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Preparation and Evaluation of Film Forming Methacrylic Acid Copolymers

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Copolymers of methacrylic acid (MA) and 2-ethylhexyl acrylate (EHA) were synthesized by emulsion polymerization technique. These were characterized for their physicochemical properties and evaluated for their potential application in pharmaceutical film coating through free film studies and film coating tablets of diclofenac sodium. The copolymers were found to produce flexible, internally plasticized films with low water vapour permeability and adequate mechanical strength that remain insoluble below pH 5 but swell and become permeable to water at and above pH 5. The copolymers may find usefulness as film-forming agents in modified-release applications and as protective coatings against moisture. Preliminary acute oral toxicity studies in mice have indicated that these are quite safe.

Methacrylic acid copolymers are described in USP/NF as fully polymerized copolymers of methacrylic acid and an acrylic or methacrylic ester. These are exemplified by the commercially available anionic Eudragit copolymers based on MA and methyl methacrylate or ethyl acrylate (the ester comonomer) that require external plasticization and afford gastroresistant, enterosoluble coatings[1]. In an earlier study, a copolymer of MA and EHA synthesized by solution polymerization was found to produce flexible internally plasticized films useful for sustained release applications[2]. As an extension of this work, the present study was aimed at synthesizing copolymers of MA and EHA by emulsion polymerization, their characterization and assessing their suitability as pharmaceutical film-forming agents.

EXPERIMENTAL

Three copoiymers were synthesized by emulsion polymerization technique using three different ratios, *viz.*, 30:70, 40:60, and 50:50 (by weight), of MA:EHA in the monomer feed. These were coded as POLY-Q, POLY-R, and POLY-S, respectively. The monomer mixture (40 g) was added gradually to the aqueous phase (160 ml of water containing 0.8 g of sodium lauryl sulphate, 2.0 g of Polysorbate 80 and 0.4 g of sodium persulphate) under stirring at 80±1° and the reaction mixture stirred for an additional 2.5 h at the same temperature. Finally, the temperature was raised to 90±1° and held for 30 min. The total reaction time was 6 h 45 min, which yielded a latex from which the copolymer was isolated by addition of 10% NaCl solution at 80±1°. The isolated copolymer was washed well with water till the washings were free of chloride ions, dried at 50±1° for 3 h, powdered and stored in airtight containers.

The synthesized copolymers were characterized and the following properties were assessed. The solubility in various solvents was determined by agitating 100 mg of each copolymer with 3 ml of solvent system at room temperature for 24 h. The content of MA units in the copolymers was determined by acid-base titration. The rheology was studied on a Brookfield Synchro-Lectric viscometer Model RVT using a spindle bearing number RV2. Moisture absorption by the copolymers was determined at 52, 74.9 and 96% RH at 30±1°. Infrared spectra of thin films of the copolymers on KBr disc were recorded on a Jasco FT/IR 5300 spectrometer. Differential scanning calorimetric studies were conducted using a Mettler TA 4000 (DSC-30) thermoanalyzer at a heating rate of 10° per min in nitrogen atmosphere.

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Free films of the copolymers were prepared by solution casting using 12.5% w/w solutions in 1:1 isopropyl alcohol-acetone mixture (by volume). The film density of the free films was determined from mass and volume data. The tensile strength and percent elongation at break were recorded on Zwick 1435 tensile tester. Folding endurance was determined by manually folding and unfolding the film at a rate of 30 folds per minute. The moisture absorption by the free films was measured at 96% RH and 30±1°. A modification of ASTM:E96-53T was used to measure the water vapour permeability of the free films[3,4]. The behaviour of the free films in buffers[4] was evaluated at pH 1.2, 2, 3, 4, 5, 6, 7, and 8 and 37±1°.

