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SUSTAINED RELEASE FROM INERT MATRIXES II. EFFECT OF POLYETHYLENE GLYCOLS ON THEOPHYLLINE RELEASE

HASAN AL-SHORA, SOBHI SAID * and ABDUL-LATIF HAMMAD **

*Department of Pharmaceutics and Research Center **, College of Pharmacy, Riyadh University, Riyadh (Saudi Arabia)*

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SUMMARY

Sustained release theophylline tablets constituting carnauba wax, (matrix) and polyethylene glycols (channeling agent) were prepared using fusion or solvent evaporation techniques for blending the drug, the matrix and the channeling agent. The channeling agent increased the release rate according to its concentration and molecular weight. Tablets prepared through fusion technique achieved quicker release than those prepared by solvent evaporation. At a certain period of dissolution, the drug release processed by zero-order process; this period was dependent on channeling agent concentration.

INTRODUCTION

Waxy matrixes were extensively used for sustaining the release of drugs (e.g. Johnson, 1974; Goodhart et al., 1974; Dakkuri et al., 1978a and b).

Goodhart et al. (1974) reported that phenylpropylamine hydrochloride was released from a typical wax matrix by a diffusion mechanism. The dissolution was carried out at lower stirring speed to keep the tablet surface constant. Dakkuri et al. (1978a) found that surfactants increased the dissolution rate of tripelennamine hydrochloride from tablets of carnauba wax matrix, and that the release followed zero-order process over the first 4 h. Furthermore, Dakkuri et al. (1978b) found that povidone increased the release of tripelennamine hydrochloride from the wax matrix; between 0.5 and 8 h the drug released by zero-order process. The authors explained the effect of surfactants and povidone as being due to formation of channels formed inside wax matrix and reached a conclusion that while it was possible to design a sustained release form using 10% of channeling agent, total drug release might, however, be difficult to achieve.

* On leave of absence from Faculty of Pharmacy, Cairo University, Cairo, Egypt.

The aim of the present work was to use a channeling with the following properties: (a) that it has a higher solubility in the dissolution fluid; (b) that it has a relatively low melting point to ensure adequate mixing with wax, carnauba wax; and (c) that it causes no higher increase in viscosity of the medium by increasing its concentration. Polyethylene glycols have been used to enhance the dissolution and bioavailability of drugs by solid dispersion (Said et al., 1974, 1975), and exhibit the properties already specified. In view of all of these, the effect of polyethylene glycols as a channeling agent on the release of theophylline embedded in matrix of carnauba wax was studied.

MATERIALS

Theophylline (Merck, Darmstadt, Germany), carnauba wax (Giffin and George, London), polyethylene glycols 1500, 4000, 6000 and magnesium stearate (BDH, Poole, England) were used as supplied.

Manufacturing procedure for theophylline tablets

The granules composed of equal proportions of theophylline, and carnauba wax–polyethylene glycol were prepared by the two techniques; fusion and solvent evaporation. Different batches were prepared such that carnauba wax–polyethylene glycol fraction constituted 0–20% of polyethylene glycol.

The fusion technique involves the melting of carnauba wax at 86°C adding polyethylene glycol, and when homogeneity was attained theophylline powder (40 mesh) was gradually mixed in. The whole mass was constantly stirred until congealed, then passed through sieve no. 16, and left to solidify spontaneously. The fraction between no. 12 and no. 16 sieves (1000–14,000 μm) was collected and mixed with 1% magnesium stearate powder by gentle rotation in a capped box.

The solvent evaporation method was carried out by dissolving carnauba wax in hot chloroform, and polyethylene glycol and theophylline in hot ethanol. The two solutions were mixed, and the solvents were allowed to evaporate at 70°C. The congested mass still containing traces of the solvents (0.7–5%) was passed through sieve 16 and left to dry spontaneously in a hot air oven, until free from the solvents. The granulates were treated as above.

The granulates were tabletted * into 506 mg tablets using a 12 mm diameter flat-faced punch and die. Considerable efforts were made to ensure uniform tablet weight and hardness to avoid variations in porosity. The hardness of the tablets was around 5 kg (measured on Erweka hardness tester) *. The friabilities * were less than 1.1%.

