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Drug release profile of malic acid-succinic acid-butane 1, 4-diol Co-polyester

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Abstract
Five samples (I-V) of malic acid-succinic acid-butane-1,4-diol co-polyesters were synthesized from five mixtures of malic acid and succinic acid in mole combinations (1.0+0.0), (0.9+0.1), (0.8+0.2), (0.7+0.3) and (0.6+0.4) respectively in each case with 1 mole of butane-1,4- diol following Dean-stark apparatus using $FeCl_3$ (approximately 0.4% of the total weight) as catalyst. These co-polyesters were characterized by their molecular weights, IR-spectra, elemental analysis, hydrolytic degradation and swelling behavior in water and ethanol and solubility test in common organic solvents. The co-polyester-II had the highest molecular weight and it was selected for subsequent experiments. Its probable structure was assigned considering the hydroxyl and carboxyl groups of the monomers. Molecular weights were determined by end group analysis and viscosity method. At room temperature, the hydrolytic degradation study of the co-polyesters in solutions of different pH values showed that it remained intact in solutions of pH values 1.5-6.0, but gradually degraded in solutions of pH values >6.0. The co-polyester was investigated as an enteric coating material on diclofenac sodium core tablets. It was found that the coated tablet did not degrade or swell in the simulated gastric fluid (pH-1.2) for 2 hours. But it gradually degraded in the simulated intestinal fluid (pH-7.4) and within 45 minutes around 80% of diclofenac sodium released indicating the BP drug delivery profile. The toxicological test of the polymer is yet to be performed. If the polymer be proved to be non-toxic, it might be usable as an enteric coating material.

Keywords: Malic acid-succinic acid-butane-1, 4-diol co-polyester, microbial degradation, enteric coating

Introduction
The invention of synthetic polymer has brought a new era in the history of modern science and technology. Biodegradable polymers represent a growing field and has a brilliant aspects of polymer science at the present time [1-3]. A vast number of biodegradable polymers have been synthesized or are formed in natural environment during the growth cycles of organisms. Some microorganisms and enzymes capable of degrading such polymers have been identified [1, 4]. Recently considerable interest is being focused on the development of biodegradable polymers for biomedical carriers [5-9]. Many of the existing biodegradable carriers are linear polyesters [10] such as polylactic acid, polyglycolic acid and their copolymers [11-12] which are being used for specialized application such as controlled release drug formulation [13-15], insecticide and pesticide carriers as well as non-toxic surgical implant materials. A large number of polymers have a built-in self-destruct mechanism by which they undergo slow hydrolytic and microbial degradation releasing the impregnated material at controlled rates. Poly (L-lactic acid) is a biodegradable polyester having good biocompatibility, it has been utilized as an useful biodegradable material in the medical and pharmaceutical fields. But the application scope of poly LA is limited because it is highly crystalline polyester [5].
Apart from the high molecular weight polyesters producedby microorganismsand by ring-opening polymerization of lactones or lactides, aliphatic polyesters from the condensation of hydroxycarboxylic acid or the condensation of diols with dicarboxylic acids have also attracted the attention of many researchers [16].
Ongoing research in our laboratory is directed towards the synthesis and characterization of new biodegradable, flexible materials based on aliphatic polyester for controlled and sustained drug delivery [17-20]. The aim of this work is to develop novel commercially viable polymers specially designed to degrade under controlled biological conditions and in this connection, an attempt had been taken to synthesize polymer from malic acid, succinic acid and butane 1, 4-diol. This paper reports its synthesis, characterization, hydrolytic and microbial degradation and drug release behavior.

Experimental

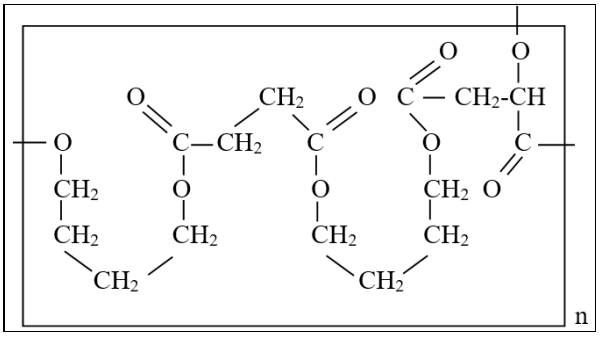
Materials

Malic acid, succinic acid, butane 1, 4-diol and $FeCl_3$ were reagent grade chemical from BDH, England. All chemicals were A.R. grade products and were used as such. $FeCl_3$ was sublimed before use.

