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Controlled Release of Glipizide from Ethylene Vinyl Acetate Microcapsules

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An industrially feasible technique of microencapsulation by ethylene vinyl acetate copolymer and the resulting microcapsules were investigated. Ethylene vinyl acetate microcapsules of glipizide were prepared by an emulsion solvent evaporation method employing various proportions of coal and core materials and chloroform as solvent for the polymer ethylene vinyl acetate. The microcapsules are spherical, discrete, free flowing and monolithic, multinucleate type. Microencapsulation efficiency was in the range of 89-97%. Glipizide 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 zero order kinetics after a lag period of 1 h. Good linear relationships were observed between wall thickness and release rate and T_{50} (time for 50% release) values. Release from some of the microcapsules was very close to that from a commercial SR tablet formulation of glipizide.

Microencapsulation by various polymers and their applications are described in standard text books[1,2]. Ethylene vinyl acetate copolymer (EVA) is 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 a few reports[5,6] 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 1x1 cm squares. In the present work an industrially feasible technique of microencapsulation by EVA copolymer was developed and the resulting EVA microcapsules were investigated. Glipizide, an effective antidiabetic which requires controlled release owing to its short biological half life of 3.4±0.7 h was microencapsulated by EVA and the resulting microcapsules were studied. A few sustained release formulations of glipizide (10 mg) are available commercially.

Glipizide 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) and sodium carboxymethylcellulose (sodium CMC with a viscosity of 1500-3000 cps of a 1% w/v solution at 25°, Loba-Chemie) were procured from com-

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mercial sources. Glytop SR (10 mg) tablets of M/s Sidmark Laboratories; Valsad, Gujarat, (Batch No. 11007; Mfg. Date: Aug., 2001; Exp. Date: July., 2003) were procured from local market.

EVA copolymer (2 g) was dissolved in warm chloroform (100 ml) to form a homogenous polymer solution. Core material, glipizide, (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 microcapsules. 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 19:1 (MC 1), 9:1 (MC 2), 8:2 (MC 3) and 7:3 (MC 4) were used to prepare microcapsules with varying coat thickness.

Glipizide content in the microcapsules was estimated by an UV spectrophotometric method[7] based on the measurement of absorbance at 276 nm in phosphate buffer of pH 7.4. The method was validated for linearity, accuracy, and precision. The method obeyed Beer's law in the concentration range 0-10 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 0.8% and 1.6% respectively.

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. Microencapsulation efficiency was calculated using the equation, microencapsulation efficiency=(estimated percent drug content/theoretical percent drug content)x100. Wall thickness of the 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 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. 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).

Release of glipizide from the microcapsules of size 20/35, and 35/60 was studied in phosphate buffer of pH 7.4 (900 ml) using an USP XXIII three-station Dissolution Rate Test Apparatus (Model DR-3, M/s Campbell Electronics) with rotating paddle at 50 rpm and 37°±1° as prescribed for glipizide tablets in USP XXIV. A sample of microcapsules equivalent to 10 mg of glipizide were used in each test. Samples were withdrawn through a filter (0.45 μ) at different time intervals and were assayed at 276 nm for glipizide using a Shimadzu UV-150 double-beam spectrophotometer. The drug release experiments were conducted in triplicate. For comparison the release of glipizide from a commercial SR product was also studied.

EVA microcapsules of glipizide could be prepared by an emulsion-solvent evaporation method employing chloroform as solvent for the polymer. The microcapsules were found to be discrete, spherical, free flowing and multinucleate and monolithic type. SEM indicated that the microcapsules are spherical with smooth surface and completely covered with the polymer coat (figure not shown). 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 55 and 35 percent were in the size range of -20+35 (670 μm) and -35+60 (375 μm) mesh size respectively. A log-normal size distribution of the microcapsules was observed in all the batches prepared.

Low c.v (< 1.5%) in percent drug content indicated uniformity of drug content in each batch of microcapsules (Table 1). The microencapsulation efficiency was in the range 89-97% with various products. Drug content of the microcapsules was found to be the same in different sieve fractions. As the microcapsules are spherical the wall thickness of the microcapsules was calculated as per Luu *et al.*[8] Microcapsules prepared employing various ratios of coat:core were found to have different wall thickness (Table 1).

Glipizide release from the microcapsules was studied in phosphate buffer of pH 7.4 for a period of 12 h. Glipizide release from the microcapsules was slow and spread over extended periods of time. Release followed zero-order kinetics ($r>0.98$) after a lag period of 1 h and the release rate (K_o) depended on coat:core ratio, wall thickness and size of the microcapsules. As the proportion of coat increased, glipizide release rate decreased. The release rate increased as the size of the microcapsules decreased. Good linear relationships were observed between wall thickness of the

TABLE 1: GLIPIZIDE CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE CHARACTERISTICS OF EVA MICROCAPSULES.

Microcapsules (size)	Glipizide content (%)	Microencapsulation efficiency (%)	Wall thickness (μ)	T_{50} (h)	K_o (mg/h)
MC1 (20/35)	89.11 (0.60)*	93.80	11.66	4.24	0.716
MC1 (35/60)	91.09 (0.68)	95.88	6.52	3.90	0.765
MC2 (20/35)	81.20 (0.92)	90.22	23.25	5.12	0.620
MC2(35/60)	86.11 (1.09)	95.67	13.01	4.95	0.679
MC3(20/35)	71.84 (1.14)	89.80	46.29	7.19	0.507
MC3 (35/60)	74.70 (0.20)	93.37	25.91	7.10	0.482
MC4 (20/35)	68.02 (0.85)	97.17	69.13	12.03	0.422
MC4 (35/60)	68.21 (0.27)	97.44	69.13	8.66	0.470

T_{50} is time for 50 % release and K_0 is zero order release rate constant * Figures in parenthesis are coefficient of variation (CV) values.

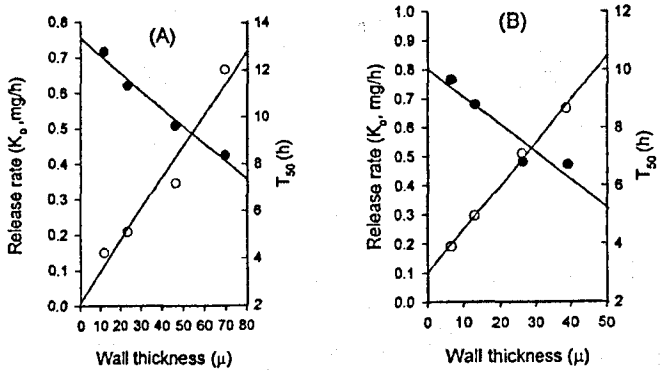

Fig. 1: Relationship between wall thickness, release rate and T_{50} value of EVA microcapsules.

Relationship between wall thickness of microcapsules and release rate (●) and T_{50} values (o) for microcapsules of size 20/35 (A) and 35/60 (B).

microcapsules and drug release rate and T_{50} (time for 50% release) values (fig. 1). 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, MC1 gave release close to that of commercial SR tablets of glipizide tested.

Thus, spherical microcapsules of EVA copolymer could be prepared by the emulsion-solvent evaporation method employed. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely. Microencapsulation efficiency was found to be in the range of 89-97%. Glipizide 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 zero order kinetics. As the microcapsules (size 35/60) could pass through syringe No. 18, these EVA microcapsules were found suitable for both oral and parenteral SR formulations.

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