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Title Page

Injectable pasty biodegradable polyesters derived from castor oil and hydroxyl-acid lactones

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Running Title Page

Pasty biodegradable polyesters and polycarbonates

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Abstract

Pasty polymers offer a platform for injectable implants for drug delivery. A library of biodegradable pasty polymers was synthesized by bulk ring opening polymerization of lactide, glycolide, trimethylene carbonate or caprolactone using castor oil or 12-hydroxy stearic acid as hydroxyl initiators and stannous octoate as catalyst. Some of the polymers behaved as Newtonian liquids. Pasty polymers of poly(caprolactone) and poly(trimethylene carbonate) were stable under physiological conditions for over one month *in vitro*, whereas polymers of poly(lactic-*co*-glycolic acid) degraded within ten days. These pasty polymers offer a platform for pasty injectable biodegradable carriers for drugs and fillers.

Significance Statement

New injectable pasty, in situ forming drug delivery systems are described and are advantageous due to their ease of administration, tuneable viscosity and biodegradability. Polyesters based on lactide, glycolide, trimethylene carbonate and caprolactone, commonly used as absorbable implants and drug carriers, were conjugated onto natural hydroxyl fatty acids. These polymers have potential use as wrinkle fillers and drug carriers.

Introduction

Biomaterials have made an enormous beneficial impact on human healthcare as tissue engineering scaffolds and drug delivery systems (Prestwich and Luo 2001, Ulery, Nair et al. 2011, Ramot, Haim-Zada et al. 2016). The design of biomaterials for specific biomedical applications has rapidly expanded during recent years. (Basu, Haim-Zada et al. 2016, Lei, Guo et al. 2018, Ning, Zhou et al. 2018, Recek 2019). Drug delivery platforms in particular have been developed as ubiquitous and integral contributors to modern medicine. Their continued development is therefore of paramount importance.

Drug delivery systems often comprise biodegradable polymers that may be employed as drug carriers in the human body (Doppalapudi, Jain et al. 2014). Poly(caprolactone), poly(trimethylene carbonate), and poly(lactic-*co*-glycolic acid) are examples of safe polymers with varying degrees of hydrophilicity and hydrophobicity that each display unique mechanical properties and patterns of hydrolytic or enzymatic degradation based on the chemical linkages along the polymer backbone (Chen, Qi et al. 2018, Duval, Rahouadj et al. 2018, Spearman, Irin et al. 2018, Zhang, Arceneaux et al. 2018), allowing for the fine-tuning of polymers for a given delivery system.

A significant *in vivo* drawback of hydrolytically degradable polymers stems from the high acidity of the degradation products {Fu 2000}. The acidic microenvironment may lead to the degradation of encapsulated therapeutic material, especially in the delivery of proteins {Estey 2006}. Thus, the development of hydrophobic polymers with less acidic degradation products, released over a longer time, is expected to minimally reduce the local pH during degradation.

Drug-eluting injectable polymer implants offer an effective route of localized drug administration (Exner and Saidel 2008). Drugs may be incorporated into the implant

and injected in order to effect highly localized delivery with minimal invasion and highly predictable rates of drug release. Highly viscous, or pasty, injectable polymers offer the distinct advantage of immobility post-injection (Krasko, Golenser et al. 2007), releasing a drug at a defined rate at the desired site of delivery. Hence, the development of pasty, biodegradable, and biocompatible polymers is of utmost importance.

We present here a library of pasty, biocompatible, and hydrolytically degradable injectable polymers based on castor oil and 12-hydroxystearic acid for potential use as drug-eluting implants (**Fig. 1**).

Materials and Methods

Materials

Castor oil was obtained from Tamar Pharma (Jerusalem, Israel). 12-Hydroxystearic acid was purchased from Holland Moran (Yehud, Israel). Trimethylene carbonate was purchased from Richman Chemical (Lower Gwynedd, PA). D,L-Lactide and glycolide were purchased from Purasorb, Purac (Gorinchem, Netherlands). Ɛ-Caprolactone was purchased from Tzamal D-Chem (Petach Tikva, Israel). Stannous octoate was purchased from Sigma–Aldrich (Jerusalem, Israel). All solvents were of analytical grade from Biolab (Jerusalem, Israel).

