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Controlled release tamsulosin hydrochloride from alginate beads with waxy materials

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Abstract

The objective of this study was to develop oral controlled release delivery systems for tamsulosin hydrochloride (TSH) using alginate beads with various waxy materials, such as Compritol 888 ATO, Precirol ATO 5 and Gelucires. The beads were prepared from sodium alginate–waxy material–TSH slurry dropped onto calcium chloride to form spherical beads. The effects of the addition of various waxy materials to alginate beads on the drug encapsulation efficiency, bead size and morphology were investigated. The drug encapsulation efficiency significantly increased with the addition of waxy materials. The TSH-loaded alginate beads with and without waxy materials were almost spherical particles with an average diameter of 1.44 and 1.22 mm, respectively. In dissolution study, the TSH-loaded alginate beads with waxy materials exhibited controlled release behaviour over a 6-h period, while beads without waxy materials showed release of 100% TSH within 2 h. These results may be attributed to the formation of a more rigid alginate matrix structure due to incorporated waxy materials. From the Dunnett's *t*-test and the f_2 factor, the release of TSH from alginate beads, a similar dissolution pattern to that of the marketed product (Harunal capsules) could be achieved by adding Gelucire 50/13 into TSH-loaded alginate beads. From these results, oral controlled release of TSH could be achieved with loading in alginate beads with waxy materials, such as Compritol 888 ATO, Precirol ATO 5 and Gelucires.

Introduction

Tamsulosin hydrochloride (TSH) is a highly selective alpha 1_A-adrenoreceptor antagonist that has been used for treatment of lower urinary-tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). As compared with other alpha-antagonists, TSH has greater specificity for alpha 1_A receptors and does not affect alpha receptors on blood vessels (Beduschi et al 1998; O'Leary 2001). Moreover, following oral administration of 0.2–0.4 mg TSH, TSH is absorbed from the intestine and almost completely bioavailable (Wilde & McTavish 1996). However, many LUTS/BPH patients are elderly subjects with an impaired cardiovascular regulation. They are particularly at risk for cardiovascular adverse events, which are not only unpleasant, but can also lead to serious morbidity, such as falls and fractures potentially resulting in hospitalization, nursing home placement or death (Chapple & Andersson 2002). Therefore, a controlled-release formulation of TSH is required to improve the absorption of drug in the intestinal tract.

Sodium alginate has been used as a controlled-release matrix material in medicine (Badwan et al 1985; Kulkarni et al 2001) and agriculture (Pepperman et al 1991) after cross-linking it with calcium chloride. In addition, Chan et al (Chan et al 1997; Chan & Heng 1998) attempted to sustain release of the model drug by incorporating poly (vinylpyrrolidone) and different types and viscosity grades of cellulose derivatives as co-polymers with sodium alginate. Mirghani et al (2000) dispersed the drug in a waxy matrix (Compritol 888 ATO) and then coated it with alginate to sustain the release of diclofenac sodium. In a previous study, the effects of the addition of excipients (microcrystalline cellulose and sodium starch glycolate, etc.) on loading efficiency and drug release from alginate beads were investigated (Hwang et al 1995; Lee et al 2003).

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The Gelucires are a family of lipid-based excipients comprising mono-, di- and triglycerides mixed with mono- and diesters of fatty acids and polyethylene glycol (PEG). These materials are classified by two numbers, the first referring to the approximate melting point of the base and the second to the hydrophile–lipophile balance (HLB) number that reflects the proportion of water-soluble to lipid-soluble moieties in each material. Gelucires have been widely studied as controlled-release matrices, particularly with respect to two such materials, G 50/13 and G 44/14 (Sutananta et al 1995; Ratsimbazafy et al 1999; Khan & Craig 2003). Moreover, Compritol 888 ATO (atomized glyceryl behenate) consists of about 28–32% tribehenate, 52–54% dibehenate and 12–18% monobehenate, and Precirol ATO 5 is synthesized by esterification of glycerol by palmitostearic acid. These materials were also used to obtain controlled-release dosage forms by several techniques, such as hot-melt extrusion and hot-melt coating (Barthelemy et al 1999; Hamdani et al 2003).

