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(54) Title: STENT WITH POLYMER COATING CONTAINING AMORPHOUS RAPAMYCIN

(57) Abstract: A coated coronary stent, comprising: a stainless steel sent framework coated with a primer layer of Parylene C; and a rapamycin-polyrner coating having substantially uniform thickness disposed on the stent framework, wherein the rapamycin-polymer coating comprises polybutyl methacrylate (PBMA), polyethylene-co-vinyl acetate (PEVA) and rapamycin, wherein substantially all of the rapamycin in the coating is in amorphous form and substantially uniformly dispersed within the rapamycin-polymer coating.

STENT WITH POLYMER COATING CONTAINING AMORPHOUS RAPAMYCIN

BACKGROUND OF THE INVENTION

[0001] It is often beneficial to provide coatings onto substrates, such that the surfaces of such substrates have desired properties or effects. It is useful to coat biomedical implants to provide for the localized delivery of pharmaceutical or biological agents to target specific locations within the body, for therapeutic or prophylactic benefit. One area of particular interest is drug eluting stents (DES) that has recently been reviewed by Ong and Serruys in Nat. Clin. Pract. Cardiovasc. Med., (Dec 2005), Vol 2, No 12, 647. Typically such pharmaceutical or biological agents are co-deposited with a polymer. Such localized delivery of these agents avoids the problems of systemic administration, which may be accompanied by unwanted effects on other parts of the body, or because administration to the afflicted body part requires a high concentration of pharmaceutical or biological agent that may not be achievable by systemic administration. The coating may provide for controlled release, including long-term or sustained release, of a pharmaceutical or biological agent. Additionally, biomedical implants may be coated with materials to provide beneficial surface properties, such as enhanced biocompatibility or lubriciousness.

[0002] Conventional solvent-based spray coating processes are generally hampered by inefficiencies related to collection of the coating constituents onto the substrate and the consistency of the final coating. As the size of the substrate decreases, and as the mechanical complexity increases, it grows increasingly difficult to uniformly coat all surfaces of a substrate.

[0003] What is needed is a cost-effective method for depositing inert polymers and pharmaceutical or biological agents, such as rapamycin onto a substrate, where the collection process is efficient, the coating produced is conformal, substantially defect-free and uniform, and the composition of the coating can be regulated.

SUMMARY OF THE INVENTION

[0004] The present invention provides a coated coronary stent comprising: a stainless steel sent framework coated with a primer layer of Parylene C; and a rapamycin-polymer coating having substantially uniform thickness disposed on the stent framework, wherein the rapamycin-polymer coating comprises polybutyl methacrylate (PBMA), polyethylene-co-vinyl acetate (PEVA) and rapamycin, wherein substantially all of the rapamycin in the coating is in

amorphous form and substantially uniformly dispersed within the rapamycin-polymer coating. In one embodiment, the PBMA, PEVA and rapamycin are present in a ratio of about 1:1:1.

[0005] In one aspect, the invention provides coated stents, wherein rapamycin is in the form of particles having an average diameter from 2 nm to 500 nm.

[0006] In another aspect, the invention provides coated stents, wherein the rapamycin-polymer coating has a thickness of about 1 to about 30 microns. The coating is preferably substantially free of solvent residue.

[0007] In yet another aspect, the invention provides a coated stent, wherein the rapamycin-polymer coating is sintered in dense carbon dioxide at a temperature of about 40 C to about 60 C, whereby bulk properties and adhesion of the coating to the stent are improved without altering the quality of the rapamycin, PBMA or PEVA. Preferably, the rapamycin-polymer coating covers substantially the entire surface of the stent framework and/or the rapamycin-polymer coating is substantially free of aggregated particles.

