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(54) **HYDROPHILIC POLYURETHANE COMPOSITIONS**

(57) A water-swellable linear polymer is made by reacting together a polyethylene oxide of number average molecular weight less than 4000, an aliphatic diol and a difunctional isocyanate. Controlled release composition

comprises the polymer together with an active agent. The polymer is able to take up pharmaceutically active agents of molecular weight 200 to 20,000.

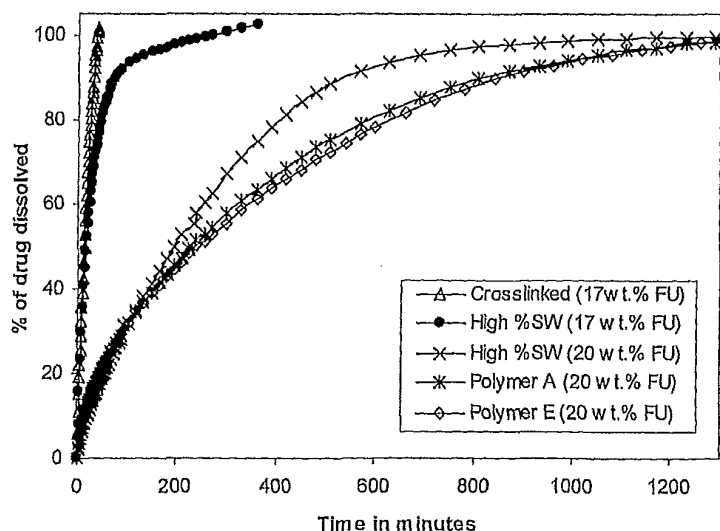


Figure 2. Comparison of the fluconazole release profiles from the crosslinked polymer, linear high-swelling polymers, polymer A and polymer E.

Description

[0001] The present invention relates to hydrophilic linear polyurethane polymers, suitable for the production of controlled release compositions for release of pharmaceutically active agents over a prolonged period of time.

[0002] Certain cross-linked polyurethane hydrogel polymers are known from European Patent Publication EP0016652 and EP0016654. 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-swellaible 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 (PEG) 8000, dicyclohexylmethane-4,4-diisocyanate (DMDI) and 1,2,6-hexane triol and which has been used commercially for vaginal delivery of prostaglandins.

[0003] However, such cross-linked 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 a chosen water content before use. As a consequence, 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 for loading. And the release properties are quite limited since prolonged release cannot be achieved; a maximum release time of 24 hours in vivo can be attained for water soluble drugs.

[0004] In addition to these disadvantages, the conventional cross-linked polyurethane polymer is essentially a non-thermoplastic polymer (thermoset), and is therefore insoluble in both water and organic solvents, making the further processing of the polymer into other solid forms, such as films, monolithic devices, foams, wafers, composites, sandwich structures, particles, pellets, foams or coatings, effectively impossible. In addition, the thermoset nature of the conventional cross-linked polyurethane polymer excludes the possibility of melt mixing drug and polymer in order to load the polymer with a suitable active agent without using solvents or water.

[0005] Certain thermoplastic polyurethane hydrogel polymers are known from patent Publication WO2004029125 (PCT/GB2003/004208). This patent specification describes linear thermoplastic polyurethanes formed by reacting a polyethylene oxide 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-swellaible 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 %-swelling from 600 up to 1700% or even above. This type of polymer has shown its suitability for diffusion loading and short-term delivery of relatively water-soluble drugs e.g. Clindamycin phosphate, Oxytocin, and Misoprostol.

[0006] However, such high-swelling thermoplastic polyurethane polymers also possess some 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, e.g. low amount of hydrophobic compound e.g. decane diol (DD) or dodecanediol (DDD), makes the polymer inappropriate for hydrophobic drugs; thus restricting its use. Furthermore, this imbalance between hydrophobic and hydrophilic regions hampers the microphase separation, reducing the mechanical strength of the polymer in both dry and wet states. 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.

