

Modification of Solute Dissolution Rate by Coprecipitation with Certain Acrylate–Methacrylate Copolymers

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Synopsis

Coprecipitates containing certain cationic acrylate–methacrylate copolymers and paracetamol (polar solute) have been prepared by evaporating to dryness an ethanolic solution of both components; their friability (i.e., degree of crumbling to dust under impact stress) and dissolution characteristics were evaluated. Friability decreased with increase in the polymer content of the coprecipitates; this effect was more marked in the polymer system containing the higher cation content. Dissolution rates also decreased with increase in polymer content, but this time the effect was slightly more pronounced in the polymer system with the lower cation content. It is thought that the polymer cationic groups interacted with polar groups of the solute to increase coherence of the particle; on the other hand, the cationic groups confer hydrophilic character and at certain concentrations, > 5% they may promote swelling in aqueous fluids and hence weaken bonding forces in the solute–polymer particle with a tendency to reduce the polymer effect on dissolution rate.

INTRODUCTION

In some practical situations, it may be desirable to control solute dissolution rate: For instance, the rate of drug absorption depends on its dissolution rate; thus a slowly dissolving system may be expected to provide a sustained drug action. Polymeric film coatings have been applied on solute particles to control dissolution rates.¹ A phenomenon which has not been fully explored to obtain controlled dissolution rates is the physical interaction between polymer chains and other solutes during their simultaneous desolvation from a common solvent (i.e., coprecipitation) to form coherent solid particles. Coprecipitation of water-soluble polymers such as poly(ethylene glycol)² and polyvinylpyrrolidone³ with poorly soluble solutes have been used to enhance dissolution rates of such solutes. Polymers used in the present study were insoluble in water but had in their chemical structure cationic quaternary ammonium groups which conferred hydrophilic swelling character.^{4,5} The objective of this work was to develop slowly dissolving forms of the test solute, and in the approach the cationic polymer was coprecipitated with a solute having hydroxyl polar group, with the hypothesis that the ionic–dipole interaction would contribute to the overall cohesive energy in the resulting solute–polymer particle and thus influence its dissolution rate.

MATERIALS AND METHODS

Two acrylate–methacrylate copolymers designated A and B (Fig. 1) were received from Rhom Rharma, Darmstadt, under the trade names Eudragit

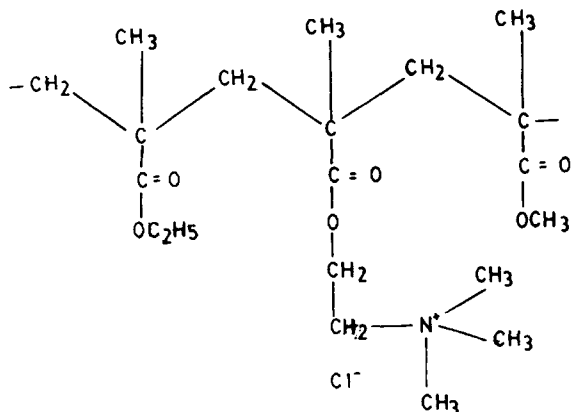


Fig. 1. Chemical structure of the acrylate-methacrylate copolymer. Cation content (mol/mol polymer chain) in polymer A = 66 and in B = 33 (see Ref. 5).

RL-100 and RS-100, respectively. They differ only in their content of quaternary ammonium (cation) groups in the ratio 2 : 1 (A : B). Paracetamol BP was selected as test solute because it has in its chemical structure polar hydroxyl groups which could undergo electrostatic bonding with the polymer cationic groups; also both paracetamol and the polymers are soluble in the selected solvent ethanol, 95% BP supplied by BDH Chemicals, Poole, England.

