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Production of an Extremly Low Dose Procaterol HCl Preparation by Fluidized-Bed Coating Method: In Vitro and In Vivo Evaluation

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ABSTRACT A convenient and reliable method to prepare procaterol HCl oral dosage form at an extremely low dosage (25 μg/cap) is presented in this paper. Procaterol HCl was mixed with the film-forming agent hydroxypropyl methylcellulose in an aqueous solution, which was then spray-coated on sugar spheres (Nupareil PG 20/25) to produce procaterol HCl pellets. The IR spectra of coated and noncoated pellets indicated that procaterol HCl was coated on the sugar spheres successfully with a weight increment less than 1%. Most of the coated pellets were able to pass through an 18-mesh screen with no agglomeration. The average weights of coated pellets filled inside of capsules were monitored during the filling process. A simple liquid chromatographic method was developed and validated for the assay and uniformity test of procaterol HCl in different dosage forms. The results of assay and content uniformity test for both in-house product and a commercial product, i.e., Meptin®-mini tablet, were satisfied. The data of f_2 function and ANOVA analysis for the dissolution profiles of both procaterol HCl products suggested that they are pharmaceutical equivalent.

In an in vivo study ($n = 24$), a single dose of 75 μg procaterol HCl was administrated to each volunteer and the plasma concentration of procaterol was determined by a LC/MS/MS method, developed by the same authors. There were no significant differences ($p > 0.05$) in the data of $AUC_{0\rightarrow 16h}$, $AUC_{0\rightarrow\infty}$, C_{max}, and MRT for both preparations. It is confirmed that the pellets capsule produced in this study is bioequivalent with Meptin®-mini tablet.

KEYWORDS Procaterol HCl pellets, Fluidized-bed coating method, In vitro and in vivo evaluation

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INTRODUCTION

Procaterol hydrochloride, (±)-*erythro*-8-hydroxy-5-[1-hydroxy-2-(isopropylamino) butyl] carbostyril hydrochloride, a potent sympathomimetic agent and a selective beta-2 adrenergic receptor agonist, is used to treat reversible

bronchospastic disease (Yamashita et al., 1978; Saitoh et al., 1979; Folco et al., 1983). Procaterol HCl can be absorbed rapidly and completely after oral administration. It is given at microgram level. The dosage for asthma treatment is 10–25 μg per day for children and 50–100 μg per day for adults (Bonder et al., 1990; Eldon et al., 1992). Although the incidences of adverse events associated with the use of procaterol HCl are relatively low, the effect of procaterol on beta-1 receptors leading to myocardial side effects remains a serious concern clinically. These adverse events are known to be dose dependent; therefore, the dose uniformity of procaterol HCl preparations turns to be an important factor to minimize possible occurrence of such events (Bonder et al., 1990; Eldon et al., 1992; Kemp et al., 1985).

Heterogeneous distribution of active components and other excipients is usually observed when traditional wet granulation method is used to produce an extremely low dose solid preparation (Hausman, 2004). It would be even worse if the production processes were under a non-well-controlled condition. Such mishap was hard to evade completely, especially for an extremely low dose (<100 μg) preparation (Yalkowsky, 1990). Therefore, it is necessary to develop a manufacturing method to improve product qualities for drugs with extremely low dose, such as procaterol HCl.

Using spherical pellets to prepare dosage forms has been extensively investigated (Hausman, 2004; Kokubo et al., 1998, Young et al., 2002; Krogars et al., 2000). Most of these results have demonstrated that spherical pellets as dosage forms generated advantages such as dosing uniformity improvement, characteristics of controlled release, and delicate appearance. They can be successfully prepared by extrusion and spheronization processes (Young et al., 2002; Krogars et al., 2000). Fluidized-bed technology is commonly employed to the film coating of pellets (Christensen et al., 1997; Cole et al., 1995). Active ingredient is usually dissolved or dispersed in solution containing coating agents and solvent. Coating solution was then sprayed an the pellets in the coater followed by solvent evaporation with the aid of heat supplied by fluidized air to form a film coated around the pellets. The coating agent of hydrophilic polymer in aqueous system is preferred to avoid any environmental pollution concerns of organic solvent. However, film coating with aqueous solution requires longer operating time to remove water content in the final coating. Such slow vaporization process may cause sticking and peeling on the surface of pellets during film coating (Rowe, 1997).

Therefore, we investigated a novel preparation method to produce procaterol HCl pellets by fluidized-bed coating process. In a preliminary study, binders of a series of water-soluble cellulose ethers were evaluated (data not shown here). Optimized coating conditions were determined to ensure the coating of procaterol HCl onto sugar spheres, and no agglomeration occurred. The qualities of procaterol HCl-coated pellets were confirmed by scanning electron microscopy (SEM), infrared spectroscopy (IR), content uniformity test, and in vitro dissolution test. An in vivo cross-over clinical trial of healthy adults was conducted for the procaterol HCl pellets-filled capsule prepared in this study and a commercial product of procaterol HCl, i.e., Meptin®-mini tablet, used as reference.