[0007] 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 exactly the same method as the one described above for the conventional cross-linked polyurethane, and the release times and profiles are very similar.

[0008] 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.

[0009] An object of certain embodiments of the present invention is to provide a hydrophilic, low-swelling, linear polyurethane polymer of the aforementioned type. Another object is to enhance the processability of the polymer to allow the use of conventional melt processing techniques e.g. extrusion, compression moulding and injection moulding, as

well as different type of solvents in the polymer processing and drug loading steps.

[0010] The present invention is based on the synthesis of low-swelling linear polyurethanes having suitable melt processing properties for drug loading, as well as good drug release characteristics, which are prepared by reacting a polyethylene glycol with a diol or other difunctional compound and a difunctional isocyanate.

[0011] In particular, the present invention provides a water-swellaable linear polymer obtainable by reacting together:

- a polyethylene oxide of number average molecular weight less than 4000;
- an aliphatic diol; and
- a difunctional isocyanate

[0012] The linear low-swelling polymer produced is swellaable in water to a certain degree, depending upon the ratio of the three components (a), (b) and (c), for example from 1% up to 200% (e.g. 20 to 100%), thus obtaining better control over the release of pharmaceutically active agents than from the known high-swelling linear polymer. The polymers of the invention may also swell in other solvents (in which they are insoluble) such as ethanol or isopropyl alcohol. The linear polymer of the present 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 the loading of thermally unstable active agents with poor water solubility but which are soluble in organic solvents, to be loaded into the polymer.

[0013] Polyethylene oxides contain the repeating unit $(-\text{CH}_2\text{CH}_2\text{O}-)$ and are conveniently prepared by the stepwise addition of ethylene oxide to a compound containing a reactive hydrogen atom. Polyethylene glycols are prepared by the addition of ethylene oxide to ethylene glycol to produce a difunctional polyethylene glycol structure $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$ wherein n is an integer of varying size depending on the molecular weight of polyethylene oxide. Polyethylene oxides used in the present invention are generally linear polyethylene glycols i.e. diols having an equivalent weight of 200 to 4000 g/mol.

[0014] The difunctional aliphatic diol is reactive with the difunctional isocyanate, and is typically at least a C_6 or C_8 diol. Diols in the range C_5 to C_{20} , preferably C_8 to C_{15} are preferred. Thus, decane diol 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 hydroxy groups are generally on terminal carbon atoms. Thus, preferred diols include 1,6-hexanediol, 1,10-decanediol, 1,12-dodecanediol and 1,16-hexadecanediol.

[0015] The difunctional isocyanate is generally one of the conventional diisocyanates, such as dicyclohexylmethane-4,4-diisocyanate, diphenylmethane-4,4-diisocyanate, 1,6-hexamethylene diisocyanate etc.

[0016] The ratio of the components (a) to (b) to (c) (in terms of equivalent weights) is generally in the range 0.01-0.1 to 1 to 1.01-1.1. Of course, the skilled man through reasonable experimentation would determine the best ratio of ingredients to give the desired properties. The amount of component (c) is generally equal to the combined amounts of (a) and (b) to provide the correct stoichiometry.

[0017] Preferably, the amount of hydrophilic PEG units is less than 50 wt%, preferably less than 40 wt%, and often less than 30 wt%. Also, the amount of hydrophobic diol preferably exceeds 20 wt%, 30 wt% or 40 wt%. The diisocyanate is generally 20-50 wt% of the polymer.

[0018] The invention also provides a method of producing the polymer, which comprises melting and drying the polyethylene oxide together with the aliphatic diol at a temperature of 85°C to 100°C under vacuum; and then adding the difunctional isocyanate.

