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# Sustained release tablet formulation of diethylcarbamazine. Part II *

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Diethylcarbamazine (DEC) has been widely used as a drug of choice for the last 3 decades in the control and treatment of human filariasis. The latter 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 DEC using its freely-soluble citrate salt were reported earlier (Kumar et al., 1975; Baveja et al., 1984). One of the simplest methods of preparing oral SR dosage forms is by using poorly soluble derivatives (salts/adducts/complexes) of a drug so that the rate of availability of drug for absorption can be monitored precisely and easily. Tannic acid and pamoic acid were reported to yield non-toxic and stable derivatives with amines, having prolonged action (Berge et al., 1977). Hence derivatives of DEC were prepared with these two acids and were successfully used in formulating SR tablets of DEC.

An adduct of DEC with tannic acid (DECT) was prepared by slowly adding the solution of acid in dry 2-propanol (10% w/v) to DEC in dry 2-propanol in equal amounts (since molecular weight of tannic acid varies). The resulting precipitate was filtered and washed repeatedly with dry 2-propanol followed by dry ether to remove the unreacted acid and base. The residue was dried in vacuum (m.p. 165–170°C; yield 90%). DECT so obtained was a buff white, fluffy powder, hygroscopic in nature and insoluble in 2-propanol, ethanol, methanol and acetone (even in hot condition). In water it is hydrolyzed slowly on storage, and is freely-soluble in dilute sodium hydroxide solution.

* For Part I, see Baveja et al., 1984.

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Salt of DEC with pamoic acid (DECP) was prepared by adding the base (1 g) to a solution of pamoic acid (2 g) in pyridine (10 ml) and refluxed for 1 h. Pyridine was distilled off, dry methanol (30 ml) was added and again refluxed for 1 h. The unreacted pamoic acid that precipitated was removed by filtering and methanol was distilled off. When the contents of the flask were cooled along with traces of methanol, DECP crystals appear as yellowish fine prismatic needles (m.p. 208–210°C; yield 90%). Soluble in hot methanol and ethanol and sparingly soluble in 0.2 M phosphate buffer (pH 7.4). (Found: C, 67.54; H, 6.68; N, 6.64. $C_{33}H_{37}N_3O_7$ requires C, 67.37; H, 6.29; N, 7.14%.)

Both DECT and DECP (10 mg each) were dissolved, respectively, in aqueous sodium hydroxide (1% w/v) and 0.2 M phosphate buffer (pH 7.4), and the resulting solutions were assayed for DEC according to the method of Baveja and Ranga Rao (1981). It was found that DECT and DECP samples contained 28 and 33.9% of the base, respectively.

To know the dissolution properties of pure DECT and DECP, they were compressed into tablets and subjected to dissolution in USP XVIII dissolution rate test apparatus with 0.2 M phosphate buffer (pH 7.4) as medium (900 ml), basket was rotated at 100 rpm. DECT tablet (200 mg) was prepared by mixing the drug with equal amount of mixture of talc and lactose (1 : 1), using 3/8 inch die (hardness $\simeq$ 5 kg/cm$^2$). DECP (120 mg) was compressed as such in 3/16 inch die (hardness $\simeq$ 11 kg/cm$^2$). The release profiles are shown in Fig. 1. Maintenance dose of DEC for 12 h was reported as 26 mg by Baveja et al. (1984). Hence tablets of number of formulations containing DECT and DECP equivalent to 26 mg of DEC were made and subjected to dissolution as above. The following formulations were considered as the best in the study since the drug was released almost uniformly for about 10–12 h.

Tablets (200 mg) containing DECT 93 mg, sodium lauryl sulfate 6 mg and talc plus lactose (1 : 1) 101 mg were prepared by mixing them well and compressed in a single punch hand-operated tablet machine using 3/8 inch die and compression

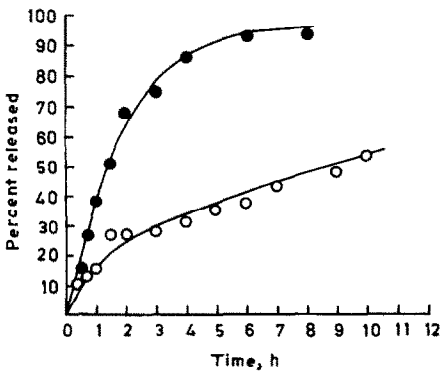


Fig. 1. Release of drug (cumulative percent) as a function of time from tablets containing (●) only DECP and (○) DECT mixed with equal amount of mixture of talc and lactose (1 : 1).

pressure was adjusted to give hardness values of ~ 5 kg/cm$^2$. This formulation of DECT (SR-I) released about 86% of drug in 10 h.