[0008] In another aspect, the invention provides a stent coated with a polymer and rapamycin comprising: a stainless steel stent framework coated with a primer layer of Parylene C; and a rapamycin-polymer coating disposed on the stent framework, wherein the rapamycin-polymer coating comprises PBMA, PEVA; and rapamycin substantially uniformly dispersed within the rapamycin-polymer coating, wherein substantially all of rapamycin in the coating is in amorphous form, wherein disposing the coating is carried out by a spray coating process whereby rapamycin spray particles are formed by rapid expansion of a supercritical or near critical fluid mixture, and the rapamycin spray particles and the stent framework are oppositely charged so that the spray particles are electrostatically attracted to the stent framework. Preferably, the spray coating process is carried out under RESS condition. The supercritical or near critical fluid mixture preferably comprises PBMA, PEVA and rapamycin dissolved in dimethylether, chlorofluorocarbon, hydrofluorocarbon, carbon dioxide or mixtures thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0010] Figure 1. Rapid Expansion of Supercritical Solutions (RESS) process equipment *see* C. Domingo et al, *Journal of Supercritical Fluids* **10**, 39-55 (1997)

[0011] Figure 2. Infrared spectra of each component and the spray coating mixture. Individual peaks for each component are labeled.

[0012] Figure 3. Stents coated (top panel) and sintered under different conditions (lower two panels) with rapamycin, PEVA and PBMA. All stent surfaces are coated

[0013] Figure 4. Infrared spectra with all components coated, before and after sintering. The spectra indicate that no damage is done to the coating during the sintering process.

[0014] Figure 5. XRD for RESS sprayed and as received rapamycin. The RESS sprayed rapamycin does not show any diffraction peaks indicating the RESS sprayed material is in amorphous form

DETAILED DESCRIPTION OF THE INVENTION

[0015] The present invention is explained in greater detail below. This description is not intended to be a detailed catalog of all the different ways in which the invention may be implemented, or all the features that may be added to the instant invention. For example, features illustrated with respect to one embodiment may be incorporated into other embodiments, and features illustrated with respect to a particular embodiment may be deleted from that embodiment. In addition, numerous variations and additions to the various embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention. Hence, the following specification is intended to illustrate some particular embodiments of the invention, and not to exhaustively specify all permutations, combinations and variations thereof.

Definitions

[0016] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0017] "Compressed fluid" as used herein refers to a fluid of appreciable density (e.g., >0.2 g/cc) that is a gas at standard temperature and pressure. "Supercritical fluid", "near-critical fluid", "near-supercritical fluid", "critical fluid", "densified fluid" or "densified gas" as used herein refers to a compressed fluid under conditions wherein the temperature is at least 80% of the critical temperature of the fluid and the pressure is at least 50% of the critical pressure of the fluid. Examples of substances that demonstrate supercritical or near critical behavior suitable for the present invention include, but are not limited to carbon dioxide, isobutylene, ammonia, water, methanol, ethanol, ethane, propane, butane, pentane, dimethyl ether, xenon, sulfur hexafluoride, halogenated and partially halogenated materials such as chlorofluorocarbons,

hydrochlorofluorocarbons, hydrofluorocarbons, perfluorocarbons (such as perfluoromethane and perfuoropropane, chloroform, trichloro-fluoromethane, dichloro-difluoromethane, dichloro-tetrafluoroethane) and mixtures thereof.

[0018] "Sintering" as used herein refers to the process by which the polymer or polymers form continuous coating by treatment of the coated substrate with a densified gas, compressed fluid, compressed gas, near critical fluid or supercritical fluid that is a non-solvent for both the polymer and the pharmaceutical agent and biological agents, but an agent that induces formation of continuous domains of polymer. Through the sintering process, the adhesion properties of the coating are improved to reduce flaking of detachment of the coating from the substrate during manipulation.