[0019] The polymers are generally produced by melting and drying polyethylene glycol together with the difunctional compound along with a typical polyurethane catalyst, e.g ferric chloride, triethylene diamine (DABCO) and/or tin(II) octoate, at a temperature of 85° to 100°C (e.g. 95°C) and under vacuum to remove excess moisture before the diisocyanate, e.g DMDI or HMDI is added thereto. The reaction mixture is then poured into moulds and reacted for a specified time. Thus, the polymer is initially formed as a solid. However, the linear polymers of the present invention are soluble in certain organic solvents such as those given in Table 2 (though not all polymers are soluble in all solvents). This allows the polymer to be dissolved and the resultant solution cast into films. The solution may also be employed for coating granules, tablets etc., in order to modify their release properties. Alternatively, the solution can be poured into a nonsolvent so as to precipitate polymer/active microparticles. In addition, the polymer can be ground, chopped, pelletised and melted using conventional techniques for processing thermoplastic polymers.

[0020] Thus, the invention also provides controlled release compositions comprising the linear polymer together with an active agent. Any suitable type of plastic processing equipment, e.g extruder, injection moulding machine, and melt mixer can be used for mixing polymer and drug and forming or reshaping them into any type of drug loaded format. 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 polymer is then removed.

[0021] The polymer may also be used for implants, which remain in the body; or for coating such implants (e.g. stents).

[0022] The linear polymer of the present invention is an amphiphilic thermoplastic polymer and is thus suitable for the uptake of hydrophilic, hydrophobic, low and high molecular weight pharmaceutically active agents (up to and exceeding a molecular weight of 3000 e.g. 10,000, 50,000, 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 patent specification EP0016652 may thus be incorporated. Furthermore, the linear polymers of the present invention may be loaded with pharmaceutically active 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 forms. 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.

[0023] The release time of the present polymers may exceed 200, 400, 800, 1200 mins or even longer - for substantially complete release of available active agent.

[0024] 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.

[0025] A detailed list of active agent includes H₂ receptor antagonist, antimuscarinic, prostaglandin analogue, proton pump inhibitor, aminosalicilic acid, corticosteroid, chelating agent, cardiac glycoside, phosphodiesterase inhibitor, thiazide, diuretic, carbonic anhydrase inhibitor, antihypertensive, anti-cancer, anti-depressant, calcium channel blocker, analgesic, opioid antagonist, antiplatelet, anticoagulant, fibrinolytic, statin, adrenoceptor agonist, beta blocker, antihistamine, respiratory stimulant, mucolytic, expectorant, benzodiazepine, barbiturate, anxiolytic, antipsychotic, tricyclic antidepressant, 5HT₁ antagonist, opiate, 5HT₁ agonist, antiemetic, antiepileptic, dopaminergic, antibiotic, antifungal, anthelmintic, antiviral, antiprotozoal, antidiabetic, insulin, thyrotoxin, female 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, antipsychotic, silver salt, topical antibacterial, vaccine.

[0026] Embodiments of the present invention will now be described by way of examples below. The effects of type and ratios of polyethylene glycols, diols and diisocyanates on the properties of polymers can be seen in the following Tables, Examples and Figures.

[0027] In the Figures, Figure 1 shows variation of molecular weight with polymerisation time for polymer A; and Figure 2 is a comparison of release profiles for various polymers.

Example 1. Polymer Manufacture

[0028] Various types of polyethylene glycols, diols and diisocyanates, in a range of stoichiometric ratios were used to demonstrate their effect on the properties of the hydrophilic linear polyurethane polymers produced. PEG400, PEG600, PEG1000, PEG1200, PEG2000 and PEG4000 are polyethylene glycols having molecular weights of 400, 600, 1000, 1200, 2000 and 4000 g/mol, respectively; DD is 1,10-decanediol and DDD is 1,12-dodecanediol; DMDI is dicyclohexylmethane-4,4'-diisocyanate and HMDI is 1,6-hexamethylene diisocyanate; FeCl₃ is Ferric chloride, DABCO is triethylene diamine; SnOct₂ is stannous octoate.