Tablets each containing 50 mg diclofenac sodium were prepared by conventional wet granulation method. The tablets were coated in a conventional coating pan (8.5 inch diameter) with a 5% w/w solution of POLY-S in 1:1 isopropyl alcohol-acetone mixture (by volume) upto 4% weight gain using a pilot spray gun. The uncoated and coated tablets were evaluated for various tablet properties. The *in vitro* drug release profile from both coated and uncoated tablets was studied using USP dissolution apparatus (basket type) at 100 rpm in pH 1.2 buffer for the first 2 h and thereafter in pH 7.2 phosphate buffer at 37±0.5°. The drug content in periodically withdrawn aliquots was analyzed by UV spectrophotometry at 276 nm[5]. The coated tablets were subjected to accelerated stability studies for a period of 30 d under the following conditions: 37±1, 45±1, 60±1° and 85% RH at room temperature.

Preliminary oral acute toxicity of the copolymers was determined in albino mice in the dose range of 1 to 8 g/kg. The test group and control group mice were observed for 14 days post-dosing for gross appearance and behaviour, body weight, food consumption and mortalities, if any.

RESULTS AND DISCUSSION

Emulsion polymerization is the method adopted for the production of the commercial anionic Eudragit copolymers[1]. It is more rapid than solution polymerization at the same temperature, affords polymers with higher molecular weights[6] and also eliminates the flammability and toxicity hazards associated with the use of organic solvents (as in solution polymerization). These, coupled with economic considerations, led to the choice of emulsion polymerization as the method of synthesis of the copolymers. The endproduct of the synthetic procedure was a milky white fluid (latex) which was found to be physically stable on overnight storage. The copolymers were isolated from the latexes by the addition of an electrolyte (10% NaCl) at 80±1°. The yields of the copolymers, calculated with reference to the monomer mixture used for synthesis, were 89.3, 83.9, and 79.3% (w/w) for POLY-Q, POLY-R, and POLY-S, respectively (mean yield of two batches for each copolymer). The washed and dried copolymers were obtained as hard, glassy, translucent to opaque grains, which on powdering yielded free-flowing, white powders with a faint characteristic odour.

A qualitative assessment of the solubility of the copolymers in various solvent systems was conducted with the aim of identifying suitable solvent systems for the copolymers, both for the preparation of free films by solution casting and for the application of the copolymers to the substrate to be coated. The three copolymers were soluble in 1N NaOH indicating the presence of MA units in them. The copolymers were found to be insoluble in water, acetonitrile, chloroform, dichloromethane and ethyl acetate. They were soluble in methanol and isopropyl alcohol, yielding slightly opalescent solutions. The copolymers were swollen in acetone, but were rapidly soluble in polar-nonpolar mixed solvent systems such as acetone-water (9:1), isopropyl alcohol-acetone (1:1), acetone-methanol (1:1) and isopropyl alcohol-dichloromethane (2:1). This is in agreement with the reported observation that the solubility of copolymers is generally low in solvents for either homopolymer, but may be high in mixtures of these solvents since maximum solvation and extension of the polar and non-polar comonomer units occur in a polar-nonpolar mixed solvent system[7]. The content of MA units in the copolymers was found to be 27.49, 33.80, and 39.02 % (w/w) respectively for POLY-Q, POLY-R, and POLY-S. The difference between the content of MA in the monomer feed used for synthesis and that incorporated into the copolymer may be attributed to the loss of the water-soluble MA from the site of polymerization by solution in the aqueous phase. The rheograms of 5% w/w solutions of the copolymers in 1:1 isopropyl alcohol-acetone mixture indicated pseudoplasticity with little evidence of thixotropy. The moisture absorption of the copolymers, calculated on a weight basis, at 52, 74.9 and 96% RH at 30±1° is represented in Fig. 1. The extent of moisture absorption by the copolymers at a given RH and temperature was in direct correlation with their content of hydrophilic MA units. The infrared spectrum of POLY-S film on KBr disc is shown in Fig. 2. The spectrum showed characteristic bands for the C=O vibrations