General Methods

Chemical reactions were performed in oven-dried glassware under N_2 gas. ^{1}H and ^{13}C NMR spectra were obtained on a Varian 300 MHz spectrometer with $CDCl_3$ as solvent and tetramethylsilane as shift reference. Molecular weights (MW) of the polymers were estimated using a gel permeation chromatography (GPC) system consisting of a Waters 1515 isocratic HPLC pump with a Waters 2410 refractive index detector and a Rheodyne (Coatati, CA) injection valve with a 20 μL loop (Waters, Milford, MA). Samples were eluted with $CHCl_3$ through a linear Styragel HR4E column (Waters; 7.8 mm I.D. × 300 mm) at a flow rate of 1 mL/min. The molecular weights were determined relative to polystyrene standards (Polyscience, Warrington, PA) using a Breeze computer program. Mass spectrometry electrospray ionization (MS-ESI) was recorded on a ThermoQuest, Finnigan LCQ-Duo instrument in positive ionization mode. FTIR analysis was performed using a Smart iTR ATR sampling accessory for Nicolet iS10 spectrometer with a diamond crystal.

Synthesis

Pasty polymers were prepared by ring opening polymerization (ROP) of Ɛ-caprolactone (CL), trimethylene carbonate (TMC) or D,L-lactide and glycolide (LA, GA) by either castor oil (CO) or 12-hydroxystearic acid (HS) in the melt in the presence of stannous octoate catalyst. A sample synthesis was as follows: 50 μL of a 0.33 g mL^{-1} solution of stannous octoate in dichloromethane was added to a melt of CO (0.65 g, 0.70 mmol) and TMC (2.1 g, 21 mmol) purged with N_2. Solvent was allowed to evaporate and the vial was purged again with N_2. The mixture was stirred at 150 °C overnight to afford CO:PTMC (**9**).

Six polymer series were synthesized by choosing one fatty acid initiator (CO or HS) and one monomer set (CL, TMC or L+G) and performing ROP in the melt. Individual polymers within the series were synthesized by modifying the relative amounts of initiator and monomer in the melt. L and G were added in a 6:1 molar ratio (Steinman, Haim-Zada et al. 2019).

Rheological Studies

Polymers' viscosities were measured on a Physica MCR 101 rheometer. Samples were measured at shear rates from 0.01 to 100 s^{-1} at 25 °C.

Degradation Studies

Polymers (50 mg) were loaded into an ampule and covered with 5 mL of 0.1 M phosphate-buffered saline solution (PBS, pH 7.4). The ampule was shaken at 37 °C for two months. Media were exchanged for fresh PBS at regular intervals (1, 5, 10, 23, 29, 57 days) to avoid solution saturation and checked for small molecules by MS-ESI. When medium was exchanged, polymers were weighed after drying to determine weight loss.

Results

Synthesis of pasty polymers

Viscosity and degradation of polymeric substances are influenced by both molecular makeup and polymer molecular weight (MW) (Colby, Fetters et al. 1987, Park 1994). In order to obtain a significant variety of polymer viscosities and degradation profiles, six series of hydrolytically degradable pasty polymers were synthesized via ring-opening polymerization (ROP) with either castor oil (CO) or 12-hydroxystearic acid (HS) as fatty acid initiator (**Scheme 1**). We chose these fatty acids due to their biocompatibility and prior use in drug delivery (Teomim, Nyska et al. 1999, Shelke, Sairam et al. 2007), and also due to the presence of hydroxyl groups available for ring opening polymerization initiation. Polymers of poly(caprolactone) (PCL), poly(trimethylene carbonate) (PTMC), or poly(lactic-*co*-glycolic acid) (PLGA) were prepared at the reactive hydroxyl positions of each fatty acid, affording a total of six polymer series. These polymers were selected based on their established use as biodegradable polymers for drug delivery, known degradation profiles and varying mechanical properties so as to afford a variety of delivery systems with varying viscosities, degradation rates, and flow behaviour. Six unique polymer series were prepared by varying the cyclic monomers and hydroxyl fatty acids employed in the reaction mixture (**Table 1**). Reaction yields were all quantitative, as homogeneous polymers were obtained without need for purification steps after ROP was performed in the melt in the presence of stannous octoate catalyst (**Fig. 2**).