[0029] Polymers were produced using the polymerisation method in patent Publication WO2004029125. The PEG was melted and vacuum dried at 95°C with diol and catalyst in a rota-evaporator, before diisocyanate addition. Table 1 shows the manufactured polymers which were produced.

Table 1. Manufactured hydrophilic polyurethane polymers.

Polymer Name	PEG			DD			DDD			DMDI			HMDI		
	Mw	mol ratio	wt%	Mw	mol ratio	wt%	Mw	mol ratio	wt%	Mw	mol ratio	wt%	Mw	mol ratio	wt%
Polymer A	4000	0.1	46.4	174	1	20.2	-	-	-	262	1.1	33.4	-	-	-
Polymer B	4000	0.1	44.9	-	-	-	202	1	22.7	262	1.1	32.4	-	-	-
Polymer C	4000	0.1	50.8	-	-	-	202	1	25.7	-	-	-	168	1.1	23.5
Polymer D *1	4000	0.1	50.8	-	-	-	202	1	25.7	-	-	-	168	1.1	23.5
Polymer E	4000	0.05	29.5	-	-	-	202	1	29.8	262	1.05	40.6	-	-	-
Polymer F	4000	0.05	34.6	-	-	-	202	1	34.9	-	-	-	168	1.05	30.5
Polymer G	4000	0.01	7.9	-	-	-	202	1	39.9	262	1.01	52.2	-	-	-
Polymer H	2000	0.1	34.1	-	-	-	202	1	34.4	-	-	-	168	1.1	31.5
Polymer I	2000	0.1	34.1	-	-	-	202	1	34.4	-	-	-	168	1.1	31.5
Polymer J	2000	0.05	20.9	-	-	-	202	1	42.2	-	-	-	168	1.05	36.9
Polymer K	1500	0.1	29.5	174	1	34.2	-	-	-	-	-	-	168	1.1	36.3
Polymer L	1500	0.05	17.6	174	1	40.9	-	-	-	-	-	-	168	1.05	41.5
Polymer M	400	0.1	10.0	174	1	43.6	-	-	-	-	-	-	168	1.1	46.3
Polymer N	400	0.1	8.0	174	1	34.7	-	-	-	262	1.1	57.4	-	-	-
Polymer O *2	400	0.1	10.0	174	1	43.6	-	-	-	-	-	-	168	1.1	46.3
Polymer P *3	400	0.1	10.0	174	1	43.6	-	-	-	-	-	-	168	1.1	46.3

*1 no catalyst

*2 DABCO

*3 DABCO + SnOct

EXAMPLE 2. Polymerisation reaction as a function of time

[0030] 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 Polymer A and is shown in Figure 1. 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 polymerisations reactions

[0031] The polymerisations were performed as in Example 1 but the ferric chloride was replaced by DABCO and SnOct₂ for Polymer P (Table 1); while DABCO alone was used for Polymer O (Table 1). Polymer D (Table 1) was prepared in the absence of a catalyst.

EXAMPLE 4. The use of different diisocyanates

[0032] The polymerisations were performed as in Example 1 but the DMDI was replaced by HMDI for Polymers C, D, F, H, I, J, K, L, M, O and P in Table 1.

EXAMPLE 5. A two step polymerisation method

[0033] A two-step polymerisation method was used for making Polymer H in Table 1. The PEG-catalyst mixture was dried in a rotary-evaporator prior to the polymerization reaction. The diisocyanate (HMDI) was first fed to the heated (95°C) stirring tank reactor followed by the addition of the molten PEG-catalyst mixture which was added in 12 minutes using a constant mixing (60 rpm). The reaction was allowed to continue for 28 more minutes at which point the diol (DDD) was fed to the reactor. The reaction mixture was stirred for 7 more minutes. At this point the mixing was stopped and the polymer was further cured for 10 hours at 95°C before it was left to cool down to room temperature.

