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[45] Date of Patent: Jan. 12, 1993

[54] FATTY ACID TERMINATED POLYANHYDRIDES

[75] Inventors: Abraham J. Domb; Manoj Maniar, both of Baltimore, Md.

[73] Assignee: Nova Pharmaceutical Corporation, Baltimore, Md.

[21] Appl. No.: 756,483

[22] Filed: Sep. 9, 1991

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 467,635, Jan. 19, 1990.

[51] Int. Cl.[5] C08G 67/04

[52] U.S. Cl. 528/271; 528/206; 528/327; 528/321; 528/360; 528/361

[58] Field of Search 526/318.2; 528/271, 528/206, 327, 321, 360, 361

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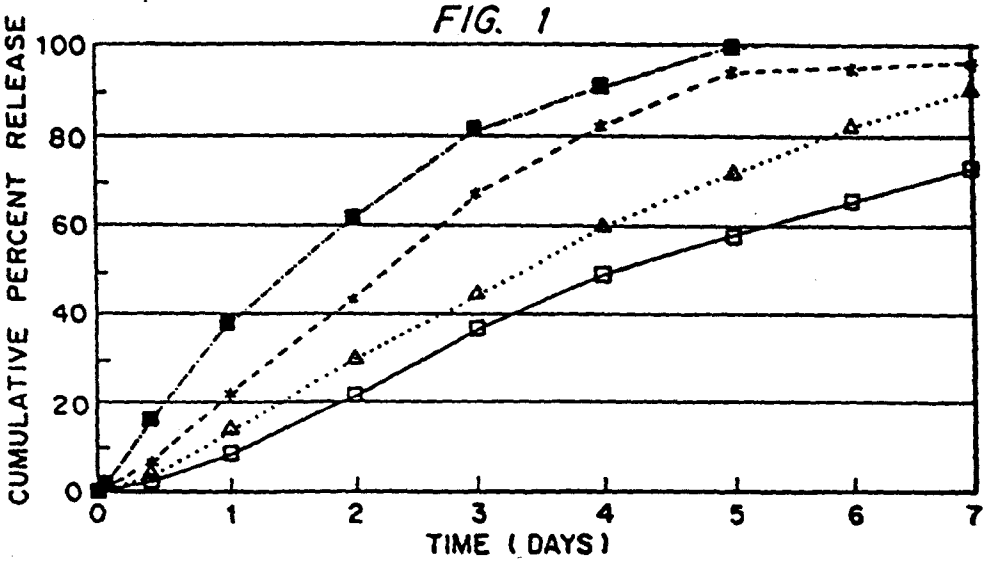
[57] ABSTRACT

Fatty acid terminated polyanhydrides suitable for use as controlled release matrices in biodegradable sustained release drug delivery systems and methods for making thereof are described. The polymers are more soluble in organic solvents, and have a lower melting point than the corresponding non-fatty acid terminated polyanhydrides. The fatty acid terminated polyanhydrides are also more hydrophobic than the corresponding polyanhydrides that are not terminated with a fatty acid, and combine the properties of thermodynamic and hydrolytic stability, and easy storage. The polymers can be produced with a controlled and low molecular weight. The polyanhydrides are useful in a number of applications, including as a matrix in biodegradable drug delivery systems.

13 Claims, 2 Drawing Sheets

FIG. 1



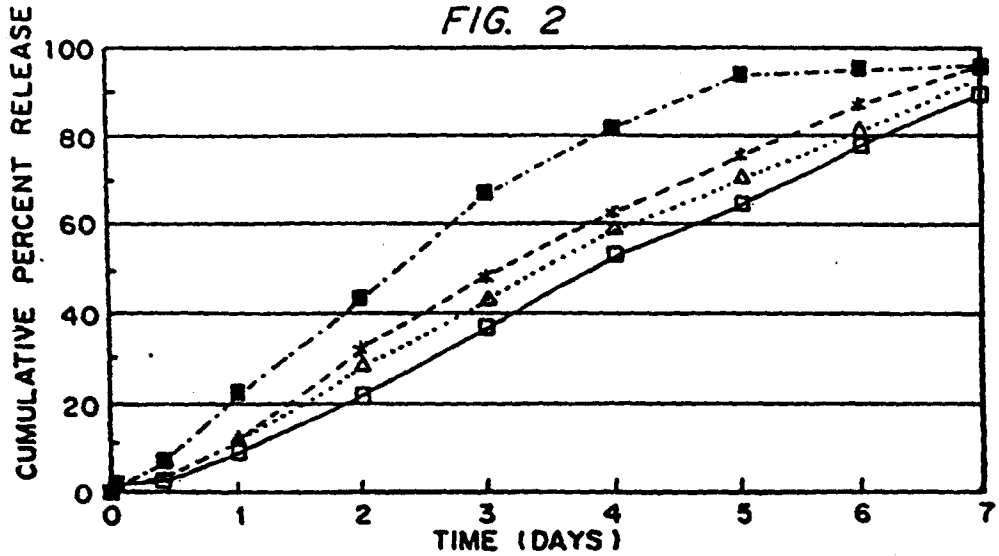
P(STA-SA) 15:85 10% MARCAIN FB

P(STA-SA)5:95 10% MARCAIN FB

P(STA-SA) 10:90 10% MARCAIN FB

P(SA) 10% MARCAIN FB

FIG. 2



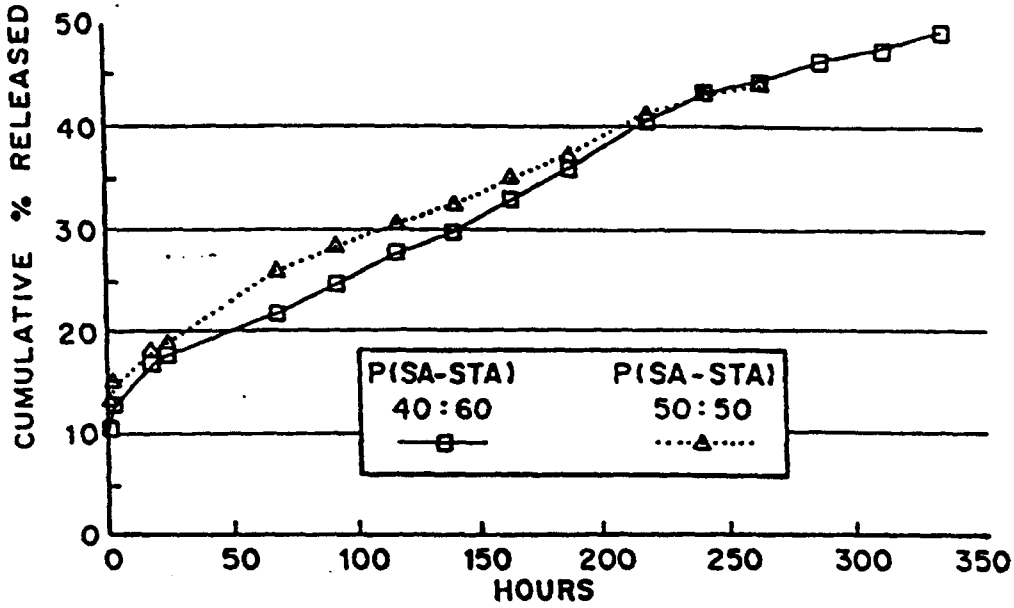
P(STA-SA) 15:85 10% MARCAIN.HCl

P(STA-SA) 5:95 10% MARCAIN.HCl

P(STA-SA) 10:90 10% MARCAIN.HCl

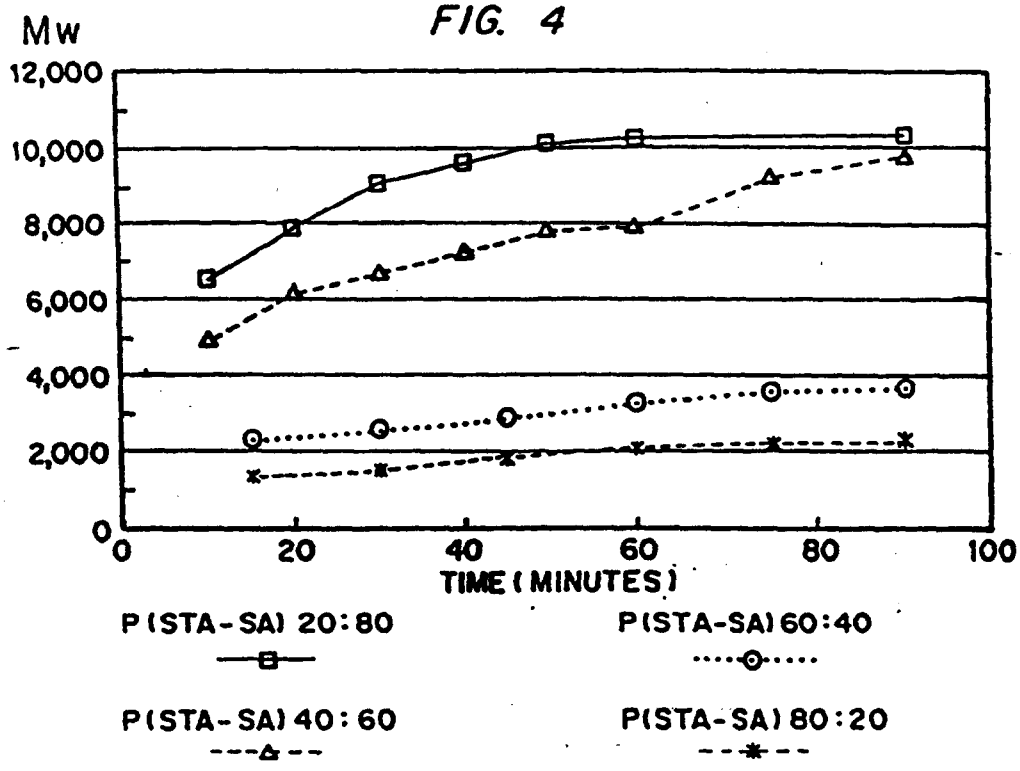
P(SA) 10% MARCAIN.HCl

FIG. 3



STUDY CONDUCTED AT ROOM TEMPERATURE
9922 - 265

FIG. 4



FATTY ACID TERMINATED POLYANHYDRIDES

This application is a continuation-in-part of U.S. Ser. No. 07/467,635, which is now pending, entitled "Polyanhydrides of Oligomerized Unsaturated Aliphatic Acids" filed on Jan. 19, 1990, by Abraham J. Domb.

BACKGROUND OF THE INVENTION

This invention is in the area of polymers for controlled delivery of substances, and more specifically encompasses biodegradable polyanhydrides whose end groups are terminated with fatty acids, and methods for making thereof.

There has been extensive research in the area of biodegradable controlled release systems for bioactive compounds. Biodegradable matrices for drug delivery are useful because they obviate the need to remove non-biodegradable drug-depleted devices. The ideal polymeric matrix would combine the characteristics of hydrophobicity, stability, organic solubility, low melting point, and suitable degradation profile. Such a polymer must be hydrophobic so that it retains its integrity for a suitable period of time when placed in an aqueous environment, such as the body, and stable enough to be stored for an extended period before use. The ideal polymer must also be strong, yet flexible enough so that it does not crumble or fragment during use.

Controlled release devices are typically prepared in one of several ways. For example, the polymer can be melted, mixed with the substance to be delivered, and then solidified by cooling. Such melt fabrication processes require polymers having a melting point that is below the temperature at which the substance to be delivered and polymer degrade or become reactive. Alternatively, the device can be prepared by solvent casting, where the polymer is dissolved in a solvent, and the substance to be delivered dissolved or dispersed in the polymer solution. The solvent is then evaporated, leaving the substance in the polymeric matrix. Solvent casting requires that the polymer be soluble in organic solvents.

Many polymers have been evaluated for their suitability for use as a matrix for a delivery device, including polyesters, polyamides, polyurethanes, polyorthoesters, polyacrylonitriles, and polyphosphazenes. None of these polymers have exhibited all of the desired characteristics for use in the controlled delivery of substances.

Polyanhydrides have also been studied for use in controlled delivery devices, as reported by Leong, et al., *J. Med. Biomed. Mater. Res.* 19, 941 (1985); and *J. Med. Biomed. Mater. Res.* 20, 51 (1986). One of the first polyanhydrides studied for its controlled release behavior was poly(bis(p-carboxyphenoxy)methane anhydride), described by Rosen, et al., *Biomaterials* 4, 131 (1983). The aromatic polyanhydride exhibited near zero order (linear) erosion and release kinetics at 37° C. and 60° C. Shortly thereafter, three related polyanhydrides: poly 1,3-(bis(p-carbophenoxy)propane anhydride (p-CPP) (an aromatic polyanhydride); the polymer formed from the copolymerization of p-CPP with sebacic acid (a copolymer of an aromatic diacid and an aliphatic diacid); and polyterephthalic acid (an aromatic anhydride), were prepared and examined for release rates by Leong, et al., *J. Med. Biomed. Mater. Res.* 19, 941 (1985).

These aromatic polyanhydrides were found to have unacceptably slow degradation rates. For example, it was estimated that it would take a delivery device prepared from p-CPP more than three years to completely degrade in vivo. Further, anhydride homopolymers based on aromatic or linear aliphatic dicarboxylic acids were found to be highly crystalline and have poor film forming properties. Aromatic polyanhydrides also have high melting points and low solubility in organic solvents.

Polymers prepared from linear aliphatic diacids are hydrophilic solids that degrade by bulk erosion, resulting in a rapid release of the drug from the polymeric matrix. Consequently, linear aliphatic diacids are unsuitable for use in controlled drug delivery systems. Hydrophobicity of such polymers can be increased by copolymerizing the linear aliphatic diacids with aromatic diacids. This approach, however, results in an increase in the polymer melting temperature and a decrease in solubility in organic solvents. Furthermore, such copolymerization does not improve the drug release profile, but instead increases the degradation and the elimination time of the polymer both in vivo and in vitro. Since both homopolymers and copolymers of linear aliphatic diacids are very sensitive to moisture, they require storage under anhydrous and low temperature conditions.

As described in U.S. Pat. No. 4,757,128 to Domb and Langer, high molecular weight copolymers of aliphatic dicarboxylic acids with aromatic diacids are less crystalline than aromatic or linear aliphatic polyanhydrides, and they form flexible films. Degradation rates are also increased by copolymerizing an aromatic dicarboxylic acid with an aliphatic diacid. However, bulk erosion still occurs because areas of the polymer containing aliphatic anhydride linkages erode faster than aromatic anhydride linkages, forming channels in the matrix through which the substance to be delivered is released in an uncontrolled fashion. For example, in the p-CPP sebacic acid copolymer described above, the aliphatic anhydride bonds are cleaved in vivo and all of the drug is released in ten days, while the aromatic regions remain intact for another five and one-half months. Further, the copolymers have inferior mechanical properties; they become brittle and crumble into flakes on exposure to moisture.