Characterization of pasty polymers

Each polymer series (I-VI) was prepared in various MW by modifying fatty acid initiator:monomer feed ratios. Mw were estimated by gel-permeation chromatography

(GPC), and fatty acid:polymer ratios as well as true Mn values were calculated by comparing relative ^{1}H NMR peaks of fatty acids and polymers (**Table 2**).

Formation of pasty polymers was confirmed spectroscopically by ^{1}H NMR and infrared (IR) spectroscopy. Ester and carbonate linkages were visualized along the polymer backbone by characteristic strong C=O bends ranging between 1746-1723 cm^{-1}. Below is an example of the spectroscopic characterization of the highest viscosity polymer of each series by IR spectroscopy. ^{1}H NMR spectra are available as supplementary information (Supplemental Figures 1-19).

IR

IR spectroscopy showed the decreasing intensity of the OH bands in fatty acid starting materials (3377 cm^{-1} in CO, 3188 cm^{-1} in HS) and the simultaneous appearance of characteristic strong C=O bands in pasty polymers. CO is a natural triglyceride with a characteristic strong ester C=O band at 1743 cm^{-1}. CO-based polymers (**1-11**) displayed new C=O bands with the polymeric carbonyls overlapping the ester bands from the starting material. HS-based polymers (**12-19**) also displayed appearance of characteristic strong C=O bands between 1746-1724 cm^{-1}. This was consistent with the terminal OH groups of fatty acids (CO or HS) having been converted to ester/carbonate bonds in pasty polymers (**Fig. 3**).

Viscosity Studies

Polymers' viscosities were measured under increasing shear rates. As MW increased within a polymer series, viscosity increased dramatically (**Table 2**). Any further increase in MW than what is reported here resulted in solid polymers, unsuitable for injectable drug delivery implants. All polymers were injectable through a 23G syringe.

Degradation Studies

Hydrolytic degradation under physiological conditions of the pasty polymers were determined. A slow rate of degradation may allow for controlled release of drugs over a significant time period, while faster degradation profiles may allow release of high levels of drug concentration over a shorter time period (Hatefi and Amsden 2002). A significant variety of polymer degradation profiles is therefore desirable, allowing fine-tuning for the desired application.

The highest MW (and hence most viscous) pasty polymer of each series was loaded into an ampule and covered with PBS (pH 7.4) at 37 °C. PLGA polymers (series III and VI) displayed rapid degradation, with only 30% weight retention after 10 days. PTMC polymers (series II and V) degraded at similar slow rates, with over 80% weight retention after 29 days and over 55% weight retention after 57 days. PCL polymers (series I and IV) also degraded slowly, although CO:PCL [I] degraded at the slowest rate (over 96% weight retention through 29 days, 78% through 57 days), while HS:PCL [IV] displayed 73% weight retention through 23 days before rapid weight loss (**Fig. 5**).

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Discussion

Biocompatible and biodegradable drug-eluting implants are essential for drug delivery (Exner and Saidel 2008, Wolinsky, Colson et al. 2012, Water, Bohr et al. 2015, Sharma, Concagh et al. 2018). Pasty polymers derived from natural fatty acids and biocompatible polymers offer the potential of acting as injectable, depot-forming implants with incorporated drugs for localized drug delivery (Krasko and Domb 2007, Krasko, Golenser et al. 2007). Ideally, an implant should be injectable, viscous enough that it maintains its localization and integrity throughout the therapeutic time frame, biocompatible to prevent unwanted side effects, biodegradable so that no post-injection implant removal would be necessary, and permeable to allow for controlled release of therapeutic material over an extended time frame. Furthermore, polymer degradation should be tuned for the desired drug release profile (Ickowicz, Abtew et al. 2016).

We present here six series of pasty polymers comprised of natural fatty acids (CO, HS) and biocompatible, hydrolytically-degradable polymers (PCL, PTMC, PLGA). Each series was synthesized in a variety of initiator:monomer ratios to afford a range of polymer MW. As polymer content was increased relative to fatty acid initiator, polymers displayed dramatic increases in viscosity (**Fig. 4**).

