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Characterization and Drug Release Studies on Ethylene Vinyl Acetate Copolymer Microcapsules

K. P. R. CHOWDARY* AND J. SURI BABU
Industrial Pharmacy Division
Department of Pharmaceutical Sciences,
Andhra University, Visakhapatnam-530 003

Microencapsulation by ethylene vinyl acetate copolymer (EVA) and the resulting microcapsules were investigated. EVA microcapsules of indomethacin were prepared by an emulsion solvent evaporation method employing various proportions of coat and core materials and chloroform as solvent for the polymer EVA. The microcapsules are spherical, discrete and free flowing. Microencap-sulation efficiency was in the range of 87-99%. Indomethacin release from the microcapsules was slow and extended over more than 12 h and depended on coat:core ratio, wall thickness and size of the microcapsules. Drug release was diffusion controlled and followed first order kinetics. Good linear relationships were observed between wall thickness and release rate and T_{50}(time for 50% release) values. Some microcapsules fulfilled the official (USP XXIII) dissolution rate test specification of indomethacin extended release capsules. Differential scanning calorimetry (DSC) indicated no interaction between the coat polymer (EVA) and the core (indomethacin).

Microencapsulation by various polymers and their applications are described in standard text books[1,2]. Ethylene vinyl acetate copolymer (EVA) is a copolymer of ethylene and vinyl acetate. Though EVA has good film forming properties[3,4], its potential in microencapsulation has not been investigated. No reports are available on microencapsulation by EVA copolymer. In the present work microencapsulation by EVA and the feasibility of preparing EVA microcapsules by an emulsion solvent evaporation method were investigated. Indomethacin, which requires controlled release owing to its short biological half-life[5] of 2.4 ± 0.4 h and gastrointestinal side effects such as peptic ulceration with bleeding, was microencapsulated by EVA and the resulting microcapsules were studied.

MATERIALS AND METHODS

Indomethacin was was a gift sample from M/s. Micro Labs Ltd., Pondicherry. Ethylene vinyl acetate copolymer (Grade 1408) was procured from M/s Polyolefins Industries Ltd., Mumbai. Chloroform GR (Merck) and sodium carboxy methyl cellulose (sodium CMC with a viscosity of 1500-3000 cps of a 1% w/v solution at 25°, Loba Chemie) were procured from commercial sources.

*For correspondence

Microcapsule preparation:

EVA copolymer (0.5 g) was dissolved in warm chloroform (25 ml) to form a homogenous polymer solution. Core material, indomethacin, (0.8 g) was added to the polymer solution (10 ml) and mixed thoroughly. The resulting mixture was then added in a thin stream to 200 ml of an aqueous mucilage of sodium CMC (0.5%) contained in a 450 ml beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A Remi Medium, Duty Stirrer with speed meter (Model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28°) for 3 h to produce spherical microcapsule. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air-dried to obtain discrete microcapsules. Different proportions of core to coat materials namely 9:1 (MC 1), 8:2

(MC 2), 7:3 (MC 3) and 6:4 (MC 4) were used to prepare microcapsules with varying coat thickness.

Estimation of indomethacin:

Indomethacin content in the microcapsules was estimated by an UV spectrophotometric method[6] based on the measurement of absorbance at 318 nm in phosphate buffer of pH 6.2. The method was validated for linearity, accuracy, and precision. The method obeyed Beer's law in concentration range 0-40 µg/ml. When a standard drug solution was assayed repeatedly (n=6), the mean error (accuracy) and relative standard deviation (precision) were found to be 1.2% and 2%, respectively.

Characterization of microcapsules:

Microencapsulation efficiency was calculated using the formula microencapsulation efficiency = (estimated percent drug content/ theoretical percent drug content)x100. For size distribution analysis, different sizes in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed. Wall thickness of microcapsules was determined by the method of Luu *et al.*[7] using the equation;

$$h = \frac{r\,(1 - p)d_1}{3[pd_2 + (1 - p)d_1]}$$

where h is the wall thickness, r is the arithmetic mean radius of the microcapsules, d_1 is the density of core material, d_2 is the density of the coat material and p is the proportion of the medicament in the microcapsules.

Drug release studies:

Release of indomethacin from the microcapsules of size 20/35, and 35/80 was studied in phosphate buffer of pH 6.2 (900 ml) using an USP XXIII three-station Dissolution Rate Test Apparatus (Model DR-3, M/s Campbell Electronics) with a basket stirrer at 75 rpm as per USP XXIII dissolution rate test prescribed for indomethacin extended release capsules[6]. A sample of microcapsules equivalent to 75 mg of indomethacin were used in each test. Samples were withdrawn through a filter (0.45 µm) at different time intervals and were assayed at 318 nm for indomethacin using a Shimadzu UV-150 double-beam spectrophotometer. The drug release experiments were conducted in triplicate.

