

Ph Responsive in-Vitro Drug Release Behavior of Poly (Malic Acid-Co-Butane-1,4-Diol-Co-Maleic Acid)

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ABSTRACT

Four mixtures of malic acid and maleic acid in mole combinations (1.0+0.1), (1.0+0.2), (1.0+0.3), and (1.0+0.4) respectively were separately polymerized with one mole of butane 1,4-diol in Dean-Stark apparatus using xylene as the reaction medium. Among the synthesized co-polyesters, sample II had the highest molecular weight and it was selected for subsequent experiments. It was characterized by its IR-spectrum, solubility in common organic solvents, elemental analysis and hydrolytic degradation test. It was found from hydrolytic degradation test that the said polyester sample did not degrade or swell in acid medium but gradually degraded in basic medium. Because of having such pH responsive behavior it was tried as an enteric coating material on diclofenac sodium core tablets. In vitro drug release pattern of co-polyester coated samples matches with the British Pharmacopoeia standard drug release profile of enteric-coating material.

Key Words: poly (malic acid-co-butane-1,4-diol-co-maleic acid), enteric coating material, drug dissolution study.

INTRODUCTION

Our gastro-intestinal tract (GIT) consists of several different sections, each with a special anatomy (structure) and physiology (function) ¹. Thus the orally administered drug passes through several regions of different environments in the GIT. The successful targeting of therapeutic agents to any specific area of the GIT, via the oral route, requires both the exploration of a unique feature of the site and also the protection of the active agent until it reaches the target site². Polymers, such as, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HMP), polyvinyl acetate phthalate (PVAP), etc. have the property to remain intact in the acidic environment of the stomach but are susceptible in the basic pH of the intestinal fluid. Because of having such pH responsive characteristics, these polymers are being commercially used as enteric coatings in oral solid formulations for targeting the drug to release in the small intestine where the pH is much higher than that in the stomach³. However, many recent *in-vivo* studies have suggested that various phthalates and their metabolites could be responsible to develop toxicity as well as liver tumors in mammals especially for long term applications^{4,5}.

Owing to their reputation as safe materials and their biodegradability, aliphatic polyesters are primarily used as biocompatible and biodegradable carriers in many types of implantable or injectable or orally administrated drug-delivery systems for both human and veterinary use⁶. Our research work is directed to synthesize and characterize new biodegradable materials based on polyesters but free of phthalates and to figure out their drug release characteristics^{7,8}. In this paper we will report synthesis, characterization, hydrolytic degradation and drug release characteristics as enteric coating material of a polymer derived from malic acid, maleic acid and butane 1,4-diol.

However, for biological applications a common prerequisite is that all polymers are to be bio-compatible. Bio-compatibility of the monomer is the foundation for the bio-compatibility of degradable polymer systems⁹. Malic acid and maleic acid are being used as excipients in the pharmaceutical industries¹⁰. So, we can expect that hydrolysis of labile ester linkages along the polyester backbone (derived from these monomers) converts it into products that the human body can easily metabolize and eliminate them without adverse effects.

EXPERIMENTAL

Materials

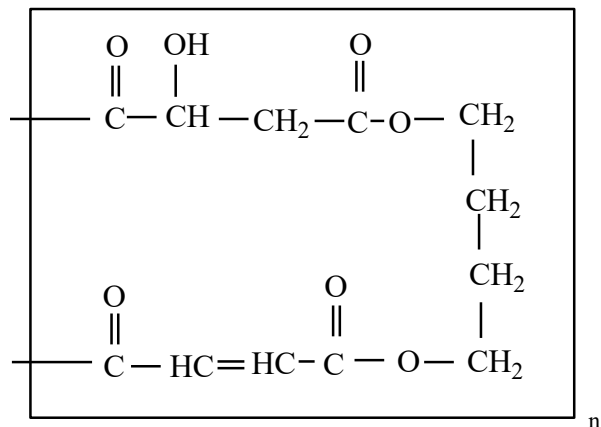
All of the monomers and chemicals were analytical reagent grade materials from either BDH-chemicals Ltd. England or E. Merck Germany. Anhydrous FeCl_3 was freshly sublimed before use as catalyst.