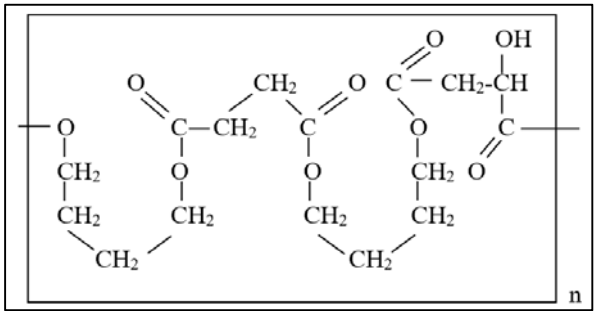
Synthesis of the Polymer

Malic acid-succinic acid-butane 1,4-diol co-polyester (MSBC) was synthesized taking the desired proportions of malic acid, succinic acid and butane 1,4-diol together with $FeCl_3$ (0.4% of the total weight) as catalyst in 250 mL R.B. flask connected by Dean-Stark apparatus for eliminating water azeotropically with xylene as the reaction medium at 145-150^{0}C under nitrogen atmosphere for about 7 hrs. When elimination of water subsided, the reaction mixture was heated for additional one hour under the same condition to ensure the completion of reaction. The co-polyester has been collected from the reaction vessel by dissolving it in acetone and purified by precipitating using water as non-solvent. It has been vacuum dried at 60^{0}C and stored in a desiccator.

Assuming the secondary hydroxyl group of malic acid to be totally reactive or totally non-reactive and the probable structure of the co-polyester would be A or B as shown below:



Structure A



Structure B

Characterization

The polymer samples were characterized by their IR spectrum, molecular weights, solubility in common organic solvents, elemental analysis, hydrolytic degradation and swelling behavior in water and ethanol. Solubility of these co-polyesters was studied in various organic solvent(toluene: ethanol, 1:3), ethyl acetate, chloroform, acetic acid and rectified sprit, slightly soluble in ethanol and insoluble in diethyl ether, xylene, benzene, carbon tetra chloride and water. The polymer was cryogenically powdered and its IR spectrum on KBr pellets was recorded by a Perkin-Elmer IR Spectrophotometer. Molecular weight determination was carried out by end group analysis and viscosity method. Elemental analysis for C and H was carried out by the standard procedure at C.D.R.I., Lucknow, India. Equilibrium swellings in the two solvents were measured gravimetrically [21] and the hydrolytic degradation test was investigated in acid and alkali solutions of various pH values.

Microbial Degradation

The microbial degradation of the co-polyester was studied using the bacteria *B. subtilis* and *E. coli* separately in a high phosphate mineral salt medium (modified M_9 medium [22]: NH_4Cl, 1gm; Na_2HPO_4, 7.5 gm; KH_2PO_4, 3.0 gm; $MgSO_4$, 0.2 gm made up to 1 liter with distilled water) containing the co-polyester granules in suspension as the source of carbon. For each type of bacteria the medium (20 ml) was taken in a number of 100 ml conical flasks in each of which the polymer granules (0.2 gm) were suspended. They were then autoclaved and inoculated aseptically with particular bacterial inoculum keeping appropriate controls. The growth of the bacteria in the inoculated flasks was then measured by turbidimetric method [23] in which absorbance of each set at a standard wave length, 440 nm was recorded taking the uninoculated medium of the corresponding set as reference for all the flasks of the same set and their O.D.'s were found out.

Coating of the core (uncoated) tablets

The malic acid-succinic acid-butane 1,4-diol co-polyester was dissolved in ethyl acetate to prepare its 40% coating solution, which was sprayed over the core tablets in a small coating pan with continuous hot air flow. The coating pan was allowed to rotate until the solvent evaporated and tablets dried.

Preparation of Diclofenac Sodium Standard Calibration Curve

0.05g. of pure diclofenac sodium (DS) was dissolved in buffer medium of pH 7.4 to make 1000 ml solution. These solutions were used for the preparation of the standard calibration curves of diclofenac sodium in experimental buffers spectrophotometrically.

Dissolution Studies

The dissolution studies for both the core tablets and the coated tablets were performed in order to evaluate the efficacy of the polymer as a coating material on the release of t e drug. A USP type II dissolution apparatus (paddle stirrer), "Electrolab TDT-04" with a rotation speed of 50 rpm was used for dissolution experiments. A solution of pH 1.2 was prepared [24] by 2g of NaCl and 9.82 mL of conc. HCl dissolved in 1 liter distilled water and used as the simulated gastric fluid. A buffer solution of pH 7.4 was prepared by KH_2PO_4 & Na_2HPO_4, and was used as the simulated intestinal fluid [24]. The simulated gastric fluid (900 mL), heated at 37 ± 0.5 ℃, was used initially for the dissolution studies which was replaced after 2 hrs. By 900 mL of simulated intestinal fluid heated previously at 37 ℃. Samples (5 mL) were withdrawn from the simulated gastric fluid at 30 minutes intervals for 2 hrs. And from simulated intestinal fluid at 15 minutes intervals for 45 minutes which were immediately compensated with the same amount of fresh medium preheated at 37 ± 0.5 ℃.