SR formulation of DECP (SR-II) contains DECP 77 mg, dicalcium phosphate 122 mg and ethylcellulose 1 mg (BDH, U.K.); viscosity of 5% w/w solution in 80 : 20 toluene–ethanol by weight at 25°C is 14 cp; ethoxy content 47.5–49.0%. DECP and dicalcium phosphate were mixed well and granulated with required amount of acetonic solution of ethylcellulose. The granules ( < 40 and > 60 mesh, BSS) were compressed in 8 mm die adjusted to give hardness of 12 kg/cm$^2$. SR-II released 100% of drug in about 12 h. Reproducibility of the in vitro release pattern of SR-I and SR-II formulations were confirmed by making different batches (3 for SR-I and 10 for SR-II). The mean in vitro results obtained are shown in Fig. 2. For both these formulations the release pattern in dilute HCl (pH 3.0) for first 3 h was found to be the same as that observed in 0.2 M phosphate buffer (pH 7.4).

Urinary excretion studies were conducted in normal volunteers (2 males for SR-I, 4 males and 1 female for SR-II, age 21–32 years, weight 50–68 kg and height 155–175 cm) to confirm the in vivo performance of SR-I and SR-II, according to the guidelines of Anthony (1979). Each volunteer received one ordinary commercial 50 mg DEC citrate tablet (initial dose) along with one tablet of SR-I or SR-II (maintenance dose). Urine samples collected for 72 h were analyzed by the method of Baveja and Ranga Rao (1981). From the plots of mean rate of excretion versus time for SR-I and SR-II (Fig. 3), it is evident that only SR-II formulation maintained steady-state levels for about 12 h.

Since DECT is a hygroscopic powder, SR-II alone was subjected to accelerated stability studies according to the guidelines of FDA, Washington so as to confirm its release integrity on storage. For this purpose 3 tablets of SR-II were placed in each amber-coloured glass vial along with a silica bag. Each vial was closed with a polyplug and sealed with an aluminium cap and exposed to 45°C, 37°C, 37°C + 80% relative humidity and 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

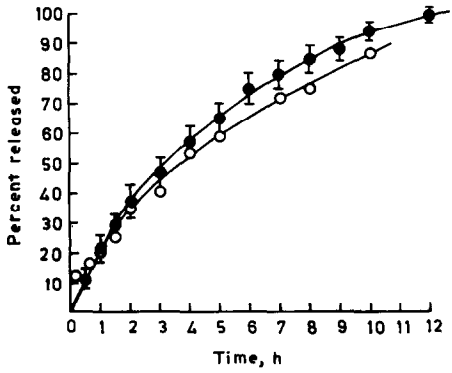


Fig. 2. Release of drug (cumulative percent) as a function of time from tablets of different batches of (●) SR-II (n = 10) and (○) SR-I (n = 3). Vertical bars indicate ± S.D.

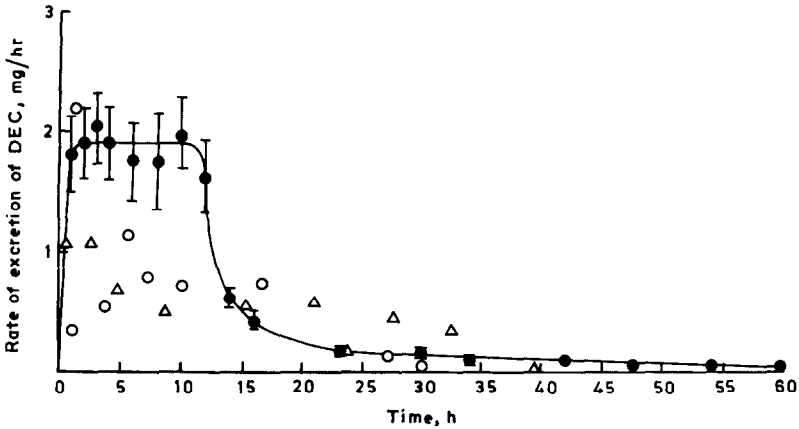


Fig. 3. Rate of excretion of DEC versus mid-point time of urinary excretion interval following oral administration of (●) 50 mg commercial DEC citrate tablet along with one tablet of SR-II (n = 5); (○) and (△) 50 mg commercial DEC citrate tablet along with one tablet of SR-I (n = 1).

subjected to dissolution as above. The results revealed that the release pattern of SR-II was almost the same as that obtained initially (Fig. 2) indicating that SR-II may be expected to remain stable for 2 years or more. No change in the colour and hardness values was observed in all the samples.

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## References

Anthony, P., An undergraduate experiment in Biopharmaceutics: serum and urine bioavailability of ampicillin. Am. J. Pharm. Educ., 43 (1979) 21—23.

Baveja, S.K. and Ranga Rao, K.V., Spectrophotometric determination of diethylcarbamazine and centperazine in urine. Analyst, 106 (1981) 726–728.

Baveja, S.K., Ranga Rao, K.V. and Amarjit Singh, Sustained release tablet formulation of diethylcarbamazine. Int. J. Pharm., 19 (1984) 229–231.

Berge, S.M., Bighley, L.D. and Monkhouse, D.C., Pharmaceutical salts. J. Pharm. Sci., 66 (1977) 1–19.

Kumar, K., Chakrabarti, T. and Srivastava, G.P., Studies on the sustained release tablet formulation of diethylcarbamazine citrate (Hetrazan). Indian J. Pharm., 37 (1975) 57–59.

Lämmler, G., Experimental chemotherapy and chemoprophylaxis of filariasis. Pestic. Sci., 8 (1977) 563–576.