1) was prepared in the absence of a catalyst.

EXAMPLE 4. The use of different diisocyanates

The polymerisations were performed as in Example 1 but the DMDI was replaced by HMDI for polymers F, G, H, I, K, L, M, N, O, P, Q and R in Table 1.

EXAMPLE 5. Solubility of polymers in different solvents

A number of polymers from Table 1 were dissolved in different solvents in order to find suitable solvents. The solubility tests were carried out for 24 hours at room temperature (RT). The solubility results for the selected polymers are shown in Table 2.

Table 2. Polymer solubility in selected solvents.

Polymer Name	DCM	THF	DCM/TEA	THF/TEA
	RT	35°C	RT	35°C
Polymer A	-	YES	-	-
Polymer B	-	YES	-	-
Polymer C	-	YES	-	-
Polymer D	-	YES	-	-
Polymer P	YES	YES	YES	YES

DCM	dichloromethane
THF	tetrahydrofuran
TEA	triethyl amine

EXAMPLE 6. Swelling capacity of polymers in different solvents

The swelling determinations for a number of selected polymers were carried out in water, ethanol, isopropyl alcohol (IPA) and in a 50% mixture of IPA/water in order to measure the amount of solvent absorbed by the polymer. The results were calculated based on the average swelling of 10 specimens and are shown in Table 3. The formula used for the calculations is shown below:

$$\%\mathbf{Swelling} = \frac{\mathbf{Swollen\ Weight - Dry\ Weight}}{\mathbf{Dry\ Weight}} \times \mathbf{100}$$

Table 3. Percent swelling of the selected polymers in different swelling media (water, ethanol, IPA and 50% IPA/water).

Polymer Name	% Swelling in Water	% Swelling in Ethanol	% Swelling in IPA	% Swelling in 50% IPA/water
Polymer A	2.5	133	113	68
Polymer B	2.5	89	73	71
Polymer C	43	N/A	130	206

EXAMPLE 7. Shore hardness testing (elasticity measurement)

The manufactured polymers were tested for Shore hardness using durometers A and D. Durometers A and D are generally used to measure elasticity of soft and hard rubber, respectively. These measurements are well known to the skilled person in the field. The results are presented as the average of four measurements and are presented in Table 4.

Table 4. Shore hardness values determined for the manufactured polymers.

Polymer Name	Durometer A		Durometer D	
	Max Hardness	Creep (15 sec)	Max Hardness	Creep (15 sec)
Polymer A	97.6	0.4	50.6	7.6
Polymer B	97.5	2.6	56.5	12.5
Polymer C	81.4	2.6	27.4	4.3
Polymer D	N/A	N/A	N/A	N/A
Polymer E	N/A	N/A	N/A	N/A
Polymer F	95.8	0.0	49.0	3.6
Polymer G	97.0	0.3	56.6	2.3
Polymer H*1	97.0	0.0	60.5	4.0
Polymer I	97.0	2.5	53.8	4.8
Polymer J	N/A	N/A	N/A	N/A
Polymer K	88.3	20.0	22.8	10.0
Polymer L	85.3	0.9	39.3	1.5
Polymer M*2	94.8	0.4	45.3	1.5
Polymer N*3	95.4	3.8	40.3	6.3
Polymer O	89.8	1.8	39.8	4.1
Polymer P	88.0	3.8	28.1	1.6
Polymer Q	60.8	3.9	N/A	N/A
Polymer R	87.0	2.0	29.8	1.8

Experimental conditions:

Temperature	21°C
Relative Humidity %RH	39

EXAMPLE 8. Polymer films manufactured by compression moulding

A number of selected polymers from Table 1 were dried over night under vacuum prior to the processing. The upper and lower plate temperatures of the compression moulding machine were set at the target processing temperature. Two Teflon sheets were placed between the mould and the hot plates. The melting time was 3-5 minutes followed by a 30 -120 seconds holding under pressure (170-200 bars). A predetermined amount of polymer was used to fill the mould. After cooling to room temperature the samples (pessary devices with dimensions 30mm x 10mm x

1mm) were mechanically punched out and kept in the freezer for further analysis. The film processing conditions are shown in Table 5.

