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Permeability of Ethylene Vinyl Acetate Copolymer Microcapsules: Effect of Solvents

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Ethylene vinyl acetate copolymer microcapsules of indomethacin were prepared by an emulsification–solvent evaporation method employing chloroform or cyclohexane or dichloromethane or 1,2-dichloroethane as solvent for the polymer ethylene vinyl acetate and the microcapsules were studied. All the microcapsules were spherical, discrete and free flowing. The microencapsulation efficiency was relatively high when chloroform was used as solvent. Indomethacin release from the microcapsules was slow and extended over more than 12 h. Drug release from all the microcapsules was diffusion controlled and followed first order kinetics. The solvent employed has significant influence on the permeability and drug release from the microcapsules. The order of increasing permeability of ethylene vinyl acetate microcapsules prepared employing various solvents was cyclohexane<dichloromethane<1,2-dichloroethane<chloroform. Relatively high permeability constants and complete drug release in 12 h were observed with microcapsules prepared employing chloroform as solvent for ethylene vinyl acetate copolymer.

Ethylene vinyl acetate copolymer (EVA), a copolymer of ethylene and vinyl acetate, has good film forming properties[1,2]. In a few reports[3,4] monolithic systems composed of ethylene vinyl acetate copolymer have been studied for the controlled delivery of macromolecular drugs such as insulin and heparin. In these studies, the drug and polymer solution were mixed together and cast as a film on a precooled plate to yield a matrix device in the form of a slab, which could be further divided into 1 cm^2 squares. An industrially feasible technique of microencapsulation by EVA copolymer based on the emulsification–solvent evaporation and characterization of the resulting EVA microcapsules was reported earlier[5]. In the present work the effect of four solvents namely chloroform, cyclohexane, dichloromethane and 1,2–dichloroethane employed in the preparation of EVA microcapsules on the permeability and drug release from the microcapsules was studied. These solvents were selected, as EVA is soluble in them. Indomethacin, which requires controlled release owing to its short biological half-life[6] of 2.4±0.4 h and gastrointestinal side effects such as peptic ulceration with bleeding, was used as core in the EVA microcapsules.

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MATERIALS AND METHODS

Indomethacin was a gift sample from M/s Micro Labs. Ltd., Pondicherry. Ethylene vinyl acetate copolymer (Grade1408) was procured from M/s Polyolefins Industries Ltd., Mumbai. Chloroform GR (Merck), dichloromethane (Loba-Chemie), 1,2-dichloroethane (S. D. Fine-Chem), cyclohexane (Loba-Chemie) and sodium carboxymethylcellulose (sodium CMC with a viscosity of 1500-3000 cps of a 1% w/v solution at 25°) were procured from commercial sources.

Microcapsule preparation:

EVA copolymer (0.5 g) was dissolved in warm solvent (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 bea-

ker 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 was then removed by continuous stirring at RT (28°) for 3 h to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules. EVA microcapsules containing indomethacin were prepared with a core to coat ratio of 8:2 employing chloroform (MC1), cyclohexane (MC2), dichloromethane (MC3) and 1,2-dichloroethane (MC4) as solvents for EVA.

Estimation of indomethacin:

Indomethacin content in the microcapsules was estimated by an UV spectrophotometric method[7] 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 the 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 these microcapsules was determined by the method of Luu *et al.*[8] using the equation, $h=\bar{r}(1-p)d_1/3[pd_2+(1-p)d_1]$ where h is the wall thickness, $\bar{r}$ is the arithmetic mean radius of the microcapsule, 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 35/60 was studied in phosphate buffer of pH 6.2 (900 ml) using 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[7]. A sample of microcapsules equivalent to 75 mg of indomethacin was 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.

Evaluation of permeability of the microcapsules:

From the drug release data, the permeability constants, P_m, were calculated as described by Koida *et al*[9] using the equation, $P_m=K_{app}.V.H./A.C_s$, where V is the volume of the dissolution medium (cm^3), H is wall thickness of the microcapsules (cm), A is the surface area of the microcapsules (cm^2), C_s is the solubility of the core material (mg) in the dissolution medium and K_{app} is the apparent release rate constant (mg/h) calculated from the slope of the early linear portion of the drug release profiles.

