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Sustained release of protein from poly(ethylene glycol) incorporated amphiphilic comb like polymers

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Abstract

Amphiphilic comb like macromonomer containing hydrophilic poly(ethylene glycol) groups covalently linked to poly(hydromethyl siloxane) (PHMS) were prepared by hydrosilylation reaction. The epoxy reacting sites were introduced to this amphiphilic system by the reaction with allyl epoxy propyl ether (AEPE). Bovine serum albumin (BSA), a model protein drug was loaded to the PEG–PDMS system and very thin membranes were made from this macromonomer adopting solution casting technique. The *in vitro* protein release studies at various pH conditions showed a controlled release profile without exhibiting any initial burst. The control of the initial burst might be due to the strong linkages of the protein with the membrane and the aggregation of the protein at the surface. The morphology of the membrane before and after the protein release, and the mechanical strength were evaluated. The surface properties of the membrane were studied using the contact angle measurements.

Keywords: Controlled drug release; Drug delivery; Siloxane; Surface energy

1. Introduction

The therapeutic potential of many pharmaceutical proteins would benefit significantly from the availability of controlled release systems for the constant or pulsed release of the intact protein. The controlled delivery of drugs permits one to maintain a drug concentration at a therapeutic level, allowing the elimination of undesirable side effects and repeated dosing (Baker, 1987). The drug release pattern may be constant, oscillating or declining. The need to engineer different release patterns for drugs of different molecular sizes, potency, and stability provides the impetus for active study of the design of new biomaterials, intelligent delivery systems and approaches for delivery through different portals in the body. For most drug delivery systems, polymers function simply as inert and biocompatible carriers. A successful controlled release device deals satisfactorily with technological factors such as protein loading efficiency, protein integrity and desired release characteristics.

Peptides and proteins are frequently administered using intravenous infusions as well as intramuscular injections or subcutaneous methods. There are many methods available like hydrogels and microspheres reported, to extend the duration of protein delivery. It has been reported that the physical denaturation of protein during fabrication and unpredicted release profiles characterized by a burst effect and incomplete release are major drawbacks in these drug delivery systems (Morlock et al., 1997, 1998; Bittner et al., 1998).

Silicones have found many uses in various healthcare applications, in the construction of medical devices, as non-metabolized active in gastro enterology or as an excipient in pharmaceutical formulations. With the emerging trend towards pain management in wound care and the revitalized interest for transdermal drug delivery forms, silicone skin adhesives are experiencing a renewed popularity, partly because they can provide gentle adhesion to skin as well as formulation options to deliver hydrophilic molecules. Many unique properties such as chemical stability, ease of use to manufacture devices of different designs and very high permeability to many active drugs can be associated with silicone-based controlled release drug delivery systems. Various poly(dimethyl siloxanes) (PDMS)-based systems are

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used in many anti-acid/anti-gas drugs, in transdermal systems, in inserts or in tropical drugs (Toddywala and Chien, 1990). The siloxane backbone is made up of very polar Si–O–Si bonds. The poly(dimethyl siloxane)s are actually very hydrophobic as the methyl groups shield the polar backbone, a feature enhanced by the very low cohesive energy of rotation which results in reduction of their interfacial energy at various surfaces by exposing a maximum number of methyl groups (Noll, 1968).

The interfacial properties contribute to the ever-increasing use of silicone adhesives for temporarily attaching therapeutic patches, wound dressings and medical devices to the skin. The excellent biocompatibility of siloxanes is due to its low chemical reactivity, low surface energy and the hydrophobicity of PDMS. Hydrophilic species may be compounded with the elastomer to improve the compatibility and solubility of hydrophilic active drugs with the very hydrophobic silicone polymers (Aguadisch et al., 1990).

Co-formulating silicone elastomers with hydrophilic polyglycols or carboxymethylcellulose allows to create pressure within the elastomer to release the hydrophilic active drugs (Etienne, 1990). This approach has been used to liberate active drugs having very low solubility in silicone elastomers e.g. using poly(ethylene glycol)s (PEG) in adhesive silicone elastomers. Recently, PEG has attracted considerable attention on controlled release technology because of their good biocompatibility and excellent physicochemical properties (Graham and McNeill, 1984; Zhang and Zhuo, 2005; Merrill et al., 1993; Iza et al., 1998). Possible routes for the introduction of PEG on hydrophobic groups include physical blending with additives containing PEG (Wesslen et al., 1994; Kober and Wesslen, 1992) and covalent bonding by various chemical reactions (Desai and Hubbell, 1991; Bergstorom et al., 1992).

However, it is always desirable to incorporate PEG with covalent bonding for stable maintenance of the surface than physical blending. There is only limited useful chemistry available in the literature for the modification of hydrophobic PDMS with hydrophilic PEG by covalent bonding (Park et al., 1999). A drug polymer dispersion can be utilized to yield a polymer matrix for diffusion mediated controlled drug release. A drug polymer matrix film may be adaptable for transdermal drug delivery (Jenquin et al., 1990). PEG, which is soluble in a wide range of organic and aqueous solvents, endows solubility to the hydrophobic siloxane backbone. It is important in the pharmaceutical industry to develop a simple and reliable administration form (Jiang et al., 2005). The aim of our research is to develop a synthetically challenging polymer matrix having covalently linked PEG with PDMS and easy to vary the hydrophobic–hydrophilic ratio in the matrix for various controlled release studies The polymer matrix synthesized here is tested for its capability in absorbing and releasing the drug in a controlled manner so that it could be suitable for transdermal drug delivery system. We chose siloxane covalently linked with PEG as a polymer matrix, capable of releasing bovine serum albumin (BSA), a model protein drug. Thus, the present study describes the approach to assess the release behaviour of BSA from the PHMS–PEG graft polymer matrix.