MATERIALS AND METHODS

Materials

Procaterol HCl hemihydrate was purchased from Edmond Pharma s.r.l. (Milano, Italy). Sugar spheres (Nu-pareil PG 20/25) were obtained from Ingredient Technology Corporation (Mahwah, NJ). Hydroxypropyl methylcellulose (HPMC, Pharmacoat® 606) was the product of Shin-Etsu Chemical Co., Ltd. (Japan). Talc was obtained from Wako Pure Chemical Industries Ltd. (Japan). Acetonitrile of HPLC-grade was obtained from Merck KGaA (Darmstadt, Germany). Meptin®-mini tablets (25 μg/tab, lot no. 1K84) were purchased from Taiwan Otsuka Pharmaceutical Co., Ltd. Betaxolol HCl, ammonium acetate, formic acid, and hydrochloric acid were the products of Sigma, Inc. (Steinheim, Germany).

Preparation of Procaterol HCl-Coated Pellets

Preparation

A batch of 3 kg of sugar spheres (Nu-pareil PG 20/25) in a particle size range of 710–840 μm was sieved through an 18-mesh (1000 μm) U.S. standard sieve and placed in a bottom-spray Wurster fluidized-bed coater (Hüttlin®, model HKC-5-TJ, Technik GmbH Daimlerstr, Germany). A freshly prepared solution of

procaterol HCl (450 mg in 100 mL D.I. water) was mixed with 5% (w/w) aqueous solution of HPMC (700 mL) to form the coating solution. The operation parameters for coating were set as following: 0.8-mm pneumatic atomizing nozzle, 4.5 g/min spray rate, 2.0 bar atomizing air pressure, 1.0 bar climate air pressure, 280 m^3/h air flow rate, and a fluid-bed chamber temperature of 60°C. After the spraying of coating solution, the procaterol HCl-coated pellets were then dried for 5 min with the residual heat inside of the coater. The procaterol HCl pellets were collected and sieved through an 18-mesh sieve again to ensure no agglomeration of pellets.

Pellet Morphology

Both the coated and noncoated sugar pellets were examined under a scanning electron microscope (SEM, JEOL® JSM-6300, JEOL USA, Inc., MA) equipped with a camera (350 X) at 10 kV. Each sample was fixed with silver paint (SPI®, Structure Probe, Inc., Westchester, PA) directly on a copper sample holder and gold palladium sputtered for 2 min using an Ion Sputter (JEOL® JFC-1100E, JEOL USA, Inc., MA).

FT-IR Spectroscopy

An FT-IR spectroscopy (JASCO® FT/IR 410, JASCO Co., Japan) was used to receive the IR spectra of procaterol HCl powder, mixture of noncoated sugar spheres and HPMC (1:1 ratio), and procaterol HCl-coated pellets by the KBr disk method (1% sample in 100 mg KBr). The scanning range was 800–4000 cm^{-1} with a resolution of 1 cm^{-1}.

Capsule Filling

The coated pellets were lubricated with 0.75% talcum powder in a polyethylene bag and handshaken for 1 min. The coated pellets were then filled into hard gelatin capsules (shell size #4, gray/pale blue, Shin Lin Fang Enterprise Co., Taiwan) by a capsule filling and closing machine (Bosch® GFK 700S, Robert Bosch GmbH, Waiblingen, Germany) under a filling speed of 500 capsules/min. The net filled weight of coated pellets inside the capsule was monitored (157.5–192.5 mg/capsule) during the filling process. An analytical balance (Type A 200 S-RC, Sartorius, Gmbh, Gottingen, Germany) with a precision of 0.0001 g was used.

Quality Controls of Prepared Coated Pellets

Assay and Uniformity Test

HPLC System

A high-performance liquid chromatograph (HPLC) method modified from literature (Wright et al., 1987) was used to determine procaterol HCl content in each preparation as well as in the dissolution media. The HPLC system (Allianace 2695 pump, Alliance 2487 UV Detector, Waters Corporation, USA) was equipped with a Hypersil® ODS column (250 mm × 4.6 mm i.d., 5 μm, E. Merck Darmstadt, Germany) using a mobile phase of 81/19 (v/v) of phosphate buffer (0.1% w/w H_3PO_4 with sodium 1-octane sulfonate 0.4 g /1000 mL) versus acetonitrile, and a detection set at 260 nm. The mobile phase was degassed and eluted at a flow rate of 1.0 mL/min. For method validation, standard solutions of procaterol HCl in high concentration ranges of 0.2, 0.3, 0.4, 0.5, and 0.6 μg/mL in 0.1% EDTA solution and in low concentration ranges of 0.01, 0.02, 0.03, 0.04, 0.05, and 0.06 μg/mL in 0.1 N HCl solutions were prepared on a daily basis and analyzed (repeated three times for each standard solution). Calibration curve established by high concentration range was used for the assay and uniformity test; the one with low concentration range was for the dissolution study.