Preparation of Coprecipitates

Five grams of paracetamol (solute) and each of the following quantities of the polymer, 50, 155, 263, 556, 882, and 1250 mg, were dissolved in 30 mL ethanol, 95%. The solution in a shallow crucible was evaporated to dryness by heating in a water bath at 90°C; stirring with a glass rod was continuous during the last 10 min of the dissolution. The dried mass was first crushed with pestle and mortar and then pressed through a wire mesh sieve (aperture size, 710 μm). Particles undersize to 500 μm were removed by shaking the granular mass on a sieve of this aperture size, 500 μm . Samples were stored in a desiccator charged with dried silica gel, not longer than 48 h before their evaluation.

Particle Friability Test

This test is a measure of the particle resistance to crumbling when subjected to impact stress, and thus provides an indication of the cohesive strength within the particle. Five grams of the coprecipitate (size range 500–710 μm), was placed in the plastic drum of an Erweka friabulator (model T.A). A sigmoid-shaped baffle in the drum lifted the material and subsequently threw it against the walls of the drum, when the latter was rotated, 25 rpm for 1 h by an electric motor. At the end of a test run, fines in the material were sifted out through sieve (aperture size 150 μm). The sieve was mounted on a mechanical sieve shaker (Endecotts, 2 MK II) vibrating at 50 cps for 10 mins. Each determination was carried out in triplicate, and the mean percentage weight loss was taken as the friability index.

Dissolution Rate Test

The apparatus consisted of a pyrex glass vessel containing 1000 mL of the dissolution medium (water maintained at $37 \pm 0.5^\circ\text{C}$); a cylindrical basket which contained the test sample was made of stainless steel wire mesh (aperture size, $425 \mu\text{m}$), and it was similar in dimensions to the rotating basket for dissolution test described in the British Pharmacopoeia 1980. The basket was suspended midposition in the dissolution medium by means of a glass rod glued into a rubber bung, which also served as a closure for the open end of the basket. With an aliquot of the coprecipitate containing 500 mg of test solute in the basket, the dissolution medium was stirred, 100 rpm, using a Gallenkamp, single blade, stirrer. Two-milliliter samples were withdrawn, from the dissolution medium at selected time intervals for 90 mins, using a pipette with a cotton wool plug. Samples were filtered through no. 3 Whatman filter paper and suitably diluted before their spectrophometric analysis at $\lambda_{\text{max}} = 257 \text{ nm}$ using the unicam SP 1800, UV spectrophotometer. The experiment was carried out in triplicate; results were reproducible to $\pm 10.5\%$ of the mean.

RESULTS AND DISCUSSION

A low friability of the particles indicates stronger cohesion; the friability of the particles decreased exponentially as polymer content increased in the coprecipitates (Fig. 2). These values were slightly lower in coprecipitates

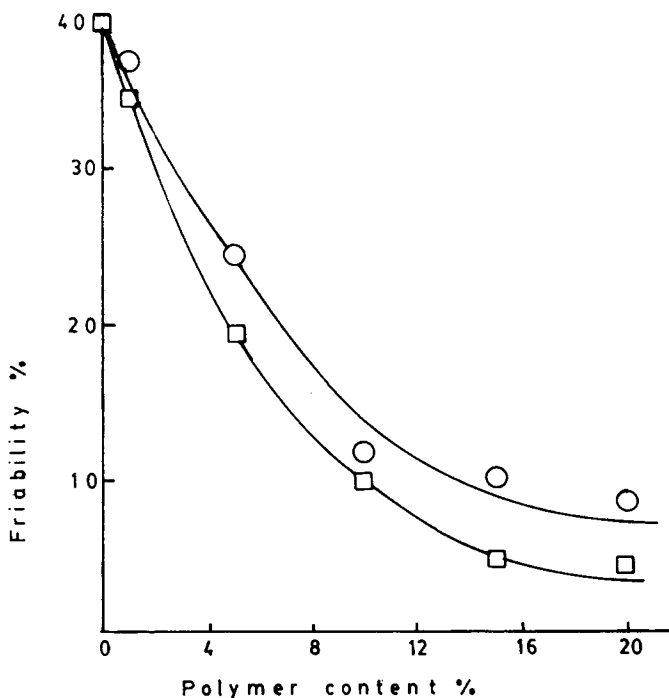


Fig. 2. Friability (i.e., degree of crumbling to fine powder) in coprecipitates containing polymer A (□) and B (○).

