Korean Journal of Clinical Pharmacy
Vol. 1, No. 1, 23-30, May 1991

서방성 Terbutaline sulfate bead의 방출특성

김기만 · 김영일† · 홍순억
유한양행 중앙연구소
(1990년 10월 15일 접수)

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 rotogranulation 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® durules 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.

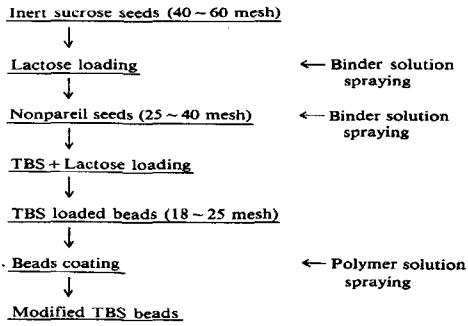
INTRODUCTION

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 rotogranulation 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]

†본 논문에 관한 문의는 이 저자에게로.



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

Terbutaline sulfate has a well-documented broncodilating effect.[12-17] 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 long time.[18-25]

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 Veghel 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

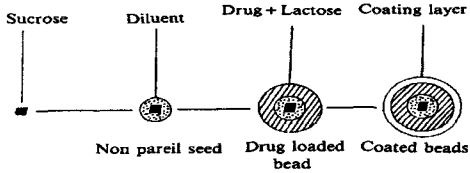


Fig. 1. Schematic representation of modified release Terbutaline sulfate beads during preparation.

CF-granulator (CF-360, Freund Co.), Vacuum dryer (VWR 430, VWR Science), Moisture tester (F-1A, Kett Electric Lab.), Laboratory mill (A10, Tekmar Co.), Dissolution tester (276-A, Hanson Research), Scanning electron microscope (JSM-35, Jeol Co.), HPLC-EC Detector (5100A, ESA Coulochem.) were used.

3. Preparation of Terbutaline sulfate beads

Sustained-release TBS beads were prepared according to rotogranulation 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 I 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 m*l* of the distilled water was poured into the vessel, the basket was rotated at

Table I. *Formulation of Terbutaline sulfate beads.*

Components \ Code	I	II	III	IV	V	VI
Uncoated TRB pellet	200	200	200	200	200	200
Hydrogenated castor oil	16	12	–	–	–	–
Ethylcellulose	4	8	14	–	–	–
PEG 6000	–	–	6	–	–	–
Eudragit-RS	–	–	–	18	19	20
Eudragit-RL	–	–	–	2	1	–
Chloroform	180 ml	180 ml	–	–	–	–
Methylene chloride	–	–	90 ml	108 ml	108 ml	108 ml
Isopropyl alcohol	–	–	–	72 ml	72 ml	72 ml
Ethyl alcohol	–	–	90 ml	–	–	–

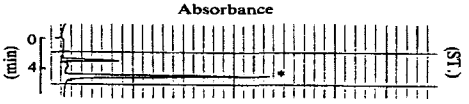


Fig. 2. HPLC chromatograms of Terbutaline sulfate.

40 rpm and the medium was allowed to 37 ± 0.5°C. The accurate amount of TBS beads (5 mg as TRB) was placed in the basket, and 3 ml of the dissolved solution was sampled at the predetermined time intervals. Immediately, the sample volume taken was replaced by the equivalent volume of fresh medium preheated at 37°C and the volume of medium in the vessel was kept constant. After the dissolved solution was filtered, the dissolved TBS was measured by HPLC using EC detector. The condition of detection and HPLC chromatograms of TBS are as follows[26,27].

Table II. *Conditions of HPLC for detection of Terbutaline sulfate.*

·Column	μ-Bondapak C_{18}, 10 μm
·Mobile phase	Methanol: pH 6 buffer soln: n-perchlorate (12: 88: 5)
·Flow rate	1.0 ml/min
·Detector	Electrochemical detetor working potential: +0.75 V

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 1 (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 caster 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

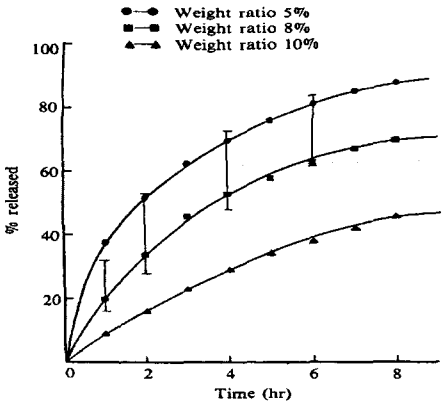


Fig. 3. Release profiles of TBS Beads coated with Formulation I (HCO: EC = 8: 2).