U.S. Patents that describe the use of polyanhydrides for controlled delivery of substances include: U.S. Pat. No. 4,857,311 to Domb and Langer, entitled "Polyanhydrides with Improved Hydrolytic Degradation Properties," which describes polyanhydrides having a uniform distribution of aliphatic and aromatic residues in the chain, prepared by polymerizing a dicarboxylic acid with an aromatic end and an aliphatic end; U.S. Pat. No. 4,888,176 to Langer, et al., entitled "Controlled Drug Delivery High Molecular Weight Polyanhydrides," which describes the preparation of high molecular weight polyanhydrides in combination with bioactive compounds for use in controlled delivery devices; and U.S. Pat. No. 4,789,724 to Domb and Langer, entitled "Preparation of Anhydride Copolymers", which describes the preparation of very pure anhydride copolymers of aromatic and aliphatic diacids.

There remains a strong need, however, for a polymer having the desired characteristics of hydrophobicity, stability, strength, flexibility, organic solubility, low melting point, and appropriate degradation profile, for use as a matrix for controlled delivery devices. It would also be useful to be able to substantially alter the degra-

dation and release kinetics of the polyanhydride for a wide variety of applications without significantly affecting the physical properties of the polymer.

It is therefore an object of the present invention to provide a biodegradable polymer that releases an incorporated substance in a controlled manner, wherein the polymer is highly hydrophobic, and degrades by surface erosion.

It is a further object of the present invention to provide a biodegradable, surface erodible polymer that is thermodynamically and hydrolytically stable, and can be stored under mild storage conditions.

It is a still further object of the present invention to provide a biodegradable controlled release microparticulate, injectable delivery system suitable for controlled in vivo administration of peptides and proteins, which is not acidic even in the absence of additives, and which stabilizes the incorporated peptides and proteins to be released without the use of additives.

SUMMARY OF THE INVENTION

Fatty acid terminated polyanhydrides, and their method of preparation, are disclosed. While not limited, in a preferred embodiment, the fatty acid terminated polyanhydrides have the general structure:

wherein R is an aliphatic, aromatic, or heterocyclic moiety, R' is a linear fatty acid residue of C_6 to C_{22}, and n is an integer from to 1 to 500. The polymers are highly hydrophobic, thermodynamically and hydrolytically stable, easily storable, and can be produced with a controlled and low molecular weight. The fatty acid terminated polyanhydrides are more soluble in organic solvents, and have a lower melting point, than the corresponding polyanhydrides that are not terminated with fatty acid moieties.

The fatty acid terminated polyanhydrides are particularly useful in biodegradable drug delivery systems since they do not create an acidic microenvironment when degrading, and they stabilize, without additives, proteins and peptides to be released from such systems.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph comparing the percent release of marcaine free base (FB) from fatty acid terminated polyanhydride as a function of time (days): p(STA-SA)(15:85) with 10% marcaine FB (open square); p(STA-SA)(10:90) with 10% marcaine FB (open triangle); p(STA-SA)(5:95) with 10% marcaine FB (-•-); and p(SA) with 10% marcaine FB (closed square).

FIG. 2 is a graph comparing the percent release of marcaine HCl from fatty acid terminated polyanhydride as a function of time (days): p(STA-SA)(15:85) with 10% marcaine FB (open square); p(STA-SA)(10:90) with 10% marcaine FB (open triangle); p(STA-SA) (5:95) with 10% marcaine FB (-•-); and p(SA) with 10% marcaine FB (closed square).

FIG. 3 is a graph comparing the cumulative percent release of BSA from fatty acid terminated polyanhydride particles as a function of time (hours) for p(STA-SA)(40:60) (open square) and p(STA-SA)(50:50) (open triangle).

FIG. 4 is a graph of the change in molecular weight of poly (STA-SA)20:80 (open square), poly(STA-SA)40:60 (open triangle), poly(STA-SA)60:40 (open circle), and poly(STA-SA) 80:20 (•) over time in minutes.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term aliphatic refers to a linear, branched, or cyclic alkane, alkene, or alkyne. Preferred aliphatic groups in the disclosed polyanhydride are C_4 to C_{22} linear, or branched moieties, particularly C_6 to C_{22} linear alkyl moieties.

As used herein, the term aromatic refers to an unsaturated cyclic carbon compound with $4n+2$ π electrons.

As used herein, the term heteroaromatic refers to an aromatic compound that has an atom other than carbon in the ring, for example, nitrogen, oxygen or sulfur.

As used herein the term fatty acid refers to a long chain (C_6 to C_{22}) aliphatic carboxylic acid.

As used herein the abbreviations STA and SA refer to stearic acid and sebacic acid, respectively.

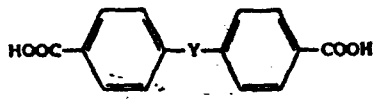
The biodegradable compositions disclosed herein are polyanhydride polymers which, during the polymerization process, are terminated with fatty acid molecules. Natural fatty acids act as polymer chain terminators because they only have one carboxylic acid group. They are, therefore, useful in controlling and limiting the molecular weight of the polyanhydride polymer. Such polymers may be either high molecular weight or low molecular weight. The low and controlled molecular weight fatty acid terminated polyanhydrides require less stringent storage conditions, due to reduced depolymerization relative to that observed with higher molecular weight polyanhydrides described by A. Domb and R. Langer, *Macromolecules*, 22, 2117 (1989). Such polymers perform equally well or better than currently known polyanhydrides as carriers for the controlled release of substances.

The incorporation of long chain fatty acids such as stearic acid into polyanhydride polymers alters the hydrophobicity of the polymer and decreases their degradation rate.

Fatty acid terminated polyanhydrides can be prepared in several ways. In a preferred embodiment, decarboxylic acids and the fatty acids are reacted separately with a lower (C_1 to C_3) aliphatic anhydride or acid chloride to form mixed anhydrides, referred to below as "prepolymers," as described in U.S. Pat. No. 4,757,128, incorporated by reference herein. These prepolymers are then mixed and co-polymerized. Once synthesized, the polymers can be combined with various substances or drugs sought to be released in a controlled manner and the mixture formed into biodegradable devices by methods well known to those skilled in the art.

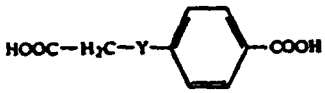
Dicarboxylic Acid Monomers

Monomers useful in the preparation of the dicarboxylic acid prepolymers are those of the structure HO_2C-R-CO_2H, wherein R is an aliphatic, aromatic, or heterocyclic moiety. Nonlimiting examples are aliphatic dicarboxylic acids, as defined by the formula: HOOC-H_2C-Y-CH_2-COOH; aromatic dicarboxylic acids, as defined by the formulas:

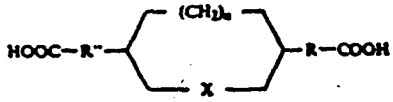


or

aromatic-aliphatic dicarboxylic acid, as defined by the formula:



aliphatic heterocyclic dicarboxylic acids defined by the formula:



wherein X=O, N or S, n=1 to 3; aromatic heterocyclic dicarboxylic acids, and aromatic heterocyclic aliphatic dicarboxylic acids.

The formulas are to be construed to include substitutions on the aromatic or aliphatic groups of the dicarboxylic acid. The Y group is any divalent organic radical, for example an aliphatic aromatic, or heteroaromatic moiety, and R=R". Any combination of these dicarboxylic acids can be copolymerized. For example, aromatic and aliphatic heterocyclic dicarboxylic acids can be used in combination with aliphatic dicarboxylic acids. Aromatic diacids can be used in combination with aliphatic acids. Further, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids can be polymerized.

The following monomers are examples of suitable dicarboxylic acids: sebacic acid, phthalic acid, terephthalic acid, isophthalic acid, adipic acid, 1,10-dodecanoic acid, bis(p-carboxyphenoxyalkane), fumaric acid, 1,4-diphenylenediacrylic acid, branched monomers such as 1,3,5-benzenetricarboxylic acid, azeleic acid, pimelic acid, suberic acid (octanedioic acid), itaconic acid, biphenyl-4,4'-dicarboxylic acid, and benzophenone-4,4'-dicarboxylic acid, p-carboxyphenoxyalkanoic acid, hydroquinone-0,0-diacetic acid, 1,4-bis-carboxymethyl benzene, 2,2-bis-(4-hydroxyphenyl)propane-0,0-diacetic acid, 1,4-phenylene-dipropionic acid, and cyclohexane dicarboxylic acid.

Monomers should be chosen that produce a fatty acid terminated polyanhydride with the desired properties. For example, aliphatic dicarboxylic acids of C_4 to C_{22} can be used to increase hydrophobicity and moldability of the polymer. Aromatic dicarboxylic acids can be used to increase the solubility of the polyanhydride in common organic solvents and to decrease the melting point of the polyanhydride.

Fatty Acid Chain Terminators

Natural fatty acids that can be used to alter the properties of the polyanhydride polymers and control their molecular weights include, but are not limited to, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, arachidic, behenic, lignoceric, heptanoic, nonanoic, undecanoic, tridecanoic, pentadecanoic, heptadecanoic, nonadecanoic, heneicosanoic, and tricosanoic acids. Naturally occurring unsaturated fatty acids, including arachidonic, docosahexanoic, elaidic, erucic, linoleic, linolenic, nervonic, oleic, palmitoleic and petriselinic acids can also be used to prepare the fatty acid terminated polyanhydrides.

The physical properties of the polyanhydride can be manipulated by careful selection of the fatty acid used to terminate the polymer. Short chain fatty acids (C_6 to C_{12}) can be used to decrease the molecular weight of the polyanhydride with minimal effect on the hydrophobicity characteristics of the polymer. Unsaturated fatty acids, such as erucic and oleic acid, which have a lower melting point than the corresponding saturated fatty acid, are useful to decrease the melting point of the polyanhydride. Long chain fatty acids (C_{12} to C_{22}), can be used to increase the hydrophobicity of the polyanhydride.

Methods for Polymerizing Fatty Acid Terminated Polyanhydrides

Any ratio of fatty acid units to dicarboxylic acid units can be used that produces a polyanhydride with the desired properties. A preferred ratio of fatty acid units to dicarboxylic acid units in the polyanhydride is 2 to 1000 fatty acid units per 500 units of dicarboxylic acid monomers. A ratio of approximately 85% by weight of dicarboxylic acid to 15% by weight of fatty acid is preferred in the preparation of certain fatty acid terminated polyanhydrides, including those made from sebacic acid and stearic acid.

Fatty acid terminated polyanhydrides can be prepared by methods known to those skilled in the art, including melt polycondensation and solution polymerization of the selected dicarboxylic acid with the desired amount of fatty acid.

Using the method of melt polycondensation, described by Domb, et al., in *J. Poly. Sci* 25, 3373 (1987), prepolymers can be prepared by heating the diacid and fatty acid separately with a lower aliphatic anhydride or lower-aliphatic acid chloride to form the corresponding dialiphatic dianhydride ("diacid prepolymer") and aliphatic fatty acid anhydride ("fatty acid prepolymer"). These prepolymers are then mixed in the desired ratio and heated neat under vacuum to form the fatty acid terminated anhydride polymer. In a preferred embodiment, acetic anhydride is used to prepare the prepolymer. The aliphatic acid is stripped off during the polymerization process. Combinations of dialiphatic dianhydrides and combinations of fatty acid prepolymers can also be polymerized with this method.

In a preferred embodiment, the fatty acid and dicarboxylic acid prepolymers are heated at 150° C. to 220° C. in a vacuum of greater than 1 mm Hg, for a time ranging from 30 minutes to six hours. The polymerization time depends on the batch size, and on the monomer composition.

Solution polymerization is preferred when either the fatty acid or the dicarboxylic acid is sensitive to heat. Solution polymerization is described in U.S. Pat. No.

4,916,204 to Domb et al., entitled "One Step Polymerization of Polyanhydrides", incorporated herein by reference. Solution polymerization involves the phosgene coupling of diacids with each other and with the fatty acid in an organic solvent. Poly(4-vinylpyridine-2% divinylbenzene) ("PVP") is added to remove the HCl from solution. For example, diphosgene (0.50 equivalents) is added dropwise to a stirred mixture of the desired ratio of dicarboxylic acid and fatty acid and poly(4-vinylpyridine-2% divinylbenzene) (in a ratio of 2 to 3 equivalents to 1 equivalent of monomer) in a suitable amount of chloroform. The solution is stirred for 3 hours at 25° C. The insoluble PVP.HCl is removed by filtration. The solvent is then removed and the precipitate is isolated, washed with ethyl ether, and then dried at 25° C. for 24 hours in a vacuum oven.

In an alternative embodiment, using either melt polycondensation or solution polymerization, the dicarboxylic acid units are allowed to polymerize alone for a given time period, and then the fatty acid terminator is added.

Materials to be Incorporated

A variety of materials, including proteins, carbohydrates, and organic molecules, can be incorporated into the polymers using known methods, including melt casting, solvent preparation, pressing, compression molding, spray drying, microencapsulation, and tableting. The polymers are particularly useful for the controlled release of proteins and peptides. Examples include drugs and other bioactive substances to be released in vivo, such as chemotherapeutic agents, antibiotics, antivirals, antifungals, antiinflammatories, and anticoagulants, as well as other substances such as fertilizers, herbicides, insecticides and repellents, that are released over a period of time. The substances to be incorporated should not chemically interact with the polymer during fabrication, or during the release process. Additives such as inorganic salts, BSA (bovine serum albumin), and inert organic compounds can be used to alter the profile of substance release.

The method of producing fatty acid terminated polyanhydrides, for ease of illustration, is described in detail below for the polymerization of sebacic acid terminated with stearic acid. The method, however, can be used to produce other polymers wherein the ratio of stearic acid to sebacic acid varies. Further, other polymers can be prepared by substituting other fatty acids for stearic acid, and other dicarboxylic acids for sebacic acid.

EXAMPLE 1

Preparation of Fatty Acid Terminated Polymers

A. Preparation of Pre-Polymers of Stearic Acid and Sebacic Acid

Stearic acid (100 g) was refluxed in acetic anhydride (500 ml) for 20 to 60 minutes. The clear solution was cooled to room air over several hours, during which time a heavy white precipitate appeared. The precipitate was collected by filtration and washed with a 1:1 hexane:diethyl ether mixture and dried. The prepolymer (>80% yield) melted at 60°-65° C. and showed typical anhydride peaks at 1740 and 1800 cm-1.

