Pak. J. Sci. Ind. Res. 2004 ***47*** *(4) 251-255*

DRUG RELEASE PROFILE OF MALIC ACID-PHTHALIC ACID BUTANE 1,4-DIOL COPOLYESTER

Md Abu Bakr*, Sefaly Khatun and Mohd Amirul Islam

Department of Applied Chemistry and Chemical Technology, University of Rajshahi, Rajshahi-6205, Bangladesh

(Received July 30, 2003; accepted April 20, 2004)

Five copolyesters **(I-V)** in varying mole ratios of malic acid and phthalic acid were separately synthesized with 1 mole of butane 1,4-diol using p-toluene sulfonic acid (0.4% of the total weight) as catalyst under vacuum at 120-125°C for about 6 h . The malic acid-phthalic acid-butane 1,4-diol copolyesters (MPBC) were characterized by their IR spectra, molecular weight, elemental analysis and solubility behavior in common organic solvents. The polymer **III** had the highest molecular weight and it was selected for subsequent experiments. Its hydrolytic degradation study in solutions of different pH values showed that it remained intact in solutions of pH values 1.2-6.0, but gradually degraded in solutions of pH values >6.0. Drug delivery profile of MPBC as an enteric coating material was investigated in simulated gastric fluid (pH 1.2) and then in simulated intestinal fluid (pH 7.4), it was found that the drug release pattern did not conform to enteric coating requirements. In the case of matrix tablets where drug was dispersed in the MPBC, it was found that the drug delivery was zero order up to 12 h releasing 88.0% of diclofenac sodium and up to 13 h releasing 86.50% of naproxen, afterwards release of drugs was negligible.

Key words: Malic acid, Phthalic acid, Copolyester, Drug delivery profile.

Introduction

In recent years, considerable interest has grown to synthesize biodegradable polymers for medical and agricultural uses, because such degradable carriers have the advantage of eliminating the necessity of their removal. Many of the existing biodegradable carriers are linear polymers (Heller 1980) such as polylactic acid, polyglycolic acid and their copolymers (Yolles *et al* 1975) which are biodegradable and are being used for specialized application such as controlled release drug formulation (Graham 1978; Rosenberg *et al* 1983), 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. Matrix tablet is one of the least complicated approaches to the manufacture of sustained release dosage forms, which consists of a drug dispersed in a polymer, the polymer playing the role of a matrix (Touitou and Donbrow 1982; Bidah and Vernaud 1991). Cellulose acetate phthalate, hydroxypropyl methylcellulose have been used as enteric coatings (Madan 1990). Aliphatic polyesters could display an excellent biocompatibility and be degraded in most biological environments. Biodegradable polymers from glycolic acid (PGA) or DL- lactic acid (PLA) are the simplest linear aliphatic polyesters, which are currently the most widely used synthetic, degradable polymers in human medicine (Engelberg and Kohn 1991; Ouchi *et al* 2000). Keeping the same view ahead, malic acid-phthalic acid-butane 1,4-diol copolyester (MPBC) has been synthesized and it has been investigated as a carrier for sustained and controlled release of drugs.

*Author for correspondence.

Experimental

Malic acid, phthalic acid and butane1,4-diol were the monomers of the synthesized copolyesters and were purchased from Sigma Chemical Co. England, E. Merck, India Ltd. and BDH, England, respectively. Core tablets of diclofenac sodium (50 mg) supplied by Chemico Laboratories, Rajshahi and naproxen (50 mg) by Beximco Pharmaceuticals Ltd. Tongi, Dhaka, were of analytical grade. Reference standard of diclofenac sodium (DS) (99.2% Purity) and naproxen (99% purity) used for analytical purpose were obtained from Beximco Pharmaceuticals Ltd. Tongi, Dhaka, Bangladesh.