2. Materials and methods

2.1. Materials

Poly(hydromethyl siloxane) (PHMS) (M_w 1902), hexachloroplatinic acid and *n*-octadecane were purchased from Lancaster and were used as received without any further purification. Monomethyoxy poly(ethylene glycol) (MPEG) of molecular weight 550 obtained from Aldrich was dried over molecular sieves. Bovine serum albumin was obtained from Sigma. Allyl bromide and potassium *t*-butoxide were obtained from sd fine chemicals and used as received. Toluene was dried over calcium hydride and tetrahydrofuran (THF) was dried over potassium hydroxide. Both the solvents were freshly distilled before use.

2.2. Characterisation

All the oligomers were characterized by ^{1}H NMR and ^{13}C NMR using JEOL 500 MHz in $CDCl_3$ solvent with TMS as internal standard. The average molecular weight of the oligomers was determined by gel permeation chromatography (GPC) (JASCO model MX-2080-31) with a RI detector using PL styra-gel column in THF with a flow rate of 1 mL/min. The molecular weights were calculated with a calibration curve relative to polystyrene standards.

The membranes before and after loading with BSA were analysed by ATR–FT-IR spectroscopy, using a Perkin-Elmer1600 spectrometer. Data were collected over 100 scans with a resolution of 4 cm^{-1}. The ATR–FT-IR measurements were made, at room temperature, on KRS-5 crystal using a variable-angle ATR unit at a nominal incident angle of 45°. Samples were taken randomly from flat sheet films, cut to ATR crystal size (2 cm × 4 cm) and mounted on both sides of trapezoid crystal. The mechanical properties were determined using Micro Tensile-Tester Instron 4501 at a speed of 10 mm/min.

The contact angles were measured at ambient temperature by Sessile Drop method using a camera mounted on a microscope to record the drop image using Digidrop (GBX) model goniometer with windrop software. Double distilled water and *n*-octadecane were used as solvents for the studies. Equilibrium contact angle was measured for a time period of 120 s depending on the stability of the drop. Average of the results obtained from three experiments was taken for contact angle measurements. The surface energy of the films was calculated using Young and Fowkes equation and the details of the experimental procedure are reported elsewhere (Holmberg, 2000).

The amount of the released BSA from the matrix was determined using Varian (model Cary Eclipse) UV spectrophotometer. Circular Dichroism spectrum was recorded at 25 °C on a J-715 spectropolarimeter in a quartz cell of 0.1 cm path length, over the range of 190–260 nm. Scanning electron

microscopy of the sample was obtained using Philips quanta 200 FEI.

2.3. Synthesis of amphiphilic membrane

PHMS backbone grafted with PEG was synthesized by following the two steps (Schemes 1 and 2) and the detailed experimental procedure is given below.

2.3.1. Synthesis of allyl monomethoxy poly(ethylene glycol) (AMPEG)

In order to covalently link PEG to PHMS via hydrosilylation, firstly PEG should be allyl functionalised at one end (Scheme 1). The allylation of monomethoxy PEG (AMPEG) is chosen to avoid the crosslinking if it were a dihydroxy terminated PEG.

AMPEG was synthesized according to the reported procedure (Nicolaou and Li, 2001). According to the procedure, 10.3 g (0.018 mol) of MPEG was reacted with potassium tertiary butoxide in 10 mL of THF by stirring for half an hour at room temperature. 3.392 g (0.028 mol) of allyl bromide was then added dropwise and stirring was continued for another 3 h at room temperature. The solution was filtered and the solvent was removed and dichloromethane solvent was added to dissolve the product. This was washed several times with water to remove unreacted MPEG and allyl bromide. A yellow liquid product was obtained by removing the solvent and the yield was calculated to be 70%. The product obtained was confirmed using FT-IR, ^{1}H NMR and ^{13}C NMR.

2.3.2. Synthesis of allyl epoxy propyl ether containing PHMS–AMPEG oligomers (AEPE–PHMS–PEG) (Scheme 2)

This work aims at the loading of BSA units to the matrix which can be done just by adsorption to the matrix or can be reacted with the functional groups in the matrix. We have tried the second method of chemically reacting BSA with the matrix and this needs a reaction site in the siloxane backbone. Epoxidation is a well-known method that allows derivatisation of the resulting oxirane ring by a variety of oxirane ring opening reactions (Antonietti et al., 1996). Epoxy groups can also be introduced to the siloxane backbone by the hydrosilylation reaction and the number of epoxy groups can be quantified by the NMR and titrimetry methods. The amine groups in the protein can open the oxirane ring and the protein can be linked via amide linkage formation.