The sebacic acid prepolymer was prepared as follows. Sebacic acid (SA, 200 gm, recrystallized twice in ethanol) was added to 500 ml of hot acetic anhydride (>100° C.) and heated for 20 to 60 minutes. The clear solution was filtered through a filter paper and evaporated to dryness. To the clear residue 100 ml of dichloromethane or hot isopropylether was added and the mixture was precipitated in 1000 mL of isopropylether at room temperature. The white precipitate was collected by filtration and stored in glass containers (yield >80%). The prepolymer melted at 75°-78° C. and showed typical anhydride peaks at 1740 and 1800 cm-1. The optical density of a 2% solution in dichloromethane at 420 nm was 0.001, indicating high purity.

B. Polymerization of the Prepolymers

Polymers containing varying combinations of sebacic acid prepolymers and stearic acid prepolymers were synthesized by melt polycondensation polymerization at 180° C. Samples were taken periodically as a function of time in order to monitor the molecular weight changes of the polymer. As illustrated in FIG. 4, it was found that the synthesized fatty acid terminated polyanhydride polymers ("p(STA:SA)") reached their maximum molecular weight within 90 minutes, and thereafter no significant change in molecular weight was observed. In contrast, the molecular weight of sebacic acid only polymer ("p(SA)") increased significantly after 90 minutes. Further, at any given time point in the polymerization process the molecular weight of the sebacic acid polymer p(SA) was significantly higher than that of the fatty acid terminated polymer p(STA:SA).

Representative molecular weights and intrinsic viscosity values of the fatty acid terminated polymer and P(SA) were measured as a function of time and are shown in Table I. p(STA:SA)(15:85) represents fatty acid terminated polymer prepared using 15% stearic acid prepolymer and 85% sebacic acid prepolymer by weight. As can be seen from Table I, stearic acid effectively acts as a chain terminator, so that the molecular weight of the p(STA:SA)15:85 fatty acid terminated polymers are lower than p(SA) and remain relatively constant during 90 to 150 minutes of polymerization.

TABLE I

Comparison of Weight Average Molecular Weights and Viscosity of p(STA:SA) and p(SA).

Time (min)	Mw of P(STA:SA) 15:85 w/w	Mw of P(SA)	Viscosity P(STA:SA) 15:85 w/w	Viscosity P(SA)
15	7537	18301	0.178	0.280
30	12419	24462	0.190	0.330
45	16570	42367	0.202	0.365
60	18792	52845	0.216	0.423
75	20059	64925	0.224	0.530
90	28233	74120	0.280	0.565
150	32986	203019	0.269	0.791

In the following examples, for ease of illustration, degradation and release profiles of fatty acid terminated polyanhydrides are described with reference to polymers prepared from stearic acid and sebacic acid. However, it should be understood that the present invention is not limited to these polymers but includes the use of all of the above described fatty acid terminated polyanhydrides to provide controlled release of substances.

EXAMPLE 2

Release of Marcaine Free Base and Hydrochloride Salt from P(STA:SA)

Marcaine HCl salt was powdered using pestle and mortar. The powdered drug was sieved through a 63μ sieve. Marcaine free base was purchased from Sigma

Chemical Company, with a particle size of less than 30 microns. P(STA:SA)(15:85) prepolymers and p(SA) prepolymers were prepared as described in Example 1. Other fatty acid terminated polyanhydrides composed of 10% stearic acid:90% sebacic acid and 5% stearic acid:95% sebacic acid were prepared by the method described in Example 1, except that the initial concentrations of stearic acid and sebacic acid were as indicated. The resulting fatty acid terminated polymers and were designated p(STA:SA)(10:90) and p(STA:SA)(5:95), respectively.

Each fatty acid terminated polymer prepared by the above method was melted separately at approximately 85° C. and powdered drug, either marcaine free base or marcaine HCl, was mixed thoroughly into it. The molten mixture was transferred into molds and allowed to solidify. The thus formed drug-polymer compositions were removed from the molds and cut into rectangular slabs weighing approximately 120 mg each. The drug content of each slab was 10% w/w.

Sustained drug release studies for each composition were conducted in 20 ml scintillation vials using 20 ml of 0.1 M phosphate buffer at 37° C. The marcaine released to the releasing medium was determined by HPLC, C18 reverse phase column using 60:40 acetonitrile:0.1 M phosphate buffer at a pH of 6.8 and a flow rate of 1 ml/minute. The amount of marcaine free base and marcaine HCl salt released from the various polymers as a function of time is represented in FIGS. 1 and 2, respectively. It is evident from the figures that increasing the ratio of stearic acid prepolymer to sebacic acid prepolymer in the fatty acid terminated polymers decreases the release rate of the drug from the compositions. The release rate of the drug becomes almost linear at a stearic acid:sebacic ratio of 15:85.

EXAMPLE 3

Release of Bovine Serum Albumin from Fatty Acid Terminated Polyanhydride

Bovine serum albumin ("BSA") (0.1 gm) was uniformly dispersed in molten samples of 40% stearic acid:60% sebacic acid and 50% stearic acid:50% sebacic acid fatty acid terminated polyanhydride (0.8 gm each) which were prepared according to the method of Example 1. The molten dispersion was compressed between two glass plates covered with teflon coated aluminum foil. After cooling, the film was separated from the foil and cut into particles of less than 1 mm in diameter. The in vitro release of BSA from the microparticles was carried out in phosphate buffer (pH 7.4) at 37° C. The concentration of BSA in the releasing medium was determined by HPLC using a size exclusion column (BioRad TSK gel) and 10% acetonitrile in pH 6.8 buffer solution at a flow rate of 1 ml/minute. The drug was detected by UV at 214 nm.

The release profile is as shown in FIG. 3. After an initial burst, the release of BSA was essentially linear for two weeks.

EXAMPLE 4

Release of Spray Dried Somatotropin from Fatty Acid Terminated Polyanhydride

Microparticles of fatty acid terminated polyanhydride containing bovine somatotropin were prepared as described in Example 3, using sebacic acid and stearic acid in a ratio of 85:15. The in vitro release of the somatotropin from the microparticles was determined over time, using the method described in Example 2.

About 60% of the drug was released in an active form from the fatty acid terminated polyanhydride over a period of 96 hours as determined by HPLC analysis. In comparison, only about 30–40% of drug was released in active form from p(SA).

EXAMPLE 5

Preparation of Microparticles of Fatty Acid Terminated Polyanhydride Containing Stabilized rbSt

A. Preparation of Stabilized Bovine Somatotropin (rbSt)

Recombinant bovine somatotropin (rbSt) (150 mg) and a stabilizer (37 mg) were dissolved in 200 ml of highly purified water. The solution was then transferred to a lyophilization flask, pre-frozen in a dry ice/acetone bath, and lyophilized by standard methods. The resulting white crystalline powder was then reduced to the desired particle size by triturating it in a mortar with pestle. The stabilizers evaluated were sucrose, potassium carbonate, sodium sulfate, deoxycholic acid and polysorbate 80. In the case of polysorbate 80, the amount of rbSt and stabilizer were 100 mg and 5 mg, respectively.

B. Preparation of rbSt Containing Fatty Acid Terminated Polymers

Microparticles of fatty acid terminated polyanhydride were prepared by combining stabilized rbSt (75 mg) with fatty acid terminated polyanhydride (85:15 SA:STA) (300 mg) to obtain 20% w/w loading. Stabilized rbSt was added to the polymer pre-melted at 82° C. The melt dispersion was mixed thoroughly with a spatula and cast into a thin film. The thin film was then ground into particles of the desired average size by methods well known to those skilled in the art.

Using the method of Example 2, it was determined that almost 100% of the drug was released in an active form over a period of 3 days.

EXAMPLE 6

In vivo Release of Porcine Somatotropin from Fatty Acid Terminated Polyanhydride In Vivo

A film of fatty acid terminated polyanhydride (85:15 SA:STA) (0.8 gm), containing porcine somatotropin (0.2 gm) was prepared as described in Example 4. The film was then crushed to obtain microparticles of less than 63μ in diameter. The microparticles were suspended in polyethylene glycol (PEG 200) and the solution was injected subcutaneously into rats. Blood samples were taken at regular time intervals and serum was analyzed for porcine somatotropin by RIA assay.

The release of porcine somatotropin from the microparticles was more prolonged than the release obtained by injecting a solution of porcine somatotropin alone.

The desirable chemical and physical properties of the fatty acid terminated polyanhydrides permit the polymers to be formed into specific structures and used, for example, as laminates for degradable or nondegradable fabrics, as coatings for implantable devices, as barriers for adhesion prevention, as tubes for nerve generation, and in guided tissue regeneration for periodontal disease, as well as for controlled drug delivery. These and other variations of the present invention will become

apparent to one skilled in the art. Such other embodiments are intended to fall within the scope of the appended claims.

We claim:

1. A fatty acid terminated polyanhydride.

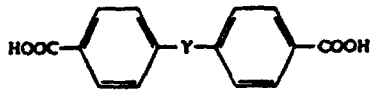
2. The fatty acid terminated polyanhydride of claim 1 of the formula:

wherein R is an aliphatic, aromatic, or heterocyclic moiety, R' is a linear fatty acid residue of C_4 to C_{22}, and n is an integer from 1 to 500.

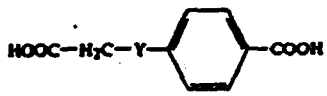
3. The fatty acid terminated polyanhydrides of claim 1 formed by polymerizing fatty acid prepolymers and dicarboxylic acid prepolymers.

4. The fatty acid terminated polyanhydrides of claim 1 wherein the fatty acid is selected from the group consisting of caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, heptanoic acid, nonanoic acid, undecanoic acid, tridecanoic acid, pentadecanoic acid, heptadecanoic acid, nonadecanoic acid, heneicosanoic acid, tricosanoic acid, arachidonic acid, docosahexanoic acid, elaidic acid, erucic acid, linoleic acid, linolenic acid, nervonic acid, oleic acid, palmitoleic acid and petriselinic acid.

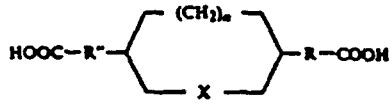
5. The fatty acid terminated polyanhydrides of claim 1 prepared by polymerization or copolymerization of a dicarboxylic acid selected from the group consisting of HOOC-H_2C-Y-CH_2-COOH; aromatic dicarboxylic acids, as defined by the formulas:



aromatic-aliphatic dicarboxylic acid, as defined by the formula:



aliphatic heterocyclic dicarboxylic acids defined by the formula:



wherein X=O, N or S, n=1 to 3; R=R"=an aliphatic, aromatic or heteroaromatic moiety, and Y is a divalent organic radical; aromatic heterocyclic dicarboxylic acids, and aliphatic aromatic heterocyclic dicarboxylic acids; with a fatty acid.

6. The fatty acid terminated polyanhydrides of claim 1 prepared by polymerization or copolymerization of a dicarboxylic acid selected from the group consisting of sebacic acid, phthalic acid, terephthalic acid, isophthalic acid, adipic acid, 1,10-dodecanoic acid, bis(p-carboxyphenoxyalkane), fumaric acid, 1,4-diphenylenediacrylic acid, branched monomers such as 1,3,5-benzenetricarboxylic acid, azeleic acid, pimelic acid, suberic acid (octanedioic acid), itaconic acid, biphenyl-4,4'-dicarboxylic acid, and benzophenone-4,4'-dicarboxylic acid, p-carboxyphenoxyalkanoic acid, hydroquinone-0,0-diacetic acid, 1,4-bis-carboxymethyl benzene, 2,2-bis-(4-hydroxyphenyl)propane-0,0-diacetic acid, 1,4-phenylene-dipropionic acid, and cyclohexane dicarboxylic acid or their anhydrides or acid chlorides with a fatty acid.

7. The fatty acid terminated polyanhydrides of claim 1 prepared by the polymerization of sebacic acid and stearic acid, or their anhydrides or acid chlorides.

8. The fatty acid terminated polyanhydride of claim 1 wherein the fatty acid and the dicarboxylic acid, or their anhydrides or acid chlorides, are combined in a ratio of 2 to 1000 fatty acid units per 500 units of dicarboxylic acid monomers

9. The fatty acid terminated polyanhydride of claim 1 wherein the fatty acid and the dicarboxylic acid are mixed in a ratio of approximately 15% fatty acid prepolymer to approximately 85% dicarboxylic acid prepolymer by weight.

10. The fatty acid terminated polyanhydride polymers of claim 1 wherein the polymers are soluble in organic solvents.

11. The fatty acid terminated polyanhydride polymers of claim 1 wherein the polymers are prepared by melt polycondensation.

12. The fatty acid terminated polyanhydride polymers of claim 1 further comprising a substance to be released from the polyanhydride polymers selected from the group of proteins, carbohydrates, and organic molecules.

13. The fatty acid terminated polyanhydride polymer of claim 12 wherein the substance to be released is selected from the group consisting of chemotherapeutic agents, antibiotics, antivirals, antifungals, antiinflammatories, and anticoagulants.

* * * * *

United States Patent [19]

Domb et al.

[11] Patent Number: 4,789,724

[45] Date of Patent: * Dec. 6, 1988

[54] **PREPARATION OF ANHYDRIDE COPOLYMERS**

[75] Inventors: Abraham J. Domb, Brookline; Robert S. Langer, Somerville, both of Mass.

[73] Assignee: Massachusetts Institute of Technology, Cambridge, Mass.

[*] Notice: The portion of the term of this patent subsequent to Jul. 12, 2005 has been disclaimed.

[21] Appl. No.: 920,724

[22] Filed: Oct. 17, 1986

[51] Int. Cl.[4] C08G 67/04

[52] U.S. Cl. 528/176; 528/193; 528/194; 528/206; 528/271

[58] Field of Search 528/176, 193, 194, 206, 528/271

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Assistant Examiner—Frederick Krass
Attorney, Agent, or Firm—Kilpatrick & Cody

[57] ABSTRACT

A method for preparation of very pure anhydride copolymers with high yield. The anhydride copolymers, consisting of aromatic and aliphatic diacids are formed by melt condensation of individually prepared, pure, isolated prepolymers. The method of preparation is characterized by high yield, reproducibility, polymer purity and controlled composition, and is a short and convenient procedure. The polyanhydrides produced by the disclosed method are particularly well suited to biomedical applications requiring low levels of toxic or inflammatory contaminants and physical and mechanical properties which closely conform to manufacturing specifications.