Viscosity and Degradation Studies

Castor oil is a low viscosity fluid that permits intramuscular injections (Behre, Abshagen et al. 1999). Biodegradable and biocompatible polymers PCL, PTMC and PLGA are all solids at physiological temperatures, and therefore may only be injected in particle dispersions, preventing their use as templates for injectable drug delivery depots (Weiniger, Golovanevski et al. 2012). Consequently, we used castor oil as a polymerization initiator of PCL, PTMC and PLGA in order to afford a platform of pasty

polymers that may be applied as injectable delivery systems. We prepared similar polymers with 12-hydroxystearic acid, a solid hydroxyl fatty acid, as the initiator for lactone polymerization. Polymerization initiated by 12-hydroxystearic acid yielded pasty materials with low MW, and so may be referred to as pasty oligomers.

CO:PLGA polymer (series [III], **11**) displayed the lowest viscosity as well as the most rapid degradation profile, consistent with low MW PLGA which is known to degrade quickly in aqueous media (Anderson and Shive 1997). Higher MW PLGA polymers with slower degradation rates were solid and thus unsuitable as injectable drug delivery implants. HS:PLGA oligomer (series [VI], **19**) displayed higher viscosity and slower degradation than CO:PLGA, and so it may be considered as a platform for drug release over several days. CO:PTMC (series [II], **9**) and HS:PTMC (series [V], **16**) each displayed great potential for application as in situ drug-eluting implants due to their high viscosities and slow rates of degradation. These polymers were slow to degrade due to the increased hydrolytic stability of the carbonate bond along the PTMC chain (Yang, Liu et al. 2010), and their injectability, high viscosity and pastiness provide excellent platforms for drug-eluting implants.

HS:PCL oligomer (series [IV], **14**) displayed high viscosity and hydrolytic stability for up to 23 days. The oligomer did not, however, maintain pasty integrity, as it formed oily globules in aqueous media.

The polymer with the highest potential for *in vivo* application as a polymeric drug-eluting implant was CO:PCL (series [I], **4**). It exhibited a viscosity of 1.1 x 10^4 Pa·s and presented as a thick paste that also maintained injectability even at MW of 8.2 kDa. Furthermore, the polymer displayed hydrolytic stability for over one month while maintaining its pastiness. Due to polymer composition (>20% castor oil or 12-

hydroxystearic acid) and its slow degradation, the local pH during degradation should be higher than unmodified polymer degradation.

Flow Behaviour

Injectable polymeric drug delivery depots should possess, in addition to biocompatibility and biodegradability, a low viscosity at time of injection and high viscosity *in situ* so that the polymer may remain affixed at the injection site and slowly release the loaded drug. It is thus highly desirable for a polymer implant to display non-Newtonian pseudoplastic behaviour so that it may undergo shear-thinning, aiding in the ease of injectability while maintaining its high viscosity *in situ* (Guvendiren et. al. 2012). The high performance of CO:PCL (**4**) in this regard is therefore advantageous. At low shear rate, (0.1 s^{-1}), the polymer exhibits high viscosity. Under high shear rate (68 s^{-1}), however, this viscosity dropped by three orders of magnitude (**Fig. 4, I)**. This dramatic shear-thinning, in addition to the slow hydrolytic degradation of the polymer, offers an encouraging platform for a pasty polymer for localized drug delivery.

Conclusions

We report on the synthesis of six series of pasty polymers based on hydroxyl fatty acids (Castor oil, 12-hydroxystearic acid) and common biocompatible and biodegradable polymers (PCL, PTMC, PLGA). Several polymer MW of each series were synthesized by modifying the fatty acid initiator:monomer feed ratios, and polymer viscosity was shown to increase with increasing MW. The highest viscosity polymer of each series formed pasty, injectable, and hydrolytically degradable depots in aqueous media. Some polymers displayed non-Newtonian pseudoplastic flow behaviour, adding a crucial element of ease of injectability while forming hard semi-solids *in situ*. This new class of polymers offers potential use as carriers for hydrophobic drugs as localized,

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injectable polymer implants. The polymer carrier is biodegradable and should eliminate from the body after the drug has been depleted. The fatty acid components of the polymers should reduce the severity of the acidic microenvironment produced upon polymer degradation, as fewer acidic units are released per polymer chain degraded. This feature should support the delivery of acid-sensitive therapeutic materials, particularly proteins.

