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EVALUATION OF TABLETED MICROSPHERES OF DIPYRIDAMOLE

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ABSTRACT

Microspheres of dipyridamole were prepared by solvent evaporation methods. The effect of additives Avicel PH 101, and beta cyclodextrin on the release rate of tableted microspheres were studied. Incorporating Avicel or beta cyclodextrin increased the dipyridamole release rates in tableted microspheres. Beta cyclodextrin was found to be a good additive for microsphere tablets to increase the drug release rates without causing disintegration.

INTRODUCTION

Dipyridamole is a weak base (pKa=6.4) and shows a pH dependent solubility profile. Its high solubility in gastric medium may cause unwanted side effects during therapy. In addition, its poor flowability and staining properties will cause problems during manufacturing. Microspheronization is a useful method to overcome such problems and to control the release rate of a drug. It was reported that the release characteristics of tableted microspheres could be modified by addition of different adjuvants such as microcrystalline cellulose and dicalcium phosphate (1-2). Beta-cyclodextrin (B-CD) was used in direct compression tableting (3). In this study, as a novel approach. B-CD was used to accelerate dipyridamole release rates from non-disintegrating microsphere tablets.

MATERIALS

Dipyridamole (Kemopharm, Geneva, Switzerland), ethyl cellulose (EC) N-10, N-20, N-100 grades (ethoxy content 47.5-49.0%) (Hercules Inc., Wilmington, DE, USA), microcrystalline cellulose (Avicel PH 101, FMC corp, Philadelphia, PA), beta-cyclodextrin (B-CD) (Selectchemie AG, Zurich, Switzerland).

METHODS

Dipyridamole microspheres were prepared by solvent evaporation method. Process I:A 5% (w/v) (EC) solution in chloroform at 1:2 drug polymer ratio was added to the aqueous solution of 0.25% w/v MC at 300 rpm, 500 rpm, or 750 rpm. Microspheres were dried, and sieved into different size fractions (Retsch Co., Haan, Germany). Process II:1% (w/v) EC in acetone, and dipyridamole were added (1:2 drug:polymer) to a mixture of mineral oil and polysorbate 80 at 750 rpm, and microspheres were washed with n-hexan. Encapsulation efficiency and loading capacity of microspheres were calculated as percentages. Dipyridamole was determined spectrophotometrically at 394 nm. Surface morphology of microspheres were determined by the scanning electron microscope (SEM) (Joel 1200 EX-11, Tokyo, Japan). Flow and compressibility, the static angle of repose of the microspheres, dipyridamole powder, and granules were determined according to a standard procedure. Tablets were prepared using a hydraulic press (Perkin-Elmer, England) equipped with a force gauge. A 13 mm die with flat-faced punches was used at 1000 kg. force. To prepare physical mixture tablets, dipyridamole powder and EC (1:7) with and without additives were mixed and directly compressed. Microsphere tablets contained EC N-10, EC N-20, and EC N-100 grades with (20% Avicel or 30% B-CD) and without additives. Tablets of wet granulation were prepared with dipyridamole, starch, lactose, Explotab, and PVP solution, then compressed as described above. Dissolution studies were carried out with USP dissolution apparatus II, at 50 rpm in pH 1.2 buffer at 37 C.

RESULTS AND DISCUSSION

In process I, a 5% EC level, 0.25% MC, and 0.03% polysorbate 80 were found as the optimum concentrations. In Process II, solubility of EC in acetone significantly decreased when the molecular weight of EC increased. Hence, a 1% EC level was used in all experiments. Mineral oil process was carried out at 18-20 C and 750 rpm. Higher temperatures altered the solvent evaporation rates and produced shapeless particles. Consequently, both processes yielded spherical, free flowing, non-staining microspheres compared to dipyridamole powder and granules. Microspheres obtained from process II were larger (250-850 μm) than the microspheres of process I (125-250 μm). The size distributions did not differ significantly for the EC grades in either of the processes. The encapsulation efficiencies were: mean (SD), 57.75% (4.08) and 85.03% (5.2), and the drug loading capacities were 94.62% (2.70), 93.77% (9.52) for process I and II. The angle of reposes were 58, 26, and 32 degrees, the compressibilities were 51.35%, 5.27%, and 14.27% for powder, granules, and the microspheres respectively. No significant difference was detected for dipyridamole release between two processes, and 125 and 250 μm sizes of Process I.

