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Synthesis and characterization of polydi(3,4-dihydro-2H-pyran-2-methyl) adipate hydrogel

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Summary
Di(3,4-dihydro-2H-pyran-2-methyl) adipate was synthesized and polymerized using different cationic initiators. The obtained polymers have been found to be both low molecular weight and water soluble. The polymeric samples were also characterized and their thermal stability was investigated. Such polymers can be considered as suitable matrices for controlled drug delivery by in-vivo biodegradation.

Introduction

It has been previously reported that some polymers made from polyols and molecules containing two or more 3,4-dihydro-2H-pyran groups were used for industrial applications to develop a variety of drug delivery devices (1-3). They had some initial problems with hydrolytic stability of the products from polyols and other vinyl ethers. Such problems have been overcome (4). Afterwards, related systems have been reported by Heller et al (5,6). On the other hand, the preferable drug delivery systems at a constant rate would be a monolithic tablet or implant. Into such systems the drug was dissolved or dispersed to provide a safe containment of the drug so that dose-dumping, by breakage of the tablet, implant or monolith, is not possible (7). The present work is aiming to synthesize and predict the possibility to use the title polymer as controlled drug delivery hydrogel. This prediction was based on the change in the glass transition temperature that is greatly influencing the permeability. Also the ease of hydrolysis of the adipate polymer resulted in need for short time to excrete its metabolites from the body.

Results and discussion

Polyethylene glycols and polyethylene oxide based hydrogels were extensively prepared and commercially produced. They have found clinical applications as drug delivery devices and wound healing (8). The crosslinking of polyethylene glycols to produce biodegradable hydrogels has been accomplished by their reaction with 3,4-dihydro-2H-pyran-2-methyl (3,4-dihydro-2H-pyran-2-yl-carboxylate) (8,9). The pyranyl monomer forms a gelled network in a ferric chloride catalyzed reaction with polyethylene glycol and 1,2,6-hexanetriol. The polymers can biodegrade by hydrolysis of the in-chain ester and glycosidic groups but can also be made in hydrolytically stable formulations. The hydrolytic stability of these polymers is determined by: a) the ease of hydrolysis of the ester or acetal groups in the polymer backbone or network and, b) the solubility of water in the polymer (10). In

the present work, di(3,4-dihydro-2H-pyran-2-methyl) adipate was polymerized in presence of three different cationic initiators, namely, complex system of boron trifluoride and diethyl ether ($BF_3.O(C_2H_5)_2$); anhydrous ferric chloride ($FeCl_3$) and p-toluene sulphonic acid (p-TSA). The polymerization solvent was chosen according to a previously reported kinetic study (11). It is reported there, that the polymerization would not go on at all in ether due to the formation of a solvated cation that is too stable to propagate. It is also reported that the polymerization rate increased with increasing dielectric constant of the solvent used(11). Therefore, dichloromethane was used as solvent in the present work. In another work, it is reported that the mechanism of breakdown and clearance of biodegradable matrices from the body is very important and an accumulation of non-degraded polymer in the body is to be avoided. For instance, continued injection of insulin in aqueous polyvinyl pyrolidone over many years caused polyneuropathy. The polymer was of higher molecular weight than would now be considered acceptable (12). Thus, the low molecular weight polymers are preferable to use as by in-vivo biodegradable controlled drug delivery polymers. In our case, the adipate polymer was synthesized under the same conditions except for the type of the initiator used. It is obvious that the used initiators affect the molecular weight of the obtained polymer and can be arranged according to this effect in the order of $BF_3.O(C_2H_5)_2$> $FeCl_3$> p-TSA. It is noticeable also that in all cases, the polydispersity index determined by GPC is slightly higher than unity indicating that the obtained polymers have a narrow molecular weight distribution (exp. part). Such narrow dispersion networks are helping to produce precisely defined networks. This would reflect its effect on the drug diffusion process for instance. On the other hand, the glass transition temperature (Tg) is an important factor affecting the diffusion process. Such process occurs by movement of the diffusate into the molecular size holes present in the polymer and known as free volume. The free volume increases significantly with increasing temperature above Tg. It would be expected that an increase of Tg in a polymer will reduce its permeability. It is generally assumed that the incorporation of water into a hydrogel increases permeability and this is compatible with a decreasing Tg(7). The amount of water incorporated into a hydrogel designated as swelling degree depend mainly on the chemical structure of such hydrogels (13). The crystalline melting points determined by DSC for polymer samples IVa,b,c were found to be decreased with increasing the molecular weight of the polymer (Figure 1: 174,182 & 190 K, respectively).

