

Colloidal and Chemical Properties of Polyesters Based on Glutamic Acid and Diols of Different Nature

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(Received 28 June 2012; published online 08 August 2012)

The paper describes synthesis method and colloid-chemical properties of novel α -amino acid based polyesters with controllable hydrophilic-lipophilic balance. Glutamic acid and diols of different nature based polyesters were obtained via low-temperature activated polyesterification. Such polymers are able to form micellar structures in self-stabilized water dispersion. Solubilization of water insoluble dyes Sudan and toluene in polymer water solution was studied. Due to micelle forming ability and prognosticated biodegradability to non-toxic products, obtained polymers are promising materials for formation of novel dispersed drug delivery systems.

Keywords: Pseudo-poly(amino acid), Biodegradability, N,N'-dicyclohexylcarbodiimide, Polymer micelle, Solubilization, Surface tension, Drug delivery systems.

PACS numbers: 81.16.Dn, 82.35.Jk

1. INTRODUCTION

Biodegradable and biocompatible polymer materials with non-toxic degradation products are widely used for different biomedical applications. Hereby, development of new synthesis methods thereof becomes important scientific task.

Nature acid based polyesters have been used as synthetic suture materials [1] and biodegradable drug delivery systems [2] long before. In this work novel method of α -amino acid and its derivatives based polyesters is described. Control of hydrophilic-lipophilic balance (HLB) of polyesters via polypolyethylene and polyoxypropylene fragments introduction gives opportunity to form polymers able to self-assembly in core-shell micellar structure in water medium.

Due to amino acid bonding in main polymer chain via ester bond, such compounds refer to the pseudo-poly(amino acid) class- amino acid based polymers with non-peptide bond in main polymer chain. Such structure provides a set of advantages over nature occurring poly(amino acid)s, e.g. no immune response in recipient organism (due to the peptide bond absence), on the other hand, compatibility to the poly(amino acid)s structure provides biodegradability and low toxicity of polymers and degradation products thereof. Accordingly, such polymers are promising materials for formation of novel dispersed drug delivery systems.

2. SYNTHESIS OF POLYESTERS BASED ON GLUTAMIC ACID AND DIOLS OF DIFFERENT NATURE

Glutamic acid and diols of different nature based polyesters were obtained via low-temperature activated polyesterification, according to the Fig. 1. As activator of esterification reaction was used N,N'-dicyclohexylcarbodiimide known agent of carboxyl group activation. Reagent ratio in pseudo-poly(amino acid)s synthesis allows to control in this system poly-

condensation degree and terminal functional groups.

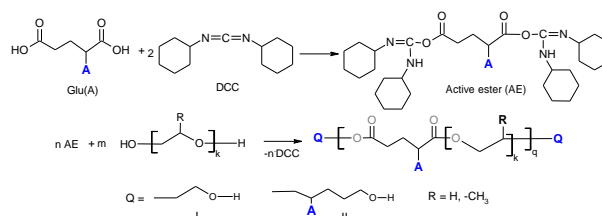
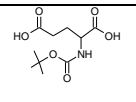
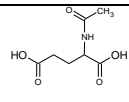
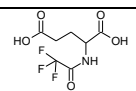
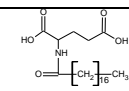


Fig. 1 – Synthesis of glutamic acid and diols based polyesters using coupling agent DCC

As amino group is more nucleophilic center than hydroxyl group, it was necessary to provide amino group protection. We optimized conditions of amino group blocking and deblocking, one can observe in Table 1 protective groups and N-derivatives of glutamic acid which were used in this work.

Table 1 – Protective groups and N-derivatives of glutamic acid

Tert-butoxycarbonyl protective group (Boc)		Acetyl protective group (Ac)	
Trifluoroacetyl protective group (TFA)		N-stearoyl glutamic acid	

Accept reaction of peptide bond formation, other side reactions influence on the reaction selectivity – cyclic esters formation and rearrangement of active ester according to fig.2.