5 Claims, 2 Drawing Sheets

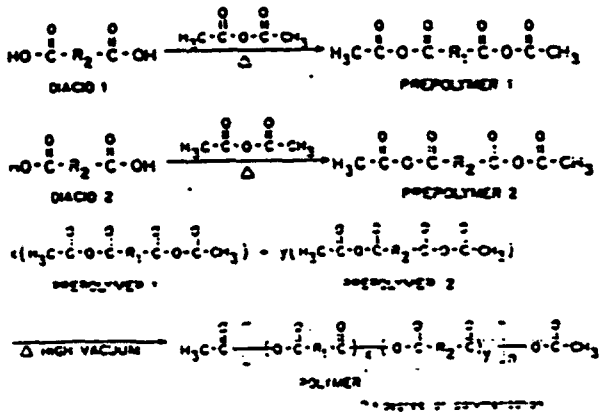


FIGURE 1

DIACID 1
PREPOLYMER 1
DIACID 2
PREPOLYMER 2
PREPOLYMER 1
PREPOLYMER 2
Δ HIGH VACUUM
POLYMER
n = degree of polymerization

FIGURE 2

x (HO-C-R1-C-OH) + y (HO-C-R2-C-OH)
H3C-C-O-C-CH3
Δ
PREPOLYMER MIXTURE OF UNDEFINED COMPOSITION
Δ VACUUM
H3C-C
O-C-R1-C
O-C-R2-C
Q
R
n
O-C-CH3
Q≠X , R≠y
n = degree of polymerization

PREPARATION OF ANHYDRIDE COPOLYMERS

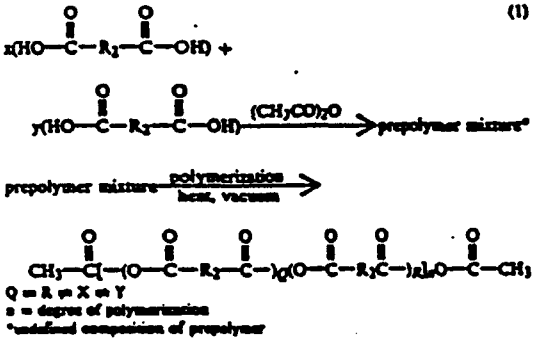
The United States Government has rights in this invention by virtue of National Institute of Health Grant No. 98000.

BACKGROUND OF THE INVENTION

The present invention is in the area of organic synthesis and, in particular, methods of synthesizing high purity anhydride copolymers.

Aromatic polyanhydrides were first synthesized in 1909 by Bucher and Slade, as reported in *J. Am. Chem. Soc.* 31, 1319 (1909). Aliphatic polyanhydrides were first prepared in 1932 by Hill and Carothers, as described in *J. Am. Chem. Soc.* 54, 1569 (1932) and 55, 5023 (1933). A number of aromatic and heterocyclic polyanhydrides, intended as substitutes for polyesters in textile applications, were further investigated over the next thirty years.

Only a few papers have been published on the preparation of anhydride copolymers. In these studies anhydride copolymers were produced by mixing a calculated amount of two diacids, e.g., aromatic and aliphatic diacids, and treating with acetic anhydride to yield the mixed prepolymer. The mixed prepolymer was then polymerized by heating under vacuum. The reaction is shown in equation 1. The mixed prepolymer was not isolated nor purified prior to polymerization.



Using this method of preparation, N. Yoda et al. prepared anhydride copolymers composed of terephthalic acid, sebacic acid, adipic acid and five membered heterocyclic diacids, as described in *Makromol. Chem.* 56, 32 (1962), and *Bull. Chem. Soc. Japan* 1120 (1959) 32. Another anhydride copolymer composed of methylene bis(p-carboxyphenyl)amide and adipic acid was reported by N. Yoda in *Chem. High Polymers Japan* 19, 613 (1962). Unpurified mixed prepolymers were used in all these studies.

In a recent study by Leong et al., reported in *J. Biomed Mat. Res.*, 19, 941 (1985), anhydride copolymers composed of bis(p-carboxyphenoxy)propane and sebacic acid were prepared. The copolymers were prepared from the mixed prepolymers obtained when the calculated amount of CPP and sebacic acid were treated with acetic anhydride. The mixed prepolymer was isolated after several weeks of crystallization at −20° C. The composition of the final polymer was not controlled. Polymerization of the mixed prepolymers yielded polymers with molecular weights of 12,030. Unsuccessful attempts were made to obtain the copolymers by polycondensing the mixture of individually prepared prepolymers, especially sebacic acid prepolymers.

It is therefore an object of the present invention to provide a method for preparation of highly pure anhydride copolymers having a controlled composition, especially for use in biomedical applications.

It is a further object of the present invention to provide a method for preparation of highly pure anhydride copolymers with controlled composition which is reproducible, has a high yield and is quick.

It is a still further object of the present invention to provide a method for preparation of highly pure anhydride copolymers wherein prepolymers of the diacids are produced which can be combined to yield a wide variety of copolymers having an actual composition which is close to the calculated composition.

It is another object of the invention to provide a method for preparation of highly pure anhydride copolymers for use in preparing high molecular weight polyanhydrides.

SUMMARY OF THE INVENTION

The invention is a method of synthesis of highly pure anhydride copolymers of known composition wherein the key element is the use of individually prepared, pure prepolymers. Calculated amounts of the individual prepolymers, e.g. aromatic and alphatic prepolymers, are mixed together and polymerized to form copolymers. High molecular weight polyanhydrides are produced by polymerization of the prepolymers at a temperature between 150° C. and 220° C. for 10 to 240 minutes, preferably 180° C. for 90 minutes, under high vacuum.

Examples of anhydride copolymers composed of the following diacids: sebacic acid (SA), bis(p-carboxyphenoxy)propane (CPP), adipic acid, bis(p-carboxyphenoxy)hexane (CPH), isophthalic acid (Isoph.) 1,4 phenylene dipropionic acid and dodecanedioic acid (DD), are polymerized from pure isolated prepolymers by a melt polycondensation process.

Polyanhydrides prepared from the very pure, isolated prepolymers are especially useful for biomedical applications because of the agreement between calculated and actual composition, reproducible molecular weights and degradation kinetics, lack of inflammatory or toxic contaminants, and mechanical properties such as film formation. Higher molecular weights can be generated by the addition of coordination catalysts to the copolymer mixture.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is the synthesis of a pure anhydride copolymer according to the present invention.

FIG. 2 is the synthesis of ananhydride copolymer according to the prior art.

DETAILED DESCRIPTION OF THE INVENTION

Anhydride copolymers are synthesized by melt condensation from a mixture of individually synthesized and purified mixed anhydride prepolymers prepared by heating diacids and acetic anhydride as shown in FIG. 1. The prior art method of synthesis is shown in FIG. 2 wherein the diacids are first mixed together, then refluxed with acetic anhydride to form the prepolymers.

The method according to the present invention is used in the following non-limiting examples to synthesize anhydride prepolymers which can then be combined and polymerized to form anhydride copolymers

with controlled composition. Individually prepared, pure, isolated prepolymers are made and purified within two work days with 50 to 80% yield. Calculated amounts of the prepolymers, such as CPP prepolymers and sebacic acid prepolymers, are then mixed together and polymerized, for example, at 180° C. for 90 minutes under high vacuum.

The prepolymer data analysis is summarized in Table 1. The data for the copolymers prepared from these prepolymers is summarized in Table 2. High molecular weight anhydride copolymers with high reproducibility in polymer composition and molecular weight are obtained.

TABLE 1

	Characterization of Prepolymers					
		GPC Analysis			NMR Analysis[b]	
Prepolymer of:	Mp	Mw	Mn	Dp[a]	Dp	IR[c]
Sebacic acid	67–69	1620	825	3.9	5 (2.22:1.32)[d]	1810,1740
Dodecanedioic acid	76–77	2410	1250	4.7	9 (2.22:1.27)[d]	1810,1740
Adipic acid	62–63	1765	694	4.0	6 (2.23:1.74)[d]	1810,1740
1,4 Phenylene dipropionic acid	74–75	1985	915	4.0	5 (2.18:7.11)[d]	1800,1735
Bis(p-Carboxy-phenoxy) propane	104–106	495	484	1.3	1.4 (2.30:7.1–8.1)[d]	1800,1730
Bis(p-Carboxy-phenoxy) hexane	92–94	573	490	1.1	1.3 (2.30:7.1–8.1)[d]	1800,1735
Isophthalic acid	56–58	484	376	1.9	1.6 (2.43:7.4–8.6)[d]	1800,1735

[a]Dp based on the Mn of the GPC analysis.
[b]Determined from ^{1}H—NMR analysis.
[c]Characteristic for anhydride bonds.
[d]Chemical shift in PPM of the methyl terminal and the representative peak of the repeating unit.

TABLE 2

	Characterization of Anhydride Copolymers		
	% Aliphatic Units		
	(calculated)	(found)	
CPP:SA	80	80 ± 2	115,000 ± 5,000
	70	70 ± 2	78,000 ± 4,500
	50	50 ± 2	32,000 ± 3,000
Isoph:SA	80	81 ± 2	112,000 ± 5,400
	50	49 ± 1	30,000 ± 2,500
CPP:DD	80	79 ± 2	122,000 ± 6,100
	50	50 ± 2	31,000 ± 3,200
CPH:SA	80	79 ± 2	76,400 ± 6,800
CPH:DD	80	80 ± 2	84,900 ± 5,600
	50	51 ± 1	36,590 ± 3,420
CPP:adipic acid	80	82 ± 2	56,800 ± 3,800

Copolymers prepared from individually prepared prepolymers in Table 1 were polymerized at 180° C. for 90 min. Results are an average of five separate polymerizations.

The following materials and methods were used in the examples:

Chemicals: Sebacic acid, dodecanedioic acid and adipic acid (99%, Aldrich Chemical Co., Milwaukee, Wis.) were recrystallized three times from ethanol and 1,4 phenylene dipropionic acid (98%, Aldrich Chemical Co.) was recrystallized from acetone before use. Bis(p-carobxyphenoxy)alkanes were synthesized according to the method described by A. Conix in *Macromol. Synth.* 2, 95 (1966) and cleaned by extraction with acetone and ether before use. Isophthalic acid (99%, Aldrich Chemical Co.) was recrystallized from ethanol. All solvents were analytical grade.

Instrumentation: Infared spectroscopy was performed on a Perkin-Elmer Spectrophotometer Model 1430. Polymeric samples were film cast onto NaCl plates from solutions of the polymer in chloroform. Prepolymer samples were either pressed into KBr pellets or dispersed in nujol onto NaCl plates.

Thermal analysis of polymers was performed on a Perkin Elmer DSC-2 differential Scanning Calorimeter employing a heating rate of 20° C./min. The melting point of prepolymers was determined on a Fisher Johns melting point apparatus. The molecular weights of the polymers and prepolymers were estimated on a Perkin Elmer GPC system consisting of a series 10 pump, a 3600 Data Station with an LKB 214 - rapid spectral detector at 254 nm wavelength. Samples were eluted in chloroform through two Pl Gel columns (Polymer Laboratories; 100 Angstroms and 1000 Angstroms pore sizes) in series at a flow rate of 1.5 ml/min. Polystyrene (Polyscience) was used as the calibration standard. Viscosity of polymers was measured in an Ubbelohde Viscometer (cannon 75) at 23° C. using 1, 0.5 and 0.25% w/v polymer in chloroform solution. ^{1}H-NMR spectra were run on a Bruker AM-250 spectrometer in $CHCl_3$.

Determination of Prepolymer and Polymer Composition

The composition of anhydride copolymers is determined by ^{1}H-NMR from the ratio of the peaks integration of the copolymer units, for example, the composition of CPP:SA copolymers is determined by ^{1}H-NMR from the ratio of the peaks integration at 1.3 PPM (8H, Sebacic acid) and 6.9–8.2 PPM (8H, CPP).

General Method for Polymer Synthesis

Polyanhydrides are synthesized by melt polycondensation of mixed anhydrides of diacids and acetic anhydride. Aliphatic mixed-anhydride prepolymers are prepared by refluxing the dicarboxylic acid monomers (40 g) in acetic anhydride (200 ml) for 20 to 90 minutes. The excess acetic anhydride is removed to dryness under vacuum at 60° C. The crude prepolymer is recrystallized from dry toluene. The crystals are then immersed in a 1:1 mixture of dry petroleum ether and ethyl ether overnight to extract traces of acetic anhydride and toluene. The pure crystals are dried under vacuum over calcium chloride (75–88% yield). Aromatic monomers are refluxed for 15 to 30 minutes, then the unreacted diacid (5 to 10%) removed by filtration. The solution is concentrated to 150 ml and allowed to crystallize overnight at 0° C. The crystals are then immersed in dry

ether (200 ml) overnight with stirring to extract traces of acetic anhydride.

The purified prepolymer is washed with dry ether and dried under vacuum over calcium chloride (42–50% yield). The prepolymers are characterized by GPC, ^{1}H-NMR and IR analysis.

The amounts of prepolymers (as calculated below) then undergo melt polycondensation as follows: In a typical reaction, CPP prepolymer is mixed with sebacic acid prepolymer in a glass tube (2×20 cm) with a side arm equipped with a capillary nitrogen inlet. The tube is immersed in an oil bath at 180° C. After the prepolymers are melted, approximately 1 minute, high vacuum (10–4 mm Hg) is applied through the side arm. The condensation product, acetic anhydride, is collected in an acetone/dry ice trap. During the polymerization, a strong nitrogen sweep with vigorous agitation of the melt is performed for 30 seconds every 15 minutes. The crude polymer is purified by precipitation in dry petroleum ether from a dichloromethane solution. The precipitate is then extracted with anhydrous ether for several hours at room temperature.

Calculations

The calculated amounts of prepolymers to be mixed for the synthesis of an x:y copolymer, where x:y is the molar ratio of copolymer units, is as follows:

$$\underset{\text{grams of prepolymer 1}}{x\left(\frac{Mn_1}{Dp_1}\right)} + \underset{\text{grams of prepolymer 2}}{y\left(\frac{Mn_2}{Dp_2}\right)}$$

wherein x and y are the molar ratios of prepolymers 1 and 2 in the copolymer,

Mn is the number average molecular weight of the prepolymer as determined by GPC, and

Dp is the number of units in the prepolymer as calculated from:

$$Dp = \frac{Mn - 102}{Ru}$$

where 102 is the molecular weight of prepolymer end groups:

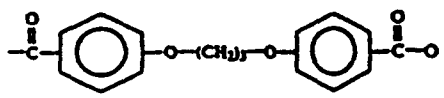
and Ru is the molecular weight of the repeating unit in the prepolymer.