6.6 g (0.003 mol) of PHMS was reacted with 41.23 g (0.0698 mol) AMPEG and 1.99 g (0.017 mol) allyl epoxy propyl ether (AEPE) by the hydrosilylation reaction (Senthilkumar and Reddy, 2004) in the presence of platinum catalyst. The reaction was standardized at 170 °C for 120 h by monitoring the reduction in intensity of Si–H peak at 2165 cm^{-1} in FT-IR and 4.6 ppm in ^{1}H NMR. The oligomer was purified by extracting in diethyl ether and then washing with methanol to remove any unreacted PHMS. The incorporations were estimated from the ^{1}H NMR spectrum employing individual characteristic integral peaks of AEPE, AMPEG and PHMS.

2.4. Loading of BSA and film formation

In order to evaluate the membranes as potential drug delivery systems, BSA was selected as a model component. BSA is a spheroidal protein with a molecular weight of approximately 66,000 Da and a hydrodynamic diameter of 72 Å (Bezemer et al., 1999). To load the BSA to the siloxane matrix, a crosslinking reaction between the synthesized AEPE–PHMS–PEG oligomer and high molecular weight PDMS was carried out. PDMS film containing 10% AEPE–PHMS–PEG oligomers was casted after the maximum loading of BSA (100 mg). A 10 mL toluene was added to this to get a homogenous liquid. Crosslinking was done by adding 0.1 mL of dibutyltindilaurate catalyst. After the solvent was evaporated, a thin dense film with thickness ranging from 100 to 200 μm were peeled from the glass plate. The membrane obtained was used for the *in vitro* protein release study of BSA.

2.5. In vitro release studies

In order to study the *in vitro* release of BSA, the membranes blended with BSA was cut into small pieces of area 1 cm × 1 cm. These pieces were incubated at 37 °C under static conditions in aqueous medium adjusted to pH 5.5, 7.0, 8.5 and in 1 M NaCl at pH 7.6. The incubation medium was checked at various intervals to maintain a constant pH. Samples of the release medium were taken at different time points varying from 1 to 240 h at regular intervals. The amount of the released BSA was determined spectrophotometrically using the protocol for Bradford method (Kruger, 1996). To 1 mL of Bradford's reagent, 0.02 mL of the sample (at experimental pH) and 50 μL of the 0.1 M NaCl was added and incubated at 37 °C for half an hour. The absorbance was measured at 595 nm. The calibration curve for a range of BSA concentrations from 0 to 100 μg/mL was obtained in the same way using standard solutions. Concentration of BSA in the experimental samples was in the range of the calibration curve.

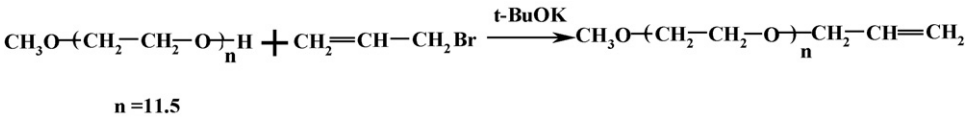
3. Results

3.1. Synthesis and characterisation of AMPEG

A new amphiphilic drug delivery system was developed by synthesizing covalently linked PEG to PHMS backbone. Introduction of epoxy groups into the backbone gives way to chemically bind the serum protein to the siloxane backbone. This involves two steps. One is to synthesise allyl PEG and the second step is to incorporate both the allyl PEG and the allyl epoxy propyl ether to the poly(hydromethyl siloxane) backbone. The experimental procedure was already discussed.

Fig. 1a shows the FT-IR spectrum of AMPEG. A strong absorption band at 1112 cm^{-1} shows the C–O–C stretch of methoxy and ethylene oxide groups. The presence of C=C is confirmed by the peak at 1644 cm^{-1}. The disappearance of –OH stretch at 3500 cm^{-1} indicates the absence of unreacted MPEG.

Fig. 1b represents the ^{1}H NMR spectrum of AMPEG. The terminal methylene protons of the allyl group shows a doublet of



Scheme 1. Synthesis of AMPEG.