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 or cyclohexane or dichloromethane or 1,2-dichloroethane 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 ob-

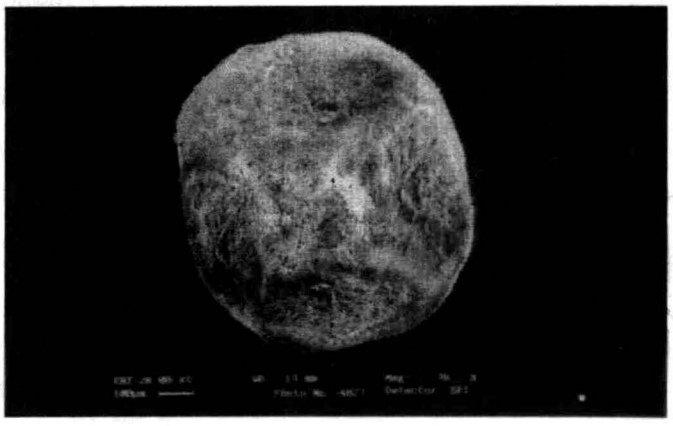

Fig. 1: SEM photograph of microcapsules MC 1.

These microcapsules prepared employing chloroform as solvent for the polymer are spherical and completely covered with the polymer.

tained. The size analysis of different microcapsules showed that about 55 and 36 percent were in the size range of -20+35 (670 μm) and -35+60 (375 μm) mesh size, respectively. A lognormal size distribution of the microcapsules was observed in all the batches prepared.

Low CV (<2.5%) in percent drug content indicated uniformity of drug content in each batch of microcapsules (Table 1). The microencapsulation efficiency was in the range 85-99% with various products. The microencapsulation efficiency was relatively high when chloroform was used as the solvent (Table1). Drug content of the microcapsules was found to be the same in different sieve fractions.

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 all the microcapsules was slow and spread over extended periods of time (Table 2). Release followed first-order kinetics ($r>0.98$) and depended on size of the microcapsules. The release increased as the size of the microcapsules decreased. The drug release mechanism from the microcapsules was diffusion controlled as plots of the amount released versus square root of time (fig. 2) was found to be linear. The correlation coefficient, r, was in the range 0.981-0.997 with various microcapsules.

In both the sizes studied the release rates were much different with the microcapsules prepared employing various solvents for the polymer. The permeability constants (P_m) calculated from the drug release data are given in Table 2. The permeability constants were found to be varying when different solvents were used in the preparation of the microcapsules. High permeability constants and complete drug release in 12 h were observed in the case of microcapsules prepared employing chloroform as solvent for the polymer EVA. The microcapsules prepared employing cyclohexane as solvent was found to be less permeable. The order of increasing permeability of the microcapsules prepared employing various solvents was cyclohexane<dichloromethane<1,2-dichloroethane <chloroform. The results, thus, indicated that the solvent employed has significant influence on the permeability of the EVA microcapsules.

The coat wall of microcapsules normally act as a barrier for drug release, the resistance of which is influenced by factors such as nature of the film former, its degree of crystallinity, inclusion of plasticizers and fillers, nature of the film, its thickness, the occurrence of pores i.e porosity and tortuosity etc. Many of these factors especially those

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

Microcapsule	Solvent*	Indomethacin content (%) of microcapsules		Microencapsulation efficiency (%)	Wall thickness (μm)
		Theoretical	Practical		
Size -20+35					
MC1	Chloroform	80	77.7 (1.24)#	97.2	59.9
MC2	Cyclohexane	80	72.4 (0.96)	90.5	72.7
MC3	Dichloromethane	80	71.4 (1.46)	89.3	75.1
MC4	1,2-Dichloroethane	80	72.7 (2.28)	90.9	70.3
Size-35+60					
MC1	Chloroform	80	78.5 (0.64)	98.2	32.4
MC2	Cyclohexane	80	69.7 (2.50)	87.2	43.4
MC3	Dichloromethane	80	68.5 (1.68)	85.6	46.1
MC4	1,2-Dichloroethane	80	71.5 (0.09)	89.3	42.0

*Solvent for the EVA copolymer employed in the preparation of the microcapsules; #Figures in parentheses are coefficient of variation (CV) values.