The main objective of this study was to develop oral controlled-release delivery systems for TSH using alginate beads with various waxy materials, such as Compritol 888 ATO, Precirol ATO 5 and Gelucires. The effects of the addition of various waxy materials to alginate beads on the drug encapsulation efficiency, bead size and morphology were investigated. The effect of waxy materials on the release profile of TSH from alginate beads was also investigated via dissolution test and compared with that of a commercial controlled-release product (Harunal capsules).

Materials and Methods

Materials

Tamsulosin hydrochloride (TSH) was purchased from Young Sung Fine Chemicals Co., Ltd (99.60% purity, Korea). Sodium alginate NSPH (Duck Algin, 500 ± 50 cP for a 1% solution at 20°C) was purchased from Kibum Food Chemifa Co. (Tokyo, Japan). The following materials were kindly donated from Gattefossè (Saint Priest Cedex, France): Compritol 888 ATO (COM), 69–74°C (melting point); Precirol ATO 5 (PRE), 53–57°C; Gelucire 50/13 (G 50/13), 46–51°C; Gelucire 44/14 (G 44/14), 42.0–46°C; Gelucire 43/01 (G 43/01), 42.0–46°C; Gelucire 39/01 (G 39/01), 37.5–41.5°C. Calcium chloride was purchased from Sigma Chemical Co. (St Louis, MO, USA). All organic solvents were high-performance liquid chromatography (HPLC) grade. All chemicals were of reagent grade. For comparison, Harunal capsules (Lot no. HRC801; Yamanouchi Pharmaceutical Co. Ltd, Korea) containing 0.2 mg of TSH were purchased.

Preparation of TSH-loaded alginate beads

Waxy material (2 g) was weighed in a beaker and heated on a water bath to 10°C above its melting point. TSH powder (20 mg) was added to the molten waxy material and mixed well with a spatula for 30 min. The alginate solution (200 mL, 2% w/v, 25°C) was added to the molten waxy materials, the mixture was homogenized (2000 rev min^{-1}, 3 min; HF 93, SMT corporation, Japan) and then cooled to 25°C. This resultant mixture formed the slurry. The slurry was dropped using a peristaltic pump (KMC-1303P2; Vision Scientific Co. Ltd, Korea) with a polyethylene tubing nozzle (i.d. 0.6 mm, o.d. 2 mm, falling distance 6 cm, pumping rate 3 mL min^{-1}) into 50 mL of saturated calcium chloride in ethanol (25°C), which was gently agitated with a magnetic stirrer. The formed beads were cured in this solution for 20 min, then filtered, and rinsed three times with 50 mL of de-ionized water. The beads were dried to constant weight in a warm air oven (30°C). As a control, 10 mg of TSH was added to 150 mL of sodium alginate solution (2% w/v) and stirred with a magnetic stirring bar in a beaker until complete dissolution was achieved. The mixture was then dropped into saturated calcium chloride in ethanol under the same conditions as described above.

Particle size analysis of TSH-loaded alginate beads

The particle sizes of 30 dry beads for each formulation were measured with a digital caliper (Mitutoyo Model 323-511-30; Kawasaki, Japan) and the mean particle size was determined.

Assay for drug content of alginate beads

Eight-hundred milligrams of TSH-loaded alginate beads with waxy materials were accurately weighed and immersed in 250 mL of pH 7.2 phosphate buffer (in accordance with USP) and heated to 10°C above the melting point of the waxy material used on a water bath and stirred for 1 h. Then, pH 7.2 phosphate buffer was added to a total 500 mL and sonicated for 1 h. For alginate beads without waxy materials, 800 mg of beads were accurately weighed and immersed in 500 mL of pH 7.2 and sonicated for 1 h. The mixture was centrifuged at 3000 rev min^{-1} for 5 min after violently stirring for 24 h. To 10 mL supernatant, 1 mL 0.5 M HCl and 2 mL internal standard solution (20 μg mL^{-1} propyl paraben in 50% acetonitrile) were added and vortex-mixed for 1 min. The solutions were filtered by 0.45-μm membrane filter (PTFE; Whatman Inc., NJ, USA) and analysed using HPLC.