Assay

About 350 mg of procaterol HCl-coated pellets were accurately weighed and sonicated with 100 mL D.I. water in a beaker until procaterol HCl released completely. The mixture was then filtered to give a clear sample solution for HPLC analysis. A reference solution was prepared by taking two Meptin®-mini tablets under the same procedures. The assay was repeated six times.

Uniformity Test

Each in-house procaterol HCl pellets capsule or Meptin®-mini tablet after trituration was placed in a beaker and sonicated with 100 mL D.I. water. The contents of procaterol HCl in the sample solutions were then determined. A total of 12 samples of each preparation were determined individually.

Disintegration Test

Disintegration tests (USP XXVI, method with disk) of procaterol HCl pellets capsules and Meptin-mini

tablets in pH 1.2 HCl solution were carried out with a VanderKamp disintegration tester (VanKel Industries Inc., Edison, NJ). The solution was maintained at 37 ± 0.5°C. Six samples of each preparation were used for this test.

Dissolution Study

The dissolution study was conducted according to USP XXVI paddle method in a dissolution tester (Vankel® D7025, Vankel Industries, Edison, NJ, USA). Twelve samples of each procaterol preparation were taken for dissolution study. The dissolution medium, i.e., 500 mL of 0.1 N hydrochloride solution in each vessel, was thermostated at 37 ± 0.5°C and stirred at 50 rpm. A volume of 1.5 mL of dissolution medium was accurately pipetted each time at 0, 5, 10, 15, 20, 25, and 30 min. The drawn sample solutions were filtered and assayed under the HPLC system described previously. The similarity factor (f_2) for the dissolution profiles was calculated as the following equation (Shah et al., 1998; El-Mahdi et al., 2000), in

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

which R_t and T_t are the average percentage of drug dissolved at each sampling time for reference (R) and the test (T) preparations, respectively, and n is the number of sampling. An f_2 value in a range of 50–100 suggests that the two dissolution profiles are similar and there is no more than 15% difference at any sampling time.

In-Vivo Clinical Trial of Human Subjects

Study Design

A single dose, nonblinded, randomized, and two-sequence crossover study was conducted on 24 male adults. Taiwanese enrolled in this study ranged from 20 to 25 years (22.0 ± 1.3 years), body weight of 52.2 to 81.1 kg (63.7 ± 7.4 kg), height of 166.9 to 183.6 cm (174.9 ± 4.3 cm), and were in good health condition based on the results of interviews, physical examinations, and biochemical tests. Before the study started, all the volunteers had read and endorsed the informed consent. Each subject received either three procaterol HCl pellets capsules (25 μg/cap) or three Meptin®-mini tablets (25 μg/tab) by oral administration with 200 mL water. After a washout period of 7 days, the subjects were scheduled to take another procaterol HCl preparation different from the previous one. A 20 mL blood sample taken from each subject before dosing was used as a blank. Ten milliliter blood samples were drawn each time at 0.33, 0.67, 1, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, and 16 h after the medication was taken. Blood samples were collected from antecubital veins using code vacutainers and were immediately centrifuged (Kubota® KN-70, Double Enterprise Co., Ltd., Japan) at 4°C and 3000 rpm for 10 min. Plasma layer was then transferred to a labeled test tube and stored at –20°C until analysis.

LC/Mass/Mass System

A highly sensitive and accurate liquid chromatography/mass spectrometry (LC/MS/MS) system has been developed to determine the plasma concentration of procaterol with a detection limit of 0.005 μg/mL (Yu et al., 2005). The chromatographic conditions included an octadecyl column and a mobile phase of ammonium acetate-acetonitrile (95:5; v/v) with a flow rate of 1.0 mL/min. Betaxolol was used as an internal standard. The Mass Selective Detector was set at ionization mode (ESI+), ESI voltage 3.0 kV, source block temperature at 90°C, and desolvation temperature at 500°C. The detection mass for procaterol (Mw 290.36 g/mole) is parent ion at m/z 290.99 and fragment ion at m/z 273.64, and for betaxolol (Mw 307.43 g/mole) is parent ion at m/z 308.33 and fragment ion at m/z 116.31, respectively.

