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COMMUNICATION

RELEASE OF FUROSEMIDE FROM SUSTAINED RELEASE MICROCAPSULES PREPARED BY PHASE SEPARATION TECHNIQUE

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SUMMARY

Furosemide Eudragit RL-100 sustained release microcapsules were prepared using phase separation technique. The results of the release studies, in sorensen phosphate buffer at PH 7.4, indicated good sustained release of the prepared microcapsules. Increasing drug to polymer ratio resulted in a decrease in the release, while increased release obtained by increasing the PH of the dissolution medium. Dosing of healthy human volunteers with sustained release microcapsules resulted in a reduced and sustained urine volume compared to the profuse diuresis obtained with the conventional furosemide capsules.

INTODUCTION

Furosemide is one of the most widely used members of the group of potent diuretics. It produces a very profuse diuresis within a very short period of time and when used in excessive amounts, serious side effects may occur (1).

The drug is effectively used in the treatment of oedema of hepatic, cardiac, pulmonary and renal failure. It has also been given in the treatment of chronic hypertension (2). During long term therapy of diseases, patient non-compliance with therapy represents a major problem. To improve the patient compliance, sustained release medications offer advantage over the conventional dosages forms. Other advantages of

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sustained release medications include maintenance of constant or nearly constant blood level, masking the unpleasent taste, protection against the environment and reducing the GIT reactions of the drug (3).

The present study was undertaken to prepare sustained release furosemide microcapsules by phase separation technique using Eudragit retard RL-100. The effect of drug-to-polymer ratio and PH of the dissolution medium on the release rate of the prepared microcapsules were studied. Urine volumes were determined after dosing healthy human volunteers with regular and sustained release formulations of furosemide.

EXPERIMENTAL

Materials :

Furosemide powder was supplied by (Hoechst, Frankfurt W. Germany), Eudragit retard RL100 (Rohm Pharma, GmbH, Darmstadt, W. Germany), Polyisobutylene PIB (Oppanol B 50, BASF, Ludwigshafe, W. Germany). All other chemicals were pure analytical grade.

Methods :

Preparation of Furosemide Sustained Release Microcapsules :

Furosemide Eudragit RL-100 microcapsules were prepared using the phase separation technique described by Benita et al. (4). The drug particle size (250-315 um) was dispersed in a chloroformic solution of the polymer and stirred at 200 rpm. A non-solvent consisting of 6% w/w PIB in cyclohexane was added to the chloroformic dispersion drop wise at a rate of 10ml/minute. Stirring was continued until complete phase separation was produced. After decantation, the product was separated by filtration and washed with cyclohexane to remove excess PIB. Drying was carried out at room temperature in the dark. Microcapsules were then subjected to sieve analysis and fractions having drug-to-polymer ratios of 1:1, 1:2, and 1:3 were prepared by varying the weight of polymer in the above menthod.

Determination of Furosemide content of Microcapsules :

A certian weight of microcapsules was dissolved in the least amount of acetone, the volume was completed with 0.1M NaOH. The solution was filtered through a sintered glass funnel (G.5).

An aliquot of the filtrate was suitably diluted with 0.1M NaOH and assayed for its furosemide content spectrophotometrically at 334 nm using Unicam SP 8800 spectrophotometer (cambridge-England). Blank experiments showed no interference from the polymer at this wavelength.

Dissolution rate studies :

Weights of microcapsules equivalent to 40 mg furosemide were filled into hard gelatin capsules. Dissolution rate studies of the conventional and sustained release capsules were carried out at 37°C using USP dissolution apparatus (Erweka, GmbH, Type DT, Frankfurt, W. Germany). Sorensen Phosphate buffer PH 7.4 (700 ml) was used as the dissolution medium and the stirring rate was 100 rpm. Samples were taken at different time intervals, suitably diluted with 0.1M NaOH and assayed spectrophotemetrically at 334 nm.