HPLC analysis

The concentration of TSH was determined by HPLC. The HPLC system consisted of a pump (Model 600, Waters, USA), an auto-sampler (Model 717 plus, Waters) and a UV detector (Model 486 Tunable Absorbance Detector; Waters). The C_{18} reverse phase column (Xterra, 5 μm, 4.6 mm × 250 mm; Waters) was used at room temperature. The mobile phase consisted of acetonitrile (50%) and 0.02% perchloric acid (50%) adjusted to pH 2.0 with 1.0 M NaOH and the flow rate was 0.8 mL min^{-1}. The injection volume was 100 μL.

Optical microscope images

Optical microscope images of the formed beads were observed using a video microscope system (Alphasystech, Korea) equipped with a Sony model Super HAD CCD camera (Tokyo, Japan) and ITPro 3.03 image analysis software (Sometech Inc., Korea).

Scanning electron microscopy (SEM)

The surface and morphology of alginate beads were investigated by scanning electron microscopy (SEM) (XL30SFEG; Philips, Netherlands). Samples were coated with gold and palladium using a vacuum evaporator and examined using SEM at 10 kV accelerating voltage.

Dissolution studies

The release of TSH from alginate beads was performed according to the USP XXV paddle method using a dissolution apparatus (Vankel VK7000; Cary, NC, USA). The TSH-loaded alginate beads containing 0.2 mg of TSH were filled into hard gelatin capsules (capsule no. 3; Su-Heung Capsule Co. Ltd, Korea). The capsules were added into 500 mL of simulated gastric fluid without pepsin (adjusted to pH 1.2 with HCl) containing polysorbate 80 (0.003% w/w) at 37 ± 0.1°C and with a paddle speed of 100 rev min^{-1}. A sinker was used to avoid capsule flotation. Each sample (5 mL) was withdrawn at pre-determined time intervals and an equal volume of fresh simulated gastric fluid was compensated. Two hours after incubation in simulated gastric fluid, 500 mL of simulated intestinal fluid without pancreatin (pH 7.2, phosphate buffer according to the USP without enzyme) was added into the vessel to adjust the pH of the medium from pH 1.2 to pH 7.2. Portions of the samples were taken and simulated intestinal fluid was added to compensate the volume. Internal standard solution (1 mL; 4 μg mL^{-1} propyl paraben in 50% acetonitrile) was added to the 5-mL sample withdrawn at pH 1.2. Meanwhile, 0.5 mL HCl (0.5 M) and 1 mL internal standard solution were added to the 5-mL sample withdrawn at pH 7.2. Each sample was vortexed for 1 min and filtered with a 0.45-μm syringe filter (PTFE; Whatman Inc., NJ). Then, the filtrate was analysed by HPLC. The resulting dissolution curves were characterized by the corresponding 360-min dissolution efficiency (Equation 1) (Khan 1975).

$$\text{D.E.\%} = \frac{\int_0^t y\,dt}{y_{100}t} \times 100 \quad (1)$$

Kinetic assessment

The drug release mechanism was investigated by fitting the dissolution data to distinct models:

$$Q_t = K_H\sqrt{t} + C \quad (2)$$

$$(100)^{1/3} - (100 - Q_t)^{1/3} = K_{HC}t + C \quad (3)$$

where Q_t is the percentage of drug released at time t, K_H is the Higuchi model release rate constant as a diffusion process based in the Fick's law and K_{HC} is the Hixson-Crowell model release rate constant as erosion release mechanism (Costa & Lobo 2001). The optimum values for the parameters presented in each equation were determined by curve fitting methods using SPSS 11.0 software (SPSS, Chicago, IL, USA). For comparison, only the points within the interval $0.1 \le Q_t/Q_\infty \le 0.9$ were used.