Dissolution procedure

The dissolution was carried out at 37°C, 100 rpm with dissolution apparatus * based on USP XIX. The basket was immersed in the vessel containing 500 ml of the dissolution medium, phosphate buffer at pH 7.4. At selected intervals over 9–12 h, 5 ml of dissolution medium was sampled and the released theophylline was assayed spectrophotometrically ** (Said and Al-Shora, in press). At each withdrawal, 5 ml of the dissolution medium was added. Three runs were made for each batch and the average was calculated.

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* Erweka-Heanson, Stamn, Offenboch, Manch., G.F.R.

** Varian Techtron, UV-VIS Model 635, U.S.A.

RESULTS AND DISCUSSION

Figs. 1 and 2 show the release profile of theophylline from its tablets prepared through fusion, or solvent evaporation techniques. As the concentration of polyethylene glycol 6000 was increased, quicker release was observed. The batch prepared through fusion techniques without polyethylene glycol released 28.9% of theophylline after 12 h, whereas the tablets constituting 20% of polyethylene glycol 6000 (calculated in proportion to wax) released 95.25% after the same period. The values for the tablets prepared through solvent evaporation technique are 12.5 and 90.5%. These results indicate that the incorporation of polyethylene glycol 6000 in carnauba wax matrix increased considerably the release of theophylline by acting as a channeling agent. Increased dissolution might be due to the formation of solid solution of theophylline in polyethylene glycol with the possible decrease in particle size to the molecular size (Said et al., 1974). Increased concentration of polyethylene glycol is accompanied by a concomitant increase in dissolution rate. Significant differences were calculated between the amounts released in pre-

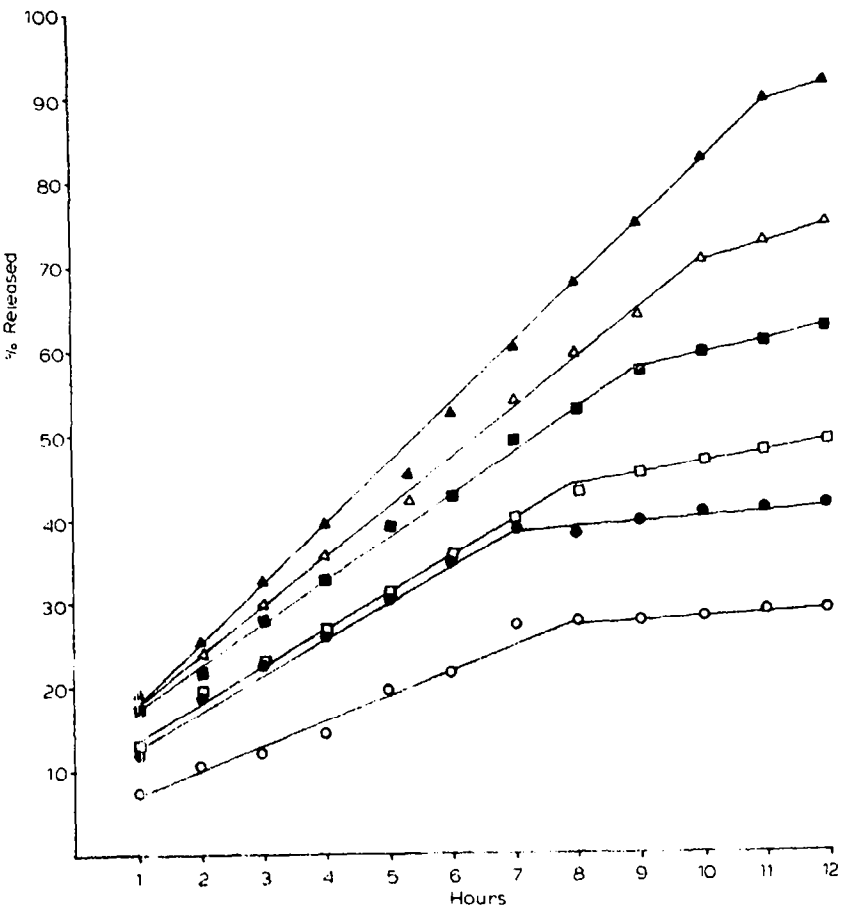

Fig. 1. Theophylline release from carnauba wax matrix tablets containing various concentrations of polyethylene glycol 6000 and prepared by fusion technique. Key: •, 1.25%; □, 2.5%, ■, 5%; △, 10%; ▲, 20%.