To simulate the in-vivo conditions, dissolution experiments over a range of PH 1.2-7.5were carried out. Dissolution media used in the study were : 250 ml of either 0.1M HCL (PH 1.2), sodium citrate buffer (PH 4.6) and sorensen phosphate buffer PHs 6.5 and 7.5. The solution was stirred at 25 rpm at 37°C. At appropriate intervals (2 hrs), the dissolution medium was changed to change the PH and to maintain sink conditions (5) .

Urine volume measurements :

Urine volume measurements were carried out in 6 healthy female volunteers, 35-44 years old. Following an overnight fasting, subjects were given regular or sustianed release furosemide capsules equivelant to 40mg furosemide with 100ml of water, Urine samples were collected and measured every hour for 12 hours, doses were administered one week apart.

RESULTS AND DISCUSSION

The results of the dissolution studies in sorensen phosphate buffer PH 7.4 are shown in Fig. 1. regular furosemide capsules showed 100% release after approximately 37 minutes. The comparison of the dissolution rate of all Eudragit-RL formulations with that of regular furosemide capsules indicated a sustained effect due to the encapsulation of the drug. This effect is dependent on the durg-to-polymer ratio. Increasing the drug-to-polymer ratio resulted in a decrease in dissolution rate as a result of increase in coat thickness surrounding the drug particles; thereby increasing the distance travelled by the drug through the coat. These findings are in agreement with previous workers (6,7).

In this study, the results showed a uniform drug release, which may be due to the uniformity of the wall thickness of the coating material surrounding the drug particles. In addition, Eudragit polymers are capable of swelling without disintegration or attrition and due to their permeability diffusion occurs.

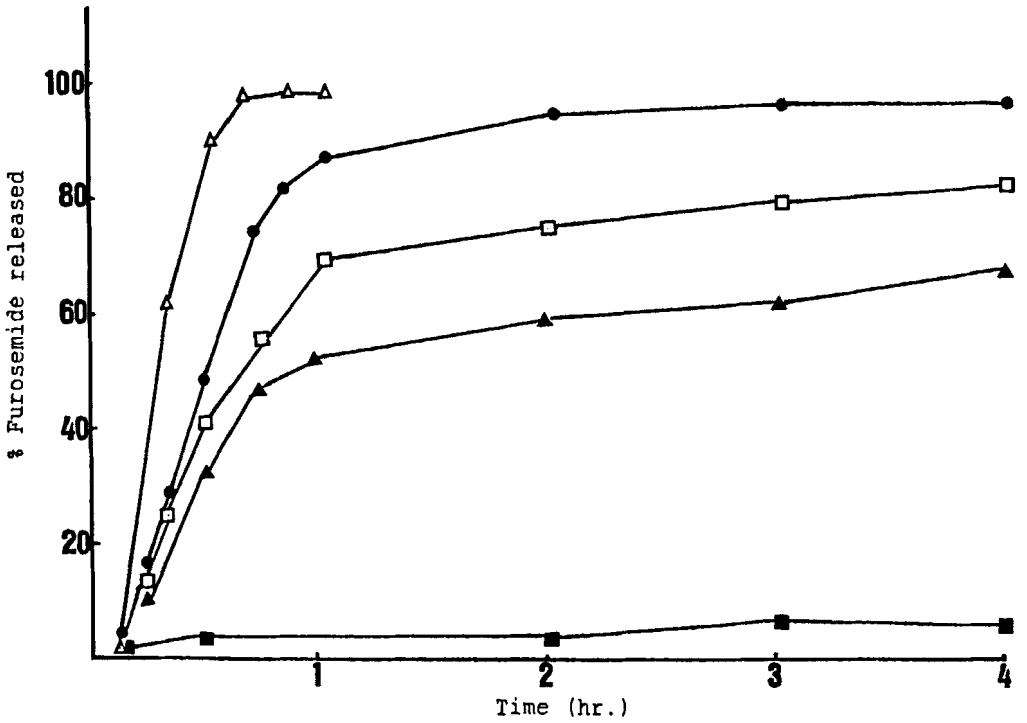

Fig.1 Dissolution rate of furosemide Eudragit-RL-100 microcapsules
● 1:1
□ 1:2
▲ 1:3
and of furosemide powder
Δ in phosphate buffer PH 7.4
■ in 0.1 M HCL