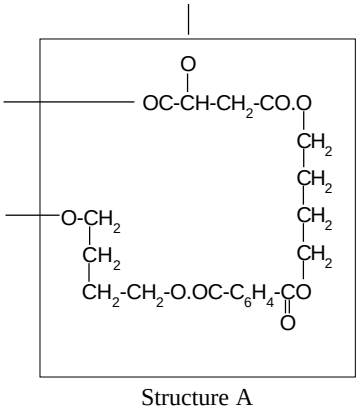
Synthesis of the polymer. Five mixtures of malic acid and phthalic acid in different mole ratios were taken separately with 1 mole of butane 1,4-diol along with *p*-toluene sulfonic acid (approximately 0.4% of the total weight) as catalyst in a 100 ml beaker and were allowed to undergo polycondensation in a reaction vessel under vacuum at 120-125°C for about 6 h. The solid polymers were then collected from the reaction

Table 1
Characterization of malic acid-phthalic acid-butane 1,4-diol copolyester by molecular weights

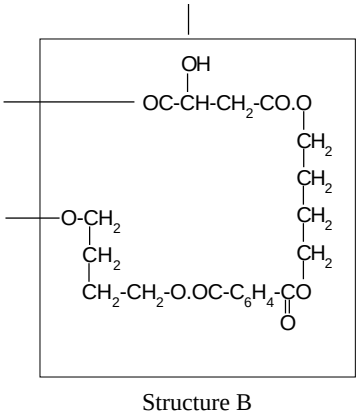
Polymer samples	Reactant composition in mole			Values of K and a in ethylacetate at 30°C		Molecular weight by	
	Malic acid	Phthalic acid	Butane 1,4-diol	$Kx\,10^3$ ml/gm	a	End group analysis	Viscosity measurement
I	1.0	0.0	1.0	5.547	0.713	15582	15771
II	0.8	0.2	1.0	6.456	0.682	16292	17279
III	0.6	0.4	1.0	5.495	0.700	20137	21379
IV	0.4	0.6	1.0	6.760	0.674	17060	17691
V	0.2	0.8	1.0	7.244	0.665	15958	16407

vessel. In this way, five samples (**I-V**) in mole combinations between malic acid and phthalic acid: (1.0+0), (0.8+0.2), (0.6+0.4), (0.4+0.6) and (0.2+0.8), respectively were separately synthesized with 1 mole of butane 1,4-diol and then purified by precipitating them using ethanol as non-solvent. The polymers were pale orange in color, solid, sticky and slightly transparent at room temperature.

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



Structure A



Structure B

Characterization. The polymer samples (**I-V**) were characterized by their IR spectra, molecular weights, solubility, elemental analysis and hydrolytic test. They were insoluble in water and ethanol, but soluble in common organic solvents e.g. acetone, ethylacetate etc. The polymer samples were cryogenically powdered and their IR spectra on KBr pellets were recorded by a Perkin-Elmer IR Spectrophotometer. Molecular weight determination was carried out by end group analysis and viscosity measurement. Elemental analysis for C and H was carried out by the standard procedure at C.D.R.I, Lucknow, India and hydrolytic test was investigated in acid, alkali and buffer solutions of various pH values. The polymer sample-**III** was chosen (for reasons to be discussed later) for further studies.

Coating of the core (uncoated) tablets. The malic acid-phthalic acid-butane1,4-diol copolyester was used as a coating material and its 40% solution in ethylacetate was sprayed over the core tablets in a small coating pan with continuous hot air flow. The drying conditions permit the removal of the solvent so as to leave a thin polymer coating around each tablet.

Preparation of drug-polymer matrix tablets. Malic acid-phthalic acid-butane 1,4-diol copolyester has been used to prepare diclofenac sodium and naproxen matrix tablets. 1 g of the copolyester was taken in a separate beaker, melted until it softened sufficiently so that it could be worked. 250 mg pure diclofenac sodium or naproxen was added to the melted mass with thorough mixing. The copolyester-drug mixture was then passed through the sieve (mesh no. 25) to prepare granules, which were so weighed that they contained 50 mg of diclofenac sodium or naproxen and were compressed in a single punch tablet machine to get them in a tablet form.