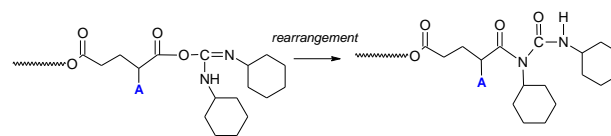


Fig. 2 – Rearrangement of active ester of glutamic acid and DCC to passive amide

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The running of these reactions was confirmed by mass spectroscopy. These reactions have significant effect on the polycondensation degree, but optimal process conditions for maximal suppression of these reactions were ascertained. Furthermore, it is well known [4], it's necessary to introduce nucleophilic additives in reaction mixture to achieve high conversion. On practice 4-dimethylaminopyridine (DMAP) is widely used. It turned more efficient in comparison with 1,4-diazabicyclo[2.2.2]octane (DABCO) and triethylamine.

Polycondensation was successfully conducted using N-stearoyl glutamic acid, glutamic acid with acetyl protective group and diols in the range of molecular mass 100-2000 Da. Polycondensation degree made 75-85% of maximal calculated one. Using glutamic acid with tert-butoxycarbonyl protective group, we obtained polyesters with polycondensation degree 1-3. We didn't succeed to obtain polyesters based on ethyleneglycol and propyleneglycol, the same as we didn't obtain polymers with terminal carboxyl groups (fig. 1, Q=I). The first can be explained by high probability of cyclization reaction for these alcohols. The second – by side reaction of rearrangement of active ester, therefore the reaction should be conducted in the condition of alcohol excess.

Hereby, developed method was used for synthesis of polymers, containing hydrophilic (polyethyleneglycol) and lipophilic (polypropyleneglycol and N-stearoyl glutamic acid) fragments. Hydrophilic-lipophilic balance of such polymers can be controlled by different fragments ratio and polyethyleneglycol and polypropyleneglycol molecular mass. Polymer structure was confirmed by NMR- and IR-spectroscopy, molecular mass was determined by gel-penetrative chromatography.

3. SURFACE-ACTIVE AND COLLOIDAL PROPERTIES OF GLUTAMIC ACID BASED POLYESTERS

Colloidal and chemical properties of obtained polyesters strongly depend on their composition. Thus polyesters co-Glu(HCl)-co-PEG or co-Glu(HCl)-co-PPG (these polyesters are formed after co-Glu(Boc)-co-PEG and co-Glu(Boc)-co-PPG deblocking, molecular mass of PEG and PPG – 100-600 Da) are water soluble. Water solutions of such polymers don't possess colloid-chemical properties even at high polymer concentration.

Co-Glu(St)-co-PEG or co-Glu(St)-co-PPG type polymers with the same molecular mass of PEG and PPG are water insoluble, they are not able to form stable self-stabilized dispersions in water and haven't ability to decrease surface tension on water-air interface. Only co-Glu(Ac)-co-DEG (synthesized via polycondensation of Glu(Ac) and diethyleneglycol (DEG)) among this type of polymers shows significant surface activity and self-stabilized water dispersions. This copolymer forms stable water dispersion with surface tension 47-49 mN/m. The last demonstrates that surface-active properties and properties of water dispersion self-stabilization can be achieved via hydrophilic/lipophilic fragments ratio in polymer chain. In this work polyesters with necessary properties were obtained due to forming of polymers with complex architecture. Thus Glu(St) based polyesters were obtained using mixture of equal molar quantities of PEG and PPG of different molecular mass as diol (Fig. 3).

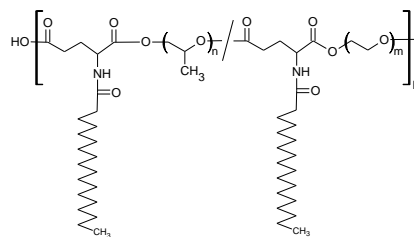


Fig. 3 – Schematic structure of polyester synthesized via polycondensation of Glu(St) and mixture of equal molar quantities of PEG and PPG

Two different diols and their part in macromolecule structure were confirmed by NMR-spectroscopy. Large majority of polyesters with different diols possess ability to form self-stabilized water dispersion. Such polyesters show higher surface activity than polyester molecules with one type of alcohol (fig. 4).

