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Sustained release tablet formulation of centperazine

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Summary

Sustained release tablet dosage form of centperazine, a pale yellow viscous oily liquid, freely soluble in water and all common polar and non-polar solvents, was prepared using hydrophilic polymers as matrix materials. A formulation containing centperazine, Aerosil 200, sodium carboxymethylcellulose (NaCMC) and hydroxypropylmethylcellulose (HPMC) in the ratio of 1 : 0.7 : 4 : 4 was found to be the best in the study when tested in vitro and in vivo (man) giving linear release for about 12 h. The release of drug from this formulation was found to be independent of hardness of tablet and pH of the dissolution medium. Sustained release of this formulation (in vivo) was compared with a quick release dosage form at the same dose level. A good in vitro–in vivo correlation was seen. Accelerated stability studies conducted according to the guidelines of FDA, Washington revealed that the formulation may be expected to remain stable for about 2 years shelf-life.

Filariasis is one of the major social and medical problems affecting about 300 million persons in the tropical zones of the world. Centperazine (3-ethyl-8-methyl-1,3,8-triazabicyclo[4,4,0]decan-2-one), an analogue of diethylcarbamazine (DEC) with greatly reduced conformational mobility, was found to be more potent than DEC against *Litmosoides carinii* infection in cotton rats (Saxena et al., 1971). Further, the therapeutic index of centperazine is much higher compared to DEC and it possesses anti-histaminic and anti-inflammatory properties which are desired in the treatment of filariasis (Saxena et al., 1970). It has no teratogenic and mutagenic effects (Anand et al., 1983). Unlike DEC, cessation of treatment with centperazine does not cause a sharp rise in microfilarial counts. At present centperazine is undergoing extensive clinical trials.

Swellable hydrophilic polymeric matrices provide a novel and simple method for preparing effective controlled drug delivery systems of highly water-soluble drugs. Sodium carboxymethylcellulose (NaCMC) and hydroxypropylmethylcellulose (HPMC) are useful gums since they hydrate rapidly and readily at body temperature (Huber et al., 1966). These two gums have been successfully used in formulating sustained release tablets of centperazine.

Centperazine was received from the Central Drug Research Institute, Lucknow and was used as such. NaCMC and HPMC were obtained from Amrut Industrial Products, Bombay and Aerosil 200 USNF from Degussa, F.R.G. The remainder of the chemicals were of analytical reagent grade.

Standardization of hydrophilic polymers. NaCMC and HPMC used in the study were standardized

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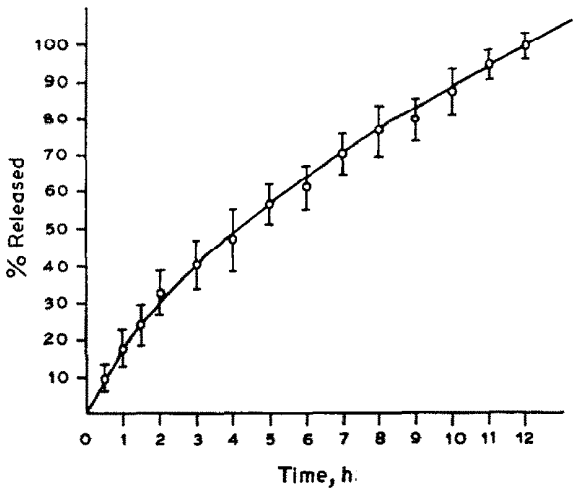

Fig. 1. Release of centperazine (cumulative percent) as a function of time from tablets of different batches containing drug: Aerosil 200: NaCMC: HPMC (1:0.7:4:4) (n = 10). Vertical bars indicate ± S.D.

by determining the pseudo-plastic properties (Metzner, 1961) of 2% w/v aqueous dispersion at 25°C using MV I bob and cup assembly of Haake Rotovisko viscometer (1965 model). Flow indices of NaCMC and HPMC were 0.655 and 0.843, respectively, and their consistency indices were 18.66 and 1.09 poise, respectively.