Differential scanning calorimetry:

DSC was performed on indomethacin, EVA and EVA microcapsules of indomethacin using Sieko (Japan) DSC model 220C. Samples were sealed in aluminium pans, and the DSC thermograms were recorded at a heating rate of 10°/min from 30° to 300°.

Scanning Electron Microscopy:

The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S430, UK). For SEM, the microcapsules were mounted directly onto the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

RESULTS AND DISCUSSION

EVA microcapsules of indomethacin could be prepared by an emulsion solvent evaporation method employing chloroform as solvent for the polymer. The microcapsules were found to be discrete, spherical and free flowing. SEM (fig. 1) indicated that the microcapsules are spherical with smooth surface and completely covered with the polymer coat. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained. The size analysis of different microcapsules showed that about 54 and 34 percent were in the size range of -20+35 (670 µm) and 35+80 (333.5 µm) mesh size respectively. A log normal size distribution of the microcapsules was observed in all the batches prepared.

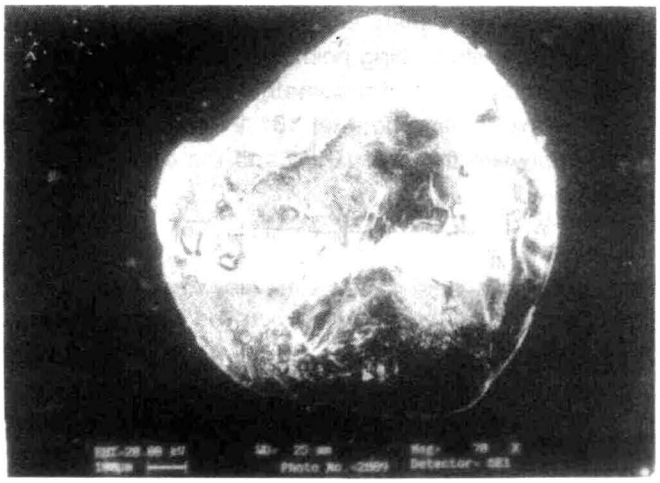

Fig. 1: SEM photograph of Microcapsules MC 2

The microcapsules are spherical and completely covered with the polymer.

Low C.V. (<3.0%) in percent drug content indicated uniformity of drug content in each batch of microcapsules (Table 1). The microencapsulation efficiency was in the

TABLE 1: DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS OF EVA MICROCAPSULES

Microcapsules (size)	Indomethacin content (%) of microcapsules		Microencapsulation efficiency (%)	Wall thickness (μm)
	Theoretical	Practical		
MC1 (20/35)	90	82.32 (0.86)	91.46	47.8
MC1 (35/80)	90	89.35 (0.90)	99.27	14.8
MC2 (20/35)	80	77.72 (1.24)	97.15	59.9
MC2 (35/80)	80	78.53 (0.64)	98.16	28.8
MC3 (20/35)	70	63.60 (2.79)	90.85	91.8
MC3 (35/80)	70	62.69 (2.61)	89.56	46.9
MC4 (20/35)	60	52.32 (0.85)	87.20	119.2
MC4 (35/80)	60	53.02 (0.84)	88.36	58.2

*Figures in parentheses are coefficient of variation (CV) values

range 87-99% with various products. Drug content of the microcapsules was found to the same in different sieve fractions. As the microcapsules are spherical the wall thickness of the microcapsules was calculated as per Luu *et al.*[7] Microcapsules prepared employing various ratios of coat:core were found to have different wall thickness (Table 1).

DSC thermogram of indomethacin of indomethacin (fig. 2) exhibited a sharp endothermic peak at 162.3° corresponding to its melting point. The DSC thermogram of EVA microcapsules of indomethacin also exhibited an endothermic melting peak at 161.1° indicating no interaction between the coat (EVA) and the core (indomethacin).

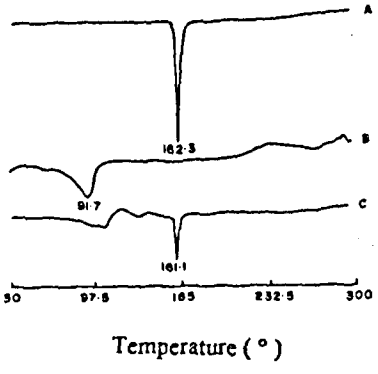

Fig. 2: DSC thermograms of Microcapsules.

DSC thermograms of indomethacin (A), EVA copolymer (B) and microcapsules MC2 (Size 20/35) (C).

