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COMMUNICATION

STUDIES ON THE RELEASE OF THEOPHYLLINE FROM POLYVINYLACETATE MICROSPHERES

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ABSTRACT

Polyvinylacetate microspheres containing theophylline were prepared by emulsification and solvent removal method. The release pattern of theophylline from the microspheres was found to be best explained by diffusion controlled process. The rates of release were found to be influenced by drug-polymer ratios, size of microspheres, concentration of surfactant used for the preparation of microspheres, and pH of the dissolution media.

INTRODUCTION

Different polymers like gelatin(1), ethylcellulose(2), and polylactic acid(3) have been used to prepare micropellets or microspheres containing different drugs. Polyvinylacetate (PVAc) has not been studied in this regard. PVAc, in combination with hydroxypropylcellulose, has only been used for fabrication of film type dosage form(4). This paper presents the preparation of PVAc microspheres by emulsification and solvent removal method and studies the release of theophylline from these microspheres.

EXPERIMENTAL

Materials

Anhydrous theophylline-Indian Pharmacopoeia, 1970 was generously supplied by Dey's Medical Stores(Mfg.)Ltd.,Calcutta, India. Polyvinylacetate resin molecular wt.40,000(Koch-Light, England), Span 80(Fluka,Switzerland) were obtained commercially and used as received. All other chemicals were of analytical reagent grade.

Preparation of Polyvinylacetate Microspheres

Theophylline and PVAc were used in the ratio of 1:1, 1.5:1, and 2:1 to prepare the microspheres. 3.5 gms. of PVAc was dissolved in 15 ml of acetone maintained at 15°C. Required amount of theophylline was dispersed uniformly in the polymer solution. This phase was, then, emulsified, at a stirring speed of 1200 r.p.m., in heavy liquid paraffin, maintained at 15°C and containing 0.1%, 0.5% and 1.0% V/V of span 80. Stirring was continued for sufficient period to evaporate off acetone at ambient temperature. The microspheres were rigidized by adding n-hexane dropwise. The microspheres were collected by filtration, washed with cold n-hexane, and kept in vacuum descicator in a cool place. Reproducibility of the methodology was evaluated by preparing triplicate batches and determining the percentage of drug embeded. Sieve analysis of each batch was carried out to determine the size distribution of microspheres.

In-vitro Dissolution Study

In-vitro release of theophylline from PVAc microspheres in 0.1(N) HCl and in phosphate buffer of pH 7.4 were determined using USP-XX rotating basket dissolution apparatus following the method reported previously(2).

Scanning Electron Micrography

After complete drug release in 0.1(N) HCl and in phosphate buffer of pH 7.4 at 37°C, the microspheres were dried and mounted onto stubs using double sided adhesive tape.

TABLE 1

Effect of Size of Microspheres and Drug-Polymer Ratios on Theophylline Content and Diffusion Controlled Release Rates of Theophylline from Polyvinylacetate Microspheres in 0.1(N) HCl and in Phosphate Buffer of pH 7.4

Theophylline : Polyvinylacetate	Concentration of Span 80 (% V/V)	Average Size d(μm)	Drug content (%)	K_H mg $min^{-\frac{1}{2}}$ in 0.1(N) HCl	K_H mg $min^{-\frac{1}{2}}$ in Phosphate Buffer(pH 7.4)
Effect of Size :		1197.5	69.05(±0.26)	5.36(±0.21)	6.55(±0.07)
2:1	0.5	922.5	69.08(±0.17)	5.66(±0.18)	6.79(±0.24)
		727	67.72(±0.44)	6.03(±0.08)	7.64(±0.33)
Effect of Drug-polymer ratio :					
1:1	1.0	550	53.61(±1.02)	4.16(±0.08)	6.56(±0.07)
1.5:1	1.0	550	59.10(±1.78)	5.78(±0.03)	7.84(±0.03)
2:1	1.0	550	65.17(±2.01)	7.88(±0.17)	9.72(±0.84)