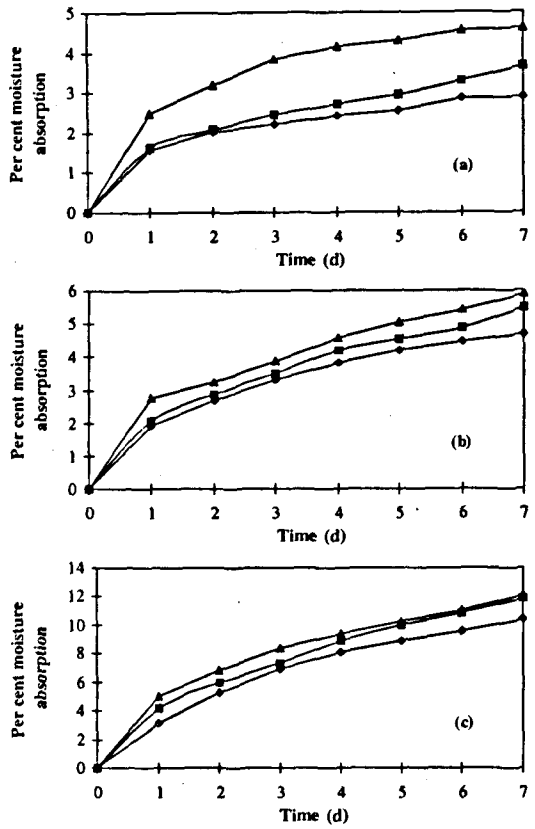

Fig. 1: Moisture absorption patterns of various copolymers

Moisture absorbed by the copolymers POLY-Q (—▲—), POLY-R (—■—), and POLY-S (—◆—) at 30 (1° under relative humidities of (a) 52%, (b) 74.9% and (c) 96%

of the esterified carboxyl groups at 1736 cm^{-1} and of the carboxylic acid groups at 1705 cm^{-1} as well as further ester vibrations at 1170 and 1263 cm^{-1}. CH_x vibrations were observed at 1460 and 1385 cm^{-1}. The band due to C=C stretching (typical of unsaturated monomers) at 1640 cm^{-1} was absent as expected. Similar infrared spectra were obtained for POLY-Q and POLY-R. The DSC scans of the copolymers are shown in fig. 3. The glass transition temperatures (T_g) were found to be 34.5, 38.5, and 35.4° and the melting points (T_m) were observed at 222.8, 220.9, and 227.9° for POLY-Q, POLY-R and POLY-S, respectively.

Results of studies performed on free films prepared by casting 12.5% w/w solutions of the copolymers in 1:1 isopropyl alcohol-acetone mixture are listed in Table 1. The values of tensile strength and percent elongation at