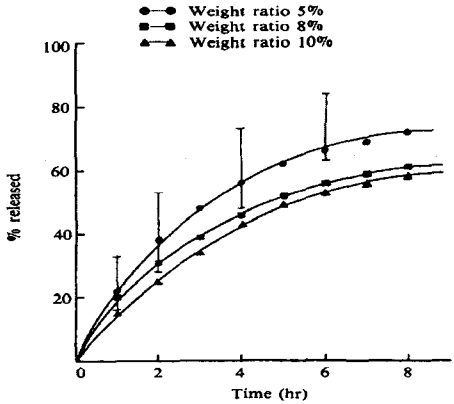


Fig. 5. Release profiles of TBS Beads coated with Formulation II (EC: PEG 6000 = 7: 3).

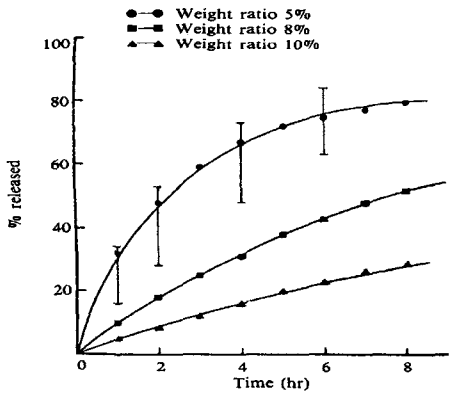


Fig. 4. Release profiles of TBS Beads coated with Formulation II (HCO: EC = 6: 4).

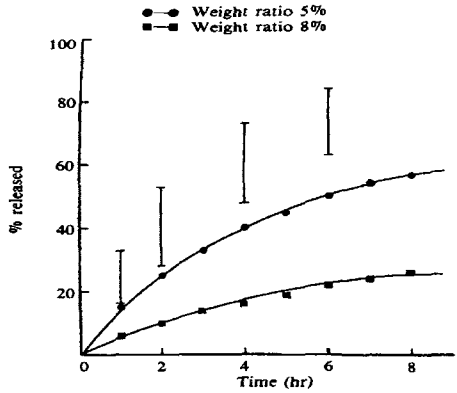


Fig. 6. Release profiles of TBS Beads coated with Formulation IV (Eudragit-RS: Eudragit-RL = 10: 0).

made the membrane somewhat hydrophylic 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

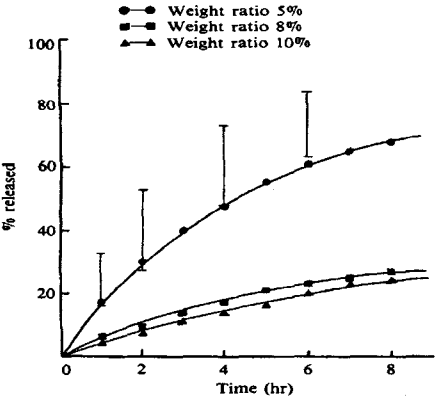


Fig. 7. Release profiles of TBS Beads coated with Formulation V (Eudragit-RS: Eudragit-RL = 9.5: 0.5).

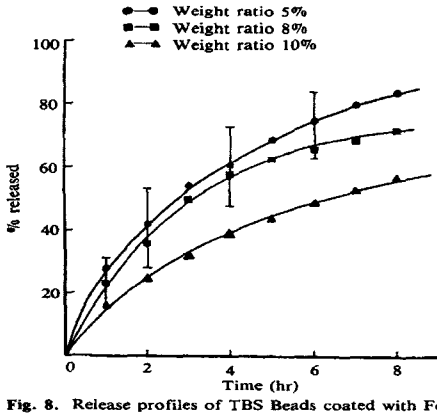


Fig. 8. Release profiles of TBS Beads coated with Formulation IV (Eudragit-RS: Eudragit-RL = 9: 1).