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Authorship Contributions

Participated in research design, performed experiments: Steinman, Noam Y.

Analysed results: Steinman, Noam Y. and Domb, Abraham J.

Wrote or contributed to the writing of the manuscript: Steinman, Noam Y. and Domb, Abraham J.

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Legends for Figures

Figure 1. Biodegradable pasty polymers may be injected through a syringe. These injectable polymers have the potential to be incorporated with drugs and used as site-specific drug-eluting implants.

Figure 2. Preparation of polymers from secondary alcohols on castor oil or 12-hydroxystearic acid. The cyclic monomers used were Ɛ-caprolactone, trimethylene carbonate, or a 6:1 molar ratio of D,L-lactide and glycolide.

Figure 3. FT-IR spectra of pasty polymers confirmed polymerization. Characteristic C=O bands between 1746-1723 cm^{-1} were observed for polymers, as well as the disappearance of the characteristic hydroxyl bands in CO and HS.

Figure 4. Viscosity was measured at varying shear rates. Polymers with the highest MW were the most viscous. Any further increase in MW resulted in solid polymers.

Figure 5. Hydrolytic degradation of pasty polymer in each series [I]-[VI], determined in phosphate buffer pH 7.4 at 37 °C. Weight loss was determined by drying the sample at each time point to determine the weight of the polymer.

Tables

Table 1. Six series of polymers were synthesized, each with its own fatty acid:polymer pair.

Initiator	**Polymer**	**Series ID**
CO	PCL	(I)
CO	PTMC	(II)
CO	PLGA	(III)
HS	PCL	(IV)
HS	PTMC	(V)
HS	PLGA	(VI)

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Table 2. MW and fatty acid:polymer ratios of all polymers within series [I]-[VI] (**Table 1**)

Entry	Series[a]	Initiator:Polymer (w/w)[b]	Mw (kDa)[c]	Mn (kDa)[b]	Viscosity (Pa·s)[d]	Flow Behaviour[e]
1	(I)	71:29	3.0	1.3	0.13	Newtonian
2	(I)	60:40	5.0	1.6	25	Pseudoplastic
3	(I)	41:59	6.1	2.3	81	Pseudoplastic
4	(I)	30:70	8.2	3.1	1.1*10^4	Pseudoplastic
5	(II)	80:20	2.7	1.2	1.2	Newtonian
6	(II)	68:32	3.1	1.4	1.6	Newtonian
7	(II)	56:44	3.8	1.7	2.8	Newtonian
8	(II)	44:56	4.4	2.1	7.4	Newtonian
9	(II)	23:77	7.2	4.0	63	Newtonian
10	(III)	92:8	1.9	1.0	0.92	Newtonian
11	(III)	69:31	2.6	2.3	2.8	Newtonian
12	(IV)	60:40	3.2	0.50	17	Pseudoplastic
13	(IV)	50:50	3.5	0.61	33	Pseudoplastic
14	(IV)	41:59	4.2	0.74	2.5*10^2	Pseudoplastic
15	(V)	46:54	3.2	0.65	3.0	Newtonian
16	(V)	24:76	5.8	1.3	35	Newtonian
17	(VI)	66:34	2.1	0.46	27	Newtonian
18	(VI)	56:44	2.2	0.53	5.7	Newtonian
19	(VI)	43:57	2.7	0.70	27	Newtonian

[a]Series number according to data in **Table 1**.

[b]The relative amounts (w/w) of fatty acid initiator and polymer as well as true polymer Mn values were calculated from relative ^{1}H NMR peaks of either component.

[c]Mw was estimated by GPC relative to polystyrene standards and is reported in kDa.

[d]Viscosity at shear rate 0.1 s^{-1}.

[e]Flow behaviour from shear rate 0.1 to 100 s^{-1}.