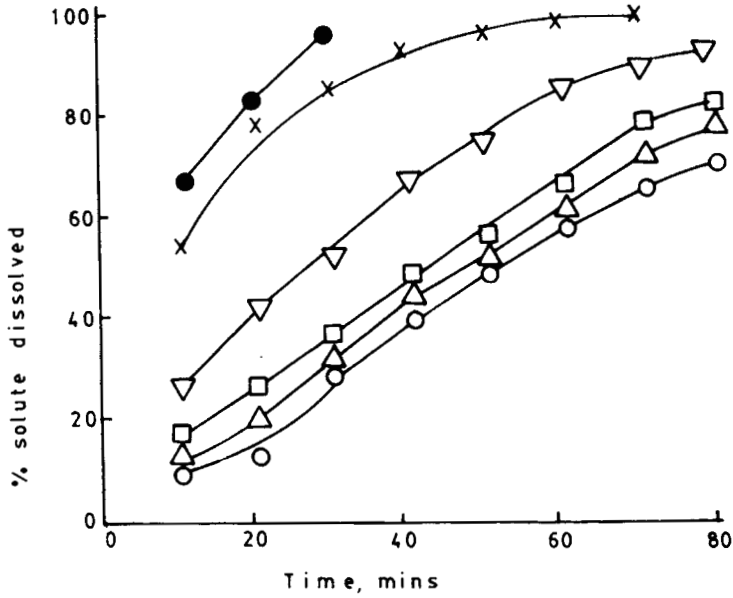


Fig. 3. Amounts of solute dissolved from coprecipitates with varying content of polymer A: (●) 0%; (×) 1%; (▽) 5%; (□) 10%; (Δ) 15%; (○) 20%.

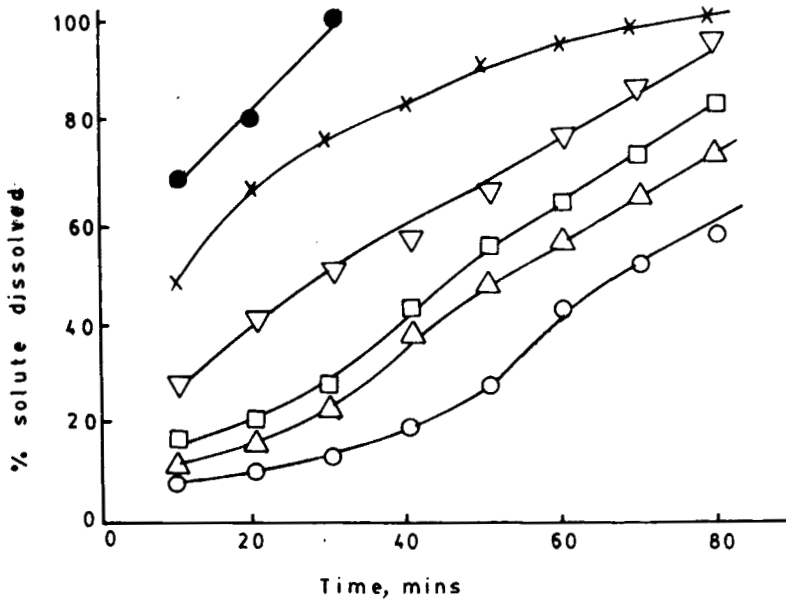


Fig. 4. Amounts of solute dissolved from coprecipitates with varying content of polymer B: (●) 0%; (×) 1%; (▽) 5%; (□) 10%; (Δ) 15%; (○) 20%.