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

Table III. *First-order release rate constants (hr^{-1}) of Terbutaline sulfate from beads in distilled water.*

Formulations	Coat ratio (w/w %)		
	5	8	10
I	0.235 ± 0.012	0.186 ± 0.008	0.076 ± 0.007
II	0.183 ± 0.011	0.092 ± 0.010	0.043 ± 0.009
III	0.148 ± 0.014	0.121 ± 0.007	0.114 ± 0.013
IV	0.213 ± 0.023	0.186 ± 0.015	0.097 ± 0.012
V	0.106 ± 0.013	0.041 ± 0.008	0.037 ± 0.009
VI	0.105 ± 0.015	0.037 ± 0.008	

Table IV. *First-order release rate constants (hr^{-1}) of Terbutaline sulfate from initial beads and the beads stored for 3 years at room temperature.*

$p < 0.05$

Formulations	Initial	After 3 years
I-8*)	0.186 ± 0.015	0.183 ± 0.010
III-5	0.148 ± 0.014	0.156 ± 0.008
IV-5	0.213 ± 0.023	0.227 ± 0.018

*) I-8 means code I beads coated with 8% coat weight ratio (w/w)

(code IV) coated with only Euragit® -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

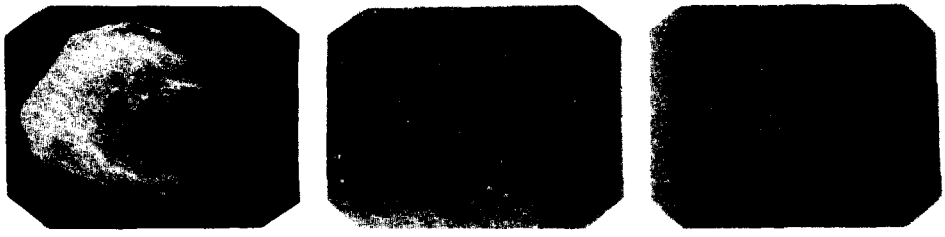
The release data were applied to zero-order, first-

(a) (b) (c)

Fig. 9. Scanning electron micrographs of TBS beads (I) at initial state (a,b) and stored for 3 years at room temperatue (c). a: ×72, b: ×1000, c: ×1000

(a) (b) (c)

Fig. 10. Scanning electron micrographs of TBS beads (III) at initial state (a,b) and stored for 3 years at room temperature (c). a: ×72, b: ×1000, c: ×1000



(a) (b) (c)

Fig. 11. Scanning electron micrographs of TBS beads (III) at initial state (a,b) and stored for 3 years at room temperature (c). a: ×72, b: ×1000, c: ×1000

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 lineality 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

1) Robinson, M.J. *et al.:* An apparatus and method for coating of solid particles., *J. Pharm. Sci.*, **57**(11), p.1983 (1968).
2) Sirianni, A.F. *et al.:* Recent experience with the spherical agglomeration process, *Can. J. Chem. Eng.*, **47**(4), p.166 (1969).
3) Bechgaard, H.: Critical factors influencing gastrointestinal absorption what is the role of pellets? *Acta. Pharm. Tech.*, **28**(2), p.149 (1982).
4) Murthy, K.S.: Solid oral controlled release dosage forms-an orerview. *Pharm. Eng.*, (July-August) p.19 (1983).
5) Suryakusuma, H. *et al.:* Encapsulated hydrophilic polymer beads containing indomethacin as controlled released drug delivery systems, *J. Pharm. Pharmacol.*, **36**, p.497 (1983).
6) Lin, S.Y. *et al.: In-vitro* dissolution behavior of spansule-type micropellets prepared by pan coating method. *Pharm. Ind.*, **51**(5), p.528 (1989).
7) Funakoshi, Y. *et al.:* Process for coating granular materials. *U.S. Patent. 3*, **671**, 296 (1972).
8) Idem, Process for coating granular materials, *U.S. Pattent*, **4**, 034, 126 (1977).
9) Idem, A novel agglomeration granulating system utilizing a centrifugal-fluidizing drive, *Powder. Tech.*, **27**(1), p.13 (1980).
10) Ishizaka, T. *et al.: In vitro* drug release from wax-coated granules prepared by dry-blending and structure of wax coat layer. *Yakuzaigaku.*, **45**(2) p.193 (1985).
11) Morimoto, M. *et al.:* Evaluation of sustained-release capsules of molsidomine (SIN-10) in dogs and monkeys, *Chem. Pharm. Bull.*, **34**(3), p.1257 (1986).
12) Gilman, A.G. *et al.*:"The Pharmaceutical Basis of Therapeutics", 7th ed Mcmillan Press, p.172 (1985).
13) Reynolds, J.E.F.: "Martindale" 29th ed. Pharmaceuticl Press, p.31 (1989).
14) Nilsson, H.T. *et al.:*The metabolism of terbutaline in man, *Xenobiotica.*, **2**(4), p.363 (1972).
15) Reed, C.E.: Physiology and pharmacology of beta 2 adrenergic agents, *Chest.*, **73**(6), p.914 (1978).
16) Mcphillips, J.J.: Terbutaline., *Drug. Information.*,. p.311 (1979).