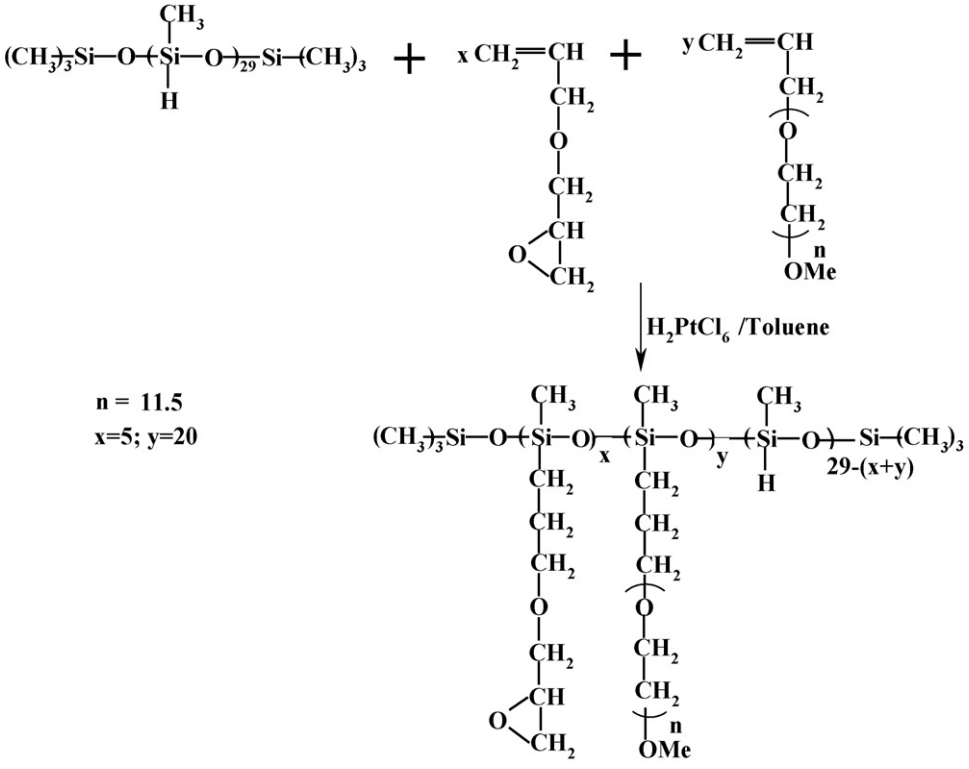
a doublet signals at 4.9 and 5.0 ppm. The methine proton of the allyl group shows a multiplet signal at 5.7 ppm. The chemical shift at 2.03 ppm corresponds to the methylene protons of the allyl group. The ethylene oxide protons show signal at 3.43 ppm and the methoxy protons show a signal at 3.1 ppm.

Fig. 1c shows the ^{13}C NMR spectrum of AMPEG. The chemical shift representing the terminal methylene carbon shows signal at 116.8 ppm. The methine carbon shows shift at 134.7 ppm. The methylene carbons of the ethylene oxide and the methoxy carbon show chemical shifts at 70.0 and 53.7 ppm, respectively.

3.2. Synthesis of AEPE linked PHMS–PEG oligomers

The second step is the incorporation of epoxy groups to the PHMS backbone along with the synthesized AMPEG. AEPE and AMPEG were reacted with PHMS by the hydrosilylation reaction. The synthesized AEPE linked PHMS–PEG was characterized by FT-IR, ^{1}H and ^{13}C NMR (Fig. 2a–c). The number of incorporations of the PEG units to the backbone was calculated from the ^{1}H NMR spectrum using the integral ratio calculations between the SiH and the ethylene oxide chemical shift of PEG at 4.6 and 3.3 ppm, respectively. The incorporation of epoxy groups was calculated by the epoxy equivalent weight (EEW) measurement according to the reported procedure (Paul and Ranby, 1975) and was found to be 50 g mol^{-1}. From this the incorporated epoxy groups were found to be five and the PEG incorporations were calculated to be 20 leaving behind four SiH units for crosslinking with the PDMS matrix. The molecular weight of the macromolecule was also estimated from the GPC analysis and was found to be $M_w = 1.4 \times 10^4$ with a polydispersity index of 1.8 ($M_w/M_n = 1.8$). The BSA was crushed and was dispersed in the PHMS–PEG oligomers together with high molecular weight PDMS and stirred until the epoxy ring cleaves and incorporates to the backbone and the maximum protein loading was taken as 100% since all the protein used (100 mg) was incorporated to the matrix. The remaining Si–H groups per mole in the epoxy functionalized PHMS–PEG oligomer were used for further crosslinking with high molecular weight PDMS in toluene using dibutyltindilaurate catalyst to get the BSA blended membrane.

The presence of BSA in the membrane was confirmed by the ATIR-IR spectra obtained from BSA loaded and unloaded membranes (Fig. 3). The stretch at 1696 cm^{-1} confirms the presence of amide group, which authenticates the blending of BSA in the membrane.



Scheme 2. Synthesis of PHMS–PEG oligomer.