Statistical analysis

In all cases, experiments were replicated and analyses were carried out in triplicate. One-way analysis of variance followed by the Student–Newman–Keuls multiple comparison test using SPSS 11.0 software was used to compare the effect of waxy materials on the size of beads, the drug encapsulation efficiency and the drug dissolution efficiency. In addition, Dunnett's *t*-test (two-sided) was performed to compare the percent dissolved between formulation and marketed product (Harunal capsules) at each time point (Yuksel et al 2000). $P < 0.05$ denoted significance in all cases.

Results and Discussion

Drug encapsulation efficiency of the beads

The drug encapsulation efficiency was 26.2–64.1% for the beads prepared. Waxy materials significantly increased the drug encapsulation efficiency over the control (without waxy materials) (Table 1). The analysis of variance showed that there are significant differences among the waxy materials ($P < 0.001$), which in order of increasing the drug encapsulation efficiency were ranked by the Student–Newman–Keuls test as follows: G 39/01 < G 50/13 = G 43/01 = G 44/14 < PRE = COM. Waxy materials with a high melting point and that were water-insoluble, such as COM and PRE, resulted in high drug encapsulation efficiency, compared with Gelucires.

Table 1 Drug encapsulation efficiency and average diameter of alginate beads

Formulation (additives)	Drug encapsulation efficiency (%)	Average diameter (mm)
G 39/01	54.90 ± 1.64	1.31 ± 0.03
G 43/01	59.90 ± 1.87	1.33 ± 0.03
G 44/14	60.30 ± 1.86	1.35 ± 0.04
G 50/13	59.50 ± 1.97	1.33 ± 0.03
PRE	63.50 ± 1.18	1.41 ± 0.04
COM	64.10 ± 1.92	1.44 ± 0.03
Control (no additive)	26.20 ± 1.36	1.24 ± 0.02

Data are means ± s.d., n = 6 (drug encapsulation efficiency) or 60 (average diameter).

Moreover, waxy materials with a high HLB and water-soluble property, such as G 44/14 and G 50/13, showed a two-fold increase in drug encapsulation efficiency. Agglomerates were observed within formed beads for waxy materials with a low HLB, such as G 39/01, G 43/01, PRE and COM (Figure 1). However, a homogeneous alginate-waxy matrix seemed to form for waxy materials with a high HLB, such as G 44/14 and G50/13. It is clear that waxy materials had a significant effect on the encapsulation efficiency of TSH in alginate beads. This may be due to impediment of the diffusion of drug from the aqueous polymer phase to the continuous ethanol phase during the formation of insoluble calcium alginate matrix and encapsulation of drug within waxy materials during the formation of gel beads (slurry) despite low drug loading (0.2 mg TSH/capsule).

Particle size and morphology of the beads

The TSH-loaded alginate beads with and without waxy materials were almost spherical particles, with an average diameter of 1.44 ± 0.03 and 1.24 ± 0.02 mm, respectively (Table 1 and figure 2). The average diameters of beads was significantly increased with the addition of waxy materials ($P < 0.001$). However, there were no significant differences in the average diameters among beads prepared with Gelucires. The ranked order for the average diameters of beads was Gelucires < PRE < COM. The surface morphology of alginate beads with waxy materials is shown in Figure 2. When waxy material was added in the alginate beads, the surface was more compact due to the formation of rigid insoluble calcium alginate beads, compared with control. Moreover, the surface of alginate beads without waxy materials was porous. This may also result in low drug encapsulation efficiency, permitting the drug (TSH) to diffuse out during the formation of alginate beads (Liu et al 1997).