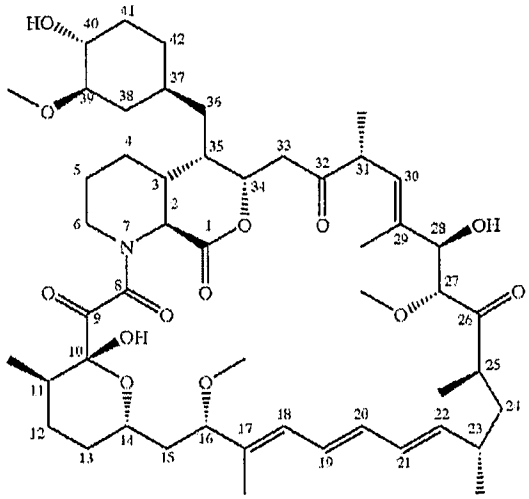
[0019] "Rapid Expansion of Supercritical Solutions" or "RESS" as used herein involves the dissolution of a polymer into a compressed fluid, typically a supercritical fluid, followed by rapid expansion into a chamber at lower pressure, typically near atmospheric conditions . The rapid expansion of the supercritical fluid solution through a small opening, with its accompanying decrease in density, reduces the dissolution capacity of the fluid and results in the nucleation and growth of polymer particles. The atmosphere of the chamber is maintained in an electrically neutral state by maintaining an isolating "cloud" of gas in the chamber. Carbon dioxide or other appropriate gas is employed to prevent electrical charge is transferred from the substrate to the surrounding environment.

[0020] "Electrostatically charged" or "electrical potential" or "electrostatic capture" as used herein refers to the collection of the spray-produced particles upon a substrate that has a different electrostatic potential than the sprayed particles. Thus, the substrate is at an attractive electronic potential with respect to the particles exiting, which results in the capture of the particles upon the substrate. i.e. the substrate and particles are oppositely charged, and the particles transport through the fluid medium of the capture vessel onto the surface of the substrate is enhanced via electrostatic attraction. This may be achieved by charging the particles and grounding the substrate or conversely charging the substrate and grounding the particles, or by some other process, which would be easily envisaged by one of skill in the art of electrostatic capture.

[0021] "Open vessel" as used herein refers to a vessel open to the outside atmosphere, and thus at substantially the same temperature and pressure as the outside atmosphere.

[0022] "Closed vessel" as used herein refers to a vessel sealed from the outside atmosphere, and thus may be at significantly different temperatures and pressures to the outside atmosphere.

[0023] Rapamycin is an immunosuppressive lactam macrolide that is produced by Streptomyces hygroscopicus, and having the structure depicted in Formula:



[0024] See, e.g., McAlpine, J. B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S. L., et al., J. Am. Chem. Soc. (1991) 113: 7433; U.S. Pat. No. 3,929,992.

[0025] The present invention provides a coated coronary stent comprising: a stainless steel sent framework coated with a primer layer of Parylene C; and a rapamycin-polymer coating having substantially uniform thickness disposed on the stent framework, wherein the rapamycin-polymer coating comprises polybutyl methacrylate (PBMA), polyethylene-co-vinyl acetate (PEVA) and rapamycin, wherein substantially all of the rapamycin in the coating is in amorphous form and substantially uniformly dispersed within the rapamycin-polymer coating.

[0026] In one embodiment, the PBMA, PEVA and rapamycin are present in a ratio of about 1:1:1.

[0027] In another embodiment, the invention provides coated stents, wherein rapamycin is in the form of particles having an average diameter from 2 nm to 500 nm.

[0028] In another embodiment, the invention provides coated stents, wherein the rapamycin-polymer coating has a thickness of about 1 to about 30 microns. The coating is preferably substantially free of solvent residue.

[0029] In yet another embodiment, the invention provides a coated stent, wherein the rapamycin-polymer coating is sintered in dense carbon dioxide at a temperature of about 40 C to about 60 C, whereby bulk properties and adhesion of the coating to the stent are improved without altering the quality of the rapamycin, PBMA or PEVA. Preferably, the rapamycin-polymer coating covers substantially the entire surface of the stent framework.

[0030] The invention encompasses embodiments wherein the rapamycin-polymer coating is substantially free of aggregated particles.

