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Sustained release tablet formulation of diethylcarbamazine. Part III *

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Summary

Sodium carboxymethylcellulose was successfully used in formulating a sustained-release tablet dosage form of diethylcarbamazine citrate, a drug of choice against human filariasis. The formulation containing DECC:NaCMC (1:7) was found to be most suitable. Urinary excretion studies in normal subjects using this formulation showed steady-state levels of DEC for about 12 h. Tablets prepared according to the formulation had a stable shelf-life of over 2 years.

Introduction

Diethylcarbamazine citrate, I.P. (DECC) is a drug of choice against human filariasis and is recommended at a dose of 50 mg t.i.d. for a period of 7–21 days. Filariasis is a major medical and social problem and affects about 250 million persons in the tropical zones of the world (Lämmler, 1977). Sustained release (SR) tablet formulations of DECC were reported earlier (Kumar et al., 1975; Baveja et al., 1984, 1985). However, compressed hydrophilic polymeric matrices also provide a cheap, simple and convenient method for achieving SR of highly water-soluble drugs (Lapidus and Lordi, 1966; Huber et al., 1966; Huber and Christenson, 1968;

* For Part II, see Baveja et al. (1985)

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Lapidus and Lordi, 1968; Machida and Nagai, 1978; Schneider et al., 1978; Salomon et al., 1979a and b; Machida and Nagai, 1980; Nakano et al., 1983; Korsmeyer et al., 1983). Huber et al. (1966) reported that sodium carboxymethylcellulose (NaCMC) is a useful gum since it hydrates readily and rapidly at body temperature. The present study reports how NaCMC was successfully used in formulating a sustained-release tablet dosage form of DECC.

Materials and Methods

Sodium carboxymethylcellulose was standardized by determining the pseudoplastic parameters (Metzner, 1961) of 2% w/v aqueous dispersion at 25°C using MV I bob and cup assembly of Haake Rotovisko viscometer (1965 model). The flow index was 0.6551 while its consistency index was found to be 18.66 poise.

Granules of NaCMC (< 40 and > 60 mesh, BS) were prepared by slugging and dried in vacuum. These dried granules were thoroughly mixed with DECC (52 mg) in various ratios and directly compressed into tablets using 9.3 mm die of a single punch hand-operated tablet machine. In vitro release rates of all these hydrophilic matrix tablets were studied using the USP XVIII dissolution rate test apparatus with 0.2 M phosphate buffer, pH 7.4 as medium and rotated the basket at 100 rpm. The samples were assayed by the method of Baveja and Ranga Rao (1981).

Results and Discussion

The formulation containing DECC:NaCMC (1:7) (I) was found to be the best in the study since nearly zero-order release was seen up to 12 h. Reproducibility of the release pattern of formulation I was studied for one tablet each from ten different batches in the above manner and the mean results are shown in Fig. 1. Hardness of the tablet (4–12 $kg \cdot cm^{-2}$) was found to have no effect on release of DECC from formulation I in agreement with the observations of Huber and Christenson (1968) and Nakano et al. (1983). Since the tablet is expected to remain in the stomach for about 3 h, release pattern of I was studied in dilute HCl (pH 3.0) for 3 h and the release rate was found to be same as that observed earlier.

Urinary excretion studies were conducted according to the guidelines of Anthony (1979) in 5 normal volunteers (4 males and 1 female, age 21–26 years, weight 50–62 kg) to confirm the in vivo performance of I. Each volunteer took one ordinary commercial 50 mg tablet of DECC (initial dose) along with one tablet of formulation I containing 52 mg of DECC (maintenance dose; Baveja et al., 1984). Urine samples collected for 72 h were analyzed by the method of Baveja and Ranga Rao (1981). From the plot of mean rate of excretion versus time (Fig. 2) it is evident that I maintained steady-state levels for about 12 h.

Accelerated stability studies of formulation I were conducted according to the guidelines of FDA, Washington (Davis, 1978) so as to confirm its release integrity on storage. For this purpose tablets of I, stored in amber-coloured glass vials along

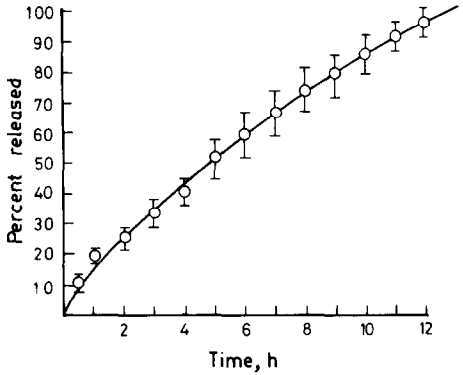

Fig. 1. Release of drug (cumulative percent) as a function of time from DECC tablets of different batches containing drug:NaCMC (1:7) (n = 10). Vertical bars indicate ± S.D.

with a silica bag were closed with a poly plug and sealed with an aluminium cap. They were exposed to: (i) 45°C; (ii) 37°C; (iii) 37°C and 80% relative humidity; and (iv) room temperature (22–41°C) for 3 months. Samples (one vial in each case) were drawn after 1, 2, 3, 4, 8 and 12 weeks and subjected to dissolution as above. The results revealed that the release pattern of I was almost same as that shown in Fig. 1, indicating that this formulation should remain stable for 2 years or more on shelf (Davis, 1978). No change in the colour and hardness values was observed during the study.