EXAMPLE 6. Solubility of polymers in different solvents

[0034] 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) or at elevated temperatures. The solubility results for the selected polymers are shown in Table 2.

Table 2. Polymer solubility in selected solvents and at different temperatures.

Polymer Name	DCM	HFIP	CHCl ₃	THF	DMAC	DMSO	NMP	NMP	NMP+LiBr
	RT	40°C	50°C	37°C	80°C	80°C	85°C	120°C	120°C
Polymer A	YES	N/A	N/A	YES	N/A	N/A	N/A	N/A	N/A
Polymer B	YES	N/A	N/A	YES	N/A	N/A	N/A	N/A	N/A
Polymer C	NO	Gel	NO	NO	NO	NO	YES	N/A	N/A
Polymer D	NO	Gel	NO	NO	NO	NO	YES	N/A	N/A
Polymer E	YES	N/A	N/A	YES	N/A	N/A	N/A	N/A	N/A
Polymer F	NO	Gel	NO	NO	NO	NO	Gel	YES	YES
Polymer G	NO	N/A	YES	NO	YES	NO	YES	N/A	N/A
Polymer H	NO	Gel	NO	NO	NO	NO	YES	N/A	N/A
Polymer I	NO	Gel	NO	NO	NO	NO	YES	N/A	N/A
Polymer J	NO	Gel	NO	NO	NO	NO	Gel	Gel	YES
Polymer K	NO	YES	NO	NO	NO	NO	NO	YES	YES
Polymer L	NO	Gel	NO	NO	NO	NO	Gel	YES	YES
Polymer M	NO	Gel	NO	NO	NO	NO	Gel	YES	YES
Polymer N	YES	N/A	YES	YES	YES	NO	YES	N/A	N/A

(continued)

Polymer Name	DCM	HFIP	CHCl ₃	THF	DMAC	DMSO	NMP	NMP	NMP+LiBr
	RT	40°C	50°C	37°C	80°C	80°C	85°C	120°C	120°C
Polymer O	NO	Gel	NO	NO	NO	NO	Gel	YES	YES
Polymer P	NO	Gel	NO	NO	NO	NO	Gel	YES	YES

DCM dichloromethane

HFIP hexafluoro isopropanol

CHCl₃ trichloromethane

THF tetrahydrofuran

DMAC dimethyl acetamide

DMSO dimethyl sulphoxide

NMP 1-methyl-2-pyrrolidone

LiBr lithium bromide

EXAMPLE 7. Swelling capacity of polymers in different solvents

[0035] 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 5-10 specimens and are shown in Table 3. The formula used for the calculations is shown below:

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

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	81	190	15	300
Polymer E	41	80	18	115
Polymer J	10	-	-	-
Polymer K	5.6	-	-	-
Polymer P*3	1.5	-	-	-

EXAMPLE 8. Shore hardness testis

[0036] The manufactured polymers were tested for shore hardness using durometers A and D. These measurements are well known to the skilled 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	95.3	0.8	59.3	5.3
Polymer B	98.0	0.0	60.6	4.1
Polymer C	97.5	0.5	53.1	2.1
Polymer D	96.0	0.0	50.5	4.3
Polymer E	98.0	0.0	67.0	6.5

(continued)

Polymer Name	Durometer A		Durometer D	
	Max Hardness	Creep (15 sec)	Max Hardness	Creep (15 sec)
Polymer F	94.5	0.0	53.5	3.3
Polymer G	97.5	0.0	65.8	6.0
Polymer H	N/A	N/A	N/A	N/A
Polymer I	96.5	1.0	53.8	0.8
Polymer J	93.0	1.5	55.8	2.3
Polymer K	99.0	0.0	63.0	3.6
Polymer L	99.0	0.0	66.0	4.8
Polymer M	99.0	0.0	68.4	4.9
Polymer N	99.5	0.0	77.8	4.9
Polymer O	99.0	0.0	70.6	2.9
Polymer P	100.0	0.0	67.8	3.8