[0031] The invention also provides a stent coated with a polymer and rapamycin comprising: a stainless steel stent framework coated with a primer layer of Parylene C; and a rapamycin-

polymer coating disposed on the stent framework, wherein the rapamycin-polymer coating comprises PBMA, PEVA; and rapamycin substantially uniformly dispersed within the rapamycin-polymer coating, wherein substantially all of rapamycin in the coating is in amorphous form, wherein disposing the coating is carried out by a spray coating process whereby rapamycin spray particles are formed by rapid expansion of a supercritical or near critical fluid mixture, and the rapamycin spray particles and the stent framework are oppositely charged so that the spray particles are electrostatically attracted to the stent framework. Preferably, the spray coating process is carried out under RESS condition. The supercritical or near critical fluid mixture preferably comprises PBMA, PEVA and rapamycin dissolved in dimethylether, chlorofluorocarbon, hydrofluorocarbon, carbon dioxide or mixtures thereof.

Examples

[0032] The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

[0033] Example 1.

[0034] The RESS process equipment used in the present studies is depicted in Figure 1. This is a common design for a RESS apparatus *see* C. Domingo et al, *Journal of Supercritical Fluids* **10**, 39-55 (1997).

[0035] A solution containing rapamycin that is saturated in a solvent or supersaturated in a solvent is sprayed at a flow rate sufficient to achieve flow into a chamber of known volume pressurized above ambient pressure and containing a coronary stent . The system temperature is held constant or allowed to vary so that any number of points in the phase diagrams of the solution or mixture or any of its individual components can be mapped in pressure –temperature, volume-pressure or pressure-volume space constituting liquid, gas or supercritical CO_2 conditions. CO_2 in any single phase or combination of phases flows through the chamber at a mass flow rate of 5 gm/min to some multiple of this flow rate. After a period of time ranging from seconds to minutes or hours have elapsed, the solute and solvent flow that is a solution of the therapeutic compound and suitable solvent for the chosen solute or solutes cease but CO_2 flow continues for an additional period of time maintaining constant pressure during this period. After this time period, the pressure is dropped to atmospheric pressure. During the spray coating process the particles are attracted to the stent by charging the substrate oppositely to that of the sprayed particle charge by applying a voltage that is greater than 5000 V but less than the ionization potential of the most easily ionized component of the mixture. The particles may also traverse an electromagnetic field such that the field is used to guide the particle to a target.

[0036] Example 2:

[0037] The ability to uniformly coat arterial stents with rapamycin with controlled composition and thickness using electrostatic capture in a rapid expansion of supercritical solution (RESS) experimental series has been demonstrated. This technique involves spraying an equal part mixture of the therapeutic compound such as rapamycin and polymers such as PBMA and PEVA using a spray coating and collection technique described herein. To determine coating composition, infrared spectroscopy was used to collect the spectrum of a silicon wafer chip coated simultaneously with an arterial stent (Figure 2). Unique absorption bands were identified for each mixture component and band area was used as a metric to determine incorporation of each compound in the coating.

[0038] The individual bands used for compositional analysis were determined by spray coating Si wafer chips with each component separately. The coating thickness was determined gravimetrically and calculated from the density of the materials. It was assumed that the layer is fully dense. The thickness can be controlled by varying the spray time.

[0039] In the as sprayed state, the coating lacks strong adhesion to the substrate. Sintering the coated substrate (see Figure 3) dramatically improves coating adhesion while leaving the components unaltered as the infrared spectra shown in figure 4 confirm. The coating is sintered in a supercritical carbon dioxide environment allowing mild sintering conditions to be used with temperature below 80 C.

[0040] Figure 4 shows Infrared spectra with all components coated, before and after sintering. The spectra indicate that no damage is done to the coating during the sintering process. The spectra demonstrate that the sintering process does not adversely impact the coating since no new stretches appear in the after sintering spectrum.