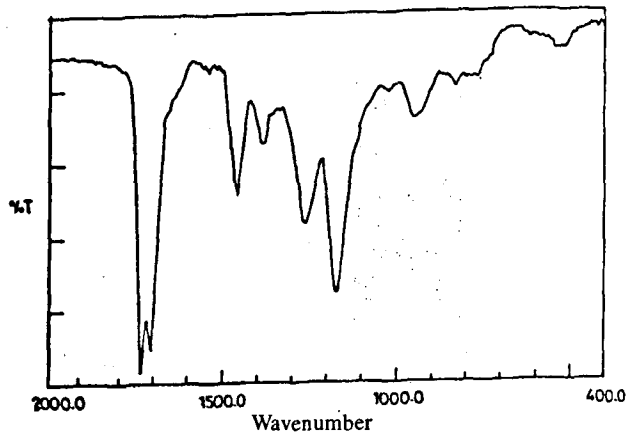

Fig. 2: Infrared spectrum of POLY-S film on KBr disc

break for the free films of the copolymers were favourably higher than those reported for plasticized free films of Eudragit L-100 and Eudragit S-100[8]. The ability of the copolymers to form internally plasticized films may be attributed to the presence of a higher proportion of the long-chain ester comonomer (EHA) in the copolymers relative to their content of MA units. POLY-Q, with its relatively higher content of EHA units, afforded films with higher values of percent elongation at break and folding endurance as compared to POLY-R and POLY-S. The low moisture absorption and water vapour permeability of the free films indicate their suitability as protective coatings against moisture. The water vapour permeability constant at a given RH and temperature, as calculated using the formula given by Patel *et al.*[9], was found to be the highest for POLY-S films, followed by films of POLY-R and POLY-Q. This is in agreement with the reported observation that the water vapour transmission is dependent on the relative polarity of the polymer[3]. The films of all three copolymers remained insoluble at pH 1.2, 2, 3 and 4 as evidenced by no change whatsoever in their character/ integrity in these buffers. In buffers of pH 5, 6, 7 and 8, the films were found to swell and become permeable to water, which was evident from a change in the clarity of the films from transparent to translucent and an increase in their volume. Also, at pH ≥ 5, the films did not crack or break in spite of perceptible softening, which render the copolymers useful as coating agents which produce films that remain intact during drug delivery. Resistance of the films to buffers of pH < 5 and swelling in buffers of pH ≥ 5 may be attributed to a combination of the pH-independent character of the nonpolar, relatively hydrophobic ester comonomer (EHA) units and the pH-dependent ionization of the polar MA units of the copolymers.

TABLE 1: FREE FILM STUDIES

	POLY-Q	POLY-R	POLY-S
Appearance	transparent, flexible, uniform in thickness, odourless, non-tacky		
Film density (g/cm^3)	1.08 ± 0.04	1.06 ± 0.04	1.06 ± 0.03
Tensile strength (N/cm^2)	1545.5 ± 196.5	1402.4 ± 102.7	1564.58 ± 64.99
Elongation at break (%)	62.18 ± 10.32	16.21 ± 2.67	5.36 ± 0.84
Folding Endurance (no. of folds to break the specimen)	628 ± 39	593 ± 19	464 ± 40
Moisture absorption at 96% RH and 30±1° (% w/w)	0.26	1.87	3.27
Water vapour permeability constant (g/cm/mm of Hg/24 h) at 30±1°			
52% RH	2.21 x 10^{-6}	3.27 x 10^{-6}	3.96 x 10^{-6}
74.9% RH	2.43 x 10^{-6}	3.43 x 10^{-6}	5.21 x 10^{-6}
96% RH	3.48 x10^{-6}	5.03 x 10^{-6}	6.45 x 10^{-6}
Behaviour in buffers	insoluble at pH < 5, swollen at pH ≥ 5		

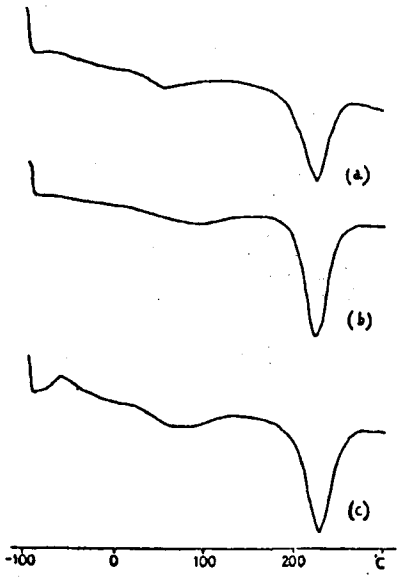

Fig. 3: Differential scanning calorimetry thermograms of copolymers

Differential scanning calorimetry thermograms of (a) POLY-Q (Tg 34.5°, Tm 222.8°), (b) POLY-R (Tg 38.5°, Tm 220.9°) and (c) POLY-S (Tg 35.4°, Tm 227.7°)

As an extension to free film studies, a study was undertaken to evaluate the performance of the copolymers in film coating diclofenac sodium tablets. The copolymer POLY-S was selected for this study. Results of tests performed on coated and uncoated tablets are given in Table 2. The uncoated tablets were found to be satisfactory substrates for film coating. The *in vitro* drug release profiles from uncoated and coated tablets are shown in Fig. 4. The copolymer POLY-S provided slow release of diclofenac sodium. No significant changes in physical appearance, drug content and *in vitro* drug release