Experimental conditions:

[0037]

Temperature 21°C
Relative Humidity %RH 39

EXAMPLE 9. Polymer films manufactured by compression molding

[0038] A number of selected polymers and a drug loaded polymer formulation 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 x10mm 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	Fluconazole (wt%)	Temperature (°C)	Cylinder Pressure (Bar)	Melting Time (s)	Pressure Time (s)	Mould Thickness (mm)
Polymer A	-	150	200	180	60	0.4
Polymer B	-	160	170	180	30	1.0
Polymer B	-	160	200	240	120	1.0
Polymer C	-	190	200	180	20	0.4
Polymer C	-	200	200	180	60	0.4

(continued)

Polymer	Fluconazole (wt%)	Temperature (°C)	Cylinder Pressure (Bar)	Melting Time (s)	Pressure Time (s)	Mould Thickness (mm)
Polymer D	-	180	200	300	60	0.4
Polymer D	-	200	200	180	50	0.4
Polymer E	-	165	200	270	60	0.4
Polymer E	20	160	200	270	60	1.0
Polymer E	-	170	200	210	60	0.4
Polymer H	-	160	170	180	30	1.0
Polymer P	-	200	200	180	50	0.4

EXAMPLE 10. Drug loading - extrusion

[0039] Selected polymers were loaded with the model drug fluconazole. A 16mm corotating 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	Drug	Drug (wt%)	Screw speed (rpm)	Temperature profile from feed to die (°C)
Polymer A	Fluconazole	20	30	96-150-150-150-155
Polymer E	Fluconazole	20	30	95-135-135-135-135

EXAMPLE 11. Drug release studies

[0040] The amount of fluconazole released from the extrusion loaded polymers was investigated by a dissolution method based on the USP paddle method. This 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.

Experimental conditions:

[0041]

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

[0042] In vitro drug release properties of the extrusion loaded polymers were compared with the diffusion loaded crosslinked and linear high swelling polymers, see Figure 2. Extrusion loaded polymers A and E were plotted with another extrusion loaded linear high swelling polymer from patent WO2004029125 (high %SW 20wt% fluconazole). The diffusion loaded crosslinked polymer from patent EP0016652/EP0016654 (crosslinked 17wt% fluconazole) is also shown in the graph below along with another linear diffusion loaded high swelling polymer from patent WO2004029125 (high %SW 17wt% fluconazole).

[0043] Further embodiments of the invention will now be described, by way of example only, with reference to the following clauses.

1. A water-swellaable linear polymer obtainable by reacting together:

- (a) a polyethylene oxide of number average molecular weight less than 4000;
- (b) an aliphatic diol; and
- (c) a difunctional isocyanate.

2. A linear polymer according to clause 1, wherein the polyethylene oxide is a diol of equivalent weight 200 to 4000 g/mol.

3. A linear polymer according to any preceding clause, wherein the aliphatic diol is C₅ to C₂₀ diol.

4. A linear polymer according to clause 3, wherein the aliphatic diol is a C₈ to C₁₅ diol.

5. A linear polymer according to clause 4, wherein the aliphatic diol is 1,6-hexanediol, 1,10-decanediol, 1,12-dodecanediol or 1,16-hexadecanediol.

6. A linear polymer according to any preceding clause, wherein the difunctional isocyanate is dicyclohexylmethane-4,4-diisocyanate, diphenylmethane-4,4-diisocyanate, or 1,6-hexamethylene diisocyanate.

7. A linear polymer according to any preceding clause, wherein the ratio of components (a) to (b) to (c) is in the range 0.01-0.1 to 1 to 1.01-1.1 in terms of equivalent weights.

8. A linear polymer according to any preceding clause, wherein the amount of hydrophilic PEG units is less than 50 wt % of the polymer.