[0041] Figure 5 shows XRD data taken for an authentic rapamycin sample (as received rapamycin) and RESS sprayed rapamycin. The RESS sprayed rapamycin does not show any diffraction peaks indicating the RESS sprayed material is in amorphous form. In other words, the RESS sprayed rapamycin lacks any crystallinity as indicated by the absence of diffraction peaks in the XRD.

[0042] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

WHAT IS CLAIMED IS:

1. A coated coronary stent, comprising:

a stainless steel sent framework coated with a primer layer of Parylene C; and

a rapamycin-polymer coating having substantially uniform thickness disposed on the stent framework, wherein the rapamycin-polymer coating comprises polybutyl methacrylate (PBMA), polyethylene-co-vinyl acetate (PEVA) and rapamycin, wherein substantially all of the rapamycin in the coating is in amorphous form and substantially uniformly dispersed within the rapamycin-polymer coating.

2. The stent of Claim 1, wherein PBMA, PEVA and rapamycin are present in a ratio of about 1:1:1.

3. The stent of Claim 1, wherein rapamycin is in the form of particles having an average diameter from 2 nm to 500 nm.

4. The stent of Claim 1, wherein said coating has a thickness of about 1 to about 30 microns.

5. The stent of Claim 1, wherein said coating is substantially free of solvent residue.

6. The stent of Claim 1, wherein the rapamycin-polymer coating is sintered in dense carbon dioxide at a temperature of about 50 C to about 60 C and a pressure below 1000 psig, whereby bulk properties and adhesion of the coating to said stent are improved without altering the quality of the rapamycin, PBMA or PEVA.

7. The stent of Claim 1, wherein said rapamycin-polymer coating covers substantially the entire surface of said stent framework.

8. The stent of Claim 1, wherein said rapamycin-polymer coating is substantially free of aggregated particles.

9. A stent coated with a polymer and rapamycin, comprising:

a stainless steel stent framework coated with a primer layer of Parylene C; and

a rapamycin-polymer coating disposed on the stent framework, wherein the rapamycin-polymer coating comprises PBMA, PEVA; and rapamycin substantially uniformly dispersed within the rapamycin-polymer coating, wherein substantially all of rapamycin in the coating is in amorphous form, wherein disposing said coating is carried out by a spray coating process whereby rapamycin spray particles are formed by rapid expansion of a supercritical or near critical fluid mixture, and said rapamycin spray particles and said stent framework are oppositely charged so that said spray particles are electrostatically attracted to said stent framework.

10. The stent of Claim 9, wherein said spray coating process is carried out under RESS conditions.

11. The stent of Claim 10, wherein said supercritical or near critical fluid mixture comprises PBMA, PEVA and rapamycin dissolved in dimethylether, chlorofluorocarbon, hydrofluorocarbon, carbon dioxide or mixtures thereof.