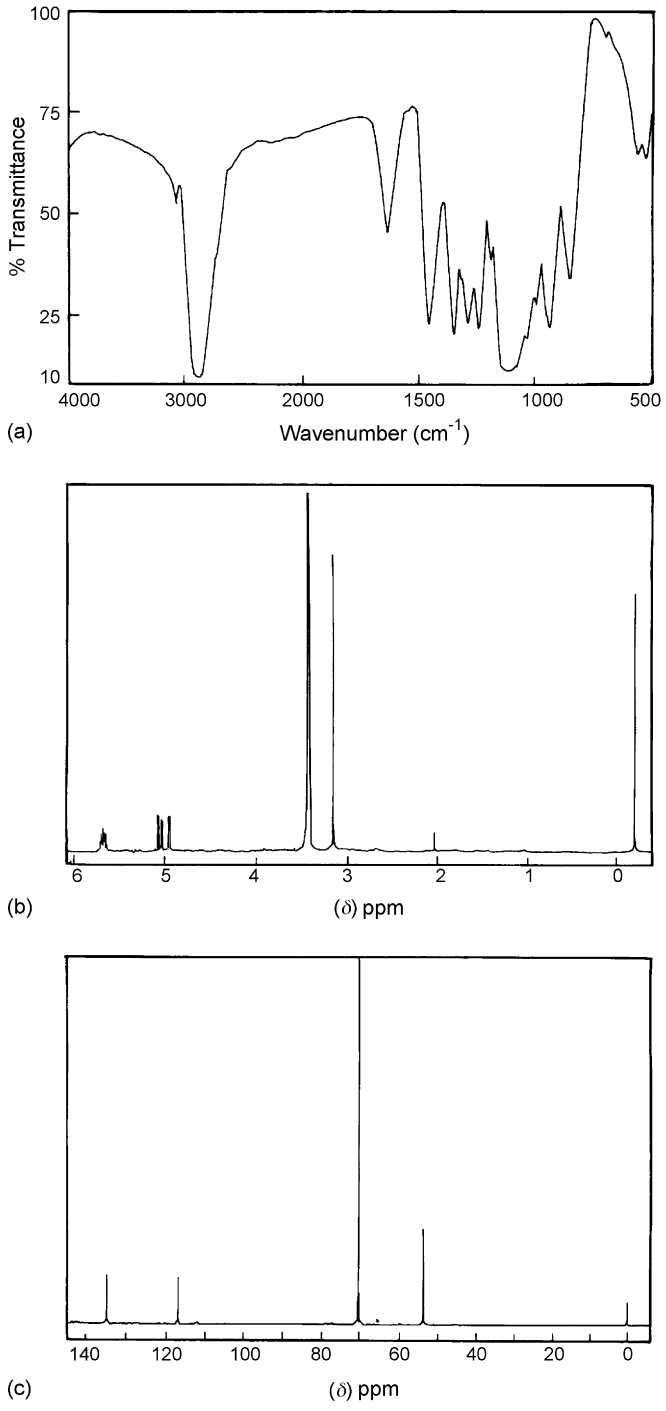


Fig. 1. (a) FT-IR, (b) ^{1}H NMR and (c) ^{13}C NMR spectrum of AMPEG.

3.3. BSA release studies

In the amphiphilic siloxane matrix, there exists the poly(ethylene glycol) units and the ethylene oxide units containing the epoxy groups as the hydrophilic groups. Studies have already been carried out by our group in stabilizing the number of PEG groups incorporation and studying their solubility in water. Flourescence and surface tension measurements demonstrated the formation of aggregates by these systems in aqueous solutions.

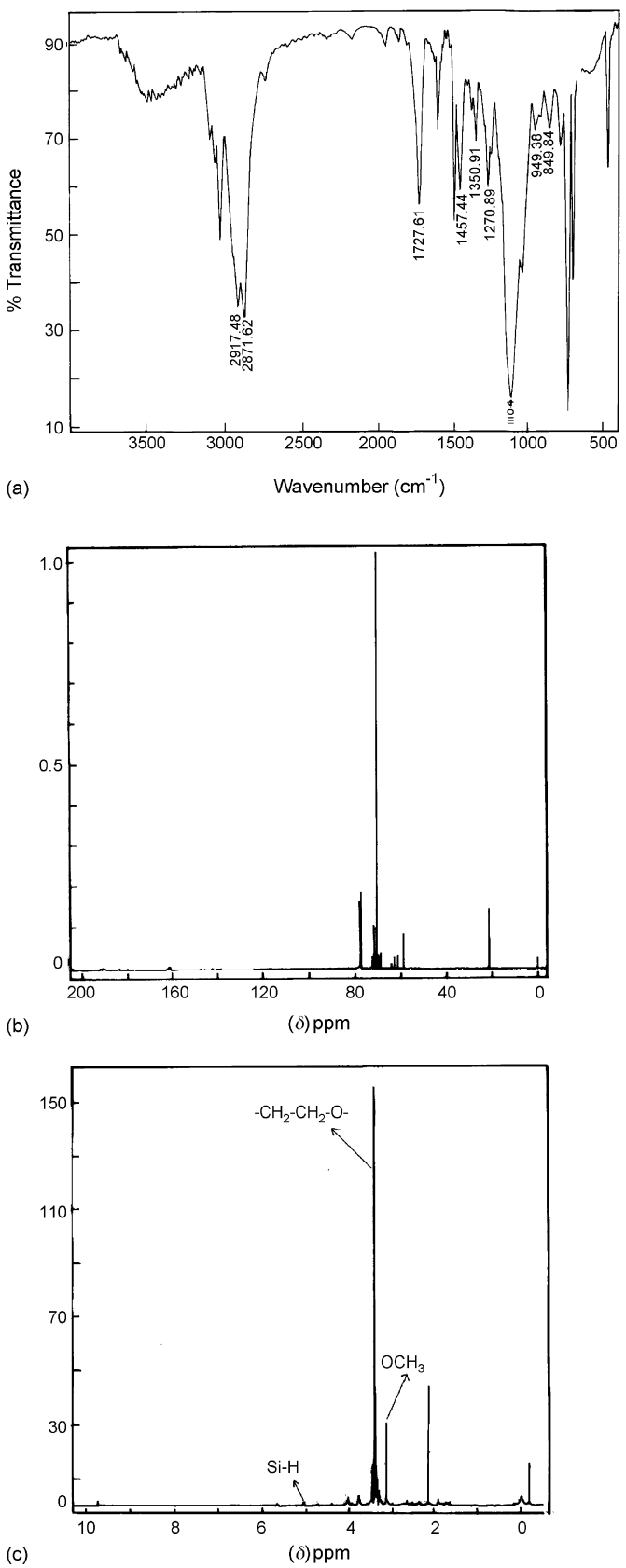


Fig. 2. (a) FT-IR, (b) ^{13}C NMR and (c) ^{1}H NMR spectrum of PHMS–PEG oligomer.