Table 5. Thermal processing of the manufactured polymers using compression moulding.

Polymer	Temperature (°C)	Cylinder Pressure (Bar)	Melting Time (s)	Pressure Time (s)	Mould Thickness (mm)
Polymer A*	160	200	240	120	1.0
Polymer A*	160	200	210	120	1.0
Polymer A	150	200	120	60	0.25
Polymer C	130	200	180	60	0.4

EXAMPLE 9. Drug loading – extrusion

Selected polymers were loaded with two different active compounds: fluconazole and oxybutynin. A 16mm co-rotating twin-screw laboratory extruder was used for loading the polymers. Table 6 shows the drug loading conditions.

Table 6. Extrusion loading conditions used for the fluconazole loaded devices.

Polymer Name	**Drug**	**Drug (wt%)**	**Screw speed (rpm)**	**Temperature profile from feed to die (°C)**
Polymer A*	Fluconazole	20	40	55-95-120-120-120
Polymer A*	Fluconazole	50	40	55-95-115-115-115
Polymer A	Fluconazole	20	60	80-110-110-110-110
Polymer A	Fluconazole	50	60	103-113-115-115-115
Polymer A	Oxybutynin	5	60	80-115-115-115-115
Polymer A	Oxybutynin	10	40	90-110-110-110-110
Polymer A	Oxybutynin	15	60	80-110-110-110-110
Polymer B	Oxybutynin	5	50	132-132-132-132-132
Polymer B	Oxybutynin	10	40	133-133-133-133-136
Polymer C	Fluconazole	20	60	95-115-115-115-115
Polymer C	Oxybutynin	5	60	85-100-105-105-105
Polymer C	Oxybutynin	10	50	80-100-105-105-105
Polymer C	Oxybutynin	15	40	80-100-110-110-110

Two different batches of the same polymer composition (Polymer A and A*) were loaded with fluconazole in two different drug amounts in order to prove the reproducibility of the polymerisation process. Release results were found to be reproducible.

The quantity of the active compound loaded into the polymers was based on the required therapeutic dosage.

EXAMPLE 10. Drug release studies – Effect of polymer

In vitro drug release properties of the extrusion loaded polymers were determined by dissolution studies. The amount of fluconazole and oxybutynin released from the extrusion loaded polymers was investigated by using dissolution method based on the USP paddle method for short term release and incubator shaker method with Erlenmeyer bottles for long term release. USP paddle technique is comprised of an automated UV dissolution system where a Distek (2100C model) dissolution paddle (speed 50rpm) is connected to a Unicam UV 500 spectrophotometer via an Icalis peristaltic pump. The system is operated using Dsolve software. In the incubator shaker method the samples were taken manually and the Unicam UV 500 spectrophotometer was used to analyse the samples.

Experimental conditions:

Temperature	37°C
Dissolution media	500ml of deionised degassed water

In this example the effect of the polymer structure on the release of fluconazole was investigated. Polymer A and C were loaded with 20wt% fluconazole and Polymer A, B and C were loaded with 5% of oxybutynin using extrusion techniques. The release of fluconazole and oxybutynin varied depending on the polymer matrix, see Figure 2a and 2b.

EXAMPLE 11. Drug release studies – Effect of drug

When the drug type was changed different release profiles were obtained. Fluconazole and oxybutynin were loaded into Polymer A. Normalised dissolution profiles are shown in Figure 3. The same dissolution method as in Example 10 was used to determine the release curves.

EXAMPLE 12. Drug release studies – Effect of drug amount

The effect of increasing loading content was investigated by dissolution studies. The effect of different drug contents on the release properties of Polymer A was investigated and is shown in Figure 4. The fluconazole loading was increased from 20wt% to 50wt%. The same dissolution method as in Example 10 was used to determine the release curves.