The T_{50} in vitro (time for 50% drug release) for regular furosemide capsules is 15 minutes and 30, 37 and 52 minutes for furosemide Eudragit-RL 1:1, 1:2 and 1:3 respectively. Results indicated increased T_{50} - invitro with increase in drug - polymer ratio. Determination of the T_{50} - invitro was reported to be the most reasonable parameter to explain the coating effect (8).

To test the adaptability of the release data to Higuchi model, percentage drug released was plotted against the square root of time (9). The results showed that the drug release process for the microcapsules obeyed the Higuchi model up to 50% drug release. This indicates that the drug is reasonably encapsulated and a matrix type drug release occurs.

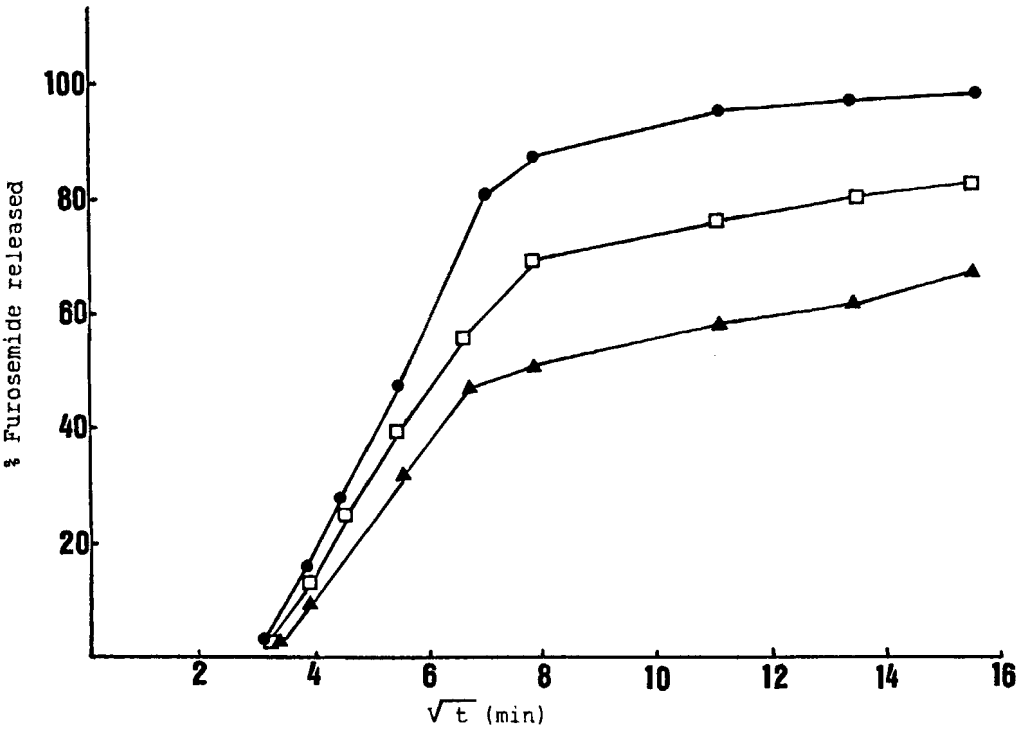

Fig.2 Release profile of furosemide Eudragit RL-100 microcapsules

● 1:1
□ 1:2
▲ 1:3
in phosphate buffer PH 7.4, according to the diffusion model of Higuchi

Figures 2 and 3 showed that the release of the drug started after a lag time of approximately 7.5 minutes. This lag time corresponded to the disintegration time for the hard gelatin capsules.

