서방성 Terbutaline sulfate bead의 방출특성

김기만·김영일†·홍순익
유한양행 중앙연구소
(1990년 10월 15일 집수)

Release Characteristics of Terbutaline Sulfate Sustained-Release Beads In Vitro

Ki Man Kim, Young Il Kim† and Soon Uk Hong
Yuhan Research Center, Yuhan Corporation, Kyung Gi Do 433-810, Korea
(Received Oct. 15, 1990)

The sustained-release beads containing terbutaline sulfate (TBS) were prepared by rotopelletization method. The drug was dusted on the non-pareil seeds in a CF-granulator. The sustained-release beads were obtained by coating the active beads with ethylcellulose or Eudragits® , using in any case the same granulator employed for active beads preparation. The release characteristics of sustained-release beads were examined in vitro by rotating basket method applied to Bricanyl® duraules which is a sustained-release TBS matrix tablet.

The release of terbutaline from the beads in vitro was first-order, and the release rate was dependent on both the coat weight ratio and membrane hydrophilicity. Both surfaces of the beads before and after dissolution were smooth. The drug release pattern from the beads could be thought the diffusion through the polymer membrane. The release rate and the surface of the beads stored for 3 years at room temperature were the same with those of the initial beads.

INTRODUCTION

The intensity of the pharmacologic or toxic effect of a drug is considered to be related to the concentration of the drug at the receptor sites, which are usually located in the tissue cells. In practice, the plasma drug level is generally employed for monitoring the course of therapy, since most of the tissue cells are richly perfused with tissue fluids or plasma. The drug concentration is determined by the rates of absorption, distribution and clearance. The effect of a drug may be controlled by reducing its rate of absorption, by delaying the rate at which it is inactivated, of by retarding its excretion. One method to prolong the plasma drug level is to employ a sustained-release formulation.

To maintain continuously effective therapeutic drug levels, multiple unit dosage forms (MUDF) such as granules, pellets or beads has been tried. Compared to single-unit dosage forms, MUDF has much more advantages such as being spreaded out uniformly in the GI tract, reproducible drug absorption, reduced local irritation and unwanted retention of the polymeric material etc.1-6)

In the present study the multiple unit beads were prepared by rotopelletization method. CF-granulator was chosen for the preparation of beads, since it has much more merits such as preparation of more round, smooth and high dense beads, simple manufacturing, uniform drug distribution, and etc.7-11)
Inert sucrose seeds (40 - 60 mesh)
  ↓
Lactose loading
  ↓
Nonpareil seeds (25 - 40 mesh)
  ↓
TBS + Lactose loading
  ↓
TBS loaded beads (18 - 25 mesh)
  ↓
Beads coating
  ← Polymer solution spraying
Modified TBS beads

**Scheme 1.** Flow chart of manufacturing the modified release Terbutaline sulfate beads by CF-granulator.

Terbutaline sulfate has a well-documented bronchodilating effect. Various types of sustained release forms such as prodrug, liquid crystalline system and matrix tablet have been developed, in order to maintain plasma drug concentration constantly without side effect for a long time.

The release characteristics of TBS sustained-release beads were examined in vitro according to the dissolution method of Bricanyl® Durules which is a sustained-release TBS matrix tablet.

**EXPERIMENTAL**

1. Materials
Terbutaline sulfate (TBS) was provided from the Astra Co, Sweden. Sucrose (40-60 mesh, Sam Yang Co.), Lactose (200 mesh, DMV Vehgel Holland), Hydroxy propyl Cellulose (Aqualon Co.), Hydrogenated Castor Oil (HCO, Caschem. Inc.), Ethylcellulose (EC, 12-16 cps, Hercules Co.), PEG 6000 (Nippon Oil & Fats Co.), Eudragit®-RSPM (Rohm Pharm, Gmbh) and Eudragit®-PLRM were used. The raw materials used were of pharmaceutical grade. All other reagents and solvents used in this study were of reagent grade.

2. Apparatus

3. Preparation of Terbutaline sulfate beads
Sustained-release TBS beads were prepared according to rotograniulation method using CF-granulator as shown in Scheme 1 and Fig. 1. In the first place, sucrose seeds were screened to 60 to 40 mesh fore preparation for minimizing the size variation of the finished product. To obtain spherical cores, nonpareil seeds (NPS) were prepared by spraying 5% HPC aqueous solution on sucrose seeds and dusting lactose in granulator rotating at 100 rpm. After dried, its water content was below 0.5% (90°C, 20 mins), NPS prepared were screened to 40 to 25 mesh. TBS-lactose mixture (below 200 mesh) was dusted on the NPS in the same process, which were dried to result in TBS loaded beads and screened to 25 to 18 mesh. The TBS loaded beads produced were coated with 5 kinds of polymeric coating solution as shown in Table 1 to prepar sustained-release TBS beads. After dried, the coated beads were sieved to 25 to 18 mesh. Finally, the contents of drug and water in beads were determined.