Calculation of maintenance dose. From the reports of clinical trials, it was concluded that the minimum effective dose of centperazine is 50 mg t.i.d. or q.i.d. (Gupta, 1983). The average elimination rate constant of centperazine in humans was found to be 0.11 h^{-1}. Therefore, according to Nelson's equation (1957) the maintenance dose required for 12 h is 66 mg.

Formulation of sustained release tablet (I). Centperazine was adsorbed over Aerosil 200 (1 : 0.7) by mixing. The mixture was blended thoroughly with dry granules of NaCMC and/or

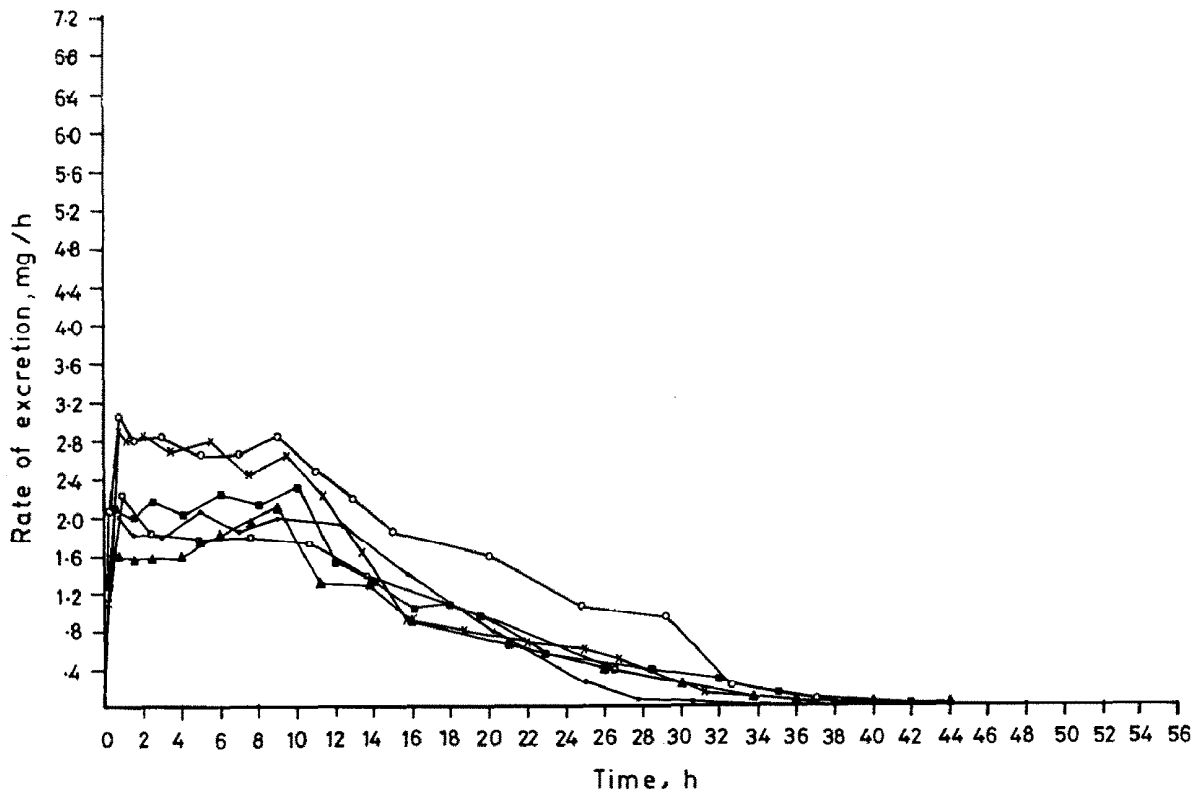

Fig. 2. Rate of excretion of centperazine versus mid-point time of urinary excretion interval following oral administration of a capsule containing 42 mg drug (initial dose) along with one tablet of formulation I (maintenance dose) to six healthy volunteers.