Pharmacokinetic Analysis

Plasma concentration profiles of procaterol versus time of the two procaterol preparations after a single dose of 75 μg procaterol HCl were evaluated by M. Gibaldi methods (Gibaldi, 1984). Values of area under the curve (AUC), maximum plasma concentration (C_{max}), time at maximum concentration (T_{max}), mean residence time (MRT), and elimination half-life ($T_{1/2}$) were obtained and compared.

Statistical Treatments

The log-transformed data (geometric means) of $AUC_{0\to16h}$, $AUC_{0\to\infty}$, C_{max}, T_{max}, MRT, and the data of $T_{1/2}$ for the patients with the two different preparations

were analyzed using an analysis of variance (ANOVA) model by Statistical Analysis System (SAS) GLM Procedure, version 8.1. Statistical inferences including 90% confidence interval and the Schuirmann's two one-sided tests were used to evaluate the differences in pharmacokinetic parameters between the two preparations. *P* values less than 0.05 were considered, having significant difference.

RESULTS AND DISCUSSION

Preparation of Procaterol HCl Pellets

Preparation

Stickiness of pellet surface resulted from film-coating agents is usually a major concern in fluidized-bed coating process, which may lead to a failure of film coating. The operation may become worse as under the conditions of using coating solution with high viscosity or having a long overall operating time (Kokubo et al., 1998). In the preliminary studies, we found that hydroxypropyl methylcellulose (HPMC, Pharmacoat 606®) of low viscosity grade in a concentration range of 3.0–6.0 % w/w and limited and small enough volume of coating solution delivered each time of spraying during spraying process were the two important operation parameters allowing us to generate coated pellets with satisfaction. We were able to produce procaterol HCl coated pellets by fluidized-bed coating with a relatively short operation time of about 55 min and at a yield of 99.2% ± 0.1% ($n = 3$). Almost all the procaterol HCl-coated pellets were able to pass through an18-mesh standard sieve with a weight loss less than 1% after sieving. There were no significant pellet agglomerations after coating, i.e., it can be ignored. The diameters of coated pellets should be not much different from those of noncoated pellets.

Theoretically, it was only about 1% weight increment for the coated pellets (about 15 μg procaterol HCl and 0.96 mg HPMC per 100 mg sugar spheres according to the formulation). The noncoated pellets are spherical shape. As visualized, the procaterol HCl-coated pellets are also spherical in shape. The photographs from SEM for noncoated sugar spheres and procaterol HCl-loaded pellets were presented in Fig. 1A and Fig. 1B. Pores and slices appeared on the surface of noncoated sugar pellets (Figure 1A); however, a continuous surface appeared on the surface of procaterol HCl coated pellets (Fig. 1B). The IR spectra of pure procaterol HCl powder, 1:1 mixture of noncoated pellets and HPMC, and procaterol HCl-coated pellets were compared in Fig. 2A, Fig. 2B, and Fig. 2C, respectively. There are absorption bands at 1646.91 cm^{-1}, 1604.48 cm^{-1}, and 1560 cm^{-1} in finger group region of spectrum of pure procaterol HCl powder (Fig. 2A). However, there were no such absorption bands in the spectrum of 1:1 mixture of noncoated pellets and HPMC (Figure 2B). The appearance of corresponding absorption bands in the spectrum of