EXAMPLE 13. Drug release studies – Comparison with high-swelling polymers

The fluconazole release profile obtained for Polymer A and Polymer C were compared with the release profiles obtained for a crosslinked and a linear high-swelling polyurethane polymer, see Figure 5. The diffusion loaded crosslinked polymer (crosslinked 17wt% fluconazole) was from patent EP0016652/EP0016654. While the linear high swelling polymer was from patent WO2004029125 and was loaded using diffusion (high %SW 17wt% fluconazole) as well as extrusion techniques (high %SW 20wt% fluconazole). The same dissolution method as in Example 10 was used to determine the release curves. These new polymers can provide an excellent control over drug release, see Figure 5.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A pharmaceutical controlled release composition in solid dosage form which comprises:

(i) a water-swellable linear polymer obtained by reacting together;

(a) a polyethylene glycol or polypropylene glycol;

(b) a PEG-PPG-PEG or PPG-PEG-PPG block copolymer;

(c) a difunctional compound, which is a C_5 to C_{20} diol; and

(d) a difunctional isocyanate; together with

(ii) a releasable pharmaceutically active agent;

wherein the molar ratio of the components (a), (b), (c) and (d) is in the range 0.01 -1 to 0.01 – 1 to 1 to 1.02 – 3, respectively.

2. A composition according to claim 1, wherein the polyethylene glycol is a linear polyethylene glycol having a molecular weight of 400 to 2000.

3. A composition according to claim 1, wherein the polypropylene glycol is a linear polypropylene glycol having an molecular weight of 400 to 2000.

4. A composition according to any one of the preceding claims, wherein the block copolymer has a molecular weight of 200 to 14,000.

5. A composition according to any one of the preceding claims, wherein the diol is a C_5 to C_{15} diol.

6. A composition according to any one of the preceding claims, wherein the diol is a C_8 to C_{15} diol.

7. A composition according to claim 1, wherein the diol is 1,6-hexanediol, 1,10-decanediol, 1,12-dodecanediol or 1,16-hexadecanediol.

8. A composition according to any one of the preceding claims, wherein the difunctional isocyanate (d) is dicyclohexylmethane-4,4-diisocyanate, diphenylmethane-4,4- diisocyanate, or 1,6-hexamethylene diisocyanate.

9. A composition according to any one of the preceding claims in the form of a suppository, ring or pessary for vaginal use, a bucchal insert, or a transdermal patch.

10. A composition according to any one of the preceding claims in the form of an implant.

11. A composition according to any one of the preceding claims, wherein the active agent has a molecular weight of up to 200,000.

12. A composition according to claim 11, wherein the active agent has a molecular weight of 200 to 20,000.

13. A method of producing a linear polymer used in a composition according to any one of the preceding claims, which comprises melting and drying PEG or PPG, and the block copolymer, together with the difunctional compound at a temperature of 85°C to 100°C under vacuum; and then adding the difunctional isocyanate.

14. A pharmaceutical controlled release composition in solid dosage form, a linear polymer, a method of producing a linear polymer substantially as herein described with reference to any one or more of the accompanying drawings and/or examples but excluding comparative examples.

Figure 1. Molecular weight analysis as a function of polymerization time for Polymers B and C.