Indomethacin release from the microcapsules was studied in phosphate buffer of pH 6.2 for a period of 12 h as prescribed in the dissolution rate test of indomethacin extended release capsules in USP XXIII. Indomethacin release from the microcapsules was slow and spread over extended periods of time (Table 2). Release followed first -order kinetics ($r>0.98$) and depended on coat:core ratio and size of the microcapsules. As the proportion of coat increased, indomethacin release decreased. The release increased as the size of the microcapsules decreased. Good linear relationships were observed between wall thickness of the microcapsules and drug release rate and T_{50} (time for 50% release) values (fig. 3). The drug release mechanism from the microcapsules was diffusion controlled as plots of the amount released versus square root of time were found to be linear ($r>0.96$). Microcapsules MC 1 and MC 2 of size 20/35 fulfilled the official (USP XXIII) dissolution rate test specification of indomethacin extended release capsules.

Thus, spherical microcapsules of EVA copolymer could be prepared by emulsion-solvent evaporation method. Microencapsulation efficiency was found to be in the range of 87-99%. Indomethacin release from the EVA microcapsules was slow and extended over longer periods of time and depended on coat:core ratio, wall thickness and size of the microcapsules. Drug release was diffusion controlled and followed first order kinetics. The EVA microcapsules were, thus, found suitable for

TABLE 2: RELEASE CHARACTERISTICS OF EVA MICROCAPSULES OF INDOMETHACIN

Micro capsule	Percent Indomethacin Released at Times (h) ($\bar{x}$± s.d.)					T_{50} (h)	$K_1 \times 10^2$ (h^{-1})
	1.0	2.0	4.0	8.0	12.0		
Size-20+35							
MC1	26.04±0.28	45.24±1.37	62.75±0.65	80.83±0.89	96.33±0.04	2.6	23.95
MC2	25.70±3.36	40.33±4.09	58.90±4.24	75.44±3.92	88.81±2.59	2.8	13.81
MC3	22.49±0.38	34.40±0.68	46.71±0.43	65.28±2.57	72.92±0.84	4.5	9.67
MC4	20.53±1.97	31.58±0.60	47.25±4.39	60.41±3.27	71.99±0.48	5.0	6.19
Size-35+80							
MC1	71.03±8.57	86.22±6.97	89.47±6.84	95.90±1.70	96.82±0.11	0.5	41.91
MC2	36.68±1.83	59.28±2.86	77.91±1.16	92.07±0.96	96.89±0.05	1.5	25.79
MC3	21.37±0.85	32.85±1.28	50.38±0.99	67.36±0.44	79.34±2.17	4.0	11.97
MC4	23.89±0.23	36.28±1.20	47.16±0.85	63.05±4.17	72.59±2.84	4.6	10.13

T_{50} is time for 50% release and K1 is first order release rate constant

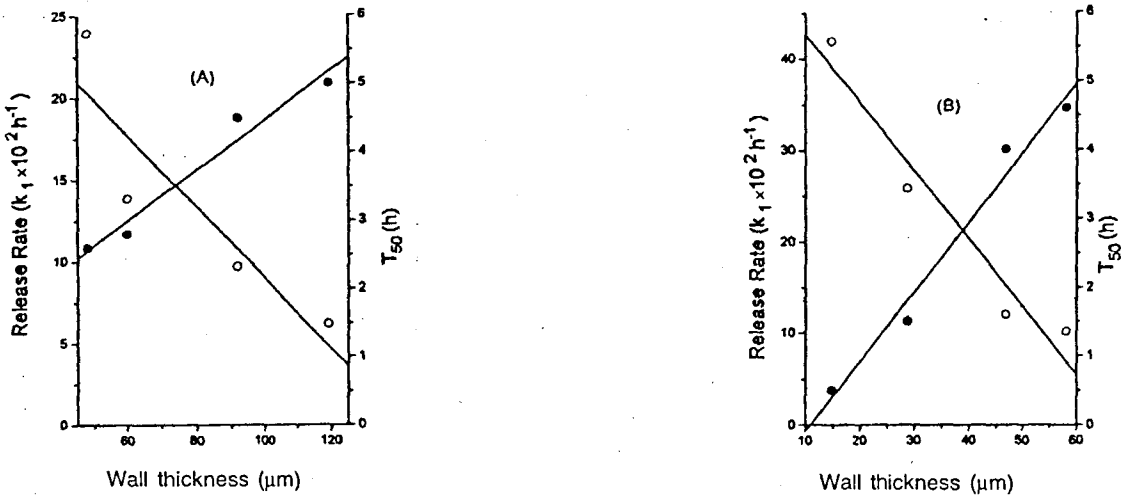

Fig. 3: Relationship between wall thickness, release rate and T_{50} values of microcapsules.
Relationship between wall thickness of microcapsules and release rate (o) and T_{50} values (●) for microcapsules of size 20/35 (A) and 35/80 (B).

formulation of oral sustained release products.

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