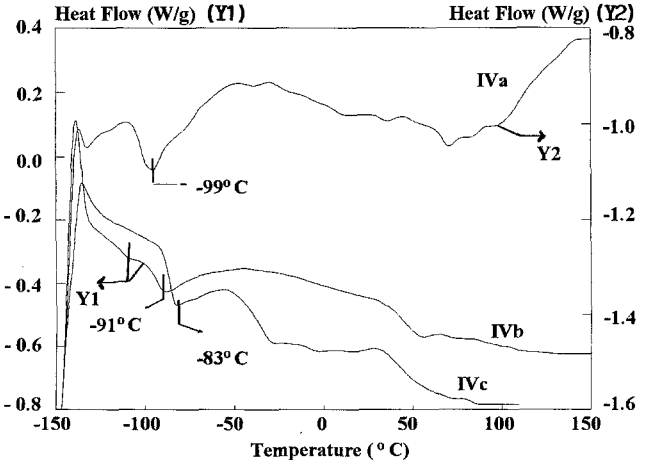
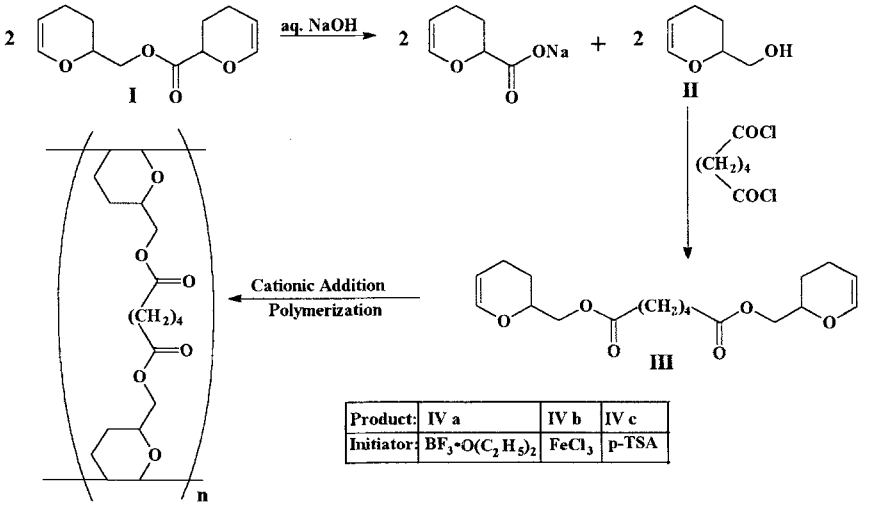


Figure 1: DSC analysis of polydi-(3,4-dihydro-2H-pyran-2-methyl) adipate synthsized in presence of: a) $BF_3.O(C_2H_5)_2$; b) Anhyd. $FeCl_3$; and c) p-Toluene sulphonic acid (p-TSA) as cationic polymerization initiators

So, the higher molecular weight polymer obtained in case of $BF_3.O(C_2H_5)_2$ changes then into the rubbery state easier than that obtained in case of p-TSA. This means that the higher crystallinity e.g. in case of **IVc**, the less mobile the polymer chains. As a result, the time of diffusion increased and consequently long release time is expected. Therefore, the polymer **IVc** may be preferable in many cases. It is previously reported that the hydrogel produced from reaction of 1,2,6-hexanetriol and polyethylene glycol and 3,4-dihydro-2H-pyran-2-methyl-(3,4-dihydro-2H-pyran-2-carboxylate) using p-TSA as a catalyst quite obviously deteriorated on storage at room temperature (7). Brønsted and Lewis acids as $HClO_4$ and BF_3 will also cause cationic polymerization but are not generally used because of undesirable side reactions (8).

