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Technical Note

Effects of a Diluent on the Retarded-Release Property of Acrylate Methacrylate–Salicylic Acid Coacervates

R. S. Okor[1] and M. A. Yahaya[1]

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A recent study (1) showed that granular coacervates containing an acrylate methacrylate copolymer and salicylic acid (ratio, 1:4) displayed retarded release. Drug release was further retarded by compressing the granules to hard and poorly disintegrating tablets (1). This observation relates to the cohesion of adjacent polymeric particles in the coacervate structure to form a continuous matrix during compression. Thus, the degree of cohesiveness in the matrix and hence drug release rates may be modified by addition of a diluent.

In the present investigation, polymer–drug coacervates were formed using the following prcedure: 1 g of an acrylate methacrylate copolymer (trade name, Eudragit RS100; received from Rhom Pharma, Darmstadt) and 4 g of salicylic acid (reagent grade, BDH) were dissolved in absolute alcohol BP (10 ml), and sodium chloride solution (0.1 *M* aq 90 ml) was added to the ethanolic solution while shaking the container. Sodium chloride (analar grade, BDH) served as a flocculant (2). The flocculated particles were collected by filtration, washed three times with water to remove the salt, dried at 80°C for 24 hr, and then pressed through a sieve (aperture size, 710 μm) to form granules of size range 710/120 μm. The granules were mixed with a directly compressible modified starch in different proportions such that as the content of starch increased, the drug content decreased (Table I). The coacervate–starch blends were compressed to tablets of mean weight 139.5 ± 0.5 mg. Tablet hardness varied depending on the starch content. Maize starch BP was acid treated (0.1 *N* HCl) for 24 hr at 30°C and subsequently washed three times with water to remove the acid. This treatment rendered the starch directly compressible.

Tablet disintegration testing was carried out using the method described in the British Pharmacopeia (BP) 1980, while tablet hardness was measured with the Pfizer hardness tester. Drug dissolution tests on the granules and tablets also followed the BP method but with the modification that the basket which contained the sample was not rotated; instead, the dissolution medium (i.e., 800 ml water at 37°C) was stirred at 100 rpm with a Gallentenkamp single-blade stirrer. After 3 hr a sample (5 ml) was withdrawn from the leaching fluid, and ferric chloride solution (5%, w/v, 1 ml) was added. The sample was allowed to stand 5 min, during which a blue color developed. Absorbance of the colored sample was read at λ_{max} 540 nm using a UV spectrophotometer (Unicam SP 500). The amount of salicylic acid released in 3 hr was expressed as a percentage of the initial drug content in the tablet or granules (see Table I). The experiment was carried out in triplicate; individual results were reproducible to ±9.5% (SD) of the mean.

Structure of the granular coacervates was studied using photomicroscopy. To prepare a slide, a drop of ferric chloride solution (5%, w/v) was added to the granules, which had been spread thinly on the slide. Photomicrographs were taken at ×16 (the magnification which gave a clear resolution).

The results (Fig. 1) showed that the diluent (starch) had profound effects on the hardness, disintegration, and drug release properties of the tablets. An increase in starch content led to decreases in tablet hardness and disintegration times (starch content >40%, w/w), while drug release increased to a maximum (82%) corresponding to a starch content of 46% (w/w). At lower starch contents (0 to 40%, w/w) the tablets did not disintegrate during the 3-hr dissolution

Table I. Composition of Tablets Used in the Dissolution, Disintegration, and Hardness Tests[a]

Content per tablet (mg:)			
Salicylic acid (drug)	Polymer	Starch	Starch content (%)
112	28	—	0
100	25	15	11
90	22	28	20
80	20	40	29
70	18	52	37
60	15	65	46
50	13	77	55
40	10	90	64

[a] The starch was added to preformed coacervates containing the polymer and the drug at a fixed ratio, 1:4; tablet weight = 140 mg.

[1] Department of Pharmaceutics, University of Benin, Benin City, Nigeria.