The amount of drug released was calculated by measuring the absorbance after suitable dilution if necessary using a Shimadzu UV – 1200 spectrophotometer at 274 nm. Concentration of the released drug were then obtained by comparing with standard calibration curve prepared from pure

drug in phosphate buffer solution of pH 7.4 in the appropriate concentration region. The in-vitro release studies were performed on coated and core tablets.

Results and Discussion

The co-polyester synthesized from malic acid-succinic acid-butane 1, 4-diol was solid, sticky and slightly transparent at room temperature. It was purified by dissolving in acetone and then by precipitating using ethanol as non-solvent.

Characterization

The band representing the –OH group at the region 3150-3450 cm^{-1} in the spectrum of the diol almost disappeared in the spectra of the polymer. In the IR spectrum of the co-polyester the >C=O stretching frequency at the region 1678-1685cm^{-1} shifted to 1645-1655cm^{-1} region. A new band representing ester linkage appeared at 1254cm^{-1} region in the spectrum of the polymer. All these indicate the formation of ester bonds of the co-polyester.

The molecular weights of the polymer samples (I-V) are shown in Table 1.

Table 1: Characterization of malic acid-succinic acid-butane 1, 4-diol co-polyester by molecular weights.

Polymer Samples	Reaction composition in mole			Molecular Weight by	
	Malic acid	Succinic acid	Butane1,4-diol	End Group analysis	Viscosity measurement
I	1.0	0.0	1.0	21132	22576
II	0.9	0.1	1.0	24678	26498
III	0.8	0.2	1.0	15987	17822
IV	0.7	0.3	1.0	14132	15865
V	0.6	0.4	1.0	10534	11538

The molecular weight of malic acid-succinic acid-butane 1, 4-diol co-polyester (MSBC) samples are shown in Table-1. Intrinsic viscosity of each fraction of MSBC was calculated and molecular weights determined by end group method (-COOH group) were utilized to get 'K' and 'a' values of Mark-Hauwink equation, $[\eta] = KM^a$, by a graphical plot of log $[\eta]$ against log $[M]$. As can be seen from the table that the molecular weight obtained by viscosity method was slightly higher than the same obtained by end group analysis. It was also observed that the sample II had the highest molecular weight and were in the order: II>I>III>IV>V.

The results of equilibrium swelling of the polymers (I-V) in water and ethanol, the swelling value was minimum for sample II which indicated higher crosslink density in the polymer sample II among other polymer samples. Results of swelling study were in the order: II>I>III>IV>V which is also supported by the molecular weight data. Hereafter, the sample II was selected for subsequent experiments.

Elemental Analysis: Calculated for structure A: C = 53.48% and H = 6.41%, Calculated for structure B: C = 53.33% and H = 6.67%. Found for sample II: C = 53.37% and H = 6.52%. Thus, the result of elemental analysis of sample II is in-between structures A and B, but nearer to B than A. It may be concluded that the polymer sample II is a mixture of about 20% of structure A and about 80% of structure B (to be designated hereafter as MSBC).

Microbial Degradation

The bacteria, *B. subtilis* and *E. coli* are enterobacter's generally present in intestine and take part in protein metabolization. Hence, the microbial degradation of this polymer using these bacteria has been studied. Fig.-2 represents the results of the degradation of this polymer by the bacteria *B. subtilis* and *E. coli* expressed in terms of the absorbance of the medium at 440 nm as a function of time.

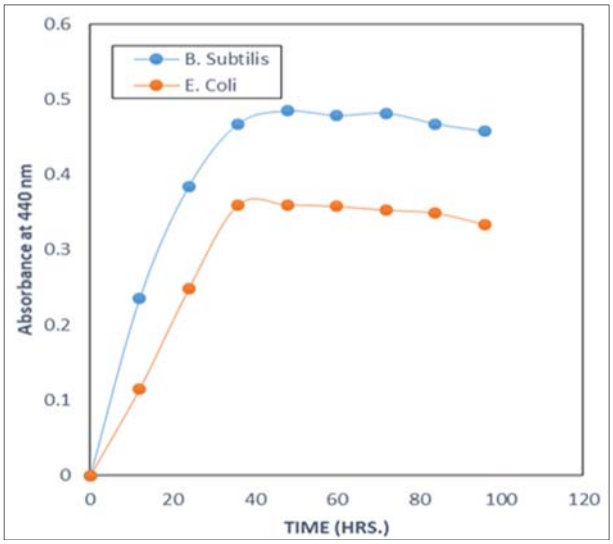


Fig 1: Microbial degradation of malic acid-succinic acid-butane 1, 4-diol co-polyester.