Dissolution studies

The dissolution profiles from alginate beads with and without waxy materials in pH 1.2 for 2 h and pH 7.2 for 4 h, respectively, are presented in Figure 3 and summarized in Table 2, in terms of the sampling time ($t_{2\,h}$) and dissolution efficiency ($D.E._{6\,h}$). As depicted in Figure 3, $99.3 \pm 2.14\%$ of TSH from beads without waxy material was released within 2 h. While only 35% of TSH from beads with COM was released, above 90% of TSH from beads with Gelucires was released in 6 h. The sampling time ($t_{2\,h}$) ranked by the Student–Newman–Keuls test was increased as follows: COM < PRE = G 50/13 < G 43/01 < G 39/01 < G 44/14. Interestingly, these results were in agreement with the increasing order of melting point of waxy materials, except G 44/14. Similarly, the $D.E._{6\,h}$ of beads with PRE and COM, which have high melting point and water-insoluble property, were also smaller than for other waxy materials. It was clear that the extent and rate of drug release was affected by the addition of waxy materials into alginate beads in comparison with the control. These results may be attributed to the formation of a rigid alginate-waxy matrix, which was able to retard the release of TSH from alginate beads.

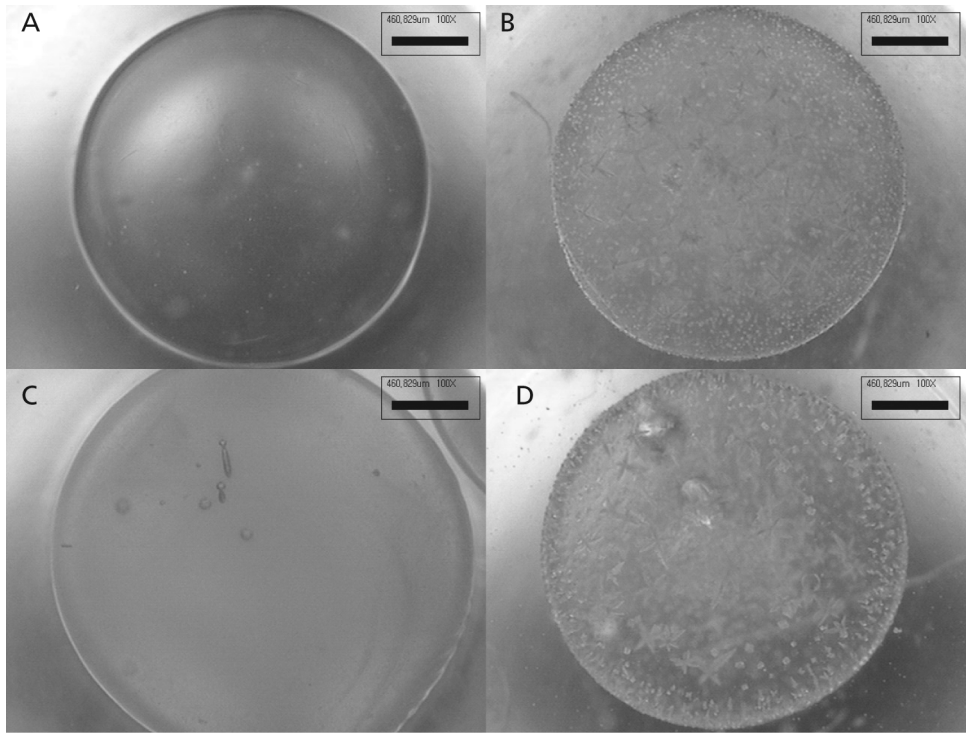

Figure 1 Optical microscope images of the formed beads after dropping slurry into ethanol saturated with calcium chloride, showing control (A), G 43/01 (B), G 50/13 (C) and PRE (D). All scale bars correspond to 450 μm (100× magnification).