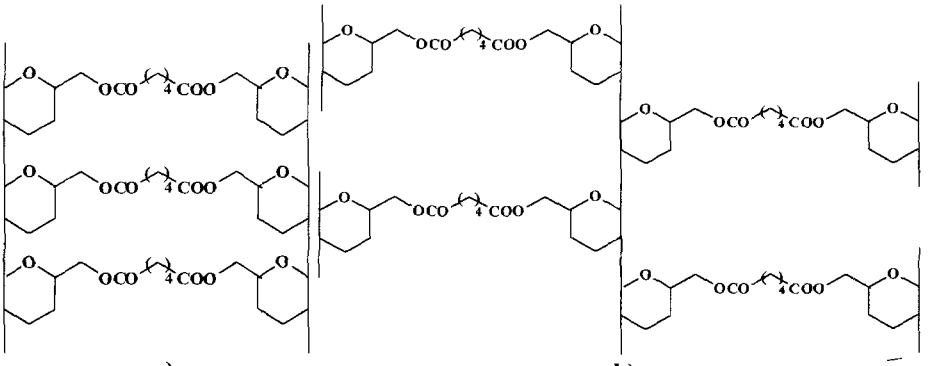
In the present work, the polymerization reaction was occured through addition mechanism (2,3) leading to backbone composed exclusively of C-C bonds (Scheme 1). They are normally resistant to hydrolysis and enzyme attack. This is in contrast to the hydrogels composed of polyethylene oxide, a compatible triol or polyol and either diisocyanates (14-16) or the pyran monomer (7-9). The pyran monomers do not have any analog of the isocyanate reaction with water and are thus easier to make bubble free products. This has been expected to overcome the storage instability problem and it was the case as the polymeric samples are still stable even after more than a year. On the other hand, the ester groups link the chains either in a form of crosslinking or in a ladder-like form or in a mixture of both (Scheme 2). These crosslinks are easily hydrolysable to adipic acid and the easily soluble linear 3,4-dihydro-2H-pyran-2-methanol addition polymer. Also synthetic water-soluble polymers can have biological activity (17,18) and it is possible to polymerize certain types of drugs such as steroid (19). In a separate experiment, the higher molecular weight polymer **(IVa)** synthesized in presence of $BF_3.O(C_2H_5)_2$ initiator was hydrolyzed in mild alkaline medium (0.1N NaOH) at 37°C. It is important to mention that the polymer is completely hydrolyzed into soluble polymer **V** after 24h. Thus, it is promising to study its utilization as drug carrier for providing prolonged action formulations.



Product:	IV a	IV b	IV c
Initiator:	BF_3•$O(C_2H_5)_2$	$FeCl_3$	p-TSA

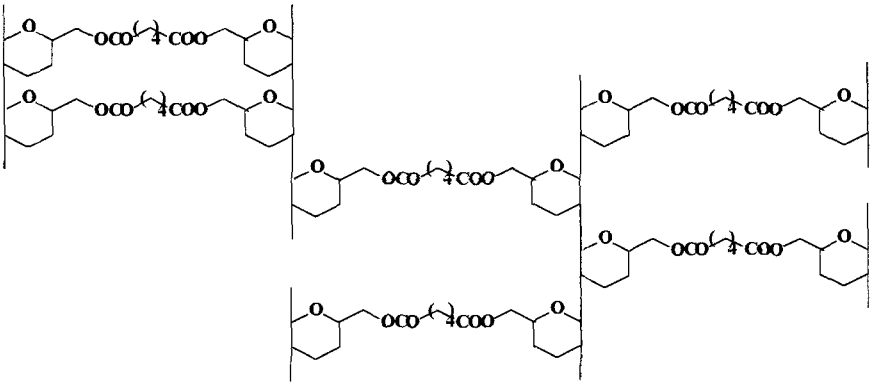
IV a, b, c

Scheme 1: Synthesis of polydi(3,4-dihydro-2H-pyran-2-methyl) adipate hydrogel through addition polymerization reaction.

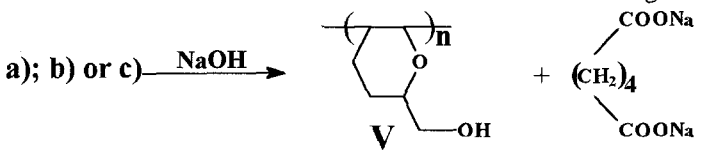


a)
Ladder - Like Structure

b)
Conventional Crosslinking



c)
Ladder - Like Structure and Conventional Crosslinking



Scheme 2: Possible structures of polydi(3,4-dihydro-2H-pyrane-2-methyl)adipate hydrogel and their alkaline hydrolysis products.

Experimental

Materials and methods

3,4-dihydro-2H-pyran-2-methyl (3,4-dihydro-2H-pyran-2-carboxylate) was supplied by Prof. N.B. Graham, University of Strathclyde, UK. Elemental microanalysis was carried out at Cairo University, Egypt. IR was recorded on Perkin-Elmer 257 Grating IR-spectrophotometer while UV analysis was achieved using Cecil CE 5501 W double beam spectrophotometer. ^{1}H-NMR was recorded on Varian 60 MHz and thermal analysis was carried out using DSC V2.2A DuPont 9900. Molecular weight measurements were carried out on 745 GPC Prosram Version 1.0 (Y/N).