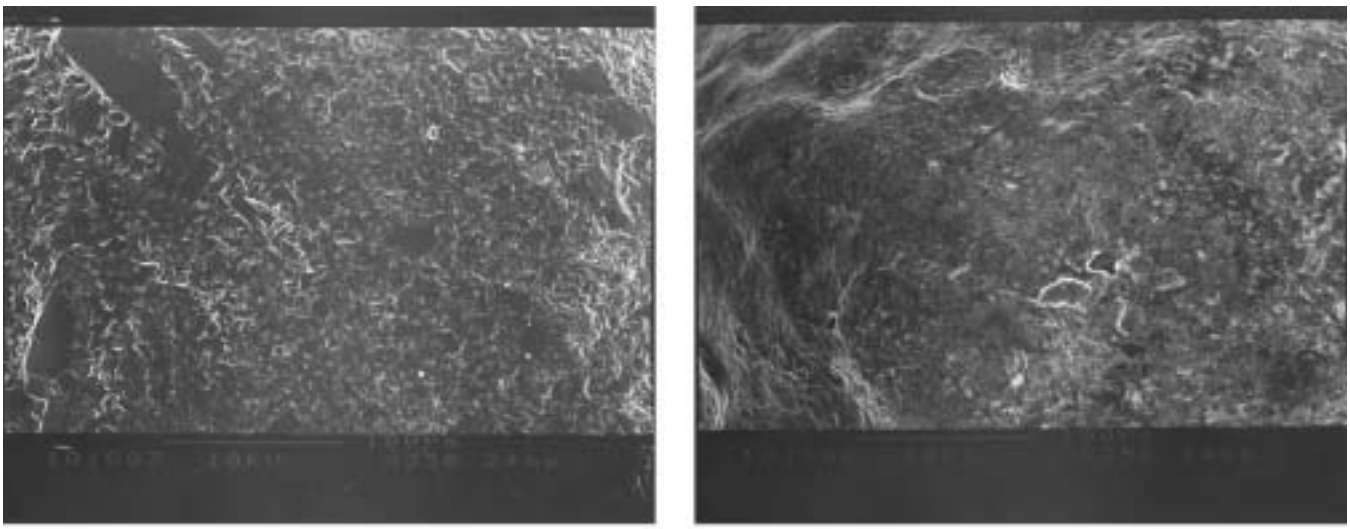

FIGURE 1 **Photographs of (A) Noncoated Sugar Sphere and (B) Procaterol HCl-Coated Pellet by Scanning Electron Micrographs at 350× Magnifications.**

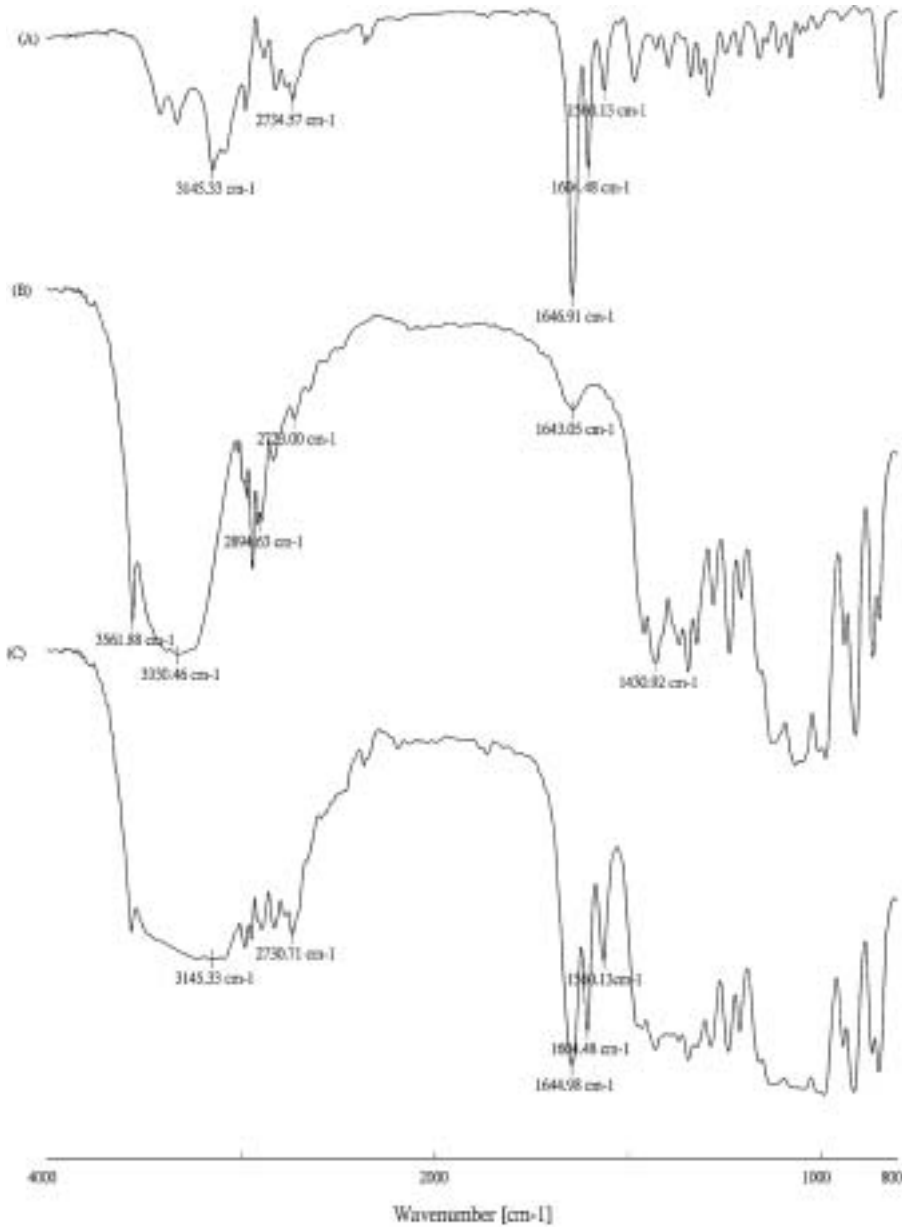

FIGURE 2 **The IR Spectra of (A) Pure Procaterol HCl Powder, (B) 1:1 Mixture of Sugar Spheres and HPMC, and (C) Procaterol HCl-Coated Pellets.**

procaterol HCl-coated pellets (Fig. 2C) suggested that procaterol HCl was successfully coated on the sugar spheres.