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Figures

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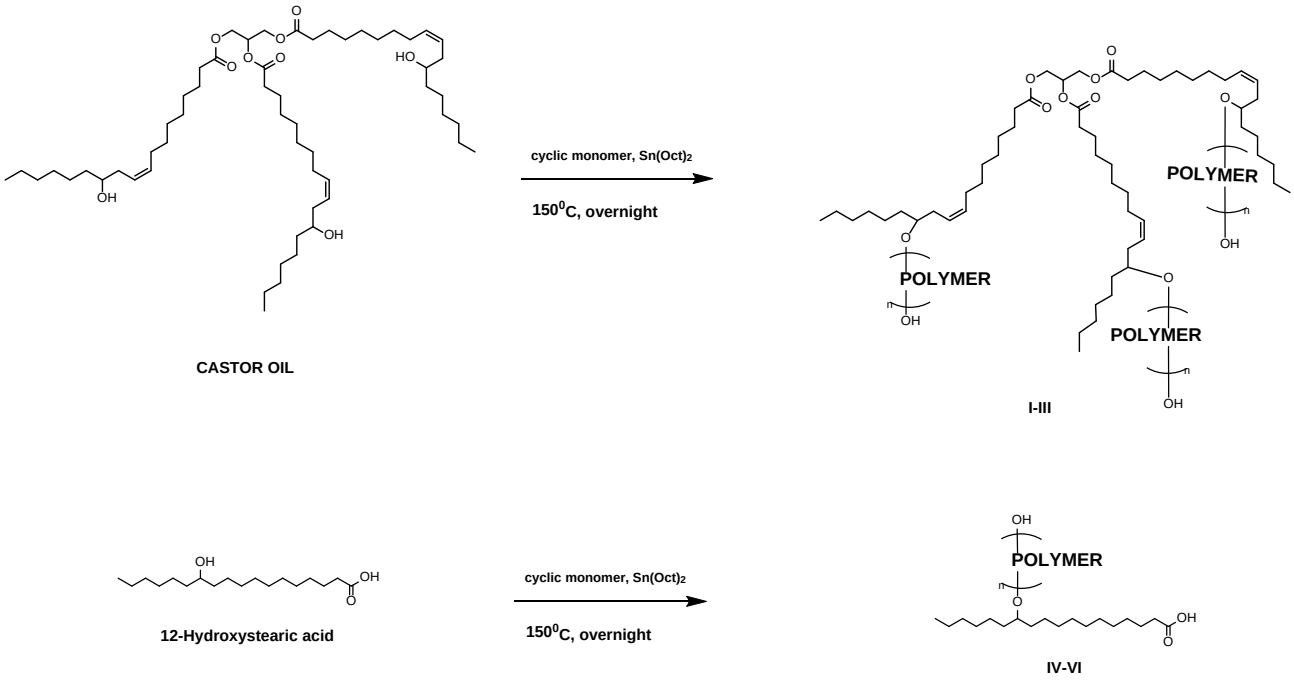