HPMC (< 40 and > 60 mesh, BS) obtained by slugging, and compressed into tablets of 11 mm diameter, using a Manesty single punch hand operated machine. In vitro release rates were studied using the USP XIX rotating basket assembly with 0.2 M phosphate buffer (pH 7.4) as medium and by rotation of the basket at 100 rpm. Samples were assayed for drug by the method of Baveja and Ranga Rao (1981). The formulation containing centperazine, Aerosil 200, NaCMC and HPMC in the ratio of 1 : 0.7 : 4 : 4 was found to be the best in this study since the release is almost uniform up to 12 h. Reproducibility of the release pattern of this formulation was studied for 10 different batches in the above manner; these results are shown in Fig. 1. The release was found to be independent of hardness of tablets (4–12 kg · cm^{-2}) in agreement with the observations of Huber and Christenson (1968), Nakano et al. (1983) and Baveja et al. (1985a). The release pattern of formulation I in dilute HCl (pH 3.0) was studied for 3 h and found to be same as that observed earlier.

In vivo evaluation of sustained release tablet.

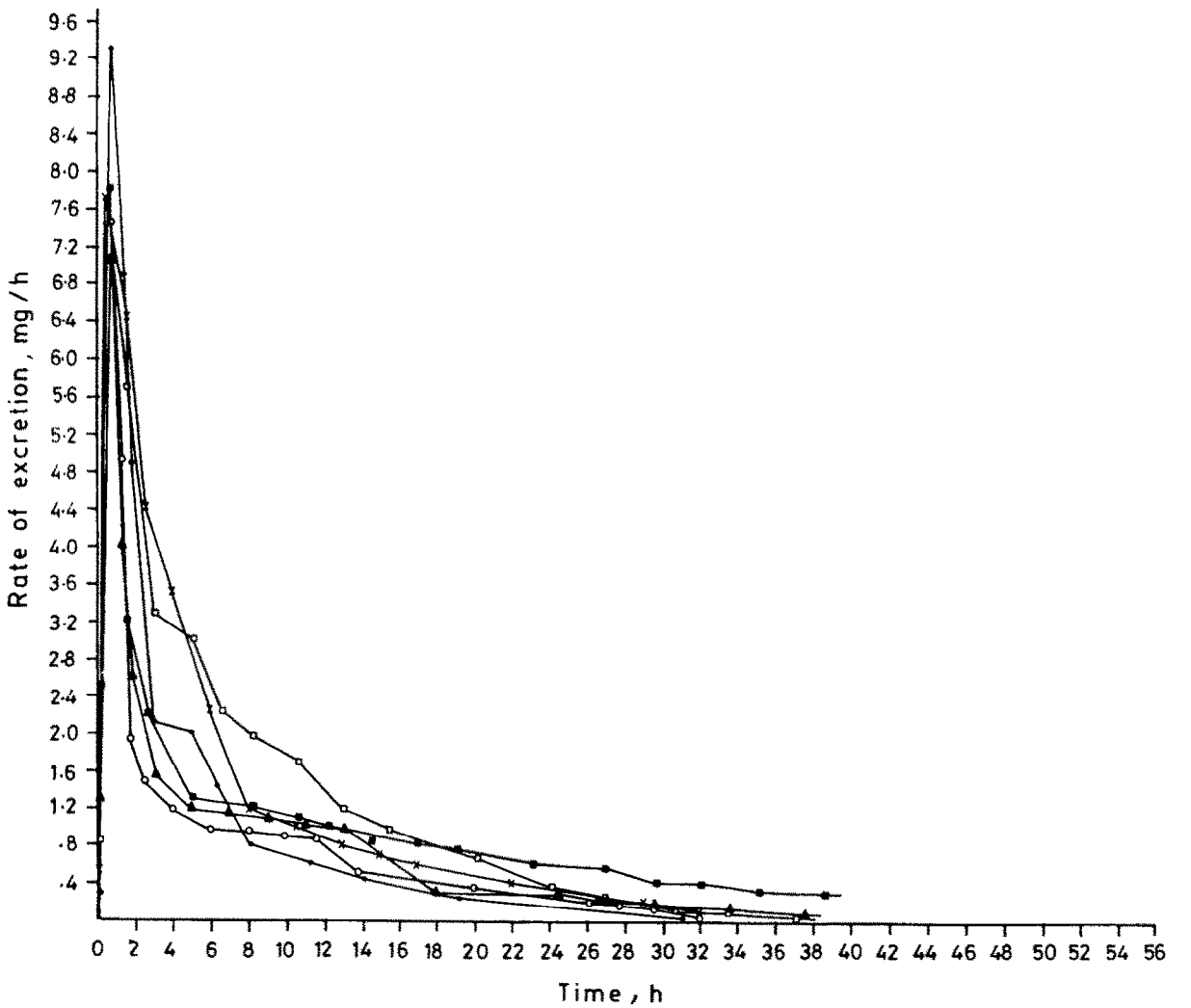

Fig. 3. Rate of excretion of centperazine versus mid-point time of urinary excretion interval following oral administration of a capsule containing 108 mg of drug to same six volunteers.

Following oral administration of centperazine, it was observed that the average peak urinary excretion rate in man was seen after about 45 min, which may be considered as the time at which blood concentration approaches maximum (Ranga Rao, 1984). Therefore, the amount of drug released from formulation I during the first 45 min, i.e., ~ 8 mg, was subtracted from normal initial dose, 50 mg, according to the method of Rowland and Beckett (1964) for maintaining the required minimum effective blood level. Hence the initial dose to be given is 42 mg.