To simulate the in vivo conditions, the release patterns were determined throughout the PH range 1.2-7.5 (Fig 3). Due to the low solubility of the drug at low PH'S, only very small amounts (3-7%) are released after 2 hrs dissolutions in 0.1M HCL PH 1.2. Increasing the PH by changing the dissolution medium resulted in a continuous increase in the amount of drug released. T_{50} in vitro was found to be 4.25, 4.30 and 5 hrs for furosemide Eudragit RL-1:1, 1:2 and 1:3 respectively.

After 7 hrs, 88% of the drug was released from furosemide Eudragit RL 1:1 capsules compared to 76% release from both 1:2 and 1:3 formulations.

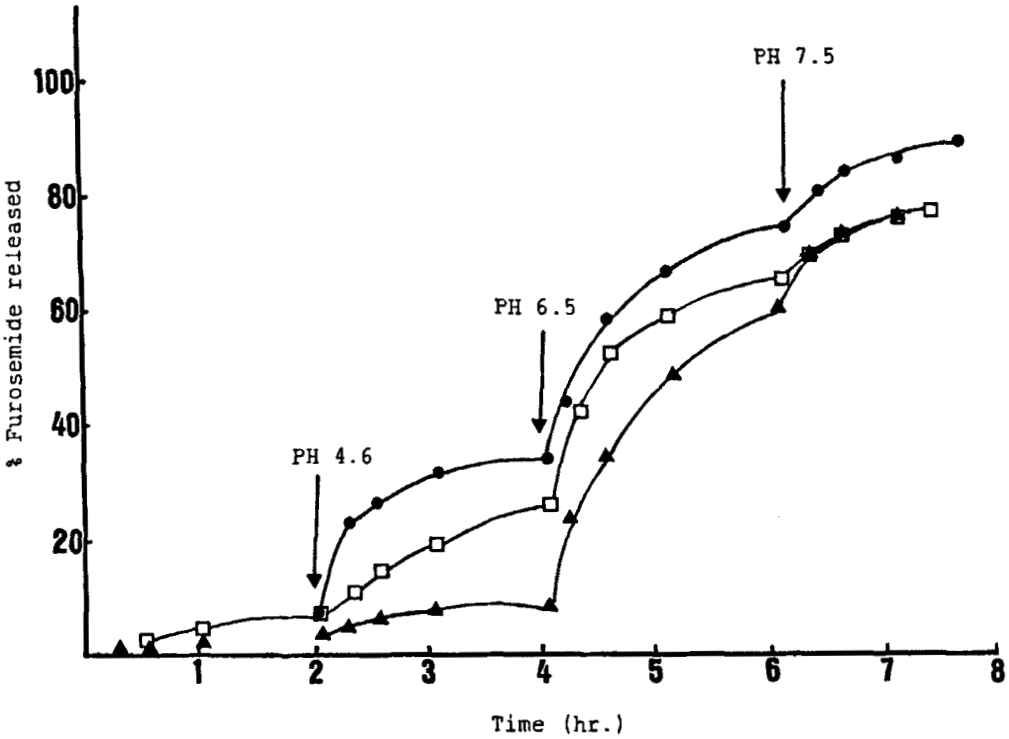

Fig.3 Dissolution rate of furosemide Eudragit RL-100 microcapsules at different PH's

● 1:1
□ 1:2
▲ 1:3

Fig. 4 shows the result of urine volume measurements at different time intervals. Administration of furosemide regular capsules resulted in a sharp increase and decrease in the mean urine volume with peaks after 2 and 8 hrs. In healthy volunteers, peak plasma concentration of the drug occurs 60 minutes after oral administration (10). However, evidence of reduced bioavailability of furosemide in oedema was noticed (11).

A significant decrease in the mean urine volume with time was produced after administraiton of furosemide Eudragit RL 1:1 and 1:3 sustained release capsules. The decrease was found to be uniform and sustained over approximately 1-6 hrs after dosing with sustained release capsules. Further increase in the mean urine volume was noticed 8-10 hrs following capsule administraiton.