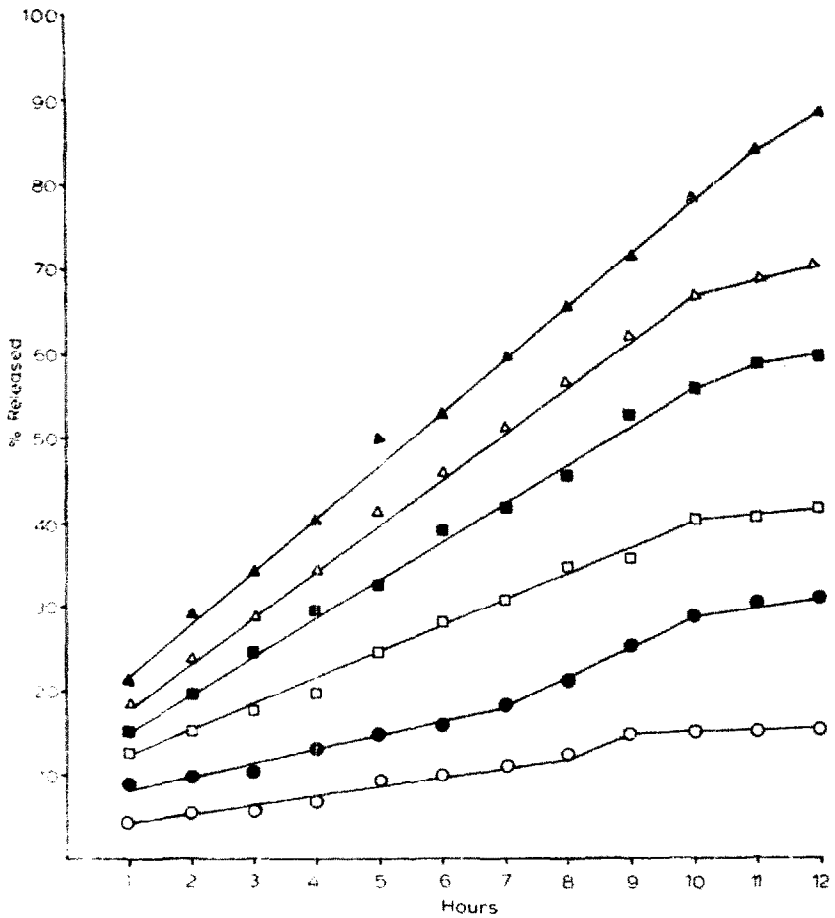

Fig. 2. Theophylline release from carnauba wax matrix tablets containing various concentrations of polyethylene glycol 6000 and prepared by solvent evaporation technique. Key: refer to Fig. 1.

sence of 10% and 20% of polyethylene glycols (Student's t-test, $P = 0.05$). Needless to say, increased concentration of the channeling agent also increases the chance for soluting more theophylline in polyethylene glycol matrix. Povidone was found to achieve an insignificant increase in the dissolution of tripelennamine hydrochloride by increasing its concentration in the wax from 10 to 20% due to increased viscosity or dissolution medium (Dakkuri et al., 1978b). The increase in concentration of polyethylene glycol 6000 within a range of concentration is always accompanied with a concomitant increase in dissolution indicating the minor effect of viscosity.

The most interesting point is that the release of theophylline follows a zero-order process within an initial period followed by a somewhat plateaued release. The time for the initial period of zero-order release is dependent on the content of polyethylene glycol 6000 in the matrix. Tablets incorporating 1.25 and 20% of polyethylene glycol and prepared through fusion and solvent evaporation techniques achieved zero-order release for the respective periods of 8–11 h respectively. Within these periods, the correlation coeffi-

cient was higher by linear regression analysis for the zero-order process ($r = 0.982$). The mechanism of theophylline release of eroding type could be expected by the fact that the channels act as a pathway for the penetration of the liquid in the tablet interior. As the eroded zone slowly dissolves in the medium, a fresh surface is exposed to the liquid with subsequent formation of a new channel.