It shows that the growth is higher for *B. subtilis* and lower for *E. coli*. It is also observed that in each case the growth increases rapidly up to 36-48 hrs. And then becomes stationary. The differences in the bacterial growth or degradation of the polymer indicate the specificity of bacterial action. This experiment shows that the polymer is susceptible to enzymatic degradation and the polymer is classed as a biodegradable polymer.

Release Characteristics of the Drugs

From the degradation study it was found that MSBC slab remained intact in the gastric fluid (pH 1.2) but gradually degraded in intestinal fluid (pH 7.4). So, the co-polyester II was selected for enteric coating. Enteric coating material resists the release of the drug from the core tablet in the gastric environment but it helps drug release in the intestine. In this study, *in vitro* drug release was carried out for MSBC coated diclofenac sodium in the simulated gastric fluid (pH 1.2) and also simulated intestinal fluid (pH 7.4). Dissolution of a drug from its dosage form is depend on many factors, which include not only the physico-chemical properties of the drug, but also the formation of the dosage form and the process of manufacture. Such statement is also true for enteric coated preparations.

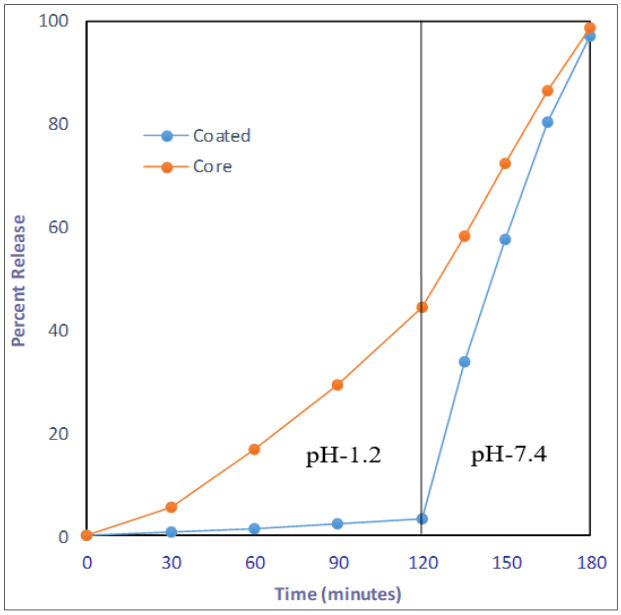


Fig 2: Mean (±SEM) percent release of diclofenac sodium core and MSBC coated tablets in simulated gastric fluid (pH 1.2) and in simulated intestinal fluid (pH 7.4).

In this study, it was found that the polymer did not degrade or swell in the gastric fluid when coated on a core tablet for as long as two hours (Fig 2) and drug release was observed not more than 4%, where as 44.40% of diclofenac sodium was released from the core tablets (uncoated tablets) in that time in the simulated gastric fluid (Fig 2). But in the intestinal fluid it gradually degraded and drug release was observed from the MSBC coated tablets. Fig. 2 also reveals that around 80% of diclofenac sodium was released in the simulated intestinal fluid within 45 min. In acid region especially in pH 1.2 the ester linkage of the compound is resistant and in alkaline region especially of pH 7.4 the compound is susceptible. As a result, ester linkage is gradually hydrolyzed. In pH 1.2 tablet coated with this co-polymer remain intact i.e., negligible release of the drug happens. But in alkaline region i.e., in pH 7.4 the co-polymer is degraded resulting the release of the drug. Therefore, the swelling and hydrolysis of the ester and diffusion of the drug particles simultaneously play an important role on the release behavior of the drug. The release pattern of MSBC coated diclofenac sodium corresponds to the BP drug release profile of enteric-coated tablets [25].

So, Malic acid-succinic acid-butane-1, 4-diol co-polyester can be used as an enteric coating material. One of the advantage of this coating material is that, no plasticizer was required to add to the formulation as the polymer itself has got sticky property. Acute toxicity and other pharmacological tests of the polymer will be reported later to utilize it as an enteric coating material.

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