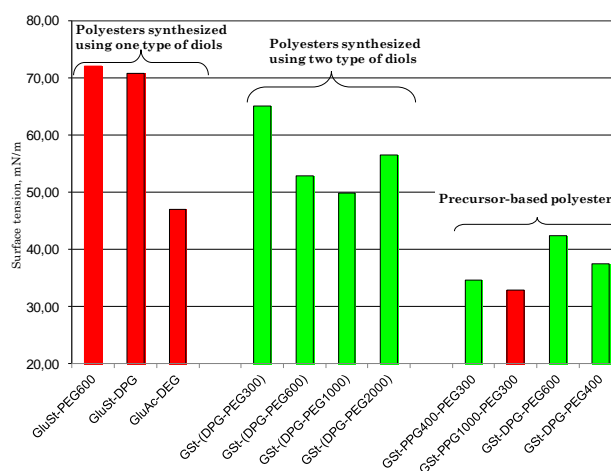


Fig. 4 – Surface-active properties of polyesters synthesized via different methods

Though, entering of diols of different structure in polymer macromolecule is not equivalent, it leads to irregular block structure and significant nonuniformity of functional distribution. In this case control of surface-active and colloidal properties of polyesters with different fragments is realized incompletely. In this case, should expect that regular sequence of blocks of different nature allows to achieve higher surface activity. Polyester synthesis with regular block sequence conducted via prior precursor synthesis with the following structure:

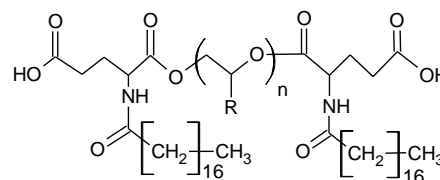


Fig. 5 – Structure of precursor used for polyester synthesis with regular block sequence. In the case R=H – Glu(St)-PEG-Glu(St), R=CH₃ – Glu(St)-PPG-Glu(St)

Synthesized precursors according to their nature are dicarboxylic acids consisting of glutamic acid residue bonded by polyoxypropylene (polyoxyethylene)

chains with different molecular mass. Such precursors were used for polyester synthesis according to the scheme on Fig. 1 instead of glutamic acid or its derivatives. NMR-spectroscopic study confirmed precursors structure and showed that 83-87% of portal carboxyl groups are γ -carboxyl groups. It facilitates reaction in comparison with glutamic acid or its derivatives due to the carboxyl group reactivity equalization. For pseudo-poly(amino acid)s synthesis we used precursors with PPG in the range of molecular mass 130-1000 Da. Obtained polyesters have the same structure as polyesters synthesized using mixture of equal molar quantities of PEG and PPG, but differ by strict regular structure. This fact was confirmed by NMR-spectroscopy. As expected, polyesters with regular molecules structure possess more strongly pronounced surface-active properties (Fig. 4). Moreover, conducted studies show that majority of precursor-based polymers have complex type of surface tension isotherm with strongly pronounced two breaking points (Fig. 6).

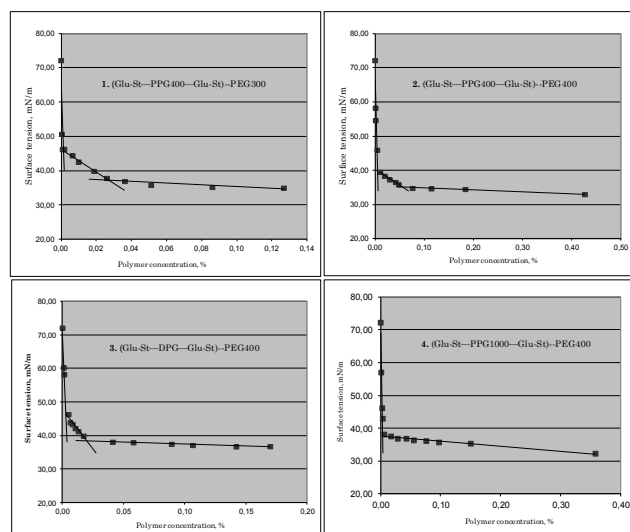


Fig. 6 – Surface tension curves of selected precursor-based polyesters

The first breaking point (starting from coordination zero) has to be considered as critical micelle concentration (CMC) (CMC values of few polymer samples are given in Table 2).

Table 2 – Selected characteristics of precursor-based polyesters

No	Polyester based on (Glu-St-DPG-Glu-St) precursor	CMC ₁ %	CMC ₂ %	Molecular mass (according to GPC)	HLB
1	Glu-St-DPG-Glu-St-PEG400	0,0042	0,0337	2980	9,4
2	Glu-St-DPG-Glu-St-PEG600	0,0051	0,0532	3405	13,7

Precursor-based polyesters form self-stabilized polymer dispersions with unimodal nanometer disperse phase distribution at negligibly higher concentration than CMC (Fig. 7.)