Effect of technique of granulation

Fig. 3 indicates that the tablets prepared by fusion technique achieved quicker release than those prepared by solvent evaporation method; tablets incorporating 20% of polyethylene glycol 6000 and prepared through fusion and solvent evaporation methods released 95.25% and 90.5% of theophylline at 12 h. By the fusion technique, a considerable time was allowed before congealing of the matrix–drug mass, during which time intimate mixing occurred allowing for the formation of more channels of polyethylene glycol 6000 in the matrix. Moreover, the presence of solvents allowed for the aggregation of drug molecules at the site of their evaporation (Said and El-Sayed, 1976).

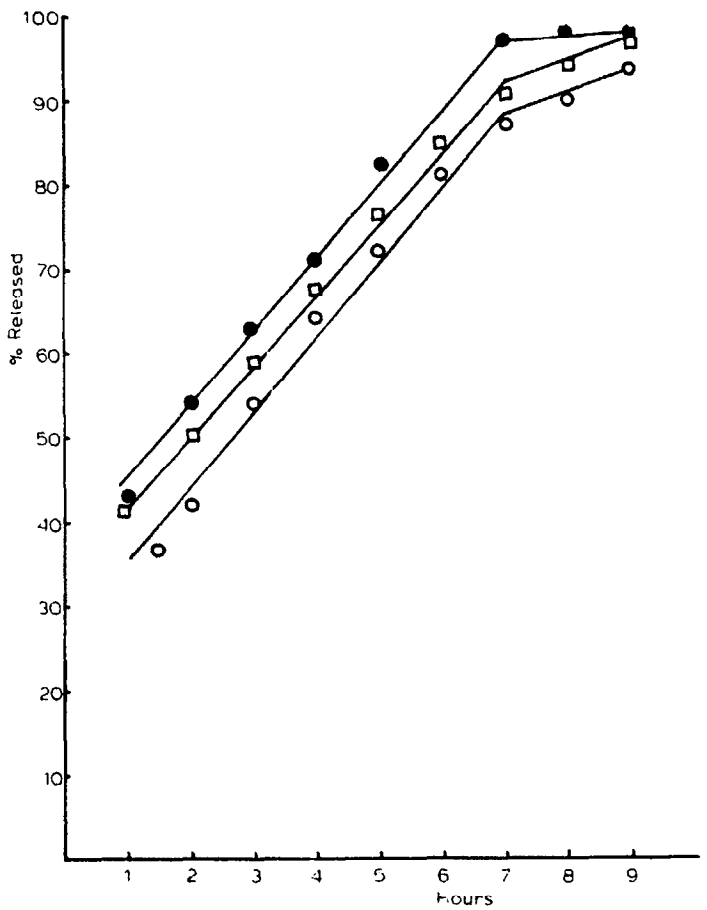

Fig. 3. Effect of polyethylene glycols on release of theophylline from carnauba wax matrix tablets prepared through fusion technique. Key: •, polyethylene glycol 1500; □, polyethylene glycol 4000; ○, polyethylene glycol 6000; all at 25%.

Effect of weight of polyethylene glycol

Fig. 3 illustrates the release profile of tablets prepared through fusion technique and polyethylene glycol 1500, 4000 and 6000 at 25%, as channeling agents. The curves follow zero-order process for the first 7 h, then plateau until the residual 2 h of release. The slopes for the curves are 1.15, 1.08 and 1.11 for the tablets containing polyethylene glycols 6000, 4000 and 1500 respectively. At 7 h, the percentage release from these tablets is 86.2, 96.3 and 96.5. Thereafter, the per cent release reaches 93.2, 94.5 and 97.5 within 9 h. The paramount effect of lower molecular weight of polyethylene glycols is due to its lower melting point and hence better chance for forming more channels in the matrix, higher water-solubility and/or viscosity differences.

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