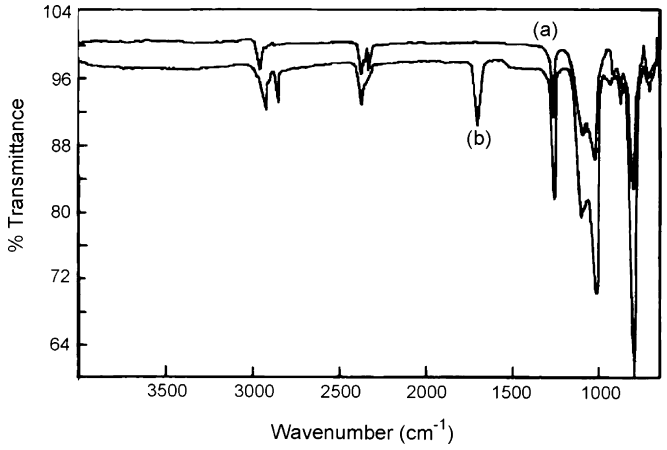


Fig. 3. ATR-IR spectra of: (a) unloaded membrane and (b) BSA loaded membrane.

The hydrophilic units will prevent the hydrophobic interaction between the siloxane matrix and the chemically bonded protein attached by the epoxy group cleavage. This may result in the aggregation of the protein at the surface of the siloxane matrix. In addition to the aggregated protein at the surface, the BSA particles are also adsorbed to the membrane via hydrogen bonding. Depending on the conformation taken by the protein, the extent of hydrogen bonding differs. BSA is a protein that undergoes pH dependant structural changes.

We have studied the *in vitro* release of BSA from the amphiphilic membrane at various physiological conditions. The kinetic study of BSA release from the membrane at various pH conditions (5.5, 7.0, 7.6 and 8.5) are shown in Fig. 4. There was no initial burst observed in any of the release conditions. This is an important condition that is aimed for the controlled release pattern for the drug delivery systems. This is mainly attributed to the aggregated protein structures formed by the proteins that are chemically linked with the matrix. These aggregated protein structures act as gates and prevent the passage of a sudden release of the protein thus controlling the burst effect. In all the pH conditions, the protein release was found to be controlled and continuous over a period of 72 h and thereafter no release was observed. However, the amount of protein released from the membrane varies with the pH conditions. An incomplete release of protein was observed in all the cases. This may be due to the inability of the pH conditions to break any chemical bond between the protein and the matrix and the release observed is the BSA that is adsorbed to the matrix via hydrogen bonds. The protein that is detached from the matrix passes out through the channels created by the hydrophilic groups of the membrane. The electrostatic interaction between the protein and the hydrophilic groups also decides the amount of protein released apart from the hydrogen bonding.

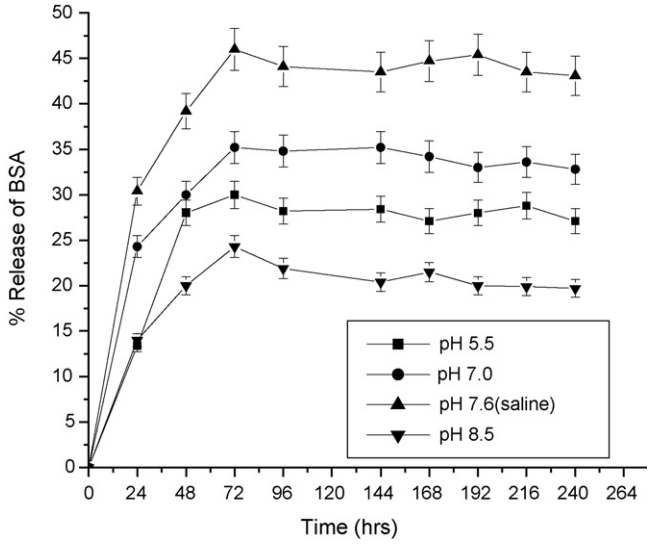


Fig. 4. Release profile of BSA from the membrane.

The maximum release of the protein was observed at the physiological saline pH (7.6) where NaCl is present as an electrolyte. The presence of electrolyte is known to decrease any electrostatic interactions present in the system and this facilitates the maximum release of protein of about 50% at this pH. At pH 5.5 and 7.0, there will be hydrogen bonding and the electrostatic attractions present that will hinder the protein release. The release at pH 5.5 was observed to be slightly less when compared to pH 7.0 with an overall release of about 32%.