Capsule Filling

The procaterol HCl-coated pellets were filled into #4 hard shell capsules to generate an oral dosage form with labeled content of procaterol HCl 25 μg per capsule. Unfortunately, the weight variation of the net weight of pellets filled inside the capsules was too high to be acceptable. Electrostatic repulsion induced by the friction between pellet particles may be the main cause of the low filling efficiency (Chopra et al., 2002). Therefore, 0.75% talc powder was added and mixed in a polyethylene bag to remove the potential electrostatic repulsion. After the modification, the filled weight inside the capsule was on-line monitored during the filling process. The average net weights of procaterol HCl pellets in the capsules ($n = 6$) were 175.3 ± 1.2 mg, 175.5 ± 1.2 mg, and 175.5 ± 1.2 mg at 10 min, 20 min, and 30 min, respectively. These average net-filled weights were consistent with the theoretical weight calculated by the material added.

Quality Control of the Coated Pellets

Assay and Content Uniformity

For the validation of the HPLC method, the linear relationship of peak response against procaterol over a high concentration range of 0.2 to 0.6 μg/mL and a low concentration range of 0.01 to 0.06 μg/mL were established to give regression lines of $y = 8.46E+05x - 3800.43$, $r^2 = 0.9999$, and $y = 8.28E+05x + 38.19$, $r^2 = 0.9996$, respectively. The validation results of within-run and between-run tests for both high and low concentration ranges are listed in Table 1. The coefficient of variances were less than 1.06% and 2.60%, respectively, indicating that the HPLC method is reliable with good linearity and suitable for this study.

From the assay, the mean percentage of labeled content of procaterol HCl in the in-house pellets capsule and Meptin®-mini tablet ($n = 6$) were 100.05% ± 0.96% and 97.27% ± 1.12%, respectively. In Table 2 are the results of content uniformity test. The percentages of labeled content of each sample for both preparations all are in the range of 85.0–115.0%, and the standard deviations of 2.29% and 2.07% are less than 6%, suggesting that both procaterol products fulfilled the requirements of content uniformity test stated in Pharmacopeias.

Disintegration and Dissolution

The disintegration time of procaterol HCl pellets capsules was 7.5 ± 0.3 min ($n = 6$), which was longer than 2.3 ± 0.4 min of Meptin®-mini tablets. It is most likely because the commercial tablet is a typical immediate release dosage form and the hard capsule shell of in-house capsule needs some time to be broken: Such observation, can be used to explain the difference of the dissolution profiles ($n = 12$) of procaterol HCl pellets capsule and Meptin®-mini tablet in 0.1 N HCl solution at 37 ± 0.5°C (Fig. 3) in the very first 10-min region. At the first sampling point, the average procaterol HCl dissolved for in-house pellets capsule was 35.3% ± 6.4% (mean ± C.V.), which was lower than 47.4% ± 7.0% of Meptin®-mini tablet. A 3–4 min lag time for capsule shell disintegrated resulted in a lower percentage of dissolution at the beginning. However, the percentage dissolved reached plateau of about 90% at 20 min for both preparations. Although according to the guidance, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997 FDA, if both test and reference products dissolve 85% or more of the labeled amount of the drug in less than or equal to 15 min, the f_2 test is not necessary. We decided to run the f_2 test since the average percentages dissolved at 15 min were 86.9% ± 3.9% and 85.7% ± 2.4%, respectively. The value of f_2

TABLE 1 **Results of Within-run and Between-run Tests When the Standard Solutions of Procaterol HCl in High and Low Concentration Ranges are Applied to the HPLC Method**

	High concentration range			
	Within-run analysis (n = 6)[a]		Between-run analysis (n = 6)[b]	
Concentration prepared (μg/mL)	Mean concentration (μg/mL)	C.V. (%)	Mean concentration (μg/mL)	C.V. (%)
0.2	0.2001	0.81	0.2009	1.06
0.3	0.3013	0.45	0.3009	0.27
0.4	0.3986	0.40	0.3987	0.46
0.5	0.4983	0.72	0.4962	0.87
0.6	0.6016	0.40	0.6033	0.55
	Low concentration range			
	Within-run analysis (n = 6)		Between-run analysis (n = 6)	
Concentration prepared (μg/mL)	Mean concentration (μg/mL)	C.V. (%)	Mean concentration (μg/mL)	C.V. (%)
0.01	0.0101	1.98	0.010	2.60
0.02	0.0199	1.70	0.0199	2.02
0.03	0.0302	0.65	0.0301	0.71
0.04	0.040	0.40	0.0401	0.49
0.05	0.0493	1.48	0.0498	1.38
0.06	0.0604	0.44	0.0601	0.94

[a]Within-run analysis was calculated from the assay values of prepared standards repeatedly on a single day.
[b]Between-run analysis was calculated from the assay values of prepared standards on 6 different days.