Preparation of diclofenac sodium and naproxen standard calibration curve. 0.05 gm of pure diclofenac sodium or pure naproxen was dissolved in buffer medium to

make 1000 ml solution. These solutions were used for the preparation of the standard calibration curves of diclofenac sodium and naproxen in experimental buffers spectrophotometrically.

*Dissolution studies.*The dissolution studies of 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 the 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 by 2 g of NaCl and 7 ml of conc. HCl dissolved in 1 liter distilled water and was used as the simulated gastric fluid and a pH 7.4 buffer solution of KH_2PO_4 and Na_2HPO_4 was used as the simulated intestinal fluid (Kawser *et al* 1996). The simulated gastric fluid (1000 ml), heated at 37°C±0.5°C, was used initially for the dissolution studies which was replaced after 2 h by 1000 ml of simulated intestinal fluid heated previously at 37°C.

For drug-polymer matrix tablets, drug release was studied by placing a drug impregnated and dried down matrix tablet weighing 250 mg and containing 50 mg drug in 1000 ml of phosphate buffer (pH 7.4) at 37°C under stirred condition. A 5 ml aliquot portion of the medium was removed at 30 min. intervals and its absorbance (after suitable dilution where necessary) was measured on a Shimadzu UV-1200 spectrophotometer at the appropriate wavelength and volume loss of the medium was immediately compensated with the same amount of fresh medium preheated at 37°C±0.5°C. Concentrations of the released drug were then obtained by comparing with standard curves prepared for each of the pure drugs in phosphate buffer solution of pH 7.4 in the appropriate concentration region. Five samples of each matrix tablet were in phosphate buffer solution of pH7.4 in the appropriate concentration region. Five samples of each matrix tablet were tested in this way and the concentrations of the released drugs were then averaged, the variations in the concentration values being within 2% (Pramanick and Ray 1990).

Results and Discussion

The MPBC polymers (**I-V**) obtained by bulk polycondensation method were pale orange in color, solid, sticky 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 is almost absent in the spectrum of the polymer. In the IR spectra of the copolyester the C=O stretching frequency shifted from 1730 cm^{-1} to 1750 cm^{-1} and a band due to –COOR appeared at 1242.1 cm^{-1}. All these indicate the formation of the ester bonds.

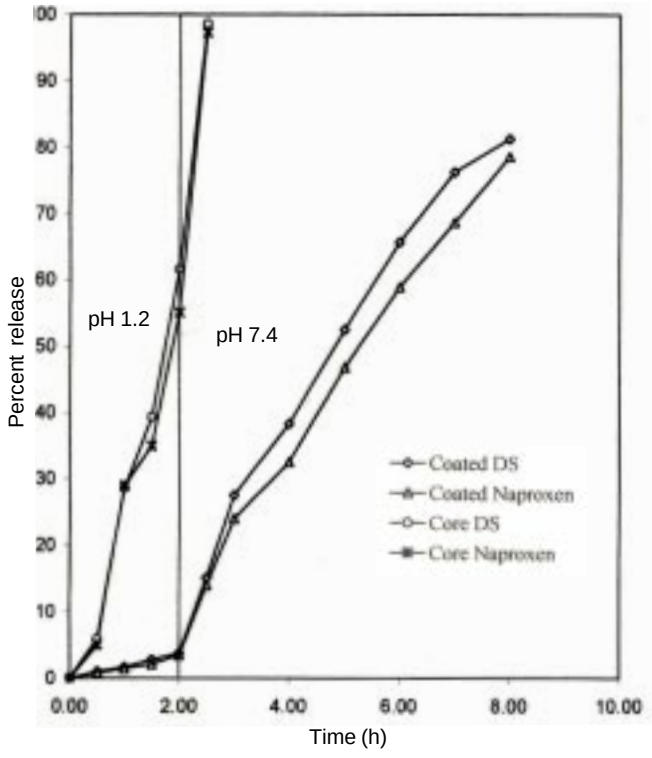


Fig 1. Mean (±SEM) percent release of diclofenac sodium and naproxen from core and MPBC coated tablets in simulated gastric (pH1.2) and intestinal (pH7.4) fluids.