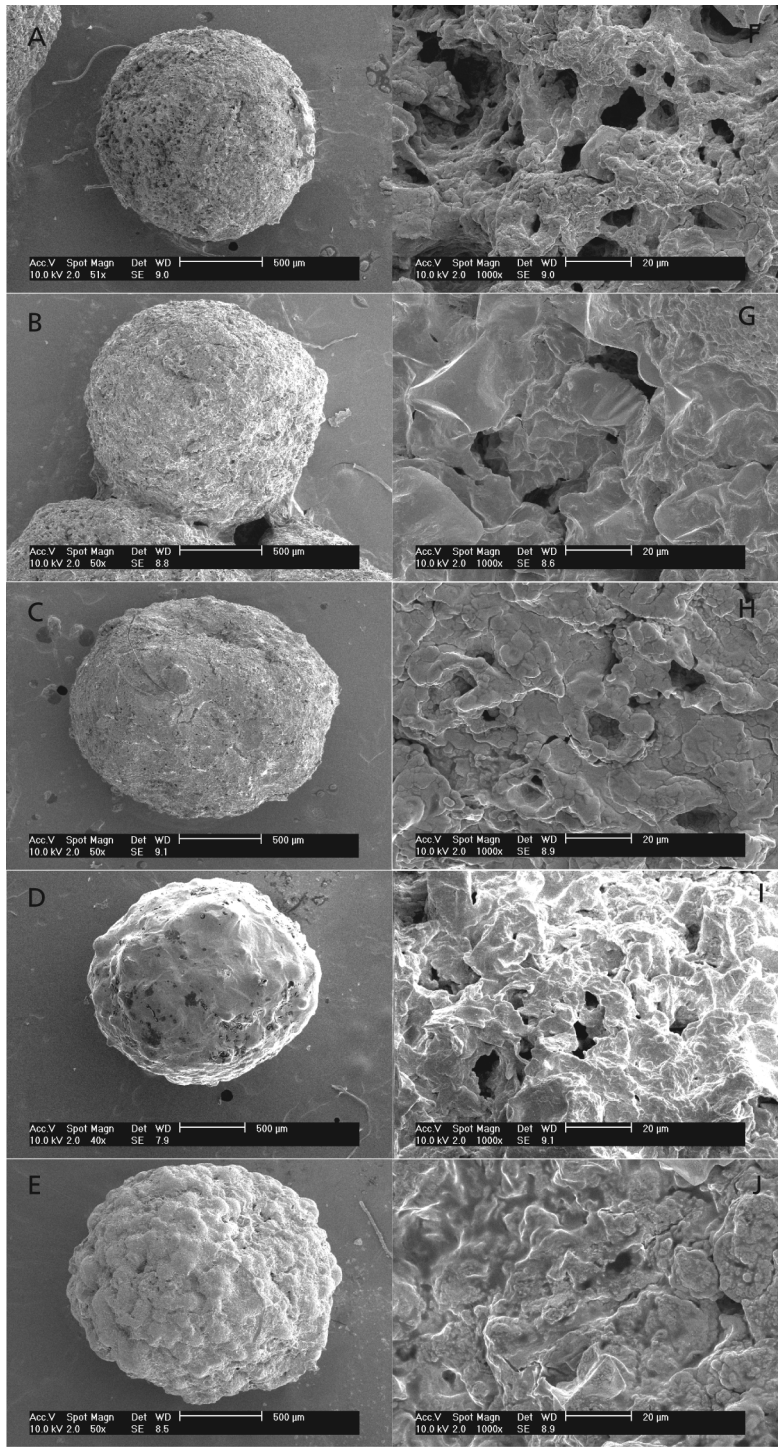

Figure 2 Scanning electron micrographs of TSH-loaded alginate beads with various waxy materials, showing control (A), G 44/14 (B), G 50/13 (C), PRE (D) and COM (E); F, G, H, I and J are 1000× magnification of A, B, C, D and E, respectively.