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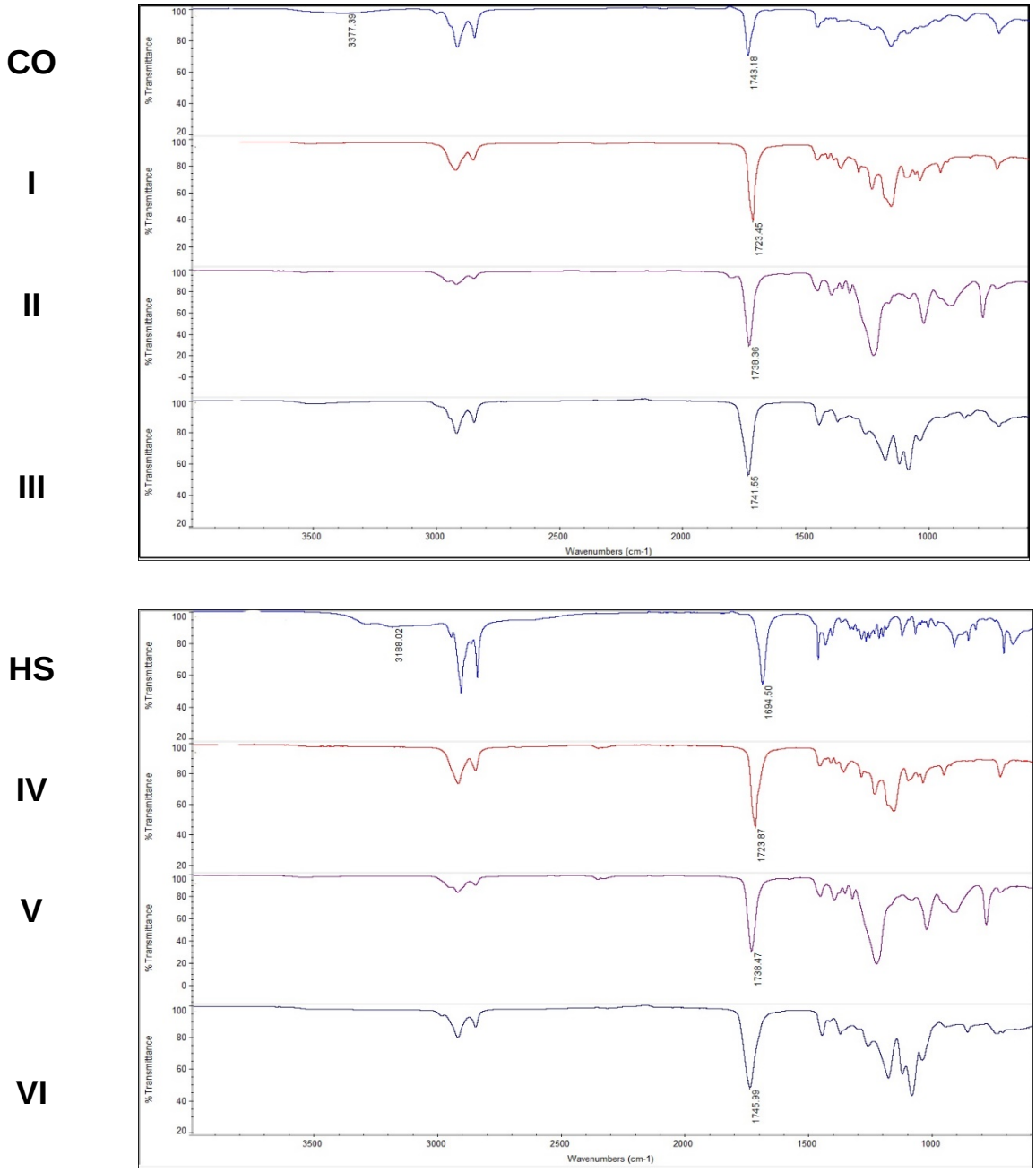

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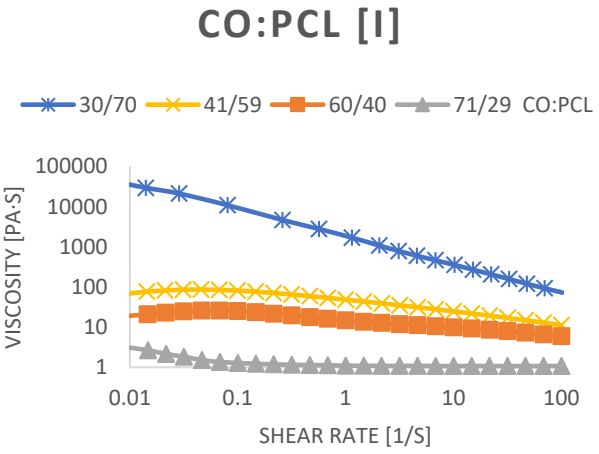