Polymer concentration increasing in water dispersion leads to complex but organized dispersed phase rearrangement. This fact is displayed by the second breaking point on the surface tension isotherm curve. Furthermore, particle size distribution curve also has dependence on the polymer concentration (Fig. 7). Presented data shows some average diameter increase of dispersed phase first mode with polymer concentration increase. Simultaneously, one can observe formation of the second mode particles (approaching the second breaking point concentration on the surface tension isotherm curve) and the third mode particles formation at the concentration higher than the second breaking point concentration on the surface tension isotherm curve.

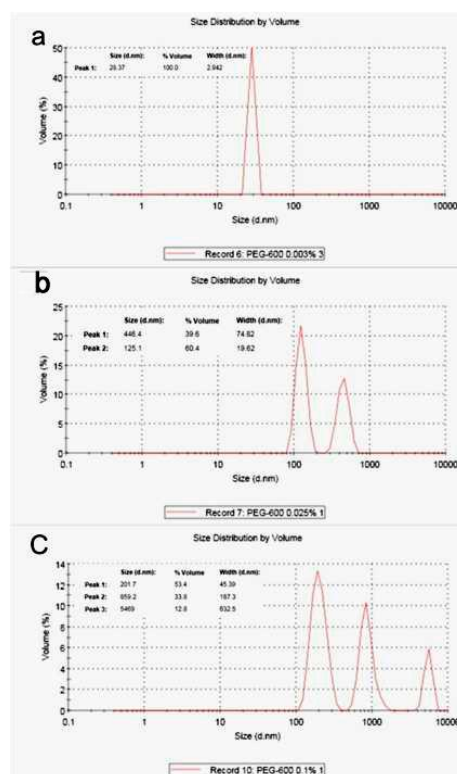


Fig. 7 – Characteristic distribution curve obtained using DLS method

The character of particle distribution changing indicates on the formation of disperse phase particle of complex structure with regions of different properties due to the hydrophilic and lipophilic fragments in polyester molecules. This conclusion is confirmed by solubilization curves of insoluble organic substances. Toluene and sudan (III) solubilization curves is presented on Fig. 7.

Noticeable solubilization of sudan is observed under CMC. As about toluene solubilization – it can be observed at concentration higher than the second breaking point concentration on the surface tension isotherm curve. Thus, regions able to solubilize toluene in disperse phase can be formed at concentration higher than the second breaking point concentration on the surface tension isotherm curve. One can observe disperse phase particle formation of the second and third mode on the size distribution curve.

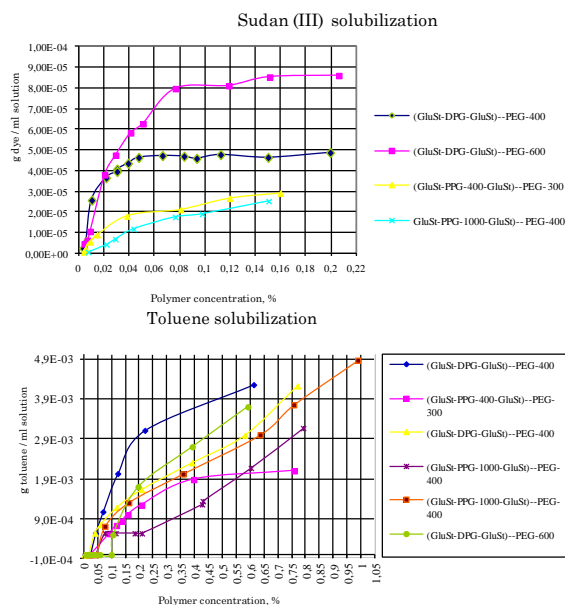


Fig. 8 – Curves of toluene and water insoluble dye Sudan (III) solubilization

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4. CONCLUSIONS

Novel polyesters based on glutamic acid (or its derivatives) and diols of polyoxyethylene/ polyoxypropylene type were synthesized. Developed technique allows to obtain polyester with different hydrophilic-lipophilic balance using the ratio of hydrophilic/lipophilic fragments in polyester molecules. The structure and composition of synthesized polymers were confirmed using NMR, IR-spectroscopy, molecular mass was settled via gel-penetration chromatography. Such polyester poses surface-active properties, and are able to form self-stabilized water dispersion. These dispersions solubilize water insoluble compounds. Thus obtained polyesters are promising materials for formation of dispersed drug delivery systems.