containing polymer A compared with polymer B, suggesting greater cohesion in A. This observation suggests strong bonding between the solute molecules and polymer chains; polar interactions of the solute with the cationic groups in the polymer structure may have contributed since polymer A with the higher cation content formed more coherent particles. Polymers in the coprecipitates were insoluble in water; therefore, the dissolution test results referred to paracetamol only as the solute. Amounts of solute dissolved decreased with increase in polymer content [Fig. 3 (polymer A) and Fig. 4 (polymer B)]. Dissolution rate constants were obtained from the slopes of the first-order equation⁶:

$$\log(a - x)/a = -kt/2.303 \quad (1)$$

where a is the initial amount of solute in the coprecipitate, x is the amount dissolved in time t , and k is the dissolution rate constant. Like the friability data (Fig. 2), the dissolution rate constants also decreased exponentially (Fig. 5), suggesting a correlation between friability and dissolution rate, i.e., the decrease in dissolution rate could be associated with particle coherence. This change was more marked at polymer content 0–5% (Fig. 5) with lower decreases at higher concentrations, 5–20%, while the cationic groups contributed to the cohesive strength on the particles; it also promoted swelling when the particles were in contact with the aqueous dissolution medium. Internal stress arising from the swelling of the particles has a potential for

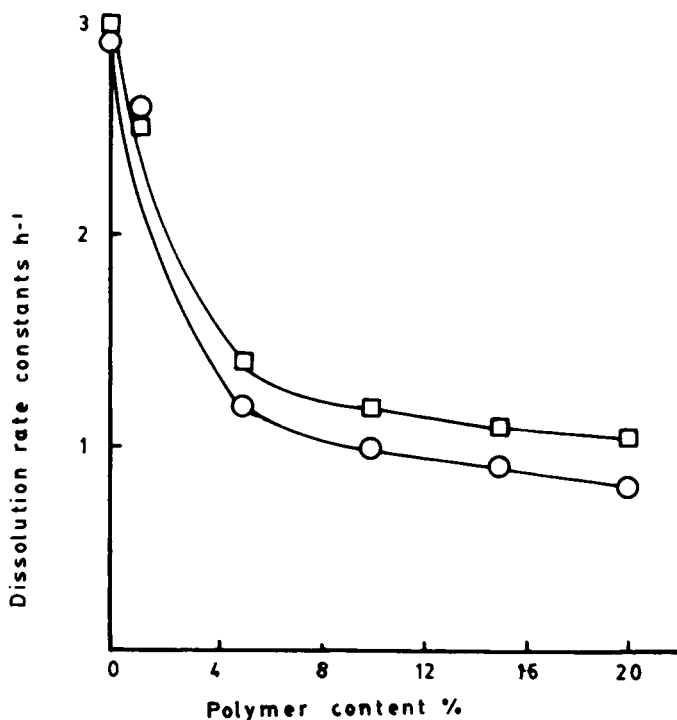


Fig. 5. Changes in the dissolution rate constants with varying concentrations of polymer in the coprecipitates; polymer A (□) and B (○).

weakening bonds in the particles; hence the polymer effect on decreasing the dissolution rate were less marked at the higher polymer contents. Higher swelling of polymer A explains the lower decreases in dissolution rate observed with this polymer.

The structural model of the system studied may be conceived as a fine dispersion of the polymer in the solute both held together by physical (van der Waals and ionic-dipole) bonds. The various molecular associations will include: P—S, S—S, and P—P, where P is the polymer chain and S the solute molecule. The observed modification of the solute dissolution rates could be attributed more particularly to the P—S bonds, notably the cationic-dipole interactions.

CONCLUSIONS

The results have shown that the coprecipitation of cationic acrylate-methacrylate copolymers with polar solutes leads to the formation of coherent particles; ionic-dipole interactions contributed to the coherence. Consequently, the water-insoluble polymers decreased the dissolution rate of the solute in a concentration-dependent manner; the system therefore lends itself to controlled release applications.

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