For example:

for sebacic acid, the repeating unit is:

Ru=184 and

for CPP, the repeating unit is:



and Ru=308

Example of the preparation of 1,3 bis(p-carboxyphenoxy) propanesebacic acid polymers (CPP:SA)

1. Preparation of pure, isolated CPP prepolymers.

A solution of 138 g (1.0 mole) of p-hydroxy benzoic acid and 80 g (2.0 moles) of sodium hydroxide in 400 ml of water is placed in a one liter three-necked flask equipped with a mechanical stirrer, a condenser, and a dropping funnel. 102 g (0.5 mole) of 1,3-dibromopropane is added through the funnel over a period of one hour, while the contents of the flask are stirred and kept at reflux temperature. The reaction mixture is refluxed for 3.5 hours after the addition of the 1,3-dibromopropane. 20 g (0.5 mole) of solid hydroxide is then added to the mixture, and the mixture refluxed for an additional two hours. Heating is then discontinued and the reaction mixture left standing overnight. The fine, powdery, white precipitate of the disodium salt is isolated by filtration and washed with 200 ml of methanol. The still wet precipitate is dissolved in one liter of distilled water with gentle heating.

The solution is extracted with 200 ml of ether to remove traces of dibromide, acidified with 6N sulfuric acid to a pH less than 2, the diacid isolated by filtration, and the diacid dried for 3 days in a lyophilizer. The yield is 120 g (76%).

40 g of CPP powder is then added to 500 ml boiling acetic anhydride (135° C.) under dry N_2. Reflux is stopped at 25 min and the solution filtered through a filter paper into another one liter round bottom flask. About 10% of the unreacted CPP is separated. The solution is concentrated to 150 ml by evaporation (evaporator with $CaCl_2$ trap). The solution is left at 0° C. to crystallize overnight. The crystals are separated by filtration and transferred to 200 ml of anhydrous diethyl ether in an Erlenmayer flask and allowed to swirl for several hours at room temperature. The white crystals are separated by filtration and dried in a $CaCl_2$ desiccator under vacuum. The CPP prepolymer is recovered with a yield of 50–60% and has a melting point of 104°–106° C. and IR-1810, 1740cm^{-1}.

2. Preparation of pure, isolated SA prepolymers.

30 g of sebacic acid are added to a 120 ml refluxing solution of acetic anhydride under N_2. Reflux is continued for 90 min. Sebacic acid is completely dissolved within 5 min. of reaction. Excess acetic anhydride is evaporated by an evaporator at 60° C. The oily material is left at room temperature to solidify. The solid is dissolved in 15 ml toluene with warming and the solution allowed to crystallize overnight at 0° C. The crystals are separated by filtration and transferred to 200 ml diethyl ether and petroleum ether 1:1 mixture, with stirring for 5 hours. The white crystals are separated by filtration and dried in a $CaCl_2$ desiccator under vacuum. The sebacic acid has a melting point of 64°–65° C. and IR-1810, 1740 cm^{-1}.

3. Polymerization of a CPP prepolymer:SA (20:80) prepolymer mixture.

CPP prepolymer (0.80 g, 2.0 mmole) is mixed with sebacic acid prepolymer (1.64 g, 8.0 mmole) in a glass tube (2×20 cm) (Kimax) with a side arm equipped with a capillary nitrogen inlet. The tube is immersed in an oil bath at 180+1° C. After the prepolymers are melted, approximately 1 min, high vacuum (less than 10^{-2} mm Hg) is applied through the side arm. The condensation product, acetic anhydride, is collected in an acetone/dry ice trap. During the polymerization, a strong

nitrogen sweep with vigorous agitation of the melt is performed for 30 seconds every 15 minutes. After 90 minutes, the polymer is removed under nitrogen to a dry glass vial. The crude polymer is ground to small particles using a micromill at low temp. (H_2O/ice cooling). The yield in this example is greater than 90%.

4. Purification of the CPP:SA (20:80) polymer.

The crude polymer is purified by precipitation in dry petroleum ether from dichloromethane solution as follows: 20 g of crude polymer is dissolved in 100 ml dichloromethane (analytical grade) at room temp. with magnetic stirring for about 20 min. The solution is pressure filtered through a 2 micron filter and dripped into 600 ml of dry petroleum ether (analytical grade) stirred with mechanical stirrer. A white fiber-like precipitate is obtained. After filtration, the precipitate is extracted with anhydrous ether (200 ml) for several hours at room temp. The ether is decanted out and the ether residue is removed by anhydrous evaporator under high vacuum (oil pump). The CPP:SA polymer has a melting point of 68°–70° C., molecular weight: M_w (weight average molecular weight)=118,000, Mn=22,400 (by GPC analysis), composition of CPP:SA (21:79) (by ^{1}H-NMR), and intrinsic viscosity of [n]=0.92 dl/g (chloroform, 23° C).

5. Polymerization of a CPP:SA (50:50) copolymer.

CPP prepolymer (2.0 g, 5 mmole) is mixed with sebacic acid prepolymer (1.15 g, 5 mmole) and polymerized at 180° C. under high vacuum (10 mm Hg) for 90 min using the same method as above. The CPP:SA (50:50) polymer has a melting point of 152° C., molecular weight: M_w=38,200, M_n=17,900 (by GPC analysis), intrinsic viscosity of [n]=dl/g (chloroform 23° C.), and composition of CPP:SA (50:50) (by ^{1}H-NMR).

Examples of the preparation of 1,3 bis(p-carboxyphenoxy) propane: dodecanedioic acid polymers (CPP:DD)

1. Preparation of pure, isolated CPP prepolymer is as previously described.

2. Preparation of dodecanedioic acid prepolymer.

50 g of dodecanedioic acid are added to 250 ml boiling acetic anhydride under dry argon. Reflux is continued for 60 minutes. Excess acetic anhydride is removed by an evaporator at 60° C. to yield a white solid. The solid is dissolved in 20 ml dry toluene with gentle warming and the solution is allowed to crystallize overnight at 0° C. The crystals are separated by filtration and extracted with 200 ml methyl ether and petroleum ether 1:1 mixture for 5 hours at room temperature. The pure crystals were dried under vacuum over calcium chloride to yield 47 g prepolymer with a melting point of 76° C. and IR-1810, 1740 cm-1.

3. Preparation of CPP:DD (20:80) copolymers.

CPP prepolymer (0.8 g, 2.0 mmole) is mixed with dodecanedioic acid prepolymer (2.0 g, 8.0 mmole) and polymerized at 180° for 90 min under high vacuum (less than 10^{-2} mm Hg). The polymer is purified as previously described. The polymer has a melting point of 75°–76° C., molecular weight: Mw =125,900, Mn =26,850 (by GPC analysis); a composition of CPP:DD (20:80) (by ^{1}H-NMR) and intrinsic viscosity of [n]=1.16 dl/g (chloroform, 23° C).

4. Polymerization of CPP:DD (50:50) copolymer.

CPP prepolymer (1.6 g, 4.0 mmole) is mixed with DD prepolymer (1.0 g, 4.0 mmole) and polymerized at 180° C. for 90 min under high vacuum (10^{-2} mm Hg). The polymer is purified as described in the first example. The polymer has a melting point of 158°–160° C., molecular weight: Mw =44,800, Mn =16,850, composition of CPP:DD (51:49) (by ^{1}H-NMR), and intrinsic viscosity of [n]=0.76 dl/g.

5. Polymerization of CPP:DD (65:35) copolymer.

CPP prepolymer (2.6 g, 6.5 mmole) is mixed with DD prepolymer (0.88 g, 3.5 mmole) and polymerized at 180° C. for 90 min under high vacuum (less than 10^{-2} mm Hg). The polymer is purified as previously described. The polymer has a melting point of 194 to 195° C., molecular weight: Mw =32,000, Mn =10,100, composition of CPP:DD (64:36), and intrinsic viscosity of [n]=0.64 dl/g.

Example of the preparation of phenylene dipropionic acid copolymer with sebacic acid and 1,3 bis(P-carboxyphenoyl)propane

1. Sebacic acid and CPP prepolymers are prepared as previously described.

2. Preparation of phenylene dipropionic acid prepolymer.

60 g of PDP (phenylene dipropionic acid) are added to 500 ml boiling acetic anhydride under dry argon. Reflux is continued for 60 minutes. Excess acetic anhydride is removed by an evaporator at 60° C. to yield a white solid. The solid is recrystallized from 30 ml toluene at 0° C. overnight. The crystals are then extracted with 200 ml of a diethyl ether and petroleum ether (1:1) mixture for 5 hours at room temperature. The pure crystals are dried under vacuum over calcium chloride to yield 61 g prepolymer with a melting point of 74°–75° C. and IR-1800, 1735 cm^{-1}.

3. Polymerization of PDP:SA (20:80) copolymer.

PDP prepolymer (0.91 g, 4 mmole) is mixed with SA prepolymer (3.28 g, 16 mmole) and polymerized at 180° C. under high vacuum (less than 10^{-2} mm Hg) for 90 min. The polymer is purified as previously described. The polymer has a melting point of 56°–59° C., molecular weight: Mw =84,920, Mn =15,650, intrinsic viscosity of [n]=0.68 dl/g, and composition of PDP:SA (20:80) (by ^{1}H-NMR).

4. Preparation of PDP:SA (50:50) copolymer.

PDP prepolymer (1.14 g, 5 mmole) is mixed with SA prepolymer (1.0 g, 5 mmole) and polymerized at 180° under high vacuum (less than 10^{-2} mm Hg) for 90 min. The polymer is purified as previously described. The polymer has a melting point of 75°–77° C., molecular weight: Mw =58,900, Mn =12,400, intrinsic viscosity of [n]=0.64 dl/g, and composition of PDP:SA (49:51) (by ^{1}H-NMR).

5. Preparation of PDP:CPP (50:50) copolymer.

PDP prepolymer (1.14 g, 5 mmole) is mixed with CPP prepolymer (2.0 g, 5 mmole) and polymerized at 180° under high vacuum (less than 10^{-2} mm Hg) for 90 min. The polymer is purified as previously described. The polymer has a melting point of 158°–160° C., molecular weight: Mw=34,400, Mn =10,100, intrinsic viscosity of [n]=0.65 dl/g, and composition of PDP:CPP (48:52) (by ^{1}H-NMR).

6. Preparation of CPP:PDP:SA (50:25:25) copolymer.

CPP Prepolymer (2.0 g, 5 mmole) is mixed with PDP prepolymer (0.57 g, 2.5 mmole) and SA prepolymer (0.5 g, 2.5 mmole) and polymerized at 180° under high vacuum (less than 10^{-2} mm Hg) for 90 min. The polymer is purified as previously described. The polymer has a melting point of 142°–144° C., molecular weight: Mw =23,900, Mn =12,400, intrinsic viscosity of [n]=0.53

dl/g, and composition of CPP:PDP:SA (48:27:25) (by ^{1}H-NMR).

Preparation of mixed prepolymer by the prior method (FIG. 2)

The yield and reproducibility of the anhydride copolymers produced by the prior art method were compared with the yield and reproducibility of anhydride copolymers produced by the method of the present invention as follows.

A calculated amount of the diacids (total of 50 g) was refluxed in acetic anhydride (500 ml) for 20 min. Unreacted material was removed by filtration, and the solution concentrated to 100 ml by vacuum evaporation. The solution was then left at −20° C. for 3 weeks to crystallize. The yield and composition of the precipitate for mixed prepolymers of CPP:SA (20:80), CPP:SA (50:50), isoph:SA (20:80), and isoph:SA (50:50) are summarized in table 3.

In a typical reaction, 10.0 g (0.0316 mole) of CPP were mixed with 25.6 g (0.126 mole) sebacic acid and refluxed in 500 ml acetic anhydride for 30 min. The unreacted material (0.6 g, identified as CPP) is removed by filtration and the solution concentrated to 100 ml by vacuum evaporation. The solution is allowed to crystallize for 3 weeks at −20° C. The precipitate is separated by filtration and washed with anhydrous ether (100 ml) to yield 14.8 g of mixed prepolymers with a composition of CPP:SA in a ratio of 35:65 (calculated 20:80), as determined by H-NMR, IR-1800, 1740 cm^{-1}.

TABLE 3

	Characterization of mixed prepolymers		
	(%) aliphatic monomer		
Prepolymer composition*	calculated	found	yield (%)
CPP:SA (20:80)	80	65	15
	80	50	21
	80	72	25
CPP SA (50:50)	50	30	25
	50	45	34
	50	32	24
Isoph:SA (20:80)	80	72	25
	80	65	33
	80	75	28
Isoph:SA (50:50)	50	65	37
	50	48	36
	50	58	31

Prepolymers prepared by a reaction between a calculated amount of diacids and acetic anhydride for 30 min.
*Determined from ^{1}H—NMR Spectrum

The preceding examples demonstrate the usefulness of the pure, isolated prepolymers in the rapid preparation of a variety of polymer compositions as well as the high yield and reproducibility of the disclosed method.

High molecular weight polyanhydrides are desirable in biomedical applications, for example, in controlled release devices because of their superior physio-mechanical properties.

These properties include film forming properties and relatively high tensile strength. The critical factors affecting polymer molecular weight are: monomer purity, temperature of reaction, time of reaction, and the removal of the condensation product.

Very high molecular weight polymers are achieved by reacting pure isolated prepolymers, prepared in accordance with this invention, under optimized conditions, for example, at a temperature of 180° C., under 10^{-4} mm Hg vacuum with a CO_2/Acetone trap, as described in co-pending application U.S. Ser. No. 892,809 filed August 1, 1986 by Abraham J. Domb and Robert S. Langer entitled "Synthesis and Application of High Molecular Weight Polyanhydrides".

Using the prior art method, with an unisolated prepolymer mixture, p(CPP:SA)(1:4) has a molecular weight of 12,030. Reacting pure, individually prepared prepolymers yields p(CPP:SA)(1:4) with a molecular weight of 116,800 and an intrinsic viscosity of $[\eta]=0.92$. Addition of a catalyst to the pure, individually prepared prepolymer mixture can further increase molecular weights, as described in U.S. Ser. No. 892,809 filed Aug. 1, 1986.

The method of preparing very pure anhydride copolymers from individually synthesized and purified diacid prepolymers has been described with reference to specific embodiments. Variations and modifications of these embodiments and preparation conditions will be obvious to those skilled in the art of chemical synthesis. Such modifications and variations are intended to be included within the scope of the appended claims.

We claim:

1. A method for preparing highly pure anhydride copolymers comprising:
providing at least two individually synthetized and purified diacids,
reacting the individual diacids and acetic anhydride separately to form mixed anhydrides of the individual diacids,
separately removing the unreacted acetic anhydride and diacids from the individual mixed anhydrides formed by the reaction of the acetic anhydride with said diacids,
combining said individual mixed anhydrides, and
polymerizing said mixture of the purified mixed anhydrides of the individual diacids to form copolymers.

2. The method of claim 1 wherein the diacids are selected form the group consisting of sebacic acid, bis(p-carboxyphenoxy-propane, bis(p-carboxyphenoxy)hexane, isophthalic acid, 1,4 phenylene diporpionic acid, adipic acid and dodecanedioic acid.