In agreement with the theory of Lapidus and Lordi (1968), the plot of mean percent drug released versus time (Fig. 3) was linear initially for about 2 h and later there was a distinct positive deviation. The latter may be attributed to the attrition

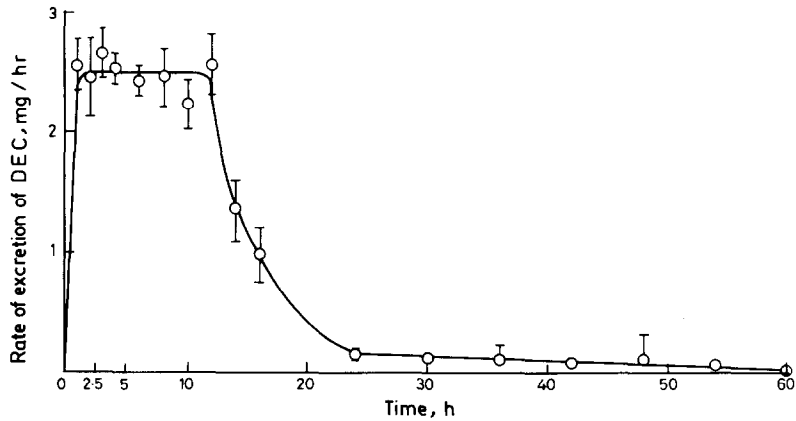

Fig. 2. Rate of excretion of DEC versus mid-point time of urinary excretion interval following oral administration of 50 mg commercial DECC tablet along with one tablet of formulation I (n = 5). Vertical bars indicate ± S.D.

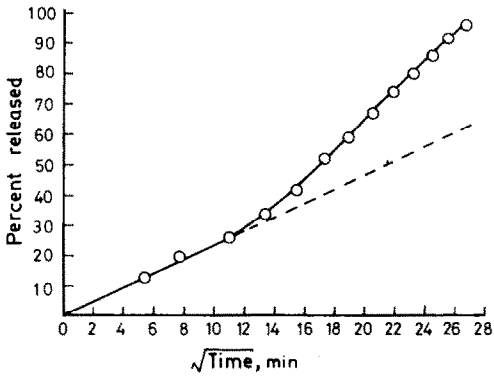

Fig. 3. Mean percent of DECC released (in vitro) versus $(\text{time})^{1/2}$ from tablets of formulation I.

of the tablet surface resulting in a decrease in diffusional path length for the drug. Hence it may be concluded that DECC is released from formulation I by diffusion process which is accelerated after 2 h due to attrition of the tablet surface.

In vitro–in vivo correlation was made for the SR dosage form in all volunteers by adapting the method of Machida and Nagai (1980). Plots of cumulative amount of DEC excreted at various times versus mean amount of DECC released (in vitro) from formulation I at those times showed a good linear relationship ($r^2 > 0.989$) with an intercept on the x-axis for each volunteer. The mean time required to release such a quantity of drug (in vitro) from I, 45 min, was considered as the average time needed for the onset of excretion of drug in urine. Hence the mean cumulative amounts of DEC excreted at 1, 2, 3, 4, 6, 8, 10 and 12 h was plotted against the mean amount of DECC released from formulation I at 0.25, 1.25, 2.25, 3.25, 5.25, 7.25, 9.25 and 11.25 h, respectively (Fig. 4). An excellent linear relationship was seen

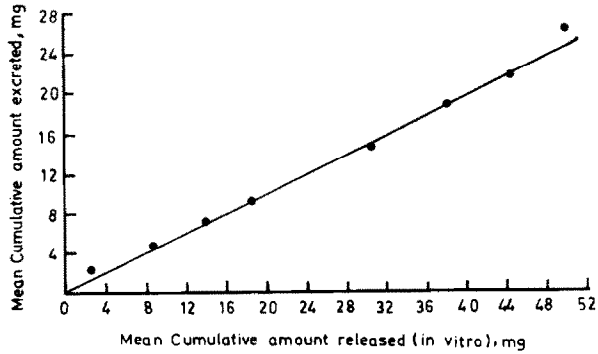

Fig. 4. Mean cumulative amount of DEC excreted at 1, 2, 3, 4, 6, 8, 10 and 12 h in urine following oral administration of sustained released dosage form versus mean cumulative amount of DECC released (in vitro) from tablets of formulation I at 0.25, 1.25, 2.25, 3.25, 5.25, 7.25, 9.25 and 11.25 h, respectively. 45 min is the mean time needed for the onset of excretion of drug in urine ($r^2 = 0.984$).

($r^2 = 0.984$) indicating that rate of absorption of drug is almost constant throughout 12 h. As a corollary it suggests that the release rate from formulation I is practically constant in all parts of the gastrointestinal tract.

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