The minimum protein release of 25% was observed at pH 8.5. Even though the pH is too alkaline, we expect a higher release when compared with pH 7.0. This decrease may be due to the "alkaline condition" effect that arises due to change in the conformation of protein structures. Depending on the environmental pH conditions, such as high alkaline pH, the conformation of BSA changes in such a way that there is higher expansion in the BSA structure (Matsumoto et al., 2003). This results in increased hydrogen bonding with the matrix and the extent of adsorption to the matrix is more, which leads to the decreased amount of protein release in pH 8.5 when compared to the other pH conditions. This effect will also be accompanied by the electrostatic interactions, which will further decrease the release of protein. In all the cases, the amphiphilic nature of the membrane plays an important role in manipulating the initial burst effect and the controlled release of protein by the aggregated structure at the surface.

3.4. Secondary structure analysis

It is known that when a protein adsorbs to the surface of a polymer, its secondary structure changes. A decrease of the α-helix content and an increase of the random fraction and/or β-sheet occur (Tanaka et al., 2000; Wang et al., 2004). The CD spectra for the native BSA, macromonomer loaded with BSA, and the BSA released from the membrane are shown in Fig. 5. Native BSA exhibited negative absorption bands with maxima around 222 and 208 nm consistent with its highly α-helical secondary structure (Woody et al., 1994). The membrane loaded with BSA shows the negative maximum at 208 nm coinciding with the α-helical secondary structure of BSA, whereas, a maximum at 222 nm is not observed. Decrease in intensity of the minima at 222 nm characteristic of the α-helix band indicating a loss of the structural element. The overlap of the minima of this type shows the dominating α-helix portion mixed with seg-

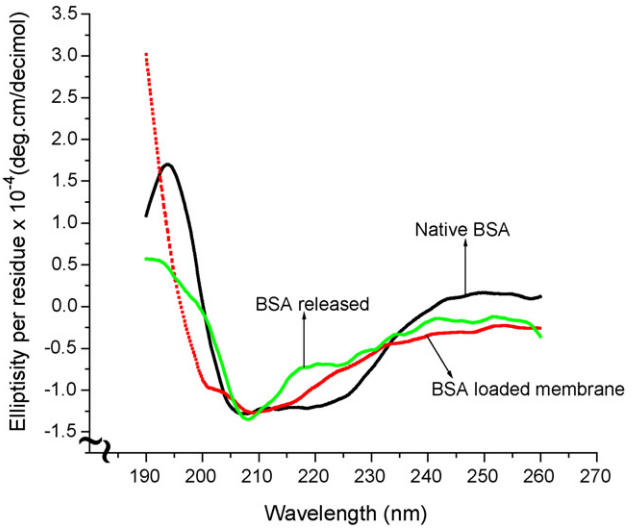


Fig. 5. CD spectrums for: (a) native BSA, (b) BSA loaded membrane and (c) released BSA.

ments of the β-sheet (Manavalan and Johnson, 1983). This is an important observation, which can be extended for the drug loading to retain the biological activity of the drug after release.

3.5. Mechanical properties

The films formed by solution casting method were tested for their mechanical properties before and after release of the loaded protein and the results are given in Table 1. The siloxane matrix shows the lowest Young's modulus of 0.56 MPa and higher tensile strength values showing the rubbery nature of the matrix due to the presence of flexible siloxane linkages. The Young's modulus of the BSA loaded membrane shows a high increase of ≅5 times due to the amide linkages present in them and this reduces the tensile strength. Considering the mechanical strength of the membrane after the release of the protein at 72 h, there is again a decrease in the Young's modulus and increase in tensile strength. We could not see the mechanical strength retaining back to the unloaded membrane and this shows that there is no complete release of BSA from the membrane.

3.6. Surface analysis

Fig. 6a shows the morphology of the unloaded membrane, which has a single phase with no pores in them. Fig. 6b and c shows the loading of 100 and 250 mg of BSA to the membrane, respectively. The membrane loaded with 250 mg of BSA shows the undissolved particles on the surface, whereas for 100 mg the surface was found to be smooth. This clearly supports the investigation that the maximum loading of protein is around 100 mg. Fig. 6b with 100 mg BSA loading shows the presence of some protein moieties at the surface, which is further confirmed by the contact angle measurements. Fig. 6d gives the surface morphology of the membrane after the release of the BSA at 72 h. This shows the release of the protein from inside the membrane by the cleavage of chemical bonds and the protein is diffused out through the channels in the network. This is shown by the cavities at the surface. If the protein were just adsorbed at the surface of the membrane, there will not be any cavity formed in the surface as observed here. This also shows some particles at the surface that are present just at the surface by adsorption.

3.7. Contact angle measurement

Contact angle measurement is the most accurate method to study the wettability of polymer surfaces and obtain the information about the organisation at the solid/liquid interface. The measurement of surface energy of solids is a thermodynamic parameter that can be influenced by the presence of any adsorbed component. There are reports for BSA that can exhibit surface active properties in the PLGA microspheres (Boury et al., 1997). We have studied the surface properties of the prepared membranes to analyse the presence of the BSA particles at the surface.