3. A highly pure anhydride copolymer consisting essentially of individually synthetisized and purified monomers selected from the group consisting of mixed anhydrides of aliphatic and aromatic diacids, wherein said diacids were individually reacted with acetic anhydride and the unreacted diacid and acetic anhydride removed after the reaction.

4. The anhydride copolymer of claim 3 wherein said mixed anhydrides are formed by
separately refluxing individual diacids with acetic anhydride to form individual mixed anhydrides,
removing the excess acetic anhydride, and
recrystallizing the individual mixed anhydrides.

5. The anhydride copolymer of claim 3 wherein the copolymers are further purified by recrystallization.

* * * * *

EXCLUSIVITY SUMMARY for NDA # 20-637 SUPPL # 016

Trade Name Gliadel wafer **Generic Name** polifeprosan 20 with carmustine implant

Applicant Name Guilford Pharmaceuticals Inc **HFD-** 150

Approval Date February 25, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /__X_/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-637 Gliadel wafer

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # T-301

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /__X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # __T-301

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # [redacted] YES /_X__/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /_ __/ NO /__X_/

If yes, explain: On 1-30-003 Nancy Link of Guilford noted that conduct of T-301 was funded by Guilford and RPR at 50% each. Follow-up and analysis was funded by Guilford.

Paul Zimmerman 1-30-2003
Signature of Preparer Date
Title: Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
2/26/03 08:40:57 AM

Richard Pazdur
2/26/03 08:54:49 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-637 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 016

Stamp Date: 10-28-2002 **Action Date:**

HFD 150 **Trade and generic names/dosage form:** Gliadel Wafer (polifeprosan 20 with carmustine implant

Applicant: Guilford Pharmaceuticals Inc. **Therapeutic Class:** 5010110

Indication(s) previously approved: GLIADEL® wafer is indicated in recurrent glioblastoma multiforme patients as an adjunct to surgery.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: GLIADEL® wafer is indicated in newly diagnosed high grade malignant glioma patients as an adjunct to surgery and radiation.

Is there a full waiver for this indication (check one)?

✔ **Yes: Please proceed to Section A.** (Newly diagnosed high grade malignant gliomas are exceedingly rare in children. Approximately 2,000 children develop a brain tumor each year in the United States. High grade malignant gliomas (glioblastoma multiforme and anaplastic astrocytoma) have a combined incidence of 5-8/100,000 in the pediatric population –per MO)

☐ **No: Please check all that apply: ___ Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ✔ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Paul Zimmerman
2/26/03 08:47:44 AM

GUILFORD PHARMACEUTICALS

GLIADEL® Wafer
NDA 20-637

DEBARMENT CERTIFICATION

Guilford Pharmaceuticals Inc. certifies that, to the best of our knowledge, it did not and will not use in any capacity the services of any person debarred under Section 306(e) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Louise Peltier
Senior Director,
Regulatory Affairs

April 5, 2001
Date

6611 Tributary Street • Baltimore, Maryland 21224 • (410) 631-6300 • (410) 631-6338 Fax

Division of Oncology Drug Products

Team Leader Memo

NDA:	20637 [S016]
Sponsor:	Guilford Pharmaceuticals
Drug Product:	Gliadel Wafers
Date submitted:	October 25, 2002

Background:

In response to a non-approval letter, Guildford Pharmaceuticals submitted this supplemental New Drug Application (sNDA) with updated survival data from study T-301, A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Polifeprosan 20 with Carmustine 3.85% Implant for Patients Undergoing Initial Surgery for Newly Diagnosed Malignant Glioma. The proposed indication is: to support the following indication: for use as an adjunct to surgery to prolong survival in patients undergoing initial resection of a high-grade malignant glioma.

T-301 was an international (14 countries), multicenter (38), randomized, double-blind placebo-controlled trial in 240 patients with newly diagnosed high grade malignant glioma. After maximal resection of tumor, up to eight wafers of either Gliadel or placebo were placed against the resection surfaces. The majority of patients received 6-8 wafers. All patients (120 in each treatment group) were to receive standard limited field radiation therapy. The protocol specified that anaplastic oligodendroglioma patients also receive systemic chemotherapy (6 cycles of PCV- lomustine 110 mg/m^2 day 1, procarbazine 60 mg/m^2 days 8-21, vincristine 1.4 mg/m^2 days 8 and 29. The primary endpoint was overall survival.

Guildford Pharmaceuticals submitted the original sNDA on April 6,2001 based on less mature survival data from T-301 study (data cut off date – June 30, 2000). The application was reviewed at an Oncology Drugs Advisory Committee (ODAC) Meeting in December 2001. The ODAC voting results are presented in the appendix to this memo. The Agency issued a non-approval letter on March 19, 2002. The primary deficiency was that the analysis of the trial's primary endpoint failed to achieve statistical significance (unstratified log-rank test p=0.08, Agency analysis). Other criticisms noted in the non-approval letter included:

1) The sponsor's primary analysis, log-rank stratified by country, was not appropriate because trial randomization was not stratified by country.

2) An imbalance occurred in the histology between the Gliadel and placebo arms, favoring the Gliadel arm (greatest contributor to the difference was the anaplastic oligoastrocytoma).
3) The Agency exploratory analyses stratifying log-rank by known prognostic factors (age, Karnofsky Performance Status, and histology) showed no significant benefit for Gliadel.
4) A subgroup analysis of glioblastoma multiforme patients showed no significant benefit for Gliadel.

Additional Concerns not identified in the non-approval letter

5) Discrepancies existed between the local pathologist's and the central pathologist's review.

Subsequently, the Agency and Guildford Pharmaceuticals had further discussions regarding this application. Jointly, they agreed that Guildford Pharmaceuticals could submit updated survival data from T-301 for review. Guildford Pharmaceuticals obtained additional survival data on patients, with cutoff date of August 16, 2002. Guildford pharmaceuticals reanalyzed the data and submitted the results to the Agency on October 25, 2002.

New Analyses

The updated results are presented below.

Issue # 1- Failure to achieve statistical significance for the primary endpoint

The Agency's primary analysis of updated survival data using the protocol specified non-stratified long-rank analysis is shown in the table below:

Note: The p-value reported below is not adjusted for multiple comparisons.

Table 1. FDA's Analysis for Overall Survival (Updated Data: 8/16/2002)

ITT Population N=240	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	P-value
Gliadel (111/120)	13.8 (12.1-15.1)	0.73	0.56-0.95	0.02*
Placebo (117/120)	11.6 (10.2-12.7)			0.02**

*Based on protocol specified non-stratified log-rank test.

** Wald test for HR.

Table from the Primary review for this submission by Drs. Ning Li and Alla Shapiro.

Issue # 2- An imbalance in histologic subtypes favoring the Gliadel arm

The sponsor performed a secondary analysis, which excluded the local pathologist's diagnosis of anaplastic oligoastrocytoma (AOA) patients who

accounted for the largest imbalance between the treatment groups. The Agency's primary analysis is shown in the table below:

Table 3. Updated Analysis for Overall Survival (excluding 10 AOA subjects)

ITT Population N=230	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	P-value
Gliadel	13.6 (12.0-14.8)	0.74	0.57-0.97	0.027*
Placebo	11.6 (10.2-12.6)			

*Based on protocol specified non-stratified log-rank test.

Table from the Primary review for this submission by Drs. Ning Li and Alla Shapiro.

Issue # 3- Lack of significance of exploratory analyses by known prognostic factors (age, Karnofsky Performance Status, and histology)

The multivariant analysis performed by Agency statisticians based on the updated survival data adjusted for known prognostic factors such as age, KPS and tumor type showed statistically significant difference between the treatment groups (p = 0.045) in favor of Gliadel.

Issue # 4- Lack of significant benefit in the glioblastoma multiforme patients

The Agency subgroup analysis using the updated survival data is shown in the table below:

Table 4. Updated Analysis for Overall Survival for GBM Subgroup*

ITT Population N=207	Median (95%CI) (Month)	Hazard Ratio	95% CI for Hazard Ratio	P-value
Gliadel	13.1 (11.4-14.7)	0.78	0.59-1.03	0.08*
Placebo	11.4 (10.2-12.6)			

*Based on protocol specified non-stratified log-rank test.

Table from the Primary review for this submission by Drs. Ning Li and Alla Shapiro.

Although the subgroup analysis did not show any statistically significant difference in overall survival, there was a trend towards an improvement in overall survival with Gliadel.

Issue # 5- Discrepancies between the local pathologist's and the central pathologist's review

Disagreements exist between the local pathologists and central pathologists for patients classified as either glioblastoma multiforme (GBM) by the local pathologist and non-GBM by a central pathologist or vice versa. These disagreements were forward to a referee neuropathologist. In all other cases, the central histopathological diagnosis was used as the final diagnosis. An imbalance in the final histologic classification exists between the Gliadel and placebo arms. This imbalance cannot be further resolved.

Although ODAC votes were mixed, a majority of members voted that the Gliadel wafer provides clinical benefit. See the appendix for the voting information.

Additional Literature submitted by the Sponsor

The sponsor submitted additional information on the use of chemotherapy as an adjunct to surgery and radiation in the newly-diagnosed high grade glioma patient population. The Glioma Meta-analysis Trialists Group published in **Lancet** (March 13, 2002 volume 359 number 9311 pages 1011-1018) "Chemotherapy in Adult High-Grade Glioma: A Systematic Review and Meta-analysis of Individual Patient Data From 12 Randomised Trials." This systematic review and meta-analysis of single and multiagent systemic chemotherapy based on 12 published and unpublished trials showed a significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI 0.78-0.91, $p<0.001$). The authors stated that the improvement in median survival was equivalent to 2 months for those who received chemotherapy.

Conclusions and Recommendations

This reviewer recommends that this submission for Gliadel wafer be approved for the following indication, "is indicated in newly diagnosed high grade malignant glioma patients as an adjunct to surgery and radiation," based on the statistically significant improvement in survival shown with the updated survival data, the significant improvement in survival when the favorable prognosis patients are excluded from the trial (i.e., patients who contributed to the imbalance), and ODAC's marginally positive recommendation of the of the original application.

Appendix

The application was reviewed at an Oncology Drugs Advisory Committee (ODAC) Meeting in December 2001. ODAC voted on the following questions:

1. Is study T-301 an adequate and well-controlled trial?
The Committee split this question into two parts.

1a. Is study T-301 a well-controlled trial?
Yes – 13/13 No - 0
1b. Is study T-301 an adequate trial?
Yes – 6/13 No – 7/13
The Committee split this question because there was a discussion about whether the trial could be considered adequate when there was a discrepancy between the local pathologist's review and the central committee's review. During the meeting, Dr. Temple commented that by answering "no" to # Ib, further votes on #3 are not necessary, since the substantial evidence can be provided only by adequate and well-controlled trials.

2. GLIADEL was considered to have a treatment effect only in patients with recurrent GBM and not in the overall population with recurrent malignant gliomas. If this were a true treatment effect, would this pattern be expected to be present in newly diagnosed patients?
Yes – 0/13 No – 13/13

3. Do the data from T-301 provide substantial evidence of a survival benefit of GLIADEL in patients with newly diagnosed malignant gliomas?
Yes – 8/13 No – 5/13

4. If the answer to #3 is YES, do trials #CL-0190 and/or #8802 together with T-301 provide convincing evidence of a survival benefit in patients with newly diagnosed malignant gliomas?
Yes – 10/13 No – 3/13

5. Is the toxicity profile of GLIADEL acceptable for patients with newly diagnosed malignant glioma?
Yes – 11/13 No – 1/13 Abstain – 1

6. Does the committee believe that GLIADEL provides clinical benefit with an acceptable safety profile in patients with newly diagnosed malignant glioma?
Yes – 8/13 No – 5/13

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/s/

Ann Farrell
2/10/03 01:51:57 PM
MEDICAL OFFICER

Grant Williams
2/11/03 10:39:51 AM
MEDICAL OFFICER
I am in complete agreement with the findings and recommendations presented in Dr. Farrell's team leader memo.

MEMORANDUM

DATE: March 4, 2002

FROM: Alison Martin, M.D.
Medical Team Leader
Division of Oncology Drug Products, HFD-150

TO: Richard Pazdur, M.D.
Director
Division of Oncology Drug Products, HFD-150

SUBJECT: Medical Team Leader Summary and Recommendation for Action
sNDA 20-637: Gliadel Wafer
Applicant: Guilford Pharmaceuticals
Indication: treatment of malignant glioma

In the supplemental NDA dated 4/6/01, Guilford Pharmaceuticals submitted results from trial T-301 to support extension of the current indication for Gliadel Wafer to the treatment of patients with all malignant gliomas.

Gliadel was initially approved in 1996 for a subgroup of malignant glioma -- patients with recurrent glioblastoma multiforme (GBM). The applicant proposes to: (1) add an indication for the treatment of patients with newly diagnosed malignant glioma; (2) add a quality of life claim; and, (3) broaden the indication in recurrent disease from GBM to all malignant glioma. The first two proposals are based on data from T-301. No new data has been submitted in the population of patients with recurrent disease. This third proposal is derivative and would only need to be addressed if the first two proposals are accepted.

The primary reviewers for this application were Dr. Alla Shapiro (medical reviewer) and Dr. Ning Li (statistical reviewer) who collaborated to produce a joint medical/statistical review. No new data were submitted in other disciplines, specifically chemistry, animal pharmacology/toxicology, microbiology or biopharmaceutics. I concur with the recommendation of both of the primary reviewers that the evidence does not warrant an extension of the current indication for Gliadel.

The central problem with this application is that data from T-301 are statistically and clinically marginal. This, in conjunction with imbalances favoring the Gliadel arm and questions about the adequacy of the trial, prevent the conclusion that efficacy has been demonstrated in patients with newly diagnosed malignant glioma. The only credible argument that can be advanced is that the collective evidence, T-301 plus the 1996 trials, allows a conclusion of efficacy. However, the efficacy question is whether the collective evidence supports an extension to newly diagnosed patients with malignant glioma.

Since this broader indication was requested in 1996 and denied, to now return to the 1996 trials to provide the needed clarity is inherently problematic. There is no safety issue that would preclude approval.

Specific issues with the efficacy data are outlined below.

Issues with the Primary Endpoint (Survival)

- Eighty-eight patients (73%) in the Gliadel group and 93 (78%) in the placebo group died before study cut-off. Median survival in the ITT population was 13.9 months (12.1, 15.3) for patients treated with Gliadel and 11.6 months (10.2, 12.9) for patients who received placebo. The difference between arms did not reach statistical significance (log-rank p = 0.08). Further data were not collected after censorship 12 months after the last enrollment; therefore, this analysis is final.