Synthesis of the polymer

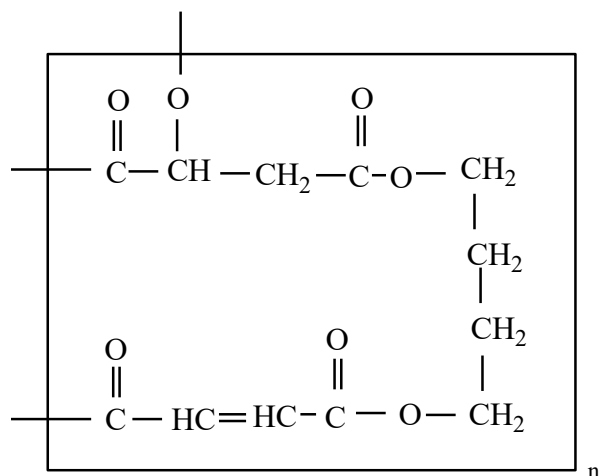
four mixtures of malic acid and maleic acid in mole combinations (1.0+0.1), (1.0+0.2), (1.0+0.3), and (1.0+0.4) respectively were taken separately with 1 mole of butane 1,4-diol together with anhydrous FeCl_3 (approximately 0.4% of the total weight) as catalyst in 250 ml round bottom flask and 80-90 ml xylene was added to it as the reaction medium. The flask was connected to a Dean-Stark apparatus for eliminating water (the by-product of the polycondensation reaction) azeotropically with xylene. The reaction mixture was heated at 130-135°C for about 5 hours. 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 polymer was collected from the reaction vessel by dissolving it in acetone and purified by precipitating using water as non-solvent. It was dried at 60°C and stored in a vacuum desiccator. In this way, four polymer samples (I-IV) were synthesized.

Assuming the secondary hydroxyl group of malic acid to be totally non-reactive or totally reactive or partially reactive, the probable structure of co-polyester would be A or B or a mixture of the two structures as shown below:

Structure A:



Structure B:



Characterization

The co-polyester was characterized by its IR-spectrum, molecular weight, solubility in common organic solvents, elemental analysis, and hydrolytic test. It was insoluble in water and ethanol but soluble in acetone and mixed solvent (toluene: ethanol = 3:1). The polymer sample was cryogenically powdered and its IR spectra on KBr pellet was recorded by a Shimadzu (model:470) IR-spectrophotometer ($500\text{--}4000\text{ cm}^{-1}$). Molecular weight determination was carried out by end group analysis and viscosity method.

Coating of the Core (Uncoated) Tablets

Malic acid-maleic acid-butane 1,4-diol co-polyester was used as a coating material. Its 40% solution in acetone was used as coating solution. The coating solution was sprayed over the core tablets in a coating pan with continuous hot air flow. The coating pan was allowed to rotate

until the solvent evaporated and the tablets dried. Drug release from coated tablets was tried as a function of weight gain by coating material on tablets and 8-10% weight gain by coating material on tablets gave the best result.

Preparation of Diclofenac Sodium Standard Calibration Curve for Drug Release Measurement

1000 ml solution was prepared by dissolving 50 mg of pure diclofenac sodium in phosphate buffer solution of pH 7.4. It was used for the preparation of the standard calibration curves of DS in experimental buffer solution spectrophotometrically.

Dissolution Studies

The dissolution for both the core and coated tablets were performed in order to evaluating the efficiency of the co-polyesters as coating material on the release of the drug. A USP type-XXII dissolution apparatus 'ELECTROLAB TDT-01' with a rotation speed of 50 rpm was used for dissolution experiments. Simulated gastric fluid was prepared by dissolving 2 g of NaCl and 7 ml of conc. HCl in 1 liter dist. water and pH was adjusted to 1.2 and simulated intestinal fluid was prepared by mixing 0.1M KH₂PO₄ and 0.1M Na₂HPO₄ solutions and then pH was adjusted to 7.4^{7,8,11}. One liter of simulated gastric fluid (pH 1.2) heated at 37±0.5°C was initially used for the dissolution studies and the solution was replaced after 2 hours by one liter of simulated intestinal fluid (pH 7.4) heated previously at 37°C. Samples (5ml) were withdrawn from the simulated gastric fluid at 30 min. intervals for 2 hours and from simulated intestinal fluid at 15 min. intervals for 1 hour. The absorbance of the release medium, after suitable dilution if necessary, was measured at 274 nm with a Shimadzu UV-1200 spectrophotometer and volume loss was immediately compensated with the same amount of fresh medium preheated at 37±0.5°C. Concentrations of the released drug were then determined spectrophotometrically. Five samples of each tablet (core and coated) were tested in the same way and the concentrations of the released drug were then averaged.

RESULTS AND DISCUSSION

The synthesized co-polyester samples (I-IV) were yellowish in color, solid and slightly transparent at room temperature. The broad band representing the -OH group at the region 3100-3500 cm⁻¹ in the spectrum of the diol almost disappeared in the spectrum of the polymer (Fig.-1). The >C=O stretching frequency at the region 1725-1735 cm⁻¹ of the spectrum of the diacid shifted to 1740-1750 cm⁻¹ region and a new band representing the ester linkage appeared at the 1280 cm⁻¹ region in the spectrum of the polymer (Fig.-1). All these indicate the reaction between -OH and -COOH groups forming ester linkage.

