A Comparative Evaluation of Permeability and Drug Release from Cellulose Acetate Microcapsules Prepared by Two Complex Emulsion Methods

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Cellulose acetate microcapsules of indomethacin and diclofenac were prepared by emulsification - coacervation (Ec) and emulsification - solvent evaporation (ESE) methods. Microcapsules prepared by ESE method were denser, less permeable, and showed slower release than those prepared by EC method. In both the cases drug release depended on wall thickness and size of the microcapsules and followed first order kinetics.

CELLULOSE acetate is a non-toxic cellulose polymer insoluble in acidic and alkaline fluids, having good film forming properties. In continuation of our work on the application of cellulose acetate in microencapsulation[1] we have tried two reported complex emulsion methods namely emulsification - coacervation [2,3] and Emulsification-solvent evaporation[4,5] for preparation of cellulose acetate microcapsules of indomethacin and diclofenac. The resulting microcapsules were studied for, among others, drug release and permeability characteristics. The results are reported here.

Materials: Indomethacin B.P., Diclofenac (obtained from YUNG-ZIP Chemical Ind. Co. Ltd., Taiwan), Cellulose acetate (D.P. 250-360; having a viscosity of 3 CPS in a 2% solution in acetone at 25°C).

Preparation of Microcapsules

Emulsification - Coacervation (EC) Method : Cellulose acetate (0.8 g) was dissolved in acetone (10 ml) to form a homogenous polymer solution. Core material, indomethacin or diclofenac, (7.2 g) was added to the polymer solution and mixed thoroughly. The resulting mixture was then added in a thin stream to liquid paraffin (300 ml) contained in a 600 ml beaker while stirring at 200 rpm. A Remi Medium Duty Stirrer with speed meter (Model RQT 124) was used for stirring. Stirring was continued for 5 minutes to disperse the added mixture as fine droplets. Cellulose acetate in the droplets was then coacervated by the addition of 100 ml of distilled water slowly to produce spherical microcapsules. The mixture was then centrifuged and the product thus separated was washed with petroleum ether to remove adhering liquid paraffin. The product was then air dried to obtain discrete microcapsules.

Emulsification - Solvent Evaporation (ESE) Method: The method is same as described under EC method upto the emulsification of the polymer solution containing the drug in liquid paraffin as fine droplets. The dispersion was then transferred to a Buchner flask and stirring was continued with a magnetic stirer. The solvent was then removed by evaporation at R.T. 28°C) under vaccum (0.86 torr) to produce spherical microcapsules. The microcapsules were collected by decanttion and washed with petroleum ether to remove adhering liquid paraffin. The product was then air dried to obtain discrete microcapsules.

In each case two proportions of coat to core materials namely 1:9 (microcapsules A) and 1:4 (microcapsules B) were used to prepare microcapsules with varying coat thickness.

Table -1:Permeability and Drug Characteristics of Various Microcapsules Prepared by EC and ESE Methods

Micro-capsules	Size	EC METHOD		ESE METHOD	
		K_1 (hr^{-1})	P_m (cm^2min^{-1})	K_1 (hr^{-1})	P_m (cm^2min^{-1})
Indomethacin Microcapsules:					
A	16/20	0.3965	0.0155	0.2328	0.0084
	20/35	0.6065	0.0265	0.4099	0.0178
	35/50	0.8414	0.0776	0.6851	0.0526
B	16/20	0.1208	0.0071	0.0843	0.0058
	20/35	0.1843	0.0153	0.1337	0.0143
	35/50	0.3567	0.0507	0.2649	0.0501
Diclofenac Microcapsules:					
A	16/20	0.6218	0.0293	0.5845	0.0127
	20/35	2.2569	0.1011	0.4674	0.0282
	35/50	2.5103	0.1965	0.6624	0.0656
B	16/20	0.2379	0.0134	0.1437	0.0126
	20/35	0.3455	0.0286	0.2233	0.0272
	35/50	0.4482	0.0693	0.3834	0.0616

Coat : Core ratios : A - 1:9; B - 1:4; K_1 - First order release rate constant

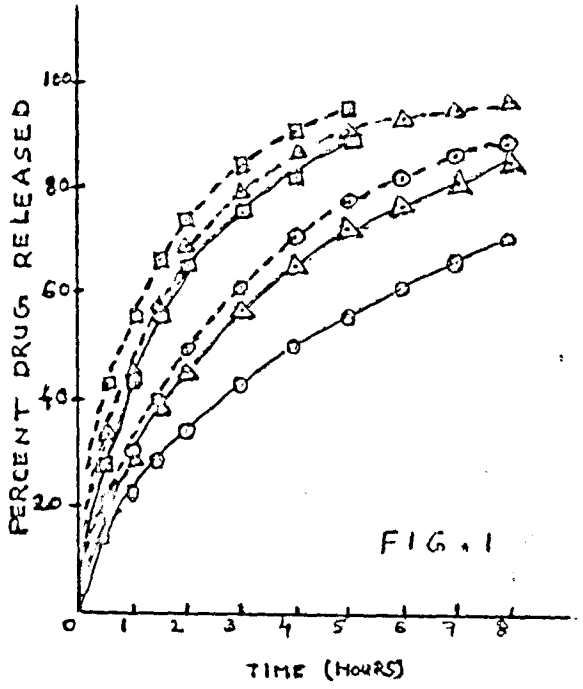
Size Analysis: For size distribution analysis different size in a batch were separated by sieving using a range of standard sieves and the amounts retained of different sieves were weighed.