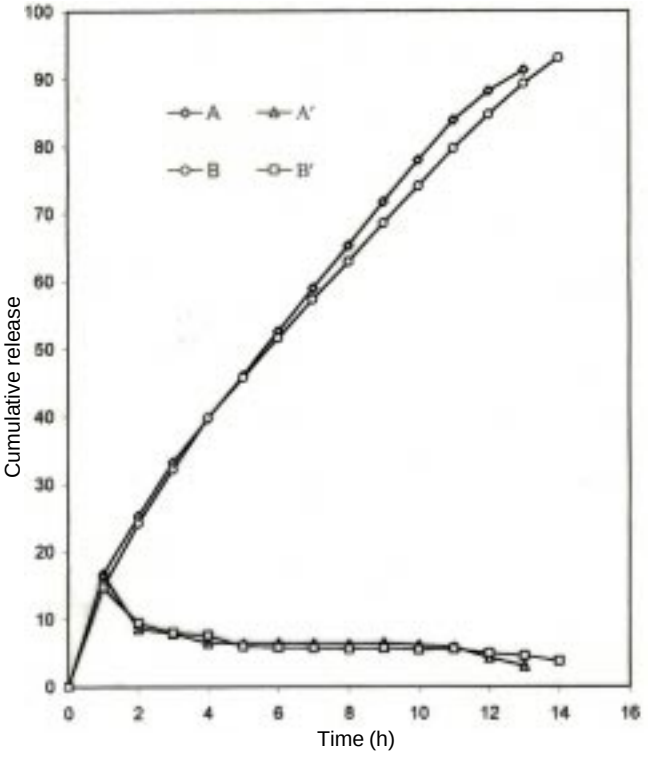


Fig 2. Plots of in-vitro release of diclofenac sodium and naproxen from malic acid phthalic acid-butane 1,4-diol copolyester matrices where A & B represent cumulative release and A′&B′ represent release rate / hour, respectively.

The molecular weights of the polymer samples (**I-V**) are shown in Table 1. As can be seen from the table that the polymer sample **III** has the highest molecular weight irrespective of the method applied. The molecular weights of the polymer samples are in order: **III** > **IV** > **II** > **V** > **I**. It is also observed from the table that the values of 'K' and 'a' of the polymer samples (**I-V**) are different, although all polymer samples (**I-V**) were obtained from the same monomer except sample **I**. This is because of the secondary hydroxyl group present in the malic acid molecule undergoes polycondensation differently for the different mole ratios of malic acid and phthalic acid.

Elemental analysis: The elemental analysis of MPBC is given below: Calculated for structure A: C, 58.97%, H, 5.65%, calculated for structure B: C, 58.82%, H, 5.88% and found for sample **III**: C, 58.37%, H, 5.98%. Thus, the result of elemental analysis of the compound **III** shows that its percentage composition is similar to that of A as well as of B, but closer to B than A. From the hydrolytic test it was found that the polymer samples remained intact in the acid medium (pH 1.2-6.0) but gradually degraded in the basic medium. In buffer solution polymer samples were intact in the pH range (1.2-6.0) but gradually degraded in buffer solutions of pH > 6. Drug release study was performed for diclofenac sodium and naproxen coated tablets as well as matrix tablets where drugs were embedded in polymer. Firstly, dissolution study of MPBC coated tablets was carried out in simulated gastric fluid (pH 1.2) and in simulated intestinal fluid (pH 7.4). The coated tablet did not degrade or swell in the gastric fluid at the time of experiment for two hours and drug release was found not more than 4% of diclofenac sodium as well as of naproxen. In the intestinal fluid the coated tablet was gradually diminished and around 80.00% of the drug was released from the tablet for next 6 h . On the other hand, the core tablet partially disintegrated and released 61.60 % of diclofenac sodium and 55.10% of naproxen in the simulated gastric fluid and ultimately dissolved faster in the intestinal fluid. The mean (±SEM) percent release of diclofenac sodium and naproxen from the core and coated tablets are given in Fig 1, which reveals that the drug release pattern did not conform to enteric coating requirements (Anon 1988).