Urinary excretion studies were conducted in 6 healthy, informed volunteers (5 male and 1 female, age 23–37 years, weight 53–74 kg, height 157–180 cm and surface area 1.42–1.9 m^2) according to the guidelines of Anthony (1979). Each subject self-administered orally in the morning with 200 ml water on fasted stomach, a gelatin capsule containing 42 mg of drug adsorbed over Aerosil 200 (1 : 0.7) (initial dose) and a tablet of I containing 66 mg of drug (maintenance dose), after collecting the blank. No food or liquid other than water was allowed for 2 h following ingestion of the dose. Urine samples were collected at regular intervals for 72 h and were frozen until analyzed by the method of Baveja and Ranga Rao (1981). After a washover period of one week, the study was repeated in the same volunteers in an identical manner by administering a capsule containing 108 mg of drug adsorbed over Aerosil 200 (1 : 0.7). From the plots of rate of excretion versus time (Figs. 2 and 3) it is obvious that formulation I maintained constant blood levels for about 10–11 h.

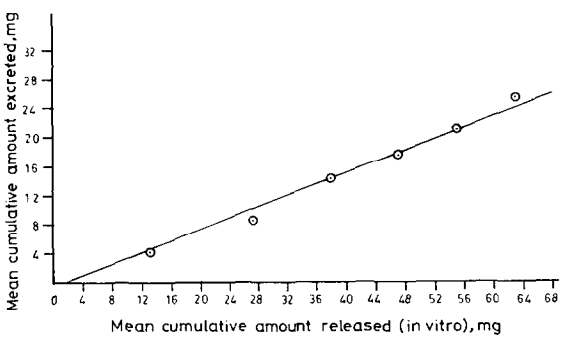

Fig. 4. Mean cumulative amount of centperazine excreted at 1, 2, 4, 6, 8, 10 and 12 h in urine following oral administration of sustained release dosage form versus mean cumulative amounts of centperazine released (in vitro) from tablets of formulation I at 0.15, 1.15, 3.15, 5.15, 7.15, 9.15 and 11.15 h, respectively. 0.85 h is the mean time needed for the onset of excretion of drug in urine ($r^2 = 0.974$).