17) Leferink, J.G., *et al.*: Pharmacokinetics of terbutaline, a β-sympathomimetic, in healthy volunteers and asthmatic patients, *Arzneim-Forsch/Drug. Res.*, **32**(I), p.159 (1982).
18) Formaren, H.: The therapeutic value of oral long-term treatment with terbutaline (Bricanyl®) in asthma., *Scand. J. Res. Dis* **56**, p.321 (1975).
19) Taudorf, E, *et al.*: Terbutaline depot tablets in asthama, *Allergy.*, **36**, p.495 (1981).
20) Keith, A.D. *et al.*: Polymeric diffusion matrix containing terbutaline, *U.S. Patent. 4*, **292**, 302 (1981).
21) Eriksson, N.E. *et al.*: A comparison of sustained-release terbutaline and ordinary terbutaline in bronchial asthma, *Br. J. Dis. Chest.*, **76**, p.202 (1982).
22) Nyberg, L. *et al.*: Pharmacokinetic of terbutaline given in slow-release tablets., *Eur. J. Res. Dis.*, **65**, (suppl 134) p.119 (1984).
23) Olsson, O.A.T. *et al.*; New lipophilic terbutaline ester prodrugs with long effect duration., *Pharm. Res.*, p.19 (1984).
24) Estilson, J. *et al.*: Short-term oral terbutaline does not induce myocardial hypertrophy in man, *Acta. Pharmacol., et Toxicol.*, **58**, p.126 (1986).
25) Rathlou, N.H.H., *et al*, Bambuterol: Dose response study of a new terbutaline prodrug in asthma., *Eur. J. Clin. Pharmacol.*, **30**, p.7 (1986).
26) Edholm, L.E.: Quantitative analysis of terbutaline (Bricanyl®) in human plasma with liquid chromatography and electrochemical detection using on-line enrichment., *J. Liq. Chromato.*, **6**(3), p.559 (1983).
27) Gupta, V.D.: Quantitative of terbutaline sulfate in pharmaceutical dosage forms using high performance liquid chromatography., *ibid.*, **9**(5), p.1065 (1986).
28) John, P.M. *et al.*: Surfactant effects of sprayed-congealed formulations of sulfaethylthiadiazole-wax. *J. Pharm. Sci.*, **57**(4), p.584 (1968).
29) Cusimano, A.G. *et al.*: Spary-congealed formulations of sulfaethylthiadiazole (SETD) and waxes for prolongel-release medication., *ibid.*, **57**(7), p.1104 (1968).
30) Raghunathan, Y. *et al.*: Spray-congealed formulations of sulfacthidole (SETD) and waxes for prolonged-release medication., *ibid.*, **57**(10), p.1748 (1968).
31) Khalil, S.A.H. *et al.*: *In vitro* release of aspirin from various wax-coated formulations., *J. Pharm. Pharmacol.*, **23**, p.72 (1971).
32) Schroeder, H.G. *et al.*: Sustained release from inert wax matrixes I: drug-wax combinations., *J. Pharm. Sci.*, **67**(3), p.350 (1978).