TABLE 2: RELEASE AND PERMEABILITY CHARACTERISTICS OF EVA MICROCAPSULES

Micro capsule	Solvent*	Percent Indomethacin Released at Times (h) ($\bar{X}$ ±sd)					T_{50} (h)	$K_1 x10^2$ (h^{-1})	P_m (cm^2/h)
		1.0	2.0	4.0	8.0	12.0			
Size -20+35									
MC1	Chloroform	25.7	40.3	58.9	75.4	88.8	2.8	13.8	3.5100
MC2	Cyclohexane	2.94	4.67	7.14	10.6	13.8	>12	1.13	0.4368
MC3	Dichloromethane	14.4	23.2	34.6	46.9	53.8	9.5	6.04	2.2570
MC4	1,2-Dichloroethane	20.1	28.1	39.7	53.1	60.2	6.7	7.18	2.4628
Size -35+60									
MC1	Chloroform	36.7	59.3	77.9	92.1	96.9	1.5	25.8	7.3032
MC2	Cyclohexane	3.70	5.76	9.27	14.4	18.6	>12	1.63	1.0404
MC3	Dichloromethane	15.7	25.7	42.4	51.9	62.8	6.8	7.21	5.4291
MC4	1,2-Dichloroethane	25.8	36.2	53.0	70.7	85.3	3.6	13.7	5.9141

*Solvent for the EVA copolymer employed in the preparation of the microcapsule; T_{50} is the time for 50 percent release; K_1 is the first order release rate constant and Pm is the permeability constant.

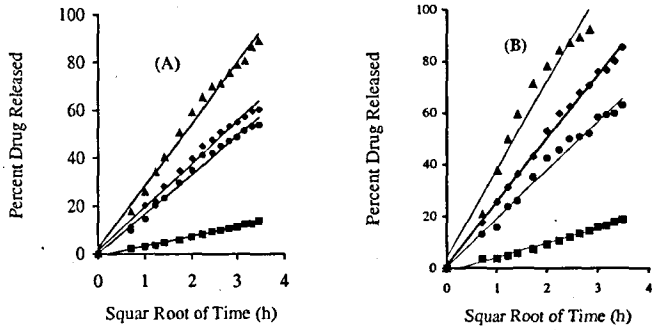

Fig. 2: Release profile of EVA microcapsules.

Percent of indomethacin released verses (time)1/2 plots of EVA microcapsules of size 20/35 (A) and 35/60 (B). EVA microcapsules are prepared employing chloroform (▲), cyclohexane (□), dichloromethane (●) and 1,2-dichloroethane (◆) as solvent for the polymer.

related to the nature of film like crystallinity of the polymer, thickness, porosity and tortuosity of film depend on the solvent for the polymer employed in the preparation of microcapsules. Thus there is every possibility that the observed differences in the permeability of EVA microcapsules to be depended on the solvent for the polymer employed in their preparation. All the microcapsules prepared employing various solvents for the polymer were found suitable for oral controlled release as drug release from these microcapsules was slow and extended over more than 12 h. The smaller microcapsules (size –35+60) were also suitable for parentral (i.m./s.c) controlled release.

Thus spherical microcapsules of EVA copolymer could be prepared by emulsion- solvent evaporation method employing chloroform or cyclohexane or dichloromethane or 1,2-dichloroethane as solvent for the polymer EVA. The microencapsulation efficiency was relatively high (97-98%) with chloroform when compared to the other solvents (85-91%). Indomethacin release from the microcapsules prepared employing chloroform as solvent was slow and complete within 12 h, whereas that form other microcapsules was extended over more then 12 h. Drug release was diffusion controlled and followed first order kinetics. The solvent employed has significant influence on the permeability and drug release from the microcapsules. Relatively high permeability constants and complete drug release in 12 h were observed with microcapsules prepared employing chloroform as solvent for EVA.

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