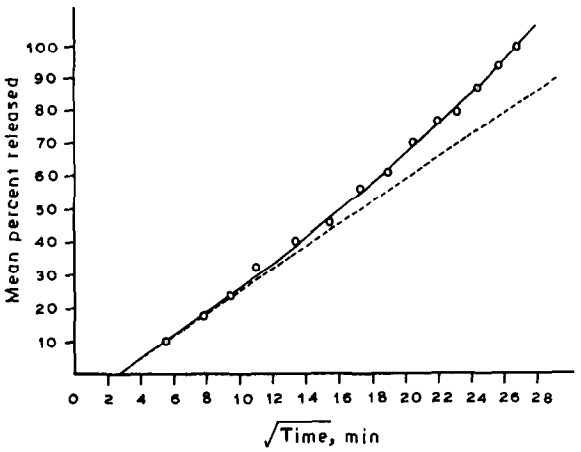

Fig. 5. Mean percent of centperazine released (in vitro) versus $\sqrt{\text{time}}$ from tablets of formulation I.

Accelerated stability studies were conducted as previously described by Baveja et al. (1985b); they revealed that formulation I may remain stable for about 2 years shelf-life.

In vitro–in vivo correlation was made for the sustained release dosage form according to the method of Baveja et al. (1985a). Initially the cumulative amount of drug excreted at various times was plotted against the cumulative amount of drug released (in vitro) from formulation I at those times. The plots were linear for all volunteers ($r^2 > 0.969$) with an intercept on X-axis. Time needed to release that quantity in vitro was considered as the time required for the onset of excretion of drug in urine for that volunteer. This mean time of six volunteers was found to be 0.85 h. Hence the mean cumulative amount of drug excreted at 1, 2, 4, 6, 8, 10 and 12 h was plotted against the mean amount of drug released (in vitro) at 0.15, 1.15, 3.15, 5.15, 7.15, 9.15 and 11.15 h, respectively (Fig. 4). A good linear relationship was seen ($r^2 = 0.974$) indicating that rate of absorption of drug is almost constant throughout 12 h. This means that the release rate from formula-

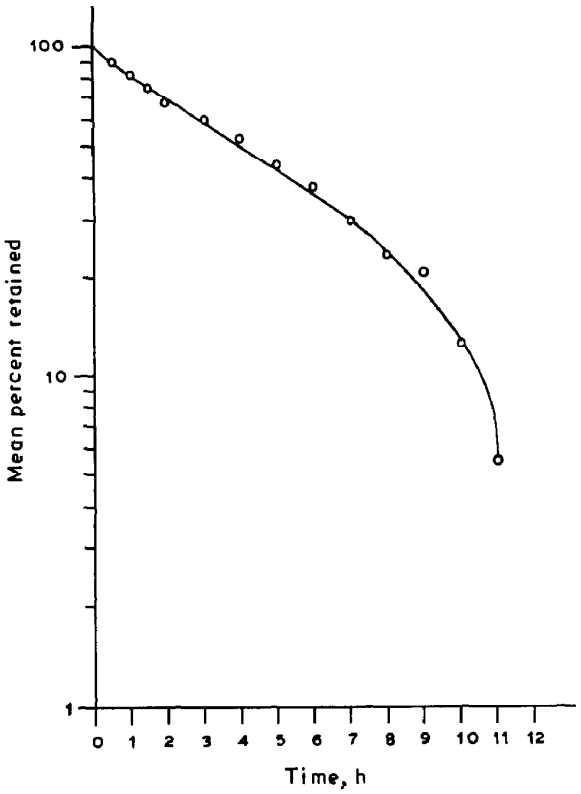

Fig. 6. Log mean percent of centperazine unreleased (in vitro) as a function of time from tablets of formulation I.

tion I is practically constant in the gastrointestinal tract.

To understand the mechanism of release of centperazine from formulation I, the mean data shown in Fig. 1 are analyzed in the following manner.