The molecular weights of the polymer samples (I-IV) are shown in Table-1. Fractionation was carried out for each of the four polymer samples. Molecular weights obtained by end group analysis as well as by viscosity method recorded in Table-1 against each sample were the average values for all the fractions. It was also observed that the sample-II had the highest molecular weight irrespective of the method applied. The MHS (Mark-Hauwink-Sakurada) constants, of this sample was found to be $K=6.98 \times 10^{-3}$ ml/gm and $\alpha = 0.67$ by viscometric method. A little lower or higher proportion of maleic acid lowered the molecular weight of the polymer. The molecular weights of the polymer samples were in order: II > III > I > IV. Hereafter, the sample-II was selected for the subsequent experiments.

Elemental Analysis

Calculated for structure A: C = 56.47% and H = 5.04 %, calculated for structure B: C = 56.25 % and H = 5.47 %, found for sample-III: C = 56.29 % and H = 5.38%. It is observed that the result of elemental analysis of the co-polyester (sample-II) is in-between structures A & B, but nearer to B than A. Synthesis and characterization of malic acid-butane 1,4-diol co-polyester have already been published ¹² and it has been reported that about 20% carboxyl groups of malic acid reacts with its own hydroxyl groups. Theoretically 50% of the carboxyl groups should take part in the reaction, but it happens so probably because of the steric effect. From functionality consideration, the structure of the selected co-polyester-II stands to be a mixture of about 80% of structure A and about 20% of structure B. To make the expression simple, the mole ratio between malic acid and maleic acid in structure A and B has been assumed to be 1:1, but actually the table -1 reveals that the selected copolyester contains malic acid and maleic acid in mole ratio 4:1.

Drug Release Pattern of the Co-polyesters

In vitro drug release study was carried out for malic acid-maleic acid-butane 1,4-diol co-polyester coated diclofenac sodium tablets in the simulated gastric fluid (pH 1.2) and in the simulated intestinal fluid (pH 7.4). Dissolution of a drug from its dosage form is dependent 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 ¹³. In this study, it was found that the polyester sample did not degrade or swell in the simulated gastric fluid for two hours when coated on a core tablet and drug release was not more than 5.8%, whereas 42% of diclofenac sodium released from the core tablets (uncoated tablets) as shown in Fig.2. But in the simulated intestinal fluid the polymer coating gradually degraded and more than 83% of diclofenac sodium released within 45 min. In acid region, especially in pH 1.2 the ester linkage is resistant and in alkaline region especially in pH 7.4 it is susceptible. As a result, ester linkage gradually hydrolyzed. In pH 1.2 the coating remains intact i.e., negligible release of the drug happens. But in alkaline region i.e., in pH 7.4 the polyester swells and degrades resulting in the release of the drug. Therefore, the swelling and hydrolysis of the ester linkage and diffusion of drug particles simultaneously play an important role on the release behavior of the drug. The drug release pattern of malic acid-maleic acid-butane- 1,4-diol polyester coated diclofenac sodium tablets correspond to the BP standard drug release profile of enteric-coated tablets ¹⁴. The toxicological investigation of malic acid-maleic acid-butane-1,4-diol polyester is in progress. If it is proved to be non-toxic, would be usable as an enteric coating material.