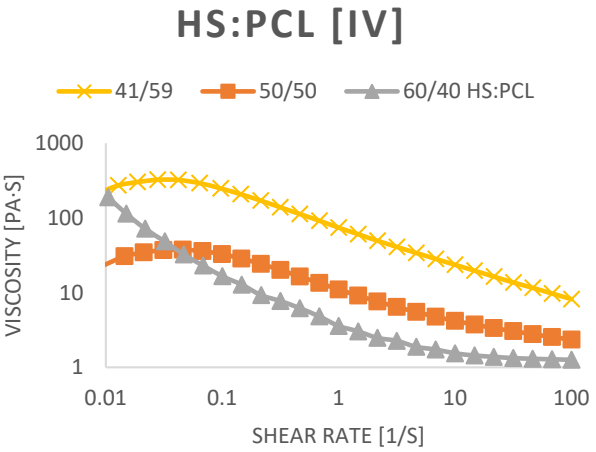

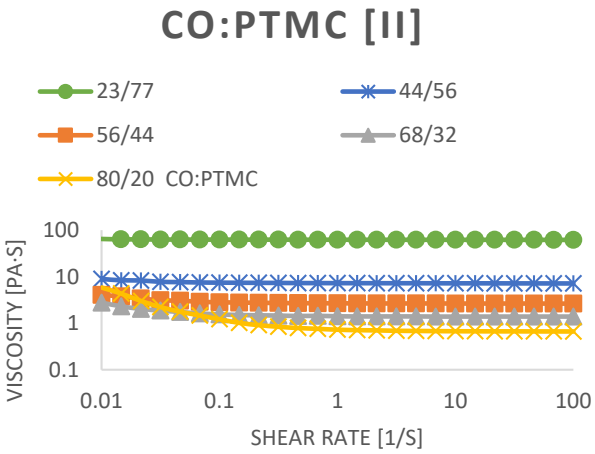

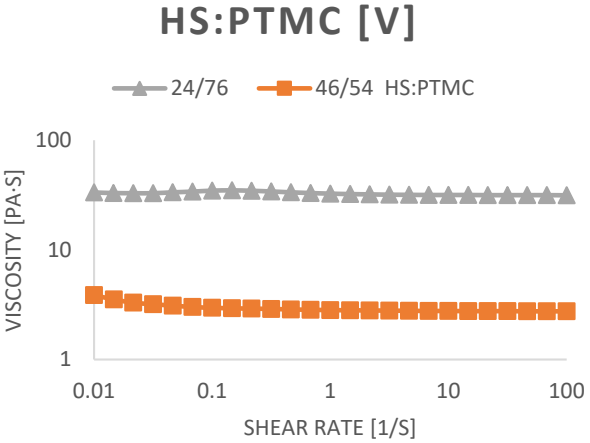

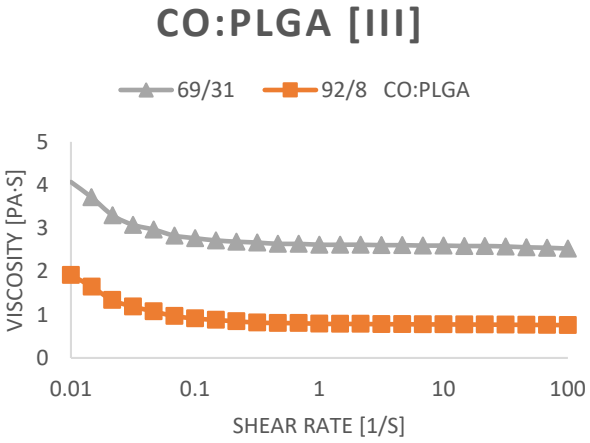

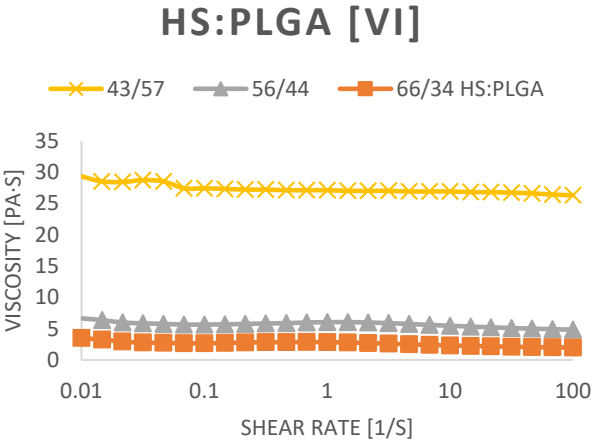

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