Note: The applicant's consultants were split with regard to the appropriate primary analysis. Dr. Steve Piantadosi argued that it is rational to stratify the log-rank for country since randomization was stratified by center and center is within country. The p-value for this analysis is 0.03. A second consultant, [redacted] agreed with the FDA that the appropriate analysis is the prespecified nonstratified log-rank test (see letter to the applicant, forwarded to the FDA, dated January 18, 2002).

The FDA performed exploratory analyses stratifying the log-rank by each of the four protocol-specified covariates of interest -- age, KPS, histology, country. Only the log-rank stratified by country reaches traditional levels of significance. The meaning of this finding is unclear. Hypotheses were not advanced during the design of the trial and are unknown even in retrospect.

- To assess the influence of known strong prognostic factors on the survival results, a multivariate cox model adjusted for age, KPS, and histology. The p-value increases to 0.16.

Note: It can be argued that a significance level of p = 0.05 should not be the final arbiter of a positive study. In this light, the secondary endpoints and collective evidence are examined in the sections below.

- The magnitude of the difference in survival between the arms is small (median of approximately 2 months). Imbalances in known prognostic factors could account for such a difference. Most importantly, more patients on Gliadel had a favorable tumor histology than patients on placebo (discussed in greater detail under Secondary Endpoints). Other imbalances favoring Gliadel included the extent of resection (prognostic factor) and treatment delivered at time of progression, e.g., reoperation, and intravenous chemotherapy.

  As an example, the greatest imbalance in favorable histologies was in patients with anaplastic oligoastrocytoma ("final" pathologist's diagnoses). If an exploratory

analysis of survival is conducted excluding these 11 patients, the observed difference between treatment arms is lost.

Issues with Secondary Endpoints

- Since Gliadel was considered to have sufficient efficacy to warrant approval in patients with recurrent GBM (and not all malignant glioma), the secondary endpoint of greatest interest (per protocol, final statistical analysis plan and regulatory meetings) was survival in the GBM subgroup of newly diagnosed patients. With 79-80% deaths, median survival was 13.5 months (11.4, 14.8) in patients receiving Gliadel and 11.4 months (10.2, 12.6) in patients treated with placebo. The difference of approximately 2 months did not reach significance in the protocol-specified analysis (log-rank p = 0.20).

Note: By design, the protocol employed two well-recognized pathologists (identified as "central" and "final") to review diagnoses made by the local pathologist. The protocol specified a sequence of review and stipulated that the "final" pathologist's diagnosis would be considered definitive and used for analyses adjusting for histology. These have been presented above. ODAC member and neuro-oncologist Dr. Jan Buckner, asked that the analysis of survival also be conducted using the "central" pathologist's diagnoses of GBM, both as a sensitivity test and measure of the reliability of the "final" diagnoses.

The "final" pathologist classified 101 patients on Gliadel and 106 on placebo with GBM. The "central" pathologist classified 88 patients on Gliadel and 99 on placebo with GBM. The imbalance in distribution of GBM, which is the histologic category associated with the worst survival, increases from 5 to 11. The observed difference in median survivals for the subgroup of patients with GBM as defined by the "central" pathologist is one month and the log-rank p-value increases to 0.40. This raises a question about the reliability of the "final" diagnoses, and returns to the issue of whether imbalances of known prognostic factors in survival could account for the observed difference between treatment arms.

- Traditional endpoints such as response rate and time to progression carry little weight in this disease since reliable tumor measurements are confounded by surgical and radiation scarring. Response rate was not assessed in T-301. Median progression-free survival was 5.9 months in both treatment groups, per applicant's analysis (not pursued by FDA).

- Time to deterioration of Karnofsky Performance Status (KPS) and time to neuroperformance deterioration were both prespecified in the protocol as secondary endpoints. The applicant claimed statistical significance in these analyses; however, the results were dependent on counting death as an event. When death is censored in the analysis of time to KPS deterioration (approximately 50% of the events in both arms), the p-value is 0.61. Approximately 40-75% of the events in the analysis of time to deterioration of neuroperformance status were death (varying by parameter, 11 parameters total). Ignoring the issue of multiplicity for the moment, when death is censored, p-values range from 0.21 to 0.94 for 10 of the parameters. One, speech,

retained significance at 0.01; however, biologic plausibility for this isolated finding is lacking. These analyses, in summary, are driven by the survival data and cannot be turned to for independent evidence of efficacy.

Note: The argument raised that efficacy is supported by the consistency of the direction of the treatment effect favoring Gliadel in the primary and secondary endpoints is flawed in that none of these secondary endpoints are independent of the primary endpoint.

- Questions #29 and #30 of the EORTC QLQ – C30 directed at global health were prespecified as the items of greatest interest on the questionnaire. FDA and applicant agree that no differences between the treatment arms were observed.

Adequacy of T-301.

Seven of the 13 ODAC members voted that T-301 was not an adequate trial, although it could be considered well-controlled (randomized, blinded, placebo wafer control). Problematic design features included (1) underpowering, based on an overly optimistic projection of the treatment effect; (2) imbalances between the arms; (3) differences in histologic diagnoses between the two expert pathologists; and, (4) if we take the applicant's arguments at face value that the intended primary analysis was meant to be stratified, there was inadequate detail in the protocol and statistical analysis plan.

Supportive Evidence: 1996 Trials.

CL-0190 was a randomized, placebo-controlled trial of Gliadel vs. placebo, also conducted in patients with newly diagnosed malignant glioma. Only 32 of the intended 100 patients were enrolled when lack of drug supply closed the trial before protocol endpoints were reached. A statistically significant treatment effect on survival was seen in the ITT population (13.4 months [9.6, --] vs. 9.2 months [8.6, 10.3]); however, the treatment arms were imbalanced in that all 5 patients with the more favorable histology randomized to Gliadel. ODAC voted unanimously in 1996 that this trial was not adequate to broaden the indication to this population.

Trial 8802 was the basis of the current approval of Gliadel for patients with recurrent GBM. The trial, however, was conducted in patients with all malignant glioma. Overall survival in the ITT population did not reach significance (log-rank p = 0.3) with median survivals of 7.2 months (6.1, 8.5) in the Gliadel arm and 5.4 (4.7, 6.4) in the placebo arm. In 1996, ODAC voted 7/8 that the indication should be limited to patients with GBM (1/7 abstention).

Note: The applicant argues that consistency in treatment effect is seen across the trials. CL-0190 produced a similar difference in survival, but the issue of imbalances in histology favoring Gliadel is also a consistent thread. Trial 8802, conducted in patients with recurrent malignant glioma, showed a nonsignificant difference in median survival of approximately 2 months; however, it could be argued that a consistent effect of 2 months in both the recurrent and newly diagnosed patients should not be seen -- that patients with previously untreated diseases should have a better outcome than patients

with relapsed disease. The applicant hypothesizes that the greater rate of reoperation in T-301 may have obscured a larger difference, but it should be noted that more patients on Gliadel had a reoperation than in the placebo arm (40% vs. 31%).

Conclusions and Recommendation.

The applicant has not provided convincing evidence of a treatment effect for Gliadel in patients with newly diagnosed malignant glioma. The reasons can be summarized as follows: (1) Supplemental NDA 20-637 contained a single, multicenter, randomized, placebo-controlled trial (T-301) whose primary and secondary endpoints did not reach statistical significance. (2) Although there was consistency in direction of the hazard ratios in the primary and some secondary endpoints favoring the Gliadel arm, these endpoints were not independent of each other. (3) The observed difference between the arms in the primary endpoint of survival was small (difference in medians of approximately 2 months). A difference of this magnitude could be due to imbalances between the arms in strong prognostic factors, particularly histology, which occurred both in T-301 and the 1996 trial, CL-0190, which was intended to be supportive. (4) The adequacy of the T-301 as a whole was called into question, with 7 of 13 members of ODAC voting that it was not adequate.

Since T-301 does not stand alone as statistically persuasive and clinically meaningful, the only credible argument for approval would be supportive evidence from other trials with Gliadel that, when taken together, provide substantial evidence of efficacy. (5) Data from the 1996 trial, 8802, can not be considered evidence in one phase of disease that could be used to provide support of efficacy in another phase of disease. The ITT population of 8802 was comprised of patients with all malignant glioma and persuasive evidence of efficacy was not demonstrated. In 1996, ODAC voted 7/8 (1 abstention) that 8802 (and CL-0190) did not provide sufficient evidence to extent the indication to newly diagnosed or recurrent patients with malignant glioma. The indication granted was limited to patients with recurrent GBM.

For the reasons stated, I recommend against approval of Gliadel Wafer for the treatment of newly diagnosed patients with malignant glioma.

Cc: NDA 20-637
HFD-150: A. Shapiro; M. Pelosi

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/s/

Alison Martin
3/19/02 08:00:56 AM
MEDICAL OFFICER

PROJECT MANAGER REVIEW OF LABELING

NDA: 20-637/S-016 resubmission after an NA letter

Drug: Gliadel (polifeprosan 20 with carmustine implant) Wafer

Applicant: Guilford Pharmaceuticals, Inc.

Submission Date: October 25, 2002 **Receipt Date:** October 28, 2002

BACKGROUND:
This submission of October 25, 2002 is a complete, class 2 response to our FDA March 19, 2002 action (NA) letter. The supplement provides for GLIADEL® wafer for use as an adjunct to surgery to prolong survival in patients undergoing initial resection of a high-grade malignant glioma.

DOCUMENTS REVIEWED:
The approved package insert dated 08/2000 is compared with the proposed revised package insert labeling text provided with the February 4, 2003 submission.

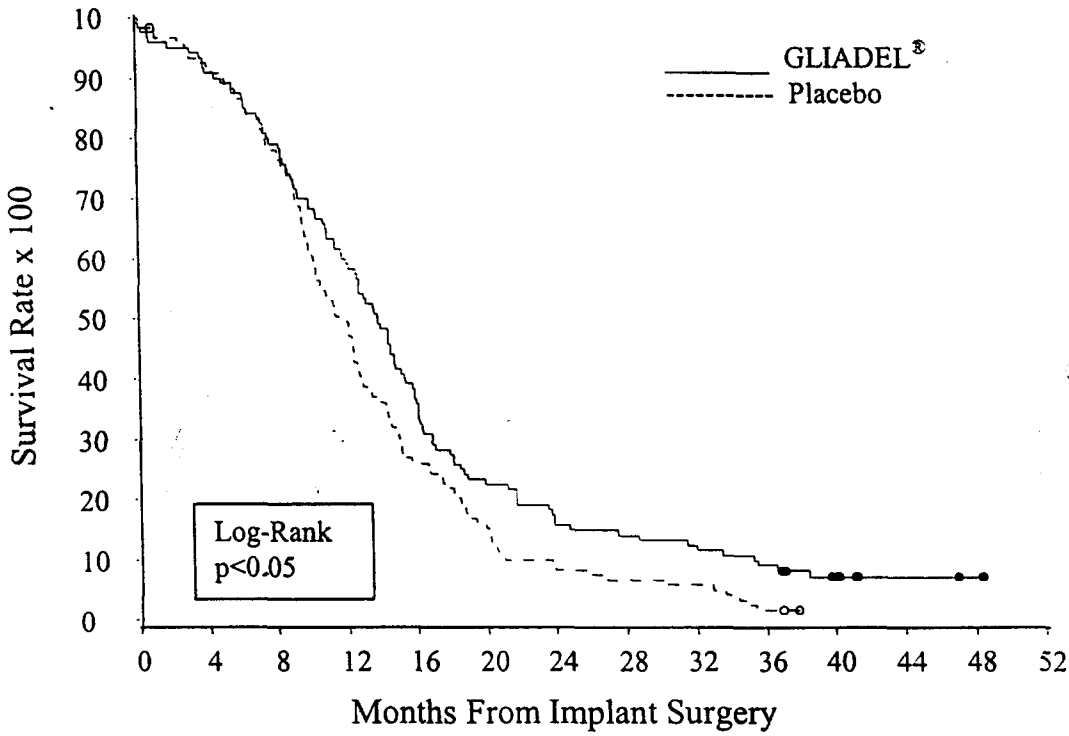
REVIEW:
Throughout the package insert GLIADEL has been changed to GLIADEL® wafer.

In CLINICAL STUDIES the following is added:

Primary Surgery

A randomized, double-blind, placebo-controlled clinical trial was conducted in adult patients with newly-diagnosed high-grade malignant glioma undergoing initial craniotomy for tumor resection. This trial determined the safety and efficacy of GLIADEL® Wafer implants plus surgery and radiation therapy compared to placebo implants plus surgery and radiation therapy. Two hundred and forty patients with newly-diagnosed malignant glioma were enrolled. The most common tumor type was Glioblastoma Multiforme (GBM) (n=207), followed by anaplastic oligoastrocytoma (n=11), anaplastic oligodendroglioma (n=11), and anaplastic astrocytoma (n=2). GLIADEL® Wafers were implanted at the time of the surgery in 120 patients and placebo wafers were implanted in 120 patients. The majority of patients received 6-8 wafers. The majority of patients (93/120, 77.5% in the GLIADEL® Wafer group and 98/120, 81.7% in the placebo group) with newly-diagnosed malignant glioma received a standard course of radiotherapy (55 to 60 Gy) typically starting 3 weeks after surgery. There were 17 patients (14.2%) in the GLIADEL® Wafer group and 12 patients (10.0%) in the placebo group who received systemic chemotherapy during the study. All six patients with anaplastic oligdendroglioma received chemotherapy within 30 days of GLIADEL® wafer implantation. Patients were followed for at least three years or until death. Only one patient was lost to follow-up. Median survival increased from 11.6 months with placebo to 13.9 months with GLIADEL® Wafer (p-value <0.05, log-rank test). The hazard ratio for GLIADEL® Wafer treatment was 0.73 (95% CI: 0.56-0.95).

Kaplan-Meier Overall Survival Curves for Patients Undergoing Initial Surgery for a High-Grade Malignant Glioma



When only patients with Glioblastoma multiforme were included in the analysis, the hazard ratio with GLIADEL® Wafer treatment was 0.78 (95% CI: 0.59-1.03, p=0.08, log-rank test).