The surface energy of the unloaded matrix results from the combination of hydrophobic contribution from the siloxane units and the hydrophilic contribution from the PEG units and ethylene oxides containing the epoxy groups. The polar and dispersion factors were calculated using the following Young and Fowkes equation:

$$\gamma_{LV}(1+\cos\theta) = 2(\gamma_L^d\gamma_S^d)^{1/2} + 2(\gamma_L^p\gamma_S^p)^{1/2}$$

where γ_{LV} (mN/m) is the surface tension at liquid/air interface, γ_L^d, γ_S^d, γ_L^p and γ_S^p are the dispersion and polar factors of the solvent and sample coated substrate in mN/m, θ is the contact angle at solid/air interface. The total surface energy γ_{SV} of the samples were estimated using the following relationship:

$$\gamma_{SV} = \gamma_S^d + \gamma_S^p$$

From the data in Table 1, it is observed that the polar and dispersion factors of the unloaded matrix are found to be almost equal. An increase in the surface energy was observed with the introduction of the hydrophobic protein to the membrane. This is also observed with the decreased contact angle of octadecane with the BSA loaded membrane. An increase in the dispersion factor with a decrease in the polar factor is characteristic of the exposure of the protein at the surface. This is in accordance with the discussion of the aggregated protein at the surface. The contact angle measurement of the membrane after the protein

Table 1
Mechanical properties and surface energies of the membranes

System	Tensile strength (MPa)	Young's modulus (MPa)	γ_S^d (mN/m)	γ_S^p (mN/m)	γ_{SV} (mN/m)
Unloaded membrane	1.714	0.556	25.04	24.9	49.9
BSA loaded membrane (100 mg)	1.424	2.463	37.7	19.8	57.5
Membrane after BSA release	1.503	1.745	23.3	12.2	35.5

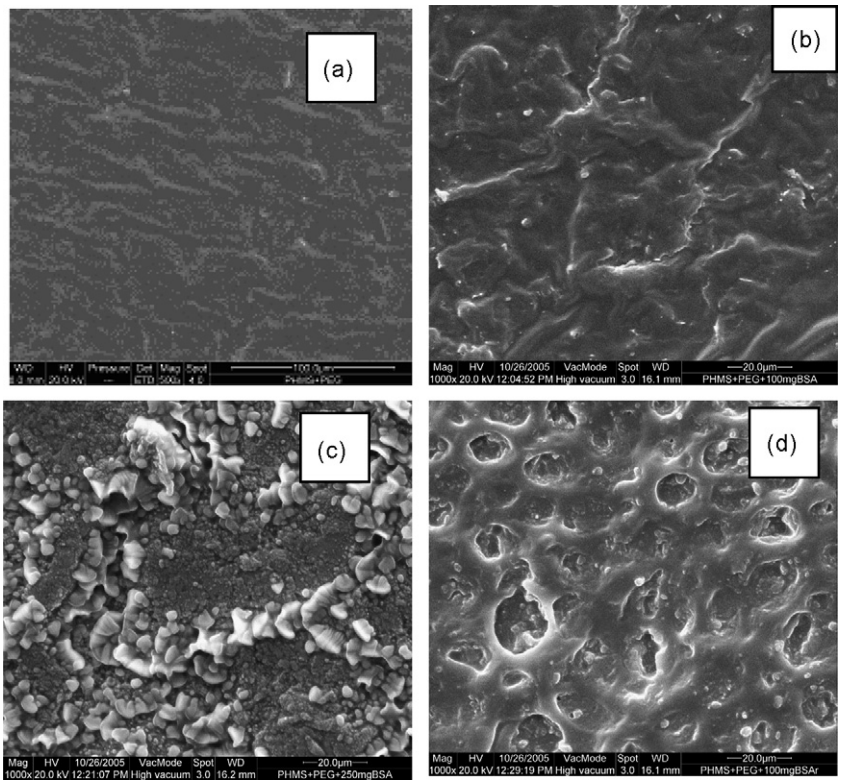


Fig. 6. SEM pictures of: (a) unloaded membrane, (b) 100 mg BSA loaded membrane, (c) 250 mg BSA loaded membrane and (d) membrane after 100 mg BSA release.

release showed a decrease in the dispersion factor and the surface energy. But, the ratio of the dispersion to the polar factor is almost same as that of the protein loaded membrane showing that there may be presence of some BSA particles that remained unreleased from the membrane. This was also confirmed from the SEM pictures showing the presence of smaller aggregated protein structures.

4. Conclusion

We have successfully synthesized the amphiphilic system PDMS–PEG via hydrosilyation. Reactive epoxy groups were also introduced into this system to provide the reaction site for the protein. Solution casting method was adopted for preparing very thin membranes loaded with BSA. The composition of the PEG and PDMS in the amphiphilic system enables the solubility of BSA in the system for homogenous casting. The release profile of the BSA from the membrane was studied in the aqueous medium at pH 5.5, 7.0 and 8.5 and physiological saline at pH 7.6. The release was found to be continuous and controlled over a period of 72 h. A maximum of 50% release was observed with pH 7.6. In all these cases there was no initial burst observed which is considered to be a major advantage. This may be attributed to the aggregated protein structures formed by the chemical bonds via the epoxy ring cleavage. The protein released shows no change in their conformation. Tensile strength was found to be 1.42 MPa for the BSA loaded membrane. The SEM pictures confirmed the maximum loading capability and the mechanism of protein release. This was also confirmed by the surface analysis using contact angle measurements and confirmed the presence of protein structure at the surface. In view of the results, it could be confirmed that the possibility of the PDMS–PEG macromonomer as a transdermal drug delivery system has enormous advantages.

Acknowledgements

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