Drug Content: In each case drug content of the microcapsules of size 16/20, 20/35 and 35/50 was determined. From each batch of microcapsules, four samples of 100 mg each were analysed by known spectrophotmetric methods for indomethacin[6] and diclofenac[7].

Wall Thickness: Assuming the microcapsules to be uniform and spherical, wall thickness of the microcapsules was determined by the method of Luu et al[8].

Density: the density of the microcapsules was determined by liquid displacement method using petroleum ether as a displacement fluid at room temperature.

Drug Release Studies: Release of medicament from microcapsules of sizes 16/20, 20/35 and 35/50 was studied using Oscillating tube dissolution rate apparatus. 900 ml of a solvent blend consisting of 1 volume of phosphate buffer of pH 7.4 and 4 volumes of distilled water was used as dissolution medium. A sample of microcapsules euivalent to 50 mg of the medicament and a speed of 36 cycles per minute were employed in each run. A 5 ml sample of dissolution medium was withdrawn at different time intervals, suitably diluted and assayed at 318



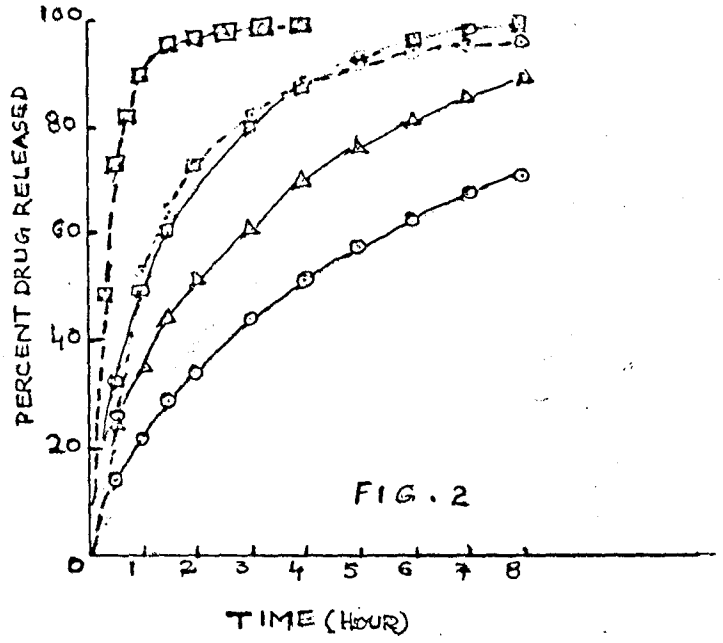


Fig.1. Drug release profiles of indomethacin microcapsules; Sizes : 16/20 (o), 20/35 (Δ), 35/50 (□); Method : EC (- - -), ESE (——).

Fig.2. Drug release profiles of diclofenac microcapsules; Sizes : 16/20 (o), 20/35 (Δ), 35/50 (□); Method : EC (- - -), ESE (——).

nm for for indomethacin and at 276 nm for diclofenac. The results are shown in **Fig.1 and 2.**

From the drug release data, the permeability constants (p_m) were calculated as described by Koida et al[9].

Both the methods produced large sized, spherical, discrete and free flowing microcapsules. EC method is less time consuming and could be completed with in half an hour. Where as ESe method is a slow process and took about 5 hours for the complete evaporation of the solvent and formation of microcapsules. In both the methods, the sizes could be separated and a more uniform size range of microcapsules could readily be obtained. Low s.d values in the percent drug content ensured uniformity of drug content in a batch of microcapsules. Drug content of the microcapsules was also found to be the same in the different sieve fractions. Smaller microcapsules were found to have thinner walls.

Drug release and permeability characteristics of various microcapsules are given in **Table 1**. Drug release from the microcapsules prepared by both the methods was found to be slow and spread over 8-10 hours. With both the medicaments per cent of drug released from the microcapsules decreased with an increase in coat material and wall thickness in all the three sizes studied. Drug release from the microcapsules followed first order kinetics. Percentage of drug released from the microcapsules and the release rate constant increased as the size of the microcapsules decreased. This may be due to the increased surface area and thinner walls associated with smaller microcapsules.

With both the medicaments and in all the sizes studied microcapsules prepared by EC method were

found to be relatively more permeable and gave higher release rates when compared to those prepared by ESE method. With both the medicaments the microcapsules prepared by ESE method were found to be denser than those prepared by EC method. the results thus indicated that the comnplex emulsion method employed has significant influence on the density, permeability and hence drug release from the mnicrocapsules. Slow removal of the solvent during the process of microencapsulation as in the ESE method produced dense microcapsules with low permeability and slow release characteristics.

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