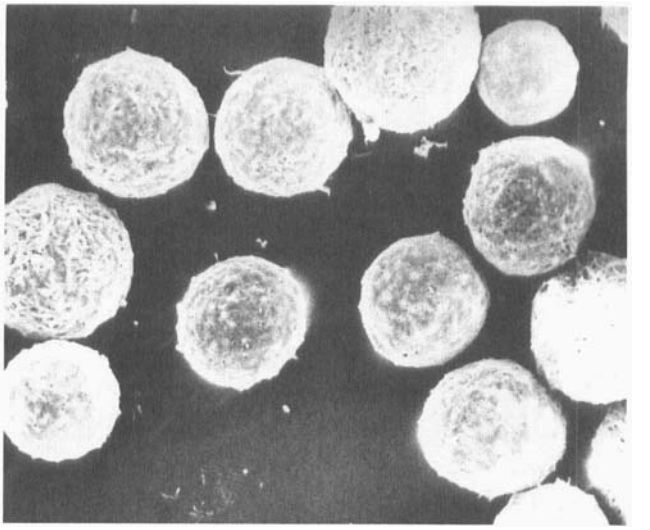

FIGURE 1a : SEM evaluation of microspheres of Process I

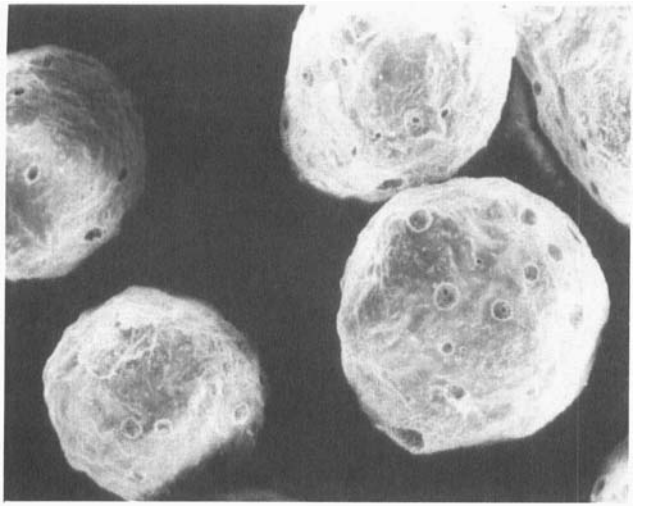

FIGURE 1b : SEM evaluation of microspheres of Process II

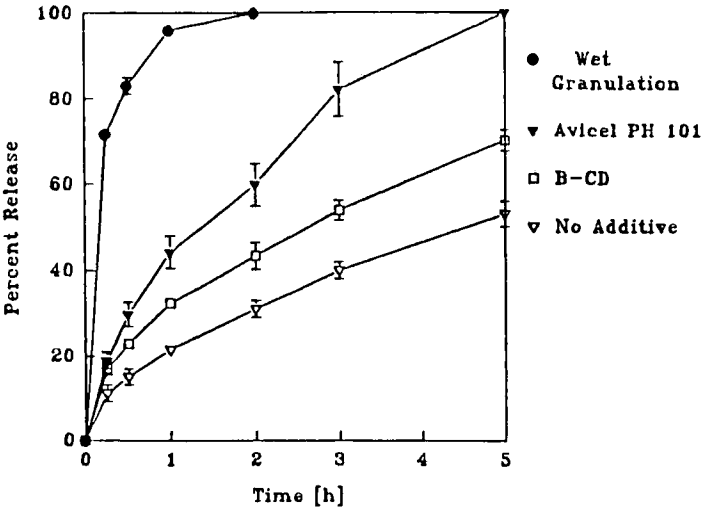

FIGURE 2a : Dipyridamole release of microsphere tablets with and without additives in comparison to wet granulation tablets

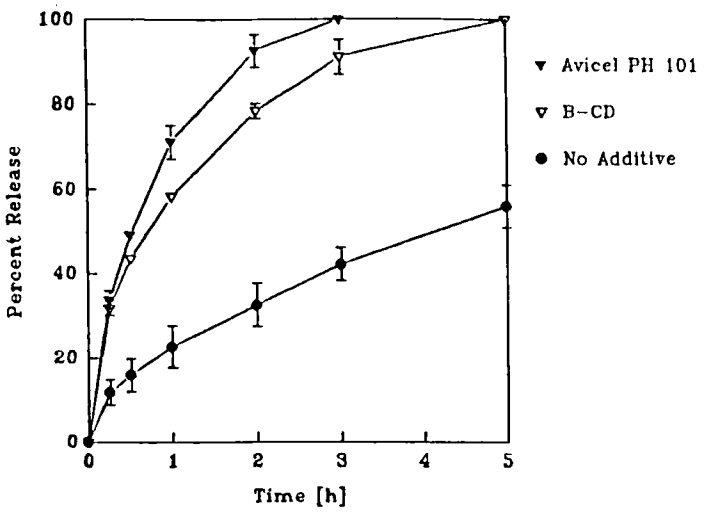

FIGURE 2b : Effect of additives on dipyridamole release of physical mixture tablets (EC N-10)

SEM Results: The high drug release of the free microspheres may be attributed to the porous structure of their surface. In process I, the microspheres were smaller, the surface shows a network of polymer fibers (Fig.1a). In process II, the presence of crater-like grooves were noted at low magnification (Fig.1b)

Dissolution Studies of Tablets: The microspheres of process II could not be compressed as uniform tablets. This might be due to the residual mineral oil entraped in the inner structure of the matrix. Microspheres of process I could easily be compressed into good quality tablets. There was a release rate difference among the EC grades in physical mixture tablets. However, there was no release rate difference among tablets prepared from different EC grades and size fractions of microspheres. As shown in Fig.2a drug release rate was faster with wet granulation tablets, followed by Avicel, B-CD, and plain microsphere tablets. Tableted microspheres containing Avicel PH 101 disintegrated in 5 minutes, but B-CD containing tablets did not disintegrate. This might be due to the solid bridges formed between B-CD and EC during tablet compression. The addition of B-CD enhanced the release rate of dipyridamole (70% at 5h). Since B-CD is a soluble agent it might accelerate the diffusion of water into the tablet. These observations correlated well with the results of tablets which were prepared with the physical mixtures (Fig.2b).

CONCLUSIONS

Forming the matrix type microspheres of dipyridamole produced a free flowing, non-staining product with a prolonged drug release rate. Tableting of free microspheres significantly decreased the release rate of dipyridamole independent of the size of the microspheres or the EC grade. Avicel PH 101 increased the drug release rate of microsphere tablets through disintegration, Beta-cyclodextrin could successfully be used as an additive in tableted microsphere formulations to enhance drug release without disintegration.

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