It is interesting to note that G 44/14 and 50/13 exhibited a remarkable difference in dissolution profile (Figure 3) despite their compositional similarities. Drug release from beads with G 44/14 showed a faster release than that from beads with other waxy materials, because of its ability to be rapidly dispersed and dissolved in aqueous dissolution medium. The difference between in-vitro properties of G 44/13 and G 50/13 could be explained by their characteristics, in that G 44/14 forms a microemulsion system on contact with water, which appears to lead to enhanced absorption (Itoh et al 2002; Barker et al 2003; Chambin et al 2004), while G 50/13 swells in water and

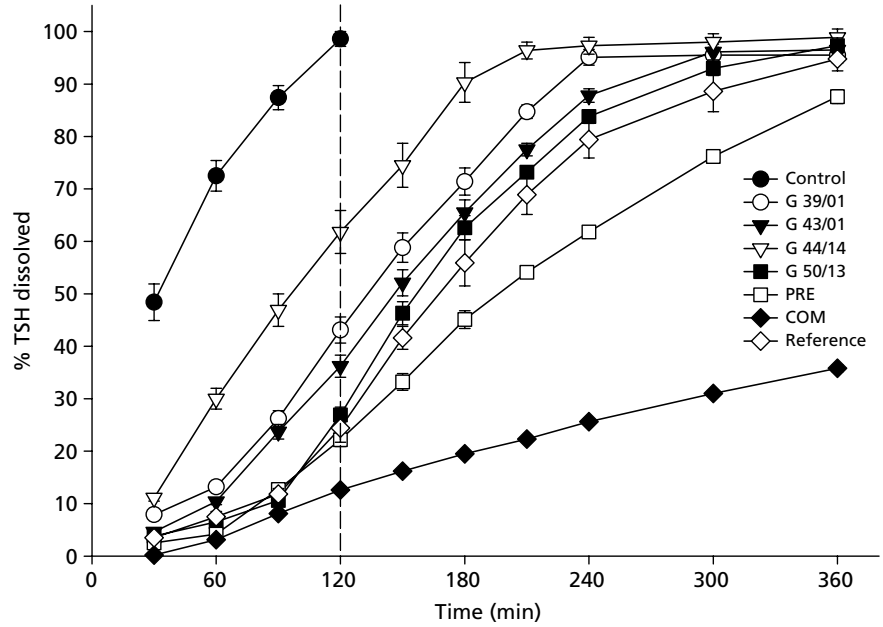

Figure 3 Drug release profiles of TSH from alginate beads with various waxy materials (dashed line shows the change in medium pH from 1.2 to 7.2). Data represent mean ± s.d., n = 12.

Table 2 Sampling time (t_{2h}) and dissolution efficiency ($D.E._{\cdot 6h}$) of TSH from alginate beads

Formulation (additives)	t_{2h}	$D.E._{\cdot 6h}$[a]
G 39/01	43.10 ± 2.46	61.20 ± 2.79
G 43/01	36.20 ± 2.07	57.60 ± 3.28
G 44/14	61.80 ± 4.10	71.00 ± 4.17
G 50/13	27.00 ± 1.54	53.00 ± 2.98
PRE	22.20 ± 1.27	42.20 ± 2.25
COM	12.60 ± 0.28	18.20 ± 1.18
Control (no additive)	99.30 ± 2.14	—

[a]Percentage of the area of the rectangle described by 100% dissolution in the same time. Data are means ± s.d., n = 12.

forms a barrier to drug release (Sutananta et al 1995). Moreover, Doelker et al (1986) and Howard & Gould (1987) reported that rapid drug release was achieved using G 44/14 matrix in hard gelatin capsules.