9. A linear polymer according to any preceding clause, wherein the amount of hydrophobic diol exceeds 20 wt % of the polymer.

10. A linear polymer according to any preceding clause, wherein the amount of diisocyanate is 20-50 wt % of the polymer.

11. A method of producing a water-swellaable linear polymer according to any preceding clause, which comprises melting and drying the polyethylene oxide together with the aliphatic diol at a temperature of 85°C to 100°C under vacuum; and then adding the difunctional isocyanate.

12. A controlled release composition, which comprises the linear polymer of any one of clauses 1 to 10 together with an active agent.

13. A composition according to clause 12 which has been processed into a solid dosage form.

14. A composition according to clause 13 wherein the dosage form is a suppository, vaginal ring or pessary, a buccal insert, or a transdermal patch.

15. A composition according to clause 13 wherein the dosage form is an implant.

16. A composition according to any of clauses 12 to 15, wherein the active agent is a pharmaceutically active agent of molecular weight in the range 200 to 20,000.

Claims

1. A pharmaceutical controlled release composition comprising:

(i) a water-swellaable linear polymer obtainable by reacting together:

- (a) a polyethylene oxide of number average molecular weight less than or equal to 4000;
- (b) an aliphatic diol; and
- (c) a difunctional isocyanate, wherein the amount of hydrophilic PEG units is less than 50 wt % of the

polymer; together with

(ii) a pharmaceutically active agent.

- 5 **2.** A composition according to claim 1, wherein the polyethylene oxide is a diol of equivalent weight 200 to 4000 g/mol.
- 3.** A composition according to any preceding claim, wherein the aliphatic diol is C₅ to C₂₀ diol.
- 4.** A composition according to claim 3, wherein the aliphatic diol is a C₈ to C₁₅ diol.
- 10 **5.** A composition according to claim 4, wherein the aliphatic diol is 1,6-hexanediol, 1,10-decanediol, 1,12-dodecanediol or 1,16-hexadecanediol.
- 6.** A composition according to any preceding claim, wherein the difunctional isocyanate is dicyclohexylmethane-4,4-diisocyanate, diphenylmethane-4,4-diisocyanate, or 1,6-hexamethylene diisocyanate.
- 15 **7.** A composition according to any preceding claim, wherein the ratio of components (a) to (b) to (c) is in the range 0.01-0.1 to 1 to 1.01-1.1 in terms of equivalent weights.
- 8.** A composition according to any preceding claim, wherein the amount of hydrophobic diol exceeds 20 wt % of the polymer.
- 9.** A composition according to any preceding claim, wherein the amount of diisocyanate is 20-50 wt % of the polymer.
- 25 **10.** A composition according to any preceding claim which has been processed into a solid dosage form.
- 11.** A composition according to any preceding claim wherein the dosage form is a suppository, vaginal ring or pessary, a buccal insert, or a transdermal patch.
- 30 **12.** A composition according to any preceding claim wherein the dosage form is an implant.
- 13.** A composition according to any any preceding claim, wherein the active agent is a pharmaceutically active agent of molecular weight in the range 200 to 20,000.
- 35 **14.** A method of producing a pharmaceutical controlled release composition according to any preceding claim, which comprises melting and drying the polyethylene oxide together with the aliphatic diol at a temperature of 85°C to 100°C under vacuum; and then adding the difunctional isocyanate.