12. The stent of Claim 10, wherein PBMA, PEVA and rapamycin are co-deposited from a single mixture.

13. The stent of Claim 10, wherein PBMA, PEVA and rapamycin are separately deposited on the stent.

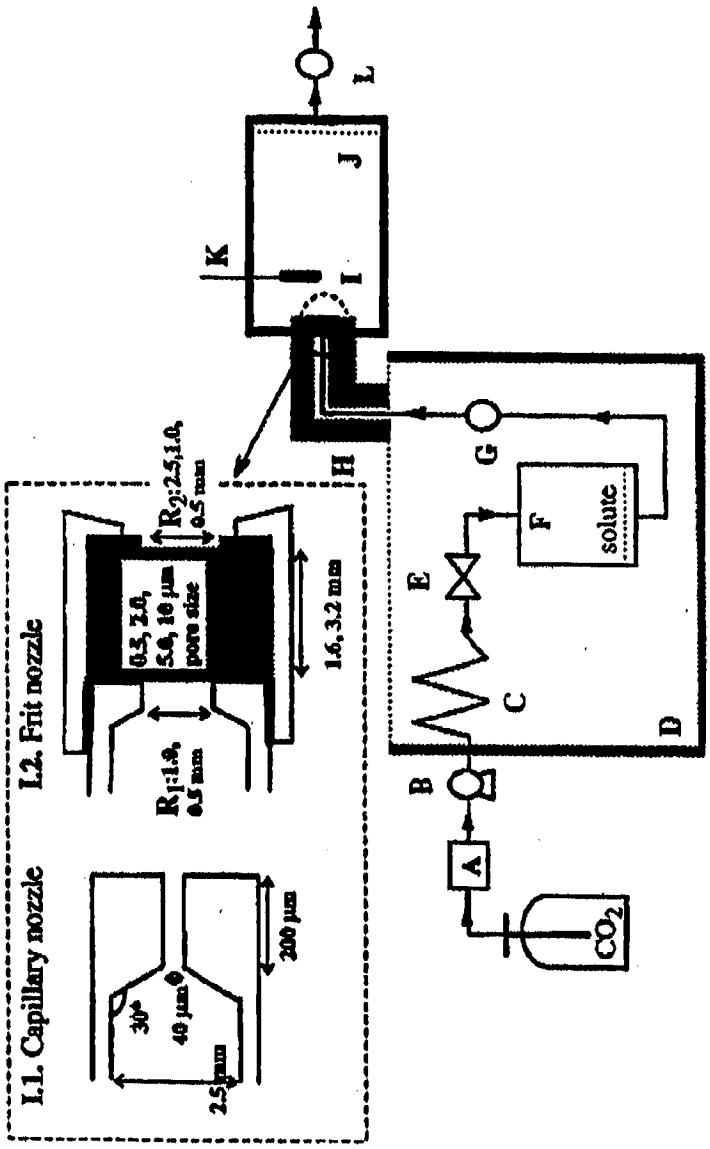

L
J
K
I
H
G
F
solute
E
C
D
B
A
CO_2
L1. Capillary nozzle
L2. Frit nozzle
30°
40 µm
2.5 mm
200 µm
R_1:1.0, 0.5 mm
0.5, 2.0, 5.0, 10 µm pore size
R_2:2.5,1.0, 0.5 mm
1.6, 3.2 mm