ACKNOWLEDGEMENT

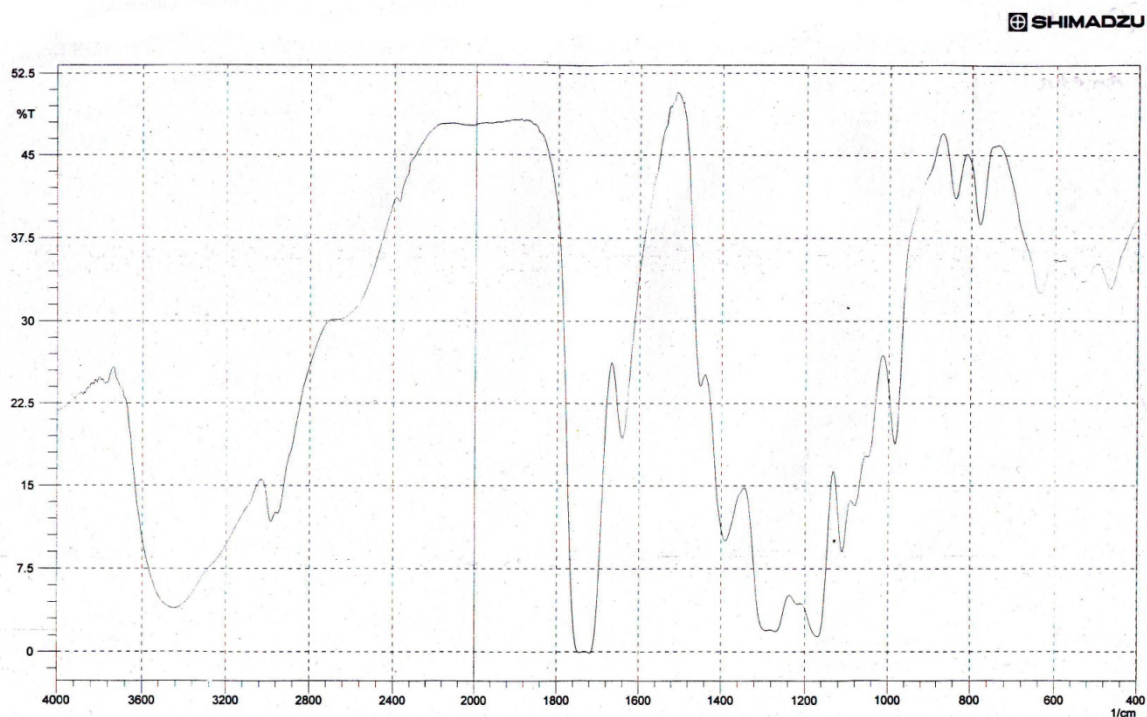
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Table- 1: Characteristics of Malic acid-maleic acid-butane 1,4-diol co-polyesters

Polymer Samples	Reactant Composition in mole			Molecular Weight by	
	Malic acid	Maleic acid	Butane 1,4-diol	End Group Analysis	Viscometry
I	1.0	0.1	1.0	16850	17940
II	1.0	0.2		20100	21320
III	1.0	0.3		18450	19600
IV	1.0	0.4		16550	17640

**Figure 1: IR-spectrum of Malic acid-maleic acid-butane 1,4-diol co-polyester**

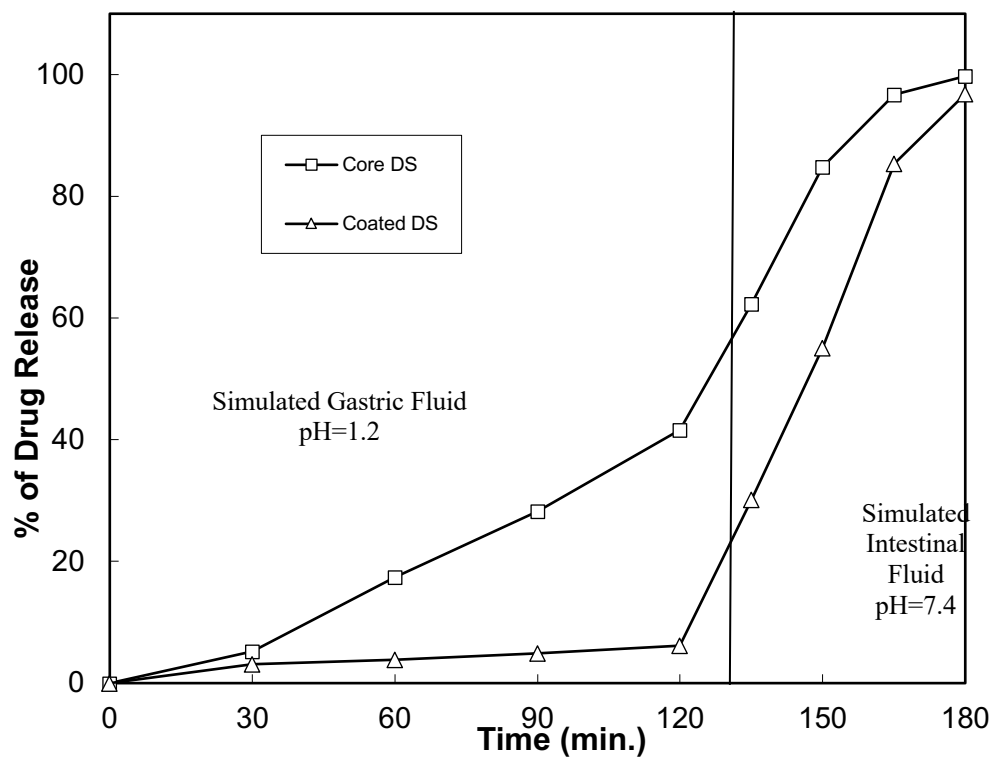


Figure 2: Mean ($\pm$ SEM) percent release of diclofenac sodium from core & Malic acid-maleic acid-butane 1,4-diol coated tablets in simulated gastric fluid (pH 1.2) & simulated intestinal fluid (pH 7.4)