TABLE 2 **Results of Content Uniformity Test of the Two Procaterol HCl Preparations with a Labeled Content of 25 μg Procaterol HCl**

Sample no.	Procaterol HCl pellets capsule (%)	Meptin®-mini tablet (%)
1	98.2	94.4
2	97.3	95.9
3	100.6	99.1
4	95.7	96.0
5	98.5	94.2
6	100.0	95.8
7	101.3	99.5
8	101.9	96.5
9	100.8	94.9
10	103.2	99.6
Mean	99.75	96.59
S.D.	2.29	2.07

function for the dissolution profile of in-house pellets capsule with respect to that of Meptin®-mini tablet was found to be larger than 50. The comparison of the two dissolution profiles was analyzed additionally using classical ANOVA. Except for the first two sampling points (5 min and 10 min), the rest of the dissolution profiles for the two preparations have no significant difference ($p > 0.05$). This is confirmed that the in-house procaterol HCl pellets capsule is pharmaceutical equivalent with a commercial preparation Meptin®-mini tablet under the same condition.

Bioequivalent Trial of Human Subjects

Figure 4 depicts the plasma concentration profiles of procaterol versus time after oral administration of single dose (75 μg) of procaterol HCl preparation. In literature, the average half-life of procaterol was 3.7 h after oral-administrated 75 μg procaterol; therefore, the blood samples for the in vivo study were designed to be collected up to the time of four half-lives, i.e., about 16 h instead of 24 h (Eldon et al., 1992). It is clear to see that blood concentration profiles of both procaterol preparations are almost superimposed. The pharmacokinetic parameters for each treatment were evaluated accordingly and summarized as mean (±S.D.) in Table 3. Also included in Table 3 are the p-values of each parameter from ANOVA analysis. There was no statistical difference ($p > 0.05$) between the two procaterol HCl preparations in terms of the pharmacokinetic parameters, i.e., $AUC_{0\rightarrow 16h}$, $AUC_{0\rightarrow\infty}$, C_{max}, T_{max}, MRT, and $T_{1/2}$. All of these data are very close to the corresponding data reported in literature, in which procaterol HCl oral preparation was administered in the same dose (Eldon, et al., 1992).

The values of 90% confidence interval for each pharmacokinetic parameter were all within the range of 80% and 125% (Table 4). The p-values from Schuirmann's

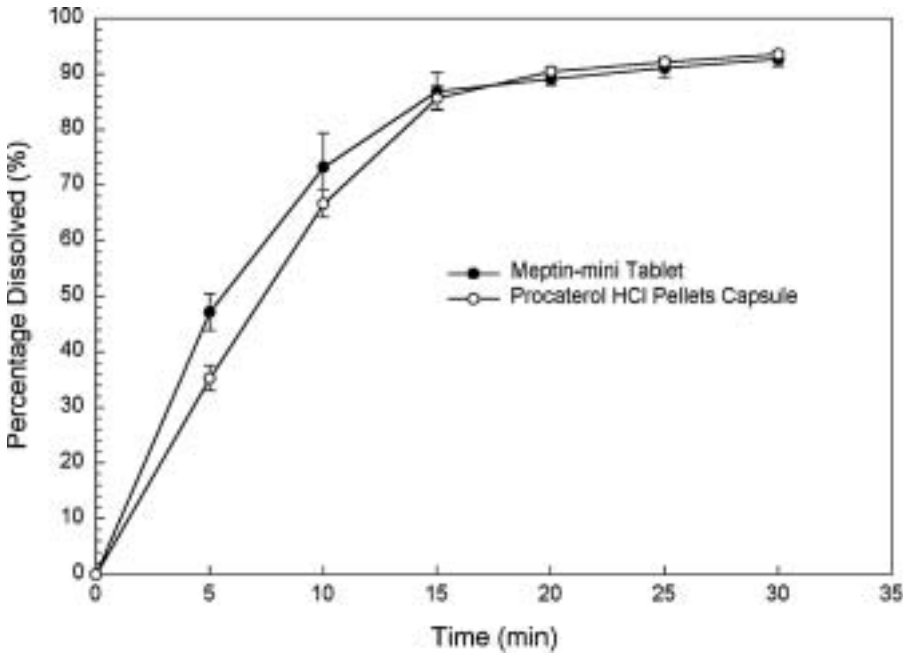

FIGURE 3 **In Vitro Dissolution Profiles of Procaterol HCl Pellets Capsule (-○-) and Meptin®-Mini Tablet (-●-) in 0.1 N HCl Aqueous Solution at 37 ± 0.5°C and 50 rpm. The Error Bar for Each Data Point is the S.D.**