Figures in the parenthesis indicate standard deviation

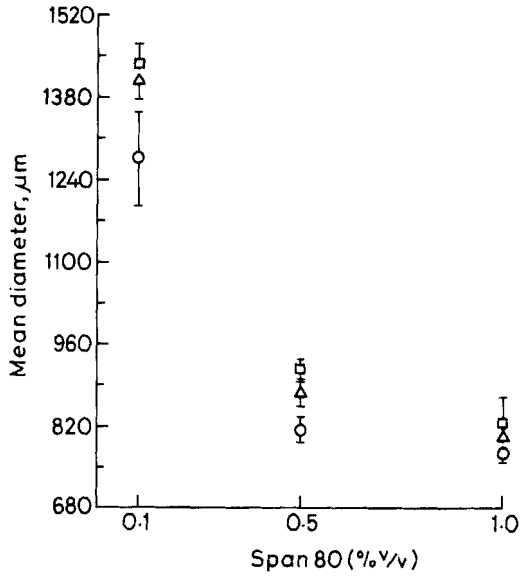


FIGURE 1

Effect of span 80 on the size-distribution of polyvinylacetate microspheres prepared at 1200 r.p.m. Key - Drug: polymer-(0) 1:1, (Δ) 1.5:1, (□)2:1

They were vacuum coated with gold film and were observed under scanning electron microscope(Hitachi scanning electron microscope, Model S-415A) for surface characteristics.

RESULTS AND DISCUSSION

Content Uniformity

The average theophylline content in different sized microspheres, having a constant drug-polymer ratio, were almost same(Table 1). Moreover, the average theophylline content of the microspheres, having a constant drug-polymer ratio, was almost same irrespective of the concentration of span 80 used during their preparation ensuring the uniformity of drug content.

Particle Size-distribution

An increase in theophylline - PVAc ratio shifted the size-distribution curves towards the bigger size leading to

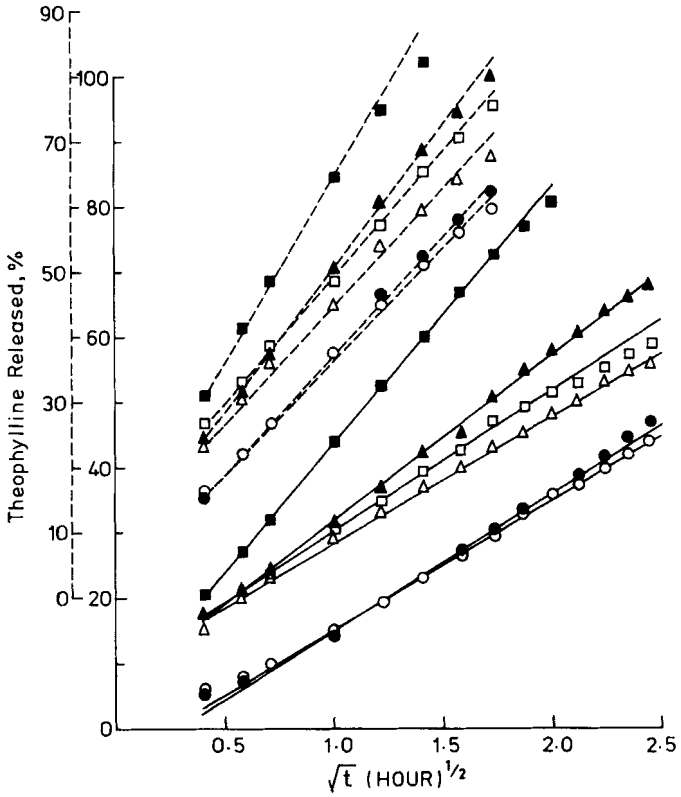


FIGURE 2

Apparent diffusion controlled release profiles of theophylline from polyvinylacetate microspheres as a function of concentration of span 80, used during their preparation, and pH of dissolution media. Key-Drug-polymer ratio and average microsphere diameter: (—) 1:1, 922.5 μm, (---) 1.5:1. 727 μm. Concentration of span 80 (% V/V) : (0) 0.1, (Δ)0.5, (□)1.0. Dissolution media : (Open symbols) 0.1(N) HCl, (closed symbols) phosphate buffer of pH 7.4

an increase in average diameter due to higher relative viscosity of the dispersed phase and higher interfacial tension. However, an increase in concentration of surfactant in the continuous phase led to the formation of smaller microspheres due to lowering of surface tension while maintaining the same trend of increasing the average diameter as the drug-polymer ratio was increased(Figure 1).

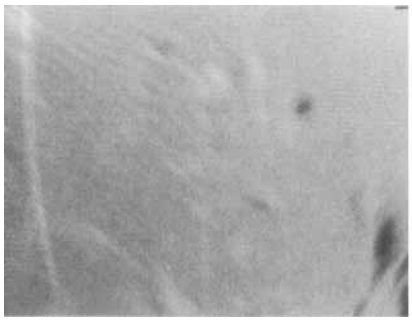
Release of Theophylline from Microspheres

The release profiles of theophylline from the microspheres were found(Figure 2) to be best explained by diffusion controlled process according to Higuchi equation(5). The rate of release of theophylline from the microspheres was found to be influenced by several factors.