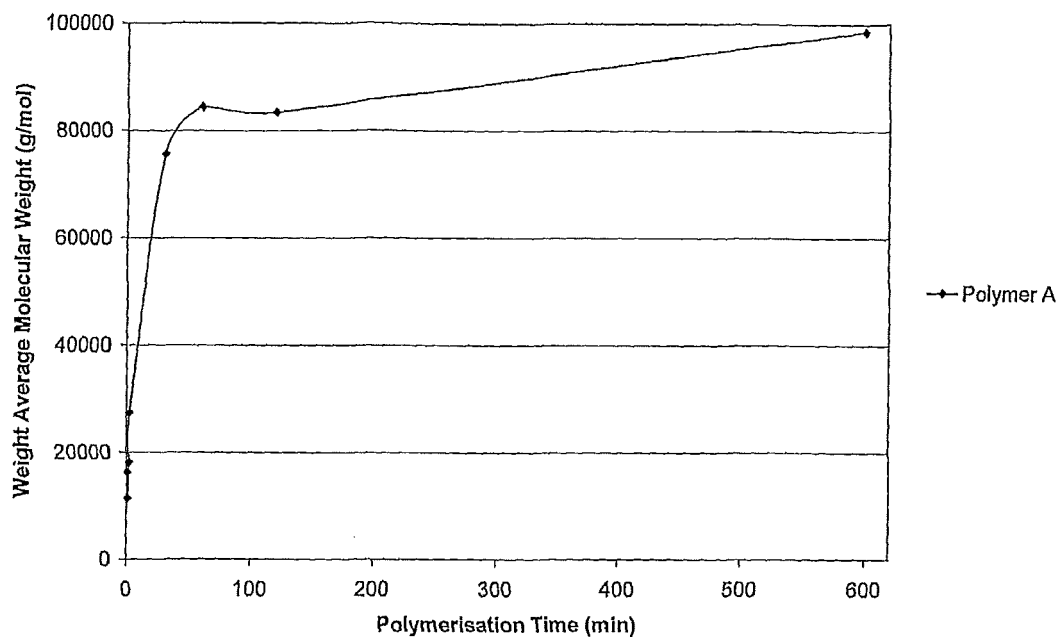


Figure 1. Molecular weight analysis as a function of polymerization time for Polymer A

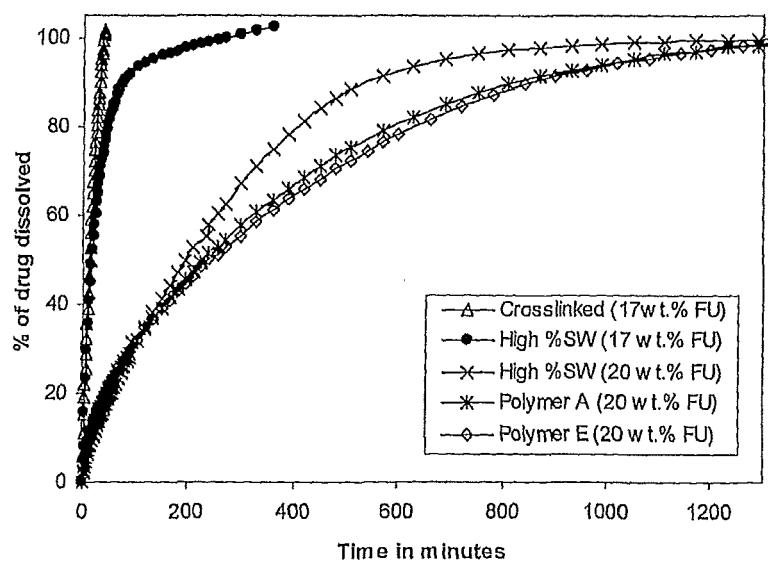


Figure 2. Comparison of the fluconazole release profiles from the crosslinked polymer, linear high-swelling polymers, polymer A and polymer E.



EUROPEAN SEARCH REPORT

Application Number
EP 15 17 8709

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摘要

本发明公开了一种水溶胀性线型聚合物，该水溶胀性线型聚合物通过将数均分子量小于4000的聚环氧乙烷、脂族二醇和双官能异氰酸酯一起反应而制成。公开了一种可控释放组合物，其包含所述聚合物以及活性试剂。所述聚合物能够吸收分子量为200至20,000的药物活性试剂。