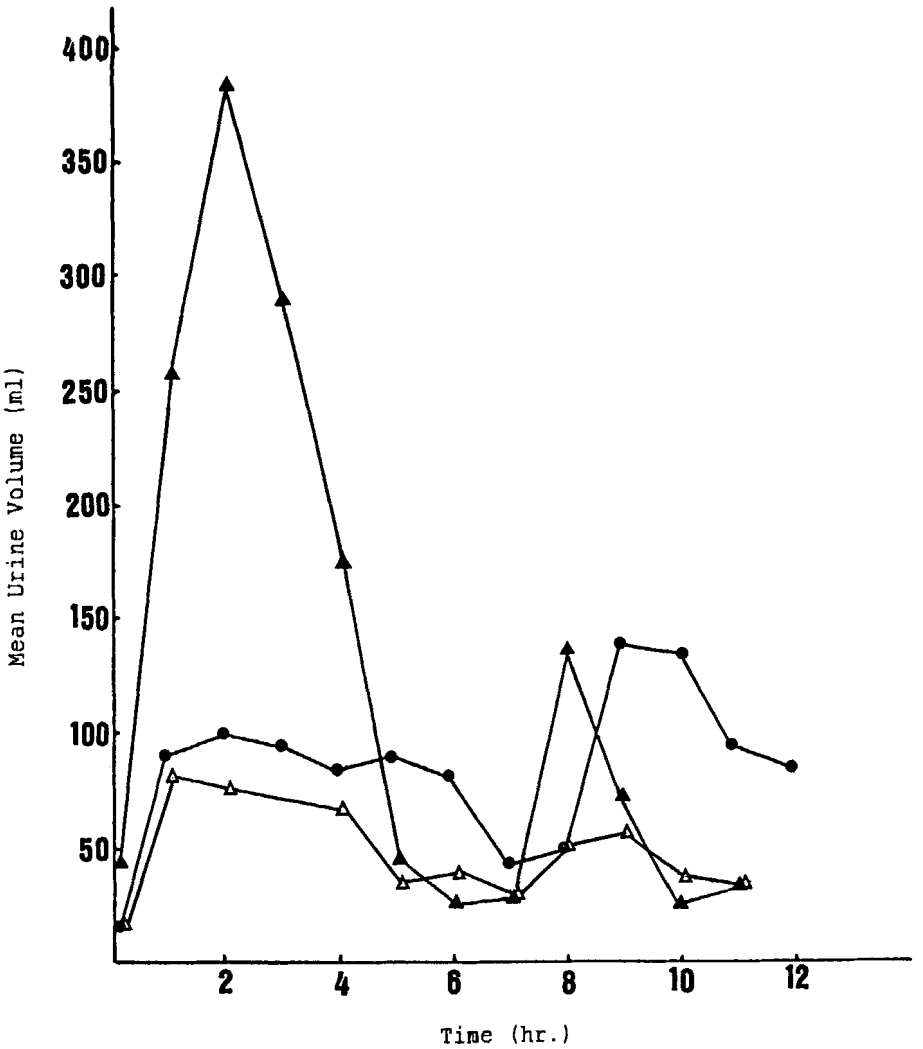

Fig.4 Urine volume obtained at different time intervals after adminstration of furosemide Eudragit RL-100 microcapsules
● 1:1
△ 1:3
▲ and of furosemide powder

previous study on the bioavailability and elimination kinetics of furosemide retard capsules showed a renewed increase of the plasma concentration and renal excretion between 9-10.5 hrs after capsule administraiton, suggesting that a further absorption of fursoemide occurs as a consequence of the delayed release from distal parts of the small intestine or from the large intestine (12).

In conclusion, encapsulation of furosemide may provide two advantages amongst which are : 1. decrease the frequency of dosing, thereby improving patient compliance, 2. sustained release formulations may attain smooth release of drug resulting in a gentle effective sustianed diuresis which is particularly desired in the long term therapy of oedema and hypertension.

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