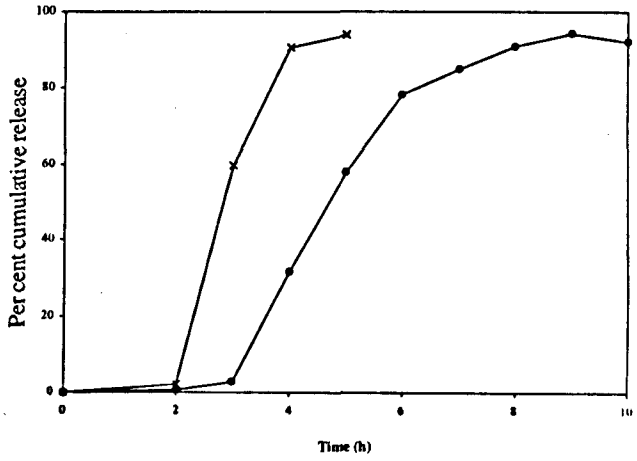

Fig. 4: *In vitro* release profiles of diclofenac sodium formulations

***In vitro* release of diclofenac was determined at various time points from uncoated (—✖—) and coated (—●—) tablets**

TABLE 2: CHARACTERISTICS OF UNCOATED AND COATED DICLOFENAC SODIUM TABLETS

Test	Uncoated tablets	Coated tablets
Appearance	Biconvex, circular, odourless, off-white, with smooth surface and no visible flaws	
Diameter (mm)	8.08 ± 0.01	8.27 ± 0.07
Crown thickness (mm)	3.57 ± 0.03	3.87 ± 0.07
Hardness (kg/cm2)	2.5-3.0	4.5-5.5
Friability (%)	0.35	—
Drug content (mg)	47.59 ± 0.20	47.31 ± 0.37
Average weight (mg)	198.85 ± 6.58	207.30 ± 7.57
Disintegration time	5 min (water)	Intact (0.1N HCl, 2 h) swollen (pH 6.8, 1 h)

profile Fig. 5 were observed during accelerated stability studies carried out on the coated tablets.

The mice administered with the copolymers orally in the acute toxicity study showed comparable behaviour with the control group. No mortalities were observed during the study period (14 d), except for one mortality in the group dosed with 4 g/kg of POLY-S. The high degree of safety of the copolymers is indicated by their oral LD_{50}>8 g/kg body weight. Further toxicological investigations (*in vivo* and *in vitro* toxicity and biological reactivity tests) are in progress to confirm the safety of the copolymers for pharmaceutical use.

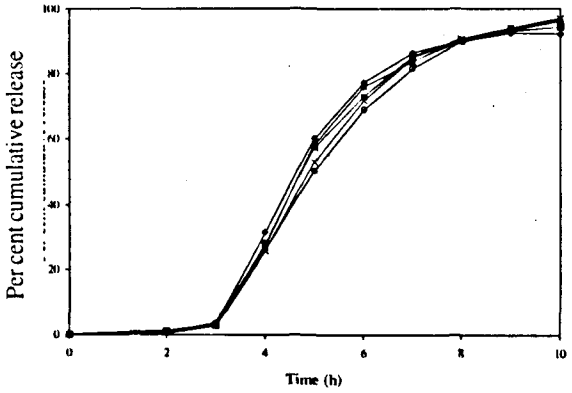

Fig. 5: *In vitro* release profiles of diclofenac sodium formulations after stability testing

***In vitro* release of diclofenac sodium was determined for 10 h from coated tablets subjected to accelerated stability testing for 30 days at room temperature (-◆-), 37 ± 1° (—■—), 45 ± 1° (—▲—), 60 ± 1°(—✖—) and 85% RH (—○—)**

In conclusion, MA copolymers prepared by emulsion polymerization using a long-chain ester (EHA) as a comonomer produced internally plasticized films having adequate mechanical strength and low water vapour permeability and may be considered for use in pharmaceutical film coating for modified-release applications and protection against moisture. Preliminary oral toxicity studies in mice have indicated that these copolymers are quite non-toxic.

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