Other studies have investigated the mechanisms by which drugs are released from Gelucires bases, using models based on the Higuchi equation for diffusion-controlled release (Howard & Gould 1987; Kopcha et al 1990, 1991; Montoussé et al 1999). Generally, these models are appropriate for Gelucires with a low HLB (< 7), although drug release from bases with high HLB values is thought to involve both diffusion and erosion mechanisms (Howard & Gould 1987; Kopcha et al 1990, 1991). In this study, both the Higuchi and the Hixson-Crowell models were applied to understand drug release mechanisms from alginate beads with various waxy materials. The parameters of the mathematical models and descriptive statistics of regression for the dissolution data are summarized in Table 3. After fitting individual unit dissolution data to the mathematical models, the selection was based on comparisons of the following features of the models: firstly, a higher determination coefficient and, secondly, a smaller residual mean square and *F*-ratio probability. Considering these criteria, the dissolution data of waxy materials with a high HLB, such as G 44/14 and G 50/13, were well fitted according to the Hixson-Crowell model, while that of waxy materials with a low HLB, such as PRE and COM, were well fitted according to the Higuchi model. For beads with G 44/14 and G 50/13, erosion can take place more than in beads with waxy materials with a low HLB, such as PRE and COM, due to their ability to dissolve in aqueous dissolution medium. This indicated that the surface erosion relative to drug diffusion inside the beads was predominant according to the Hixson-Crowell model. However, for waxy materials with a low HLB, such as G 43/01, PRE and COM, the drug release from beads was dominated by the diffusion process due to the nature of water insolubility.

Moreover, Dunnett's *t*-test (two-sided) was performed at each time point and the similarity factor (f_2) was estimated to compare the dissolution profiles between the marketed product (Harunal capsules) and alginate beads with waxy materials. It was found that the percentages dissolved of beads with G 50/13 and reference were not significantly different at all compared time points, except 240 min, while beads with G 43/01 were significantly different from reference at all compared time points. Generally, f_2 factor values > 50 (50–100) ensure sameness or equivalence of two curves according to FDA guidelines (1997). Therefore, the mean dissolution profile of beads with G 43/01 (f_2 factor 50.1) and G 50/13 (f_2 factor 61.9) could be

Table 3 Parameters of the Higuchi and Hixson-Crowell models obtained from the dissolution data

Formulation (additives)	Higuchi model			Hixson-Crowell model		
	K_H (%$h^{-½}$) (s.e.)	C	r^2 (F)	K_{HC} (%h^{-3}) (s.e.)	C	r^2 (F)
G 39/01	83.66 (1.57)	−73.46	0.9882 (7109)	0.7734 (0.0209)	−0.6748	0.9877 (1261)
G 43/01	79.57 (1.27)	−72.56	0.9969 (9162)	0.7224 (0.0178)	−0.6949	0.9881 (1653)
G 44/14	73.98 (1.58)	−42.68	0.9816 (5409)	0.8090 (0.0242)	−0.2845	0.9996 (6826)
G 50/13	84.75 (2.35)	−89.66	0.9702 (3429)	0.7325 (0.0109)	−0.9411	0.9995 (4502)
PRE	62.97 (0.64)	−65.10	0.9965 (24910)	0.4724 (0.0058)	−0.5700	0.9814 (1118)
COM	22.51 (0.22)	−19.42	0.9976 (55014)	0.1084 (0.0019)	−0.0053	0.9876 (3809)

s.e., standard error of model parameter; C, constant; r^2, determination coefficient; F, F distribution of residual variance analysis ($P = 0.000$).

considered similar to that of the reference. From the Dunnett's *t*-test and the f_2 factor, the release of TSH from alginate beads, a similar dissolution pattern to that of the marketed product (Harunal capsules) could be achieved by adding G50/13 into TSH-loaded alginate beads.

Conclusion

This study was carried out to develop oral controlled-release delivery systems for TSH using alginate beads with waxy materials as formulation strategies. In the dissolution study, the TSH-loaded alginate beads with waxy materials exhibited controlled-release behaviour over a 6-h period, while beads without waxy materials showed 100% release of TSH within 2 h. The in-vitro release of TSH from alginate beads with G 50/13 showed a controlled-release pattern, in comparison with that from the commercial product (Harunal capsules). In conclusion, this system is feasible to achieve oral controlled-release delivery systems for TSH and alginate beads with one, or a blend of, waxy material, such as Compritol 888 ATO, Precerol ATO 5 and Gelucires, and can be easily prepared and applied for controlled drug delivery systems. However, further study to improve drug encapsulation efficiency is still needed.

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