Plot of mean percent released versus $\sqrt{\text{time}}$ (Fig. 5) indicates that as per the theory of Lapidus and Lordi (1968), drug is released by a diffusion process which is accelerated after 1.5 h due to attrition of tablet surface. Time lag of ~ 5 min may be attributed to the time taken to swell and for the diffusion process to start. Semilogarithmic plot of mean percent retained versus time (Fig. 6) suggests that the release does not follow first-order kinetics (Goodhart et al., 1974). When the data were fitted to the equation of Korsmeyer et al. (1983) by drawing a log–log plot of fraction released versus time, the graph was linear ($r^2 =$ 0.969) and the release exponent, n (slope) value was found to be 0.713. The latter indicates non-Fickian release behaviour.

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References

Anand, N., Sen, A.B., Chatterjee, R.K. and Sharma, S., In Anand, N. and Sen, A.B. (Eds.), Chemotherapy and Immunology in the Control of Malaria, Filariasis and Leishmaniasis, Tata McGraw-Hill, New Delhi, 1983, p. 211.

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 Padmalatha Devi, K., Sustained release tablet formulation of diethylcarbamazine. Part III. Int. J. Pharm., 27 (1985) 157–162.

Baveja, S.K., Ranga Rao, K.V., Rajinder Kumar and Padmalatha Devi, K., Sustained release tablet formulation of diethylcarbamazine. Part II. Int. J. Pharm., 24 (1985b) 355–358.

Goodhart, F.W., McCoy, R.H. and Ninger, F.C., Release of a water-soluble drug from a wax matrix timed-release tablet. J. Pharm. Sci., 63 (1974), 1748–1751.

Gupta, P.P., (1983) Clinical Pharmacology Unit, Central Drug Research Institute, Lucknow, India, personal communication.

Huber, H.E., Dale, L.B. and Christenson, G.L., Utilization of hydrophilic gums for the control of drug release from tablet formulations I. Disintegration and dissolution behaviour. J. Pharm. Sci., 55 (1966) 974–976.

Huber, H.E. and Christenson, G.L., Utilization of hydrophilic gums for the control of drug substance release from tablet formulations II. Influence of tablet hardness and density on dissolution behaviour. J. Pharm. Sci., 57 (1968) 164–166.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm., 15 (1983) 25–35.

Lapidus, H. and Lordi, N.G., Drug release from compressed hydrophilic matrices. J. Pharm. Sci., 57 (1968) 1292–1301.

Metzner, A.B., In Streeter, V. (Ed.), Handbook of Fluid Dynamics, 1st edn., McGraw-Hill, New York, 1961, p. 5.

Nakano, M., Ohmori, N., Ogata, A., Sujimoto, K., Tobino, Y., Iwaoku, R. and Juni, K., Sustained release of theophylline from hydroxypropylcellulose tablets. J. Pharm. Sci., 72 (1983) 378–380.

Nelson, E., Mathematics of oral sustained release products. J. Am. Pharm. Assoc. Sci. Ed., 46 (1957) 572–573.

Ranga Rao, K.V., Studies on Formulation of Sustained Release Dosage Forms of centperazine, Panjab University, India, Ph.D. Thesis, 1984.

Rowland, M. and Beckett, A.H., Mathematical treatment of oral sustained release drug formulations. J. Pharm. Pharmacol., 16 Suppl. (1964) 156T–162T.

Saxena, R., Iyer, R.N., Anand, N., Chatterjee, R.K. and Sen, A.B., 3-Ethyl-8-methyl-1,3,8-triazabicyclo[4,4,0]decan-2-one: a new antifilarial agent. J. Pharm. Pharmacol., 22 (1970) 306–307.

Saxena, R., Sharma, S., Iyer, R.N., and Anand, N., Studies in potential filaricides. 5. 3-Ethyl-8-methyl-1,3,8-triazabicyclo[4,4,0]decan-2-one, a new antifilarial agent. J. Med. Chem., 14 (1971) 929–931.