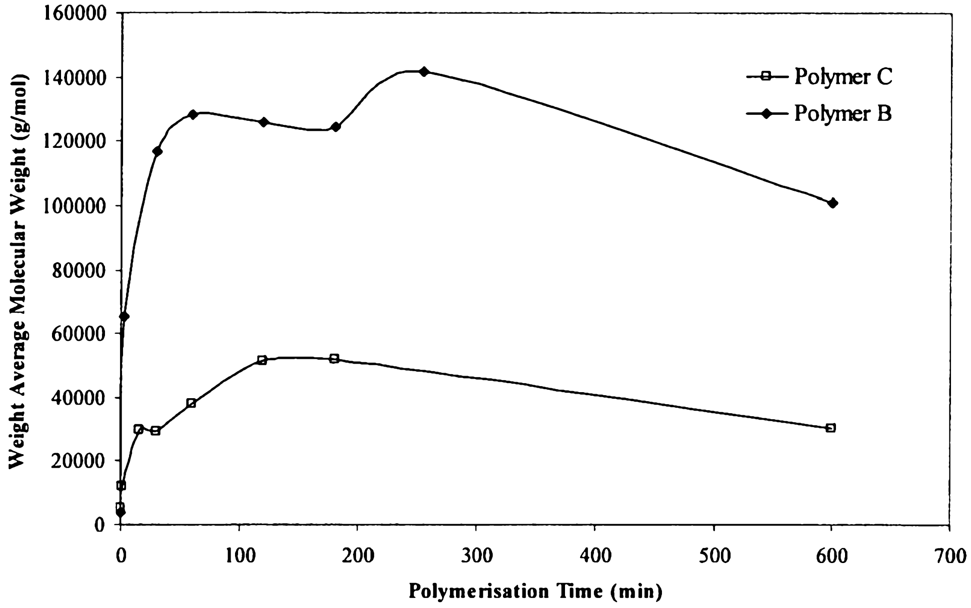

Figure 2a. Fluconazole release from Polymers A and C

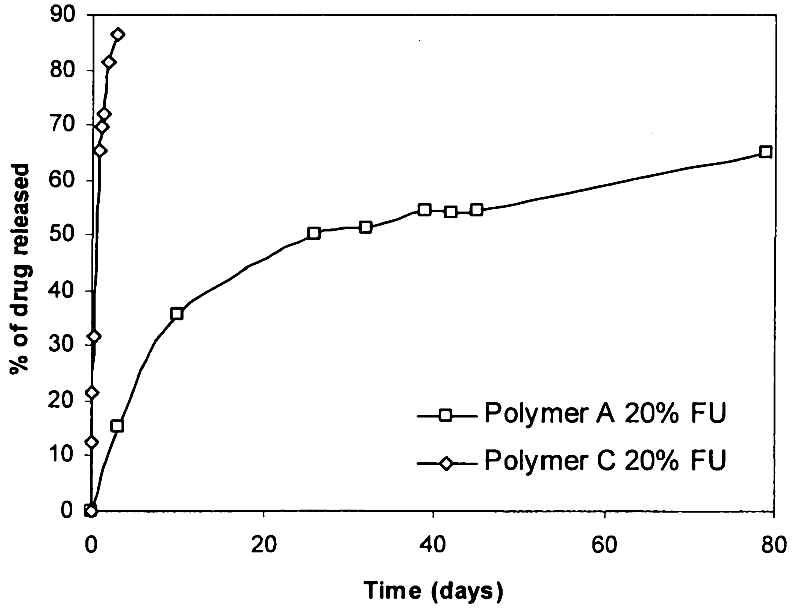

Figure 2b. Oxybutynin release from polymers Polymers A, B and C.

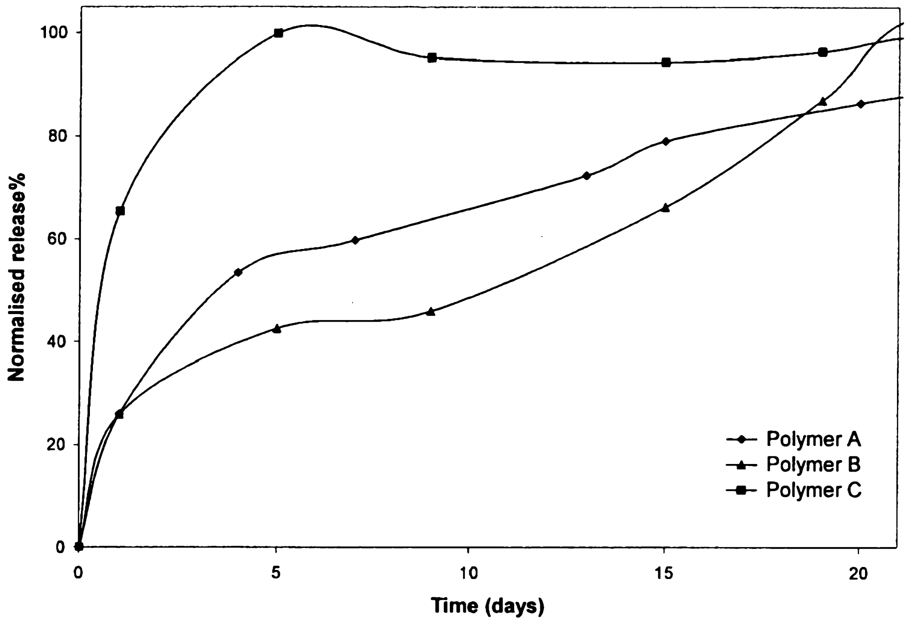

Figure 3. Release profiles obtained for Polymer A when fluconazole at 20wt% and oxybutynin at 15wt% were loaded.