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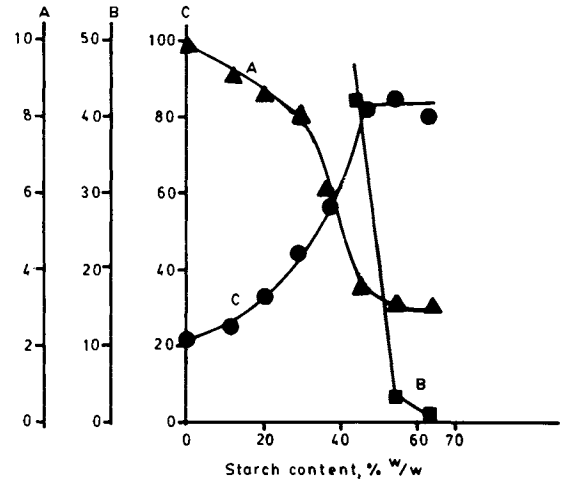

Fig. 1. Changes in tablet properties with variations in starch content in the tablets. Ordinate: A, tablet hardness (kg); B, disintegration time (min); and C, drug release (%). Note: tablets with a starch content of 40% (w/w) failed to disintegrate within the 3-hr test period.

test; instead they softened to form a gelatinous mass, perhaps as a result of hydration of hydrophilic (cationic) sites in the polymer chemical structure (3). A photomicrograph (Fig. 2) of a sample of the granular coacervate containing the polymer and drug only (no starch) revealed the presence of free (unentrapped) crystals of salicylic acid (designated a) and polymeric particles in which a portion of the salicylic acid was entrapped (designated b). Blue coloration of the polymeric particles indicated the presence of salicylic acid. It has been suggested (1) that during compression these polymeric particles interlaced (through strong cohesive forces) to form a continuous matrix in which the otherwise free portion of salicylic acid (a) was now entrapped. Drug release from such a system occurred by a slow diffusion through the matrix. This structural model is based on a previous finding that drug release was more retarded in tablets compared with granules of the coacervates (1). In the present study drug released in 3 hr from the granules of the coacervates (without starch) was 40%, and that from the corresponding tablets, 22%; the

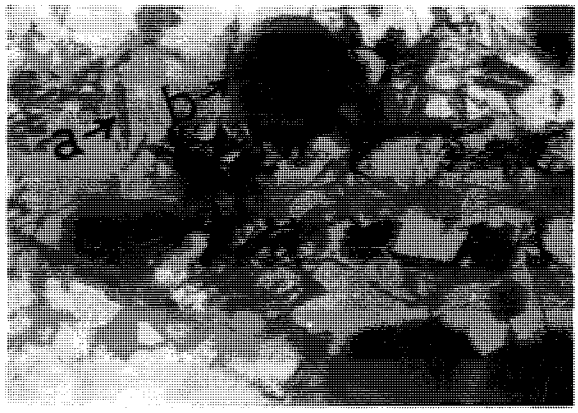

Fig. 2. Photomicrograph of the polymer–drug coacervate granules showing the free drug crystals (a) and the polymer–drug particles (b). ×16; reduced 10% for reproduction.

release from an equivalent weight of the pure drug (112 mg) was considerably higher, 80% in 3 hr.

It is expected that in the presence of a diluent the polymeric particles in the granules (Fig. 2) will be more sparsely dispersed, with a reduced tendency for polymer–polymer cohesion, resulting in lower tablet hardness and shorter disintegration times. Since tablets containing starch (0 to 40%, w/w) failed to disintegrate within 3 hr; the maximum concentration of starch which allows matrix formation will be about 40% (w/w). In spite of the poor disintegration property of the matrix tablets generally, drug release rates increased exponentially with starch content, 0 to 46% (w/w) (Fig. 1). This finding is attributable to a progressive decrease in polymer–polymer cohesiveness within the matrix structure.

The conclusion is that in certain situations the coacervate–diluent system studied may be exploited for controlled release applications.

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