4. Dissolution test
The in vitro release of TBS from the beads was determined by USP XXII basket method using a dissolution tester. 900 ml of the distilled water was poured into the vessel, the basket was rotated at
RESULT AND DISCUSSION

1. In vitro release of Terbutaline sulfate from the beads

The in vitro release profiles of TBS from the beads coated with various polymers in distilled water are shown in Fig. 3—8. Fig. 3 shows the release of TBS from the beads (code I) coated with formulation I (HCO: EC = 8:2). It is obvious that the release behavior was prolonged due to polymer coating. The bars in the figures designate the release criteria of TBS from Bricanyl® durules. Generally, the more the bead was coated, the slower the release pattern was behaved. In the Fig. 3 the release profile of the beads with 8% weight ratio was in accord with that of durules. The release of TBS from the beads (code II) coated with formulation 2 (HCO: EC = 6:4) is shown in Fig. 4. The release profile of the beads with 5% weight ratio corresponded to that of durules. We also found that the release rate of code I beads was faster than of code II beads when coated with the same weight ratio. This might be due to the physicochemical property of hydrogenated castor oil. Namely, the release through the mixed waxes was considered to give higher release due to its softening which occurred at 37°C, and distortion properties. The hydroxyl groups in hydrogenated castor oil also
made the membrane somewhat hydrophobic such that it was easily wetted\(^{28-32}\). Therefore it was thought that the diffusion through the membrane was the rate limiting step.

Fig. 5 shows the release profile of the beads (code III) coated with formulation 3 (EC: PEG 6000 = 7: 3), thought the coating layer was mixed with plasticizer, the release pattern of the beads was similar to those of code I and II beads. The release profile of the beads coated with 5% weight ratio was satisfied
the specification of Bricanyl® durules.

Fig. 6-8 show the release profiles of the beads (code IV-VI) coated with Eudragit®-RS and Eudragit®-RL in the various ratio.

As shown in Fig. 6 the release profile of the beads (code IV) coated with only Eudragit®-RS failed to get into the criterion. Although the release of the beads coated below 5% weight ratio was in accord with the criterion, the membrane strength was so weak that beads were not stable at room temperature for shelf life. So, the beads were coated with the solution added Eudragit®-RL, of which the hydrophilicity is superior to Eudragit®-RS. The release profile of the beads coated with the solution containing Eudragit®-RL 5% did not correspond to criterion. In case of the beads supplemented 10% (Fig. 8), the beads coated with 5% and 8% weight ratio released TBS according to the criterion.

2. Release mechanism from the beads

The release data were applied to zero-order, first-
order, square-root and cube-root equations and then the goodness of fit was evaluated by linear regression analysis. The first order release mechanism was the most correlated. For all the dissolution data, correlations were obtained up to 60-80% of TBS release. Once 60-80% of TBS was released, the plot
deviated from linearity and curved down. The first order release rate constants of various TBS beads are represented in Table II. It could be seen from Fig. 3-8 and Table II that the rate constants were influenced by the coat weight ratio and the membrane hydrophilicity. The release rate constant was increased with decreasing the weight ratio and with increasing hydrophilicity.

Table III shows that the constants of the beads in initial state were compared with that of the beads stored for 3 years at room temperature. The release profile of the used beads were fallen in with the criterion. From the stability test, the beads in this study had no significant difference in respect of TBS release stored for shelf life and was found to be very stable. Fig 9-11 show the scanning electron micrographs of the surfaces of TBS beads (code I, III, IV) before and after dissolution, which were stored for 3 years at room temperature. The whole shape of bead was round and the surface of bead before and after dissolution were smooth almost without cracks.

Especially, no pore was found on the surface after dissolution. This indicates that the dissolved TBS diffusion through the membrane was the major mechanism for the sustained released beads.

CONCLUSION

1. The in vitro release profile of Terbutaline sulfate from the beads showed 1st-order release pattern, and the more the bead was coated, the slower the release pattern was behaved.

2. The membrane compositions of the beads corresponding to the criterion of Bricanyl® durules were that of 1) code I bead (weight ratio: 5%), 2) code II bead (weight ratio: 8%), 3) code III bead (weight ratio: 5%), and 4) code IV bead (weight: 5%, 8%).

3. No significant change was found in the difference of the rate constants of the beads in initial state from that of the beads stored for 3 years at room temperature.

REFERENCES