Synthesis

1. Preparation of 3,4-dihydro-2H-pyran-2-methanol (II):
80 ml of 20% sodium hydroxide solution in water were added with good stirring over a period of 1-2h onto 55 ml (0.25 mole) of 3,4-dihydro-2H-pyran-2-methyl (3,4-dihydro-2H-pyran-2-carboxylate). Stirring is continued until the solution is no longer turbid and it is then extracted twice with 50 ml $CHCl_3$. The combined crude products were distilled under reduced pressure, b.p. 90°C at 20 mmHg.

2. Preparation of di(3,4-dihydro-2H-pyran-2-methyl) adipate (III):
To an ice cold solution of 34.3 g (0.32 mole) of 3,4-dihydro-2H-pyran-2-methanol in a mixture of 30 ml pyridine and 150 ml n-hexane, 29.2g (0.16 mmole) of adipoyl chloride was slowly added with stirring. Stirring for another 3h at room temperature followed by treatment with sodium bicarbonate solution and subsequent extraction with ether. The organic layer was washed repeatedly with water to get rid of pyridine completely. Distillation of the ethereal extract leads to 3.5 g of **III** (≈80 % yield). It melted at 196.8°C. IR(KBr) ν= 3050 1740, 1655, 1080 cm^{-1}; UV λ_{max}= 324.5 nm; ^{1}H-NMR($CDCl_3$): δ=1.7-2.2 ppm (aliph.CH_2); 4 & 5.2 ppm (pyran protons); 4.6 & 6.4 ppm (pyran unsat. protons); Elemental analysis: $C_{18}H_{26}O_6$ (338.4): Calculated: C, 63.89; H, 7.74; Found: C,64.1; H, 7.83.

3. Synthesis of poly di(3,4-dihydro-2H-pyran-2-methyl) adipate (IV a-c):
The novel crosslinked hydrogels were batch synthesized by a cationic bulk polymerization process. Three different cationic initiators were used in 1.0 wt % of total weight of the reactants. They are: a) solution of 7 % boron trifluoride in diethyl ether; b) anhydrous ferric chloride & c) p-toluene sulphonic acid (p-TSA). The initiator (25 mg) was added to 2 ml monomer (**III**) in 18 ml dichloroethane under nitrogen atmosphere and shaked well at 25°C for 16h. The polymerization reaction was stopped by adding 1ml of 10 % solution of tributyl amine. After evaporation of solvent and subsequent washing with dilute HCl and distilled water and finally drying at ambient temperature over P_2O_5 under vacuum, pale brownish crystals were obtained and spectroscopically characterized. IR (KBr) ν = 1740, 1030 cm^{-1}; UV λ_{max} = 230 & 269.5 nm (for a & b only); ^{1}H-NMR($CDCl_3$): δ = 1.9 - 2.4 ppm (aliph. CH_2); 4 ppm (pyran sat. protons). Number average molecular weight and polydispersity index were determined by GPC and the data obtained are listed in table 1.

Initiator	$\overline{Mn}$	Idisp	$\overline{DP}$
a ($BF_3.O(C_2H_5)_2$)	6925	1.06	22
b (Anhyd. $FeCl_3$)	5594	1.44	17
c (p-TSA)	4810	1.20	14

Table 1: Number average molecular weight ($\overline{Mn}$); polydispersity index **(Idisp)** and average degree of polymerization ($\overline{DP}$) of poly di(3,4-dihydro-2H-pyran-2-methyl) adipate determined by GPC.

Characterization

Differential scanning calorimetry
Crystalline melting points were obtained using a DuPont 9900 thermal analyzer. Small samples (10-13 mg) of polymers were sealed in aluminum pans and melting endotherms were obtained by DSC at heating rate 10 $K.min^{-1}$ under nitrogen atmosphere (Figure 1).

Hydrolysis of poly di(3,4-dihydro-2H-pyran-2-methyl) adipate:
0.25 g of **IVa** was added to 100 ml of 0.1 N sodium hydroxide solution with stirring at 37°C until it completely soluble (≈24 h). The hydrolysate was extracted with chloroform, dried over magnesium sulphate and the solvent was then evaporated.
IR (KBr) ν = 3300 - 3500, 1030 cm^{-1}.

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