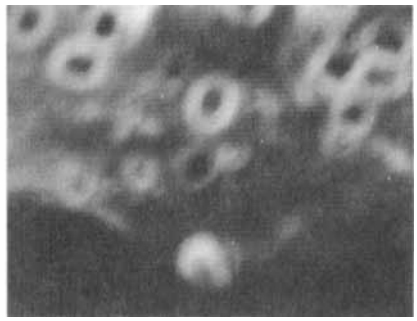
For a constant drug-polymer ratio, the rate of release of theophylline in both the dissolution media increased as the size of the microspheres decreased(Table 1). This is in accordance with the fact that the release of drug from a microsphere is inversely related to the size of the microsphere.

For a particular size of microsphere, an increase in drug-polymer ratio increased the rate of release(Table 1). An increase in drug-polymer ratio increased concentration gradient and boosted the release.

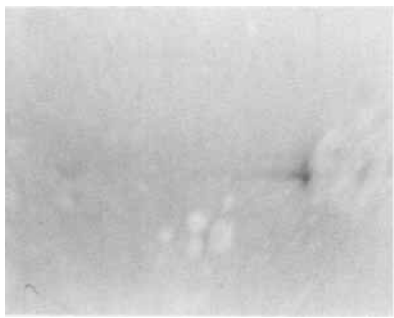
Increase in concentration of span 80, used during the preparation of microspheres, increased the rate of release of theophylline in both the dissolution media(Figure 2). Since span 80 neither increased the solubility of theophylline nor changed the wave length of maximum absorption in either of the dissolution media, there was no interaction between span 80 and theophylline. The increase in release rate may, therefore, be a consequence of increase in channels, made by increasing concentration of span 80, available for diffusion of drug. Figure 2 further shows that the rate of release of theophylline from the microspheres, prepared with 0.1% V/V of span 80, in phosphate buffer of pH 7.4 was slightly greater than that in 0.1(N) HCl. This difference in release rates in the two dissolution media enlarged as the concentration of span 80, used during the preparation of microspheres, was increased. It may be assumed that polyvinyl acetate, like polyvinyl-phosphate(6), might have undergone contraction in acidic media and expansion in alkaline media and this expansion might have been potentiated by span 80 leading to further increase in channels for diffusion with consequent increase in rate of release. Scanning



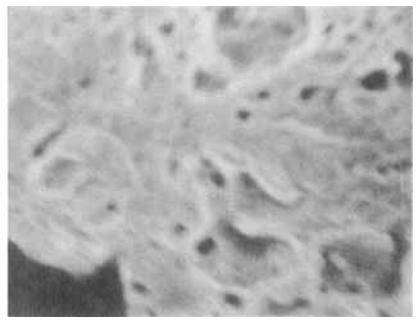
Ax Magnification X 100



Bx Magnification X 50

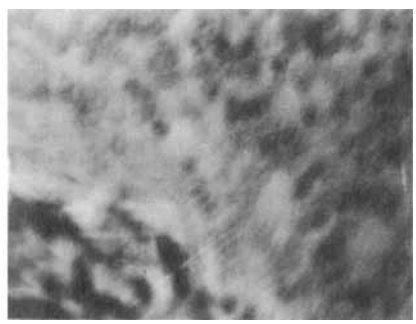


Ay Magnification X 100



By Magnification X 100

Az Magnification X 150



Bz Magnification X 100

FIGURE 3

Scanning electron photomicrographs of polyvinylacetate microspheres after complete drug release in 0.1(N) HCl (Ax, Ay, Az) and in phosphate buffer of pH 7.4 (Bx, By, Bz). Concentration of span 80 used for the preparation of microspheres : 0.1% V/V (Ax, Bx), 0.5% V/V (Ay, By), 1.0% V/V (Az, Bz). Before leaching, drug-polymer ratio in the microspheres was 2:1.

electron microscopic observations revealed that the pores on the surface of the microspheres, after complete drug release in 0.1(N) HCl, were not so prominent as were the pores on the surface of the microspheres after complete drug release in phosphate buffer of pH 7.4(Figure 3). It was also observed from Figure 3 that the number of pores on the surface of the microspheres, after complete drug release in phosphate buffer of pH 7.4, increased as the concentration of span 80, added in the continuous phase during their preparation, was increased. These observations apparently confirmed the above assumptions. However, further work is necessary to elucidate the exact mechanism of such action.

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