FIGURE 1

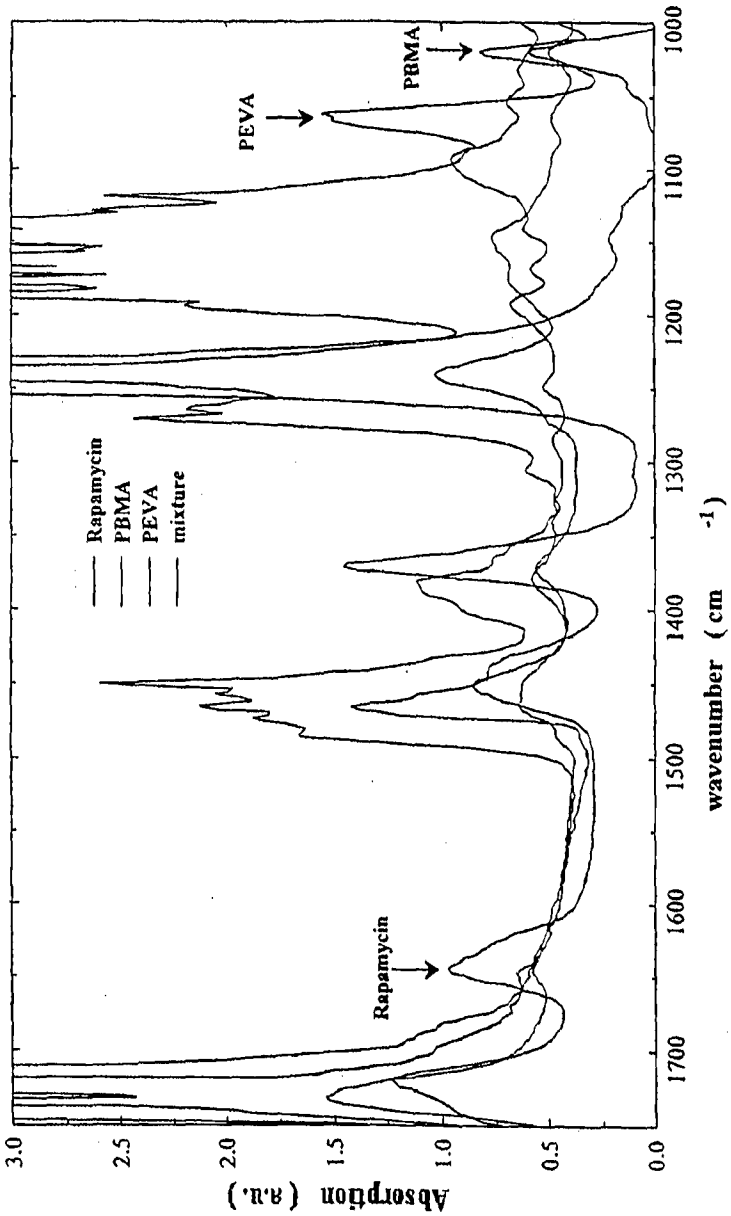

Absorption (a.u.)
wavenumber (cm -1)
Rapamycin
PBMA
PEVA
mixture
Rapamycin
PEVA
PBMA
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1700
1600
1500
1400
1300
1200
1100
1000