In CLINICAL STUDIES, a Recurrent Surgery title is added with the following recurrent surgery information modified as follows:

A randomized, double-blind, placebo-controlled clinical trial was conducted in adult patients with recurrent malignant glioma. This trial determined the safety and efficacy of GLIADEL® Wafer implants plus surgery compared to placebo implants plus surgery. Ninety-five percent of the patients treated with GLIADEL® had 7-8 wafers implanted. Chemotherapy was withheld at least four weeks (six weeks for nitrosoureas) prior to and two weeks after surgery in patients undergoing re-operation for malignant glioma. In 222 patients with recurrent malignant glioma who had failed initial surgery and radiation therapy, the six-month survival rate after repeat surgery increased from 47% (53/112) for patients receiving placebo to 60% (66/110) for patients treated with GLIADEL® Wafer. Median survival increased by 33%, from 24 weeks (5.5 months) with placebo to 32 weeks (7.4 months) with GLIADEL® Wafer treatment. In patients with GBM, the six-month survival rate increased from 36% (26/73) with placebo to 56% (40/72) with GLIADEL® Wafer treatment. Median survival of GBM patients increased by 41% from 20 weeks (4.6 months) with placebo to 28 weeks (6.4 months) with GLIADEL® Wafer treatment. In patients with pathologic diagnoses other than GBM at the time of surgery for tumor recurrence, GLIADEL® Wafer produced no survival prolongation.

In CLINICAL STUDIES, the following is deleted.

In CLINICAL STUDIES, the (2) graphs concerning recurrent surgery have been modified, rounding the log-rank values to two decimal places and deleting the Wilcoxon P values. In addition, the Overall survival graph title has been modified to "KAPLAN-MEIER OVERALL SURVIVAL....." From" OVERALL KAPLAN-MEIER SURVIVAL....."

INDICATIONS AND USAGE is changed to the following:

GLIADEL® Wafer is indicated in newly-diagnosed high grade malignant glioma patients as an adjunct to surgery and radiation. GLIADEL® Wafer is indicated in recurrent glioblastoma multiforme patients as an adjunct to surgery.

The following changes are made in PRECAUTIONS (underline=added,

strikethrough=deleted).

Computed tomography and magnetic resonance imaging of the head may demonstrate enhancement in the brain tissue surrounding the resection cavity after implantation of GLIADEL® Wafers. This enhancement may represent edema and inflammation caused by GLIADEL® Wafer or tumor progression.

Therapeutic Interactions: Interactions of GLIADEL® Wafer with other drugs have not been formally evaluated.

The short and long-term toxicity profiles of GLIADEL® Wafer when given in conjunction with chemotherapy have not been fully explored. GLIADEL® Wafer, when given in conjunction with radiotherapy does not appear to have any short-term or chronic toxicities.

In ADVERSE REATIONS, the following is deleted.

In ADVERSE REACTIONS, the following is added.

Adverse reactions for the trials are described below.

Primary Surgery

The following data are the most frequently occurring adverse events observed in 5% or more of the newly-diagnosed malignant glioma patients during the trial.

COMMON ADVERSE EVENTS OBSERVED IN ≥ 5% OF PATIENTS RECEIVING GLIADEL® AT INITIAL SURGERY

Body System Adverse event	GLIADEL® N=120 n (%)	Placebo N=120 n (%)
Body as a whole		
Aggravation reaction*	98 (82)	95 (79)
Headache	33 (28)	44 (37)
Asthenia	26 (22)	18 (15)
Infection	22 (18)	24 (20)
Fever	21 (18)	21 (18)
Pain	16 (13)	18 (15)
Abdominal pain	10 (8)	2 (2)
Back pain	8 (7)	4 (3)
Face edema	7 (6)	6 (5)
Abscess	6 (5)	3 (3)
Accidental injury	6 (5)	8 (7)
Chest pain	6 (5)	0
Allergic reaction	2 (2)	6 (5)
Cardiovascular system		
Deep thrombophlebitis	12 (10)	11 (9)
Pulmonary embolus	10 (8)	10 (8)
Hemorrhage	8 (7)	7 (6)
Digestive system		
Nausea	26 (22)	20 (17)
Vomiting	25 (21)	19 (16)
Constipation	23 (19)	14 (12)
Diarrhea	6 (5)	5 (4)
Liver function tests abnormal	1 (1)	6 (5)
Endocrine system		
Diabetes mellitus	6 (5)	5 (4)
Cushings syndrome	4 (3)	6 (5)
Metabolic and nutritional disorders		
Healing abnormal	19 (16)	14 (12)
Peripheral edema	11 (9)	11 (9)
Musculoskeletal system		
Myasthenia	5 (4)	6 (5)
Nervous system		
Hemiplegia	49 (41)	53 (44)
Convulsion	40 (33)	45 (38)
Confusion	28 (23)	25 (21)
Brain edema	27 (23)	23 (19)
Aphasia	21 (18)	22 (18)
Depression	19 (16)	12 (10)
Somnolence	13 (11)	18 (15)
Speech disorder	13 (11)	10 (8)
Amnesia	11 (9)	12 (10)

COMMON ADVERSE EVENTS OBSERVED IN ≥ 5% OF PATIENTS RECEIVING GLIADEL® AT INITIAL SURGERY

Body System Adverse event	GLIADEL® N=120 n (%)	Placebo N=120 n (%)
*Adverse events coded to the COSTART term "aggravation reaction" were usually events involving tumor/disease progression or general deterioration of condition (e.g. condition/health/Karnofsky/neurological/physical deterioration).		
Nervous system (continued)		
Intracranial hypertension	11 (9)	2 (2)
Personality disorder	10 (8)	9 (8)
Anxiety	8 (7)	5 (4)
Facial paralysis	8 (7)	5 (4)
Neuropathy	8 (7)	12 (10)
Ataxia	7 (6)	5 (4)
Hypesthesia	7 (6)	6 (5)
Paresthesia	7 (6)	10 (8)
Thinking abnormal	7 (6)	10 (8)
Abnormal gait	6 (5)	6 (5)
Dizziness	6 (5)	11 (9)
Grand mal convulsion	6 (5)	5 (4)
Hallucinations	6 (5)	4 (3)
Insomnia	6 (5)	7 (6)
Tremor	6 (5)	8 (7)
Coma	5 (4)	6 (5)
Incoordination	3 (3)	8 (7)
Hypokinesia	2 (2)	8 (7)
Respiratory system		
Pneumonia	10 (8)	9 (8)
Dyspnea	4 (3)	8 (7)
Skin and appendages		
Rash	14 (12)	13 (11)
Alopecia	12 (10)	14 (12)
Special senses		
Conjunctival edema	8 (7)	8 (7)
Abnormal vision	7 (6)	7 (6)
Visual field defect	6 (5)	8 (7)
Eye disorder	3 (3)	6 (5)
Diplopia	1 (1)	6 (5)
Urogenital system		
Urinary tract infection	10 (8)	13 (11)
Urinary incontinence	9 (8)	9 (8)

In ADVERSE REACTIONS, a Surgery for Recurrent Disease title is added under which the following recurrent surgery information is retained with the exception of the strikeout.

The following post-operative adverse events were observed in 4% or more of the patients receiving GLIADEL® Wafer at recurrent surgery
Except for nervous system effects, where there is a possibility that the placebo wafers could have been responsible, only events more common in the GLIADEL® Wafer group are listed. These adverse events were either not present pre-operatively or worsened post-operatively during the follow-up period. The follow-up period was up to 71 months.

The title of the table concerning adverse events for recurrent surgery is changed from :

To:

COMMON ADVERSE EVENTS OBSERVED IN ≥4% OF PATIENTS RECEIVING GLIADEL® Wafer AT SURGERY FOR RECURRENT DISEASE

The table is reordered listing the adverse events in order of decreasing frequency.

The footnote for the table is changed from:

To:

*p < 0.05 for comparison of GLIADEL versus placebo groups in study 8802

The following text is deleted.

In ADVERSE REACTIONS the Seizures section is changed from:

To:
In the initial surgery trial, the incidence of seizures was 33.3% in patients receiving GLIADEL® Wafer and 37.5% in patients receiving placebo. Grand mal seizures occurred in 5% of GLIADEL® Wafer-treated patients and 4.2% of placebo treated patients. The incidence of seizures within the first 5 days after wafer implantation was 2.5% in the GLIADEL® Wafer group and 4.2% in the placebo group. The time from surgery to the onset of the first post-operative seizure did not differ between the GLIADEL® Wafer and placebo treated patients.

In the surgery for recurrent disease trial, the incidence of post-operative seizures was 19% in both patients receiving GLIADEL® Wafer and placebo. In this study, 12/22 (54%) of patients treated with GLIADEL® Wafer and 2/22 (9%) of placebo patients experienced the first new or worsened seizure within the first five post-operative days. The median time to onset of the first new or worsened post-operative seizure was 3.5 days in patients treated with GLIADEL® Wafer and 61 days in placebo patients.

In ADVERSE REACTIONS the Brain Edema section is changed from:

To:
In the initial surgery trial, brain edema was noted in 22.5% of patients treated with GLIADEL® Wafer and in 19.2% of patients treated with placebo. Development of brain edema with mass effect (due to tumor recurrence, intracranial infection, or necrosis) may necessitate re-operation and, in some cases, removal of GLIADEL® Wafer or its remnants.

In ADVERSE REACTIONS the Healing Abnormalities section is changed from:

To:
The following healing abnormalities have been reported in clinical trials of GLIADEL® Wafer: wound dehiscence, delayed wound healing, subdural, subgaleal or wound effusions, and cerebrospinal fluid leak. In the initial surgery trial, healing abnormalities occurred in 15.8% of GLIADEL® Wafer treated patients and in 11.7% of placebo recipients. Cerebrospinal fluid leaks occurred in 5% of GLIADEL® Wafer recipients and 0.8% of those given placebo. During surgery, a water-tight dural closure should be obtained to minimize the risk of cerebrospinal fluid leak.

In the surgery trial for recurrent disease trial, the incidence of healing abnormalities was 14% in GLIADEL® Wafer treated patients and 5% in patients receiving placebo wafers.

In **ADVERSE REACTIONS the Intercranial Infection section is changed from:**

To:
In the initial surgery trial, the incidence of brain abscess or meningitis was 5% in patients treated with GLIADEL® Wafer and 6% in patients receiving placebo. In the recurrent setting, the incidence of brain abscess or meningitis was 4% in patients treated with GLIADEL® Wafer and 1% in patients receiving placebo.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

With the concurrence of the noted reviewer, this supplemental labeling text should be approved.

/S/

2-14-03

Paul Zimmerman, R.Ph., Project Manager/date

/S/

Alla Shapiro, M.D., Medical Officer/date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
2/19/03 11:37:08 AM
CSO

Ann Farrell
2/19/03 05:40:14 PM
MEDICAL OFFICER

TELECON MINUTES

MEETING DATE: February 4, 2003 **TIME:** 1pm **LOCATION:** room 2064

Drug Name: Gliadel **NDA:** 20-637/S-016 **Type of meeting:** labeling

Sponsor: Guilford **Preparation package:** dated February 3, 2003

FDA Invitees, titles and offices:
Richard Pazdur, M.D., Division Director
Grant Williams, M.D., Deputy Division Director
Ann Farrell, M.D., Medical Team Leader
Alla Shapiro, M.D., Medical Officer
Gang Chen, Ph.D., Statistical Team Leader
Ning Li, Ph.D., Statistical Reviewer
Catherine Miller, DDMAC
Iris Masucci, DDMAC
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:
Craig R. Smith, M.D., Chief Executive Officer
Nancy Linck, Ph.D., Senior VP, General Counsel & Corporate Sectretary
Louise M. Peltier, Senior Director, Regulatory Affairs
Valerie Riddle, M.D., Vice President, Medical Affairs
Et al

Meeting Objective(s):
To discuss Guilford's proposed changes to the FDA modified label.

Guilford agreed to the FDA proposed modifications but wanted to discuss a few of the FDA proposed modifications. Those items for discussion are found in the February 3, 2003 submission and are proposed reinsertions.

During the telecon, Guilford agreed not to include their proposed reinsertions. In addition, the typographical error and omission will be corrected. It was agreed that the proposed reference would not be used.

The meeting was concluded at 1:45pm.

/S/
_____ 2-6-03
Paul Zimmerman, Project Manager/date
Minutes preparer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
2/6/03 01:56:42 PM
CSO

TELECON MINUTES

MEETING DATE: August 7, 2002 **TIME:** 11am **LOCATION:** room 2064

Drug Name: Gliadel **NDA:** 20-637/S-016 **Type of meeting:** end of review follow-up

Sponsor: Guilford **Preparation package:** dated July 1, 2002

FDA Invitees, titles and offices:
Richard Pazdur, M.D., Division Director
Grant Williams, M.D., Deputy Division Director
Alla Shapiro, M.D., Medical Officer
Gang Chen, Ph.D., Statistical Team Leader
Ning Li, Ph.D., Statistical Reviewer
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:
Craig R. Smith, M.D., Chief Executive Officer
Enoch Bortey, Ph.D., Associate Director, Biostatistics
Nancy Linck, Ph.D., Senior VP, General Counsel & Corporate Sectretary
Louise M. Peltier, Senior Director, Regulatory Affairs
Valerie Riddle, M.D., Vice President, Medical Affairs

David Wright, President & Chief Business Officer
Robin Butler, Clinical Program Manager

Meeting Objective(s):
To discuss:
1. The Agency's concerns regarding additional surgery data.
2. An understanding as to why the Agency performed the multivariate Cox model analysis in this manner.

QUESTIONS for DISCUSSION with FDA RESPONSE:

Question 1:
What are the Agency's concerns regarding additional surgery data?

FDA response:
We are interested in evaluating additional therapies such as surgery in each arm. However, no formal statistical analyses are contemplated.

Guilford:
The applicant noted that vital status information is available on 58 of the 59 patients for the analysis. However, additional information is not available.

FDA and Guilford agreed to discuss results of the analysis at a pre-NDA meeting prior to their submission.

Question 2:
Why did the Agency performed the multivariate Cox model analysis in this manner?

FDA response:
We performed the analysis without stratifying by country to show that the treatment effect is not consistent since country is not a know prognostic factor.

Question 3:
Are there any comments regarding the June 21, 2002 submission?

a. The procedure for long term follow-up of patients, Study T-301
b. SAP
c. Further discussion of the Cox Multivariate Analysis-treating age as a dichotomous variable and stratifying by country

FDA response:

a. We believe there should be a data cut off date and you should collect complete survival follow-up information on all patients up to that date.

Guilford: The applicant proposed an August 16, 2002 cut off date.

b. The SAP for the original NDA can be used for this updated analysis but you should consider the statistical concerns presented by FDA and ODAC. Interpretation of the p value will be difficult in any case because this will be a second "final" analysis.

c. We have no objection to a Cox Multivariate Analysis stratifying by country as a secondary analysis for this updated analysis, per SAP.

There was agreement that the applicant would request a Pre-NDA meeting or telecon before submitting the supplemental amendment.

The meeting was concluded at 11:45am.

/S/

Paul Zimmerman, Project Manager/date
Minutes preparer

/S/

Concurrence:
Alla Shapiro, M.D., Medical Officer/date

/S/

Concurrence:
Ning Li, Ph.D., Statistical Reviewer/date