Secondly, release kinetics of drug-polymer matrix tablets was performed in buffer solution of pH 7.4 at 37°C. Immersed in phosphate buffer of pH 7.4 at 37°C, a drug-loaded MPBC polymer matrix tablet under stirred condition was found to maintain its shape and physical integrity while decreasing in size during the first 11 h. Thereafter, the matrix began to disintegrate into small pieces, which completely dissolved in the buffer within the next 4 h. Release of diclofenac sodium and naproxen from their drug-loaded polymer matrix tablets in simulated intestinal fluid is presented in Fig 2, which reveals a nearly constant rate of release (zero order) up to 12 h releasing around 88.00% of diclofenac sodium and up to 13 h releasing around 86.50 % of naproxen, afterwards release of the drugs was negligible. Malic acid-phthalic acid-propane1,2-diol copolyester (MPPC) as a drug carrier was investigated by the early researchers (Bakr *et al* 2002). In their investigation, a constant release of drugs from their matrix tablets was found through 11 h releasing 89.10% of diclofenac sodium and 12 h releasing 88.00% of naproxen. It may be assumed that due to the larger chain length present in the monomer of the examined copolyester, release time was increased considerably. For the use of this polymer in biomedical purposes, toxicological and pharmacological tests of the copolyester need to be investigated. The copolyester is expected to be usable as matrix for the controlled and sustained release of drugs.

Acknowledgement: The authors would like to thank the Ministry of National Science and Technology, Bangladesh and the authority of the University of Rajshahi, Bangladesh, for providing financial assistance to carry out the project. They also thank the authority of C.D.R.I., Lucknow, India, for elemental analysis of the polymer sample.

References

Anon 1988 *British Pharmacopoea* 1988 Vol 2, pp A141.

Bakr M A, Islam M A, Karim M A, Sadik G, Biswas M H U 2002 Drug delivery profile of malic acid-phthalic acid-propane 1,2-diol copolyester. *J Polym Mater* **19** 87-92.

Bidah D, Vernaud J M 1991 Dosage forms with a polymer matrix and a swelling polymer. *Int J Pharm* **77** 81-87.

Engelberg I, Kohn J 1991 Physico-mechanical properties of degradable polymers used in medical applications: a comparative study. *Biomaterials* **12**(4) 292.

Graham N B 1978 Polymeric inserts and implants for the controlled release of drugs. *J British Polym* **10** 260-266.

Heller J 1980 Controlled release of biologically active compounds from bioerodible polymers. *Biomaterials* **1** 51.

Kawser M H, Akhter B, Nargis M, Haider S S, Shahriyar S M, Chowdhury F A U 1996 In vitro dissolution pattern of marketed enteric coated diclofenac sodium tablets. *Bangladesh J Life Sci* **8**(2) 15-22.

Madan P L 1990 Sustained release dosage forms. *U S Pharmacist* October pp 39-50.

Ouchi T, Miyazaki H, Tasaka F, Hamada A, Ohya Y 2000 Architecture of polymer micelles from block-copolymers of lactide and depsipeptide as drug carriers. *J Polymer Preprints*, **41**(2) 1637.

Pramanick D, Ray T T 1990 In vitro drug release profile of

bioerodible citric acid glycerol copolymer.*J Applied Polymer Science* **40** 1511-1517.

Rosenberg H B, Chang J, Wnek G E, Linhardt R J, Langer R 1983 Bioerodible polyanhydrides for controlled drug delivery. *Biomaterials* **4** 131-133.

Touitou E, Donbrow M 1982 Drug release from non-disintegrating hydrophilic matrices – Sodium salicylate as a model drug. *Int J Pharm* **11** 355-364.

Yolles S, Leafe T D, Woodland J H R, Meyer F J 1975 Long acting delivery systems for narcotic antagonists II: release rates of naltrexone from poly (lactic acid) composites. *J Pharm Sci* **64** 349.