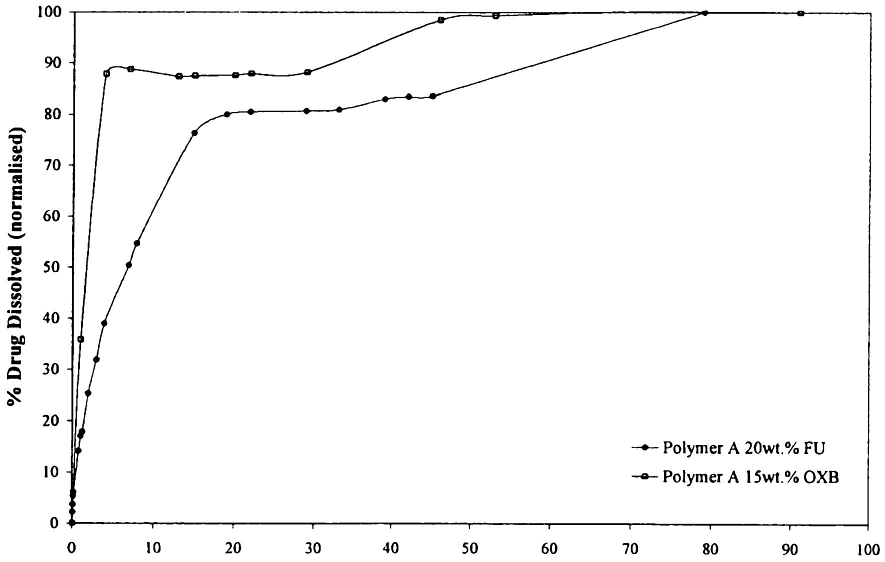

Figure 4. Release profiles obtained for Polymer A at 20wt% and 50wt% of fluconazole.

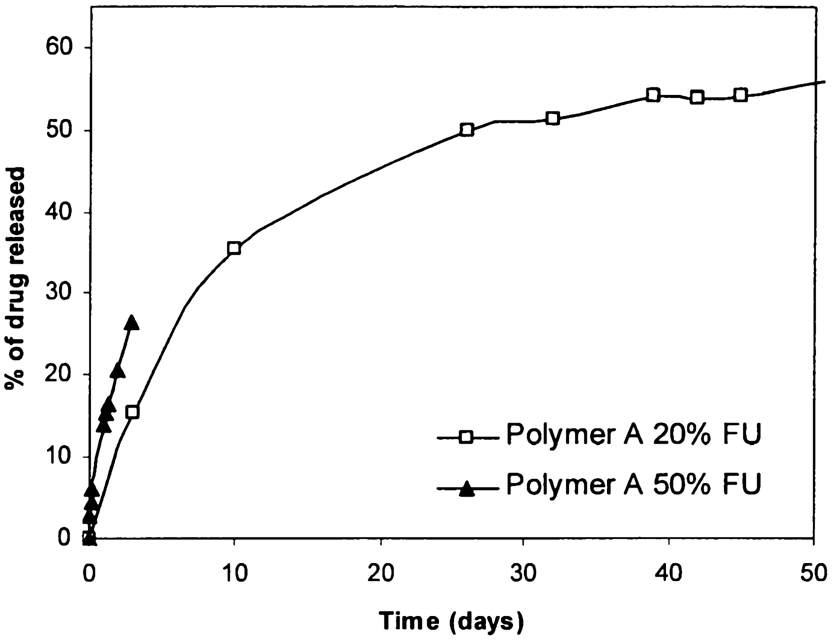

Figure 5. Comparison of the fluconazole release profiles from the crosslinked polymer, linear high-swelling polymers, Polymer A and Polymer C.