FIGURE 2

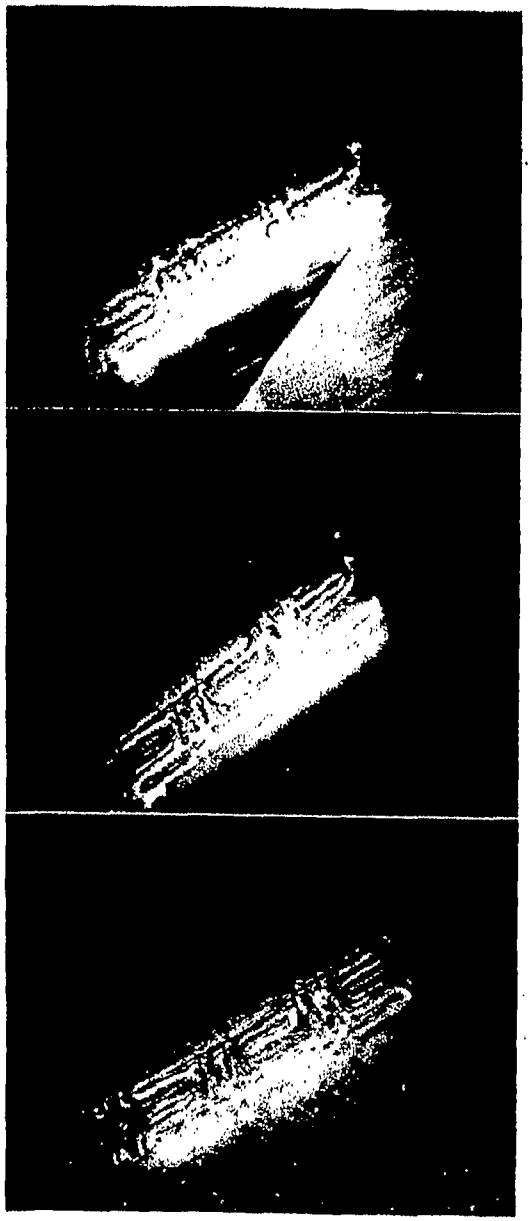


FIGURE 3

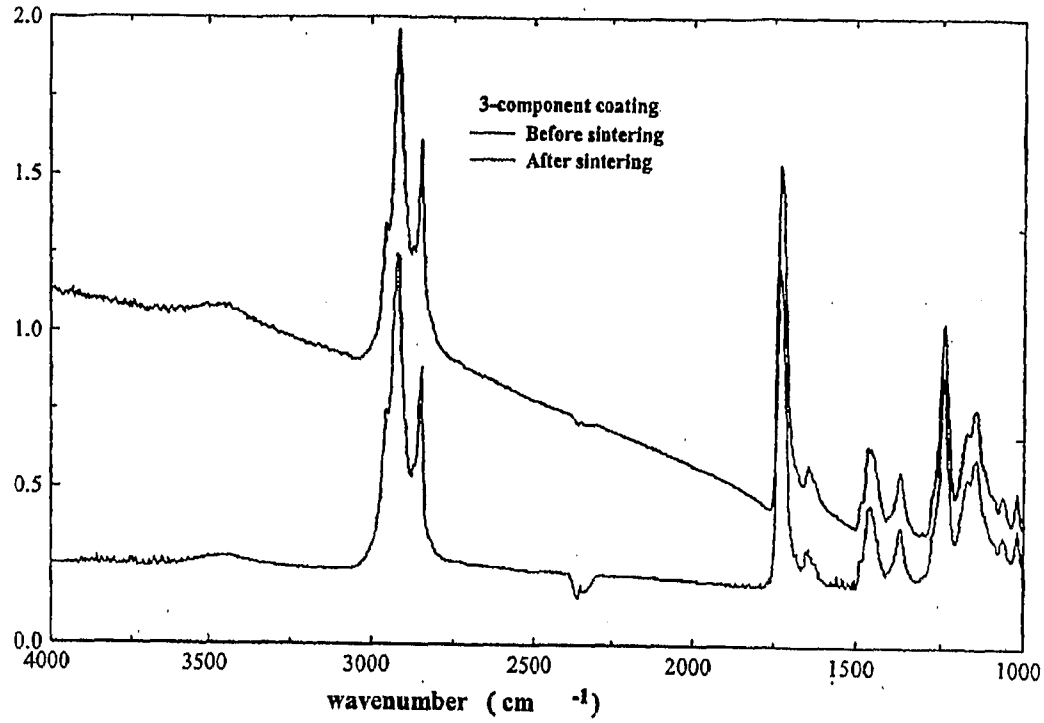


Figure 3. IR spectra of a substrate with all components coated before and after sintering. These spectra indicate that no damage is done to the coating during the sintering process.

FIGURE 4

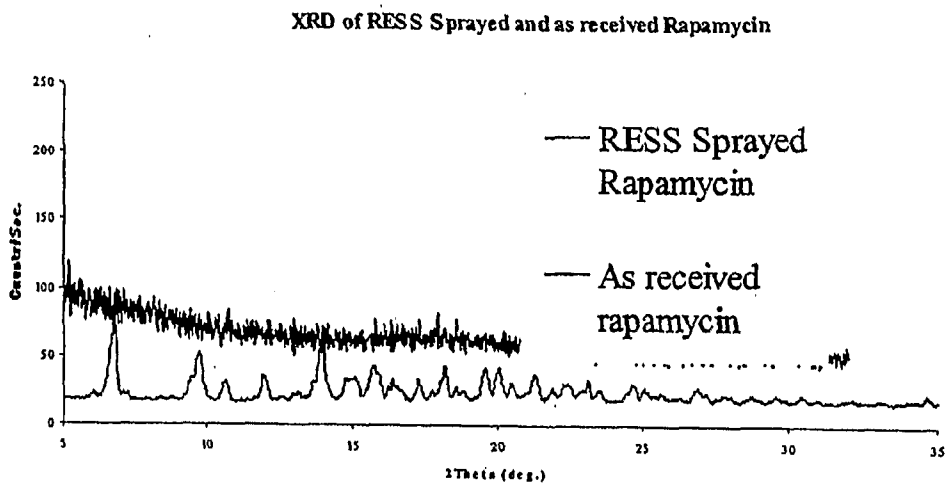


Figure 5. XRD for the RESS sprayed and as received rapamycin. The RESS sprayed rapamycin does not show any diffraction peaks indicating the RESS sprayed material is in amorphous form.

FIGURE 5