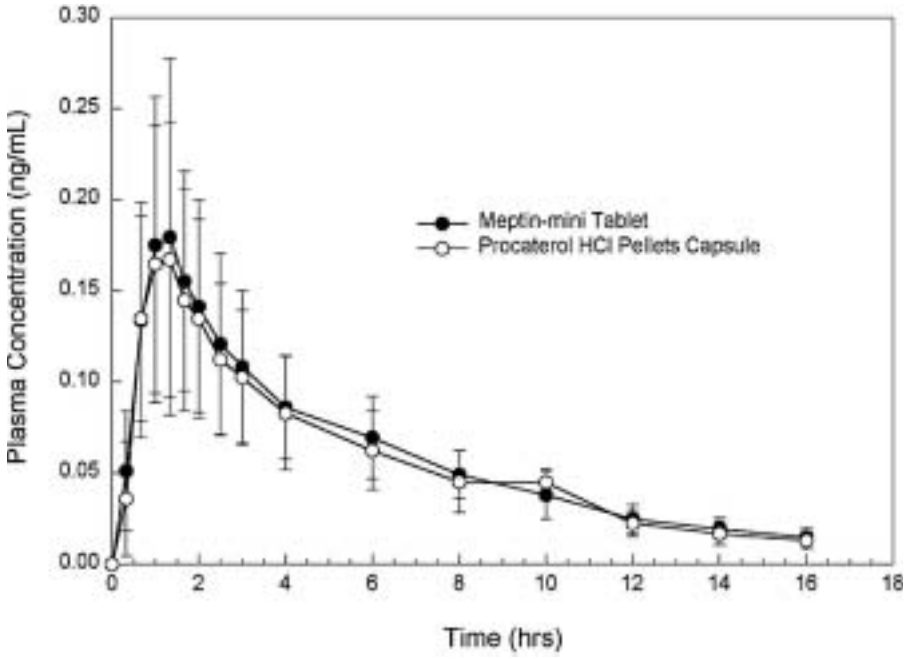

FIGURE 4 **Mean Plasma Concentration Profiles of Procaterol after Oral Administration of Single Dose of 75 μg of Procaterol HCl Pellets Capsule (-○-) and Meptin®-Mini Tablet (-●-) to Male Taiwanese Adults (*n* = 24). The Error Bar for Each Data Point is the S.D.**

TABLE 3 **The Pharmacokinetic Parameters of an In Vivo Study as Single Dose of 75 μg of Procaterol HCl Pellets Capsule or Meptin®-mini Tablet Administered to Healthy Male Adults (*n* = 24)[a]**

Parameters	Procaterol HCl pellet capsule	Meptin®-mini tablet	*p*-value[b]
$AUC_{0\rightarrow16}$(hr×ng/mL)	0.891 ± 0.272	0.975 ± 0.279	0.190
$AUC_{0\rightarrow\infty}$(hr×ng/mL)	0.978 ± 0.292	1.08 ± 0.30	0.234
C_{max} (ng/mL)	0.194 ± 0.069	0.205 ± 0.097	0.822
MRT(h)	6.68 ± 1.18	6.95 ± 1.17	0.387
T_{max}(h)	1.37 ± 0.64	1.51 ± 1.05	0.643
$T_{1/2}$(h)	4.57 ± 1.03	4.69 ± 0.87	0.553

[a]Data shown as Mean ± S.D.
[b]*P* values from ANOVA and $p < 0.05$ was considered as statistical significant difference.

TABLE 4 **Results of 90% Confidence Interval and Schuirmann's Two One-sided Test of the Pharmacokinetic Parameters for Meptin®-mini Tablet and Procaterol Pellets Capsule Administered to Healthy Male Adults (*n* = 24)**

		Schuirmann's two one-sided test *p*-value	
Parameters	90% Confidence interval (%)	$\mu_T/\mu_R \leq 0.8$	$\mu_T/\mu_R \geq 1.25$
$\ln(AUC_{0\rightarrow16})$ (hr×ng/mL)	84.3 ~ 97.6	0.0036*	< 0.0001*
$\ln(AUC_{0\rightarrow\infty})$ (hr×ng/mL)	83.9 ~ 96.6	0.0046*	< 0.0001*
$\ln(C_{max})$ (ng/mL)	84.5 ~ 114.0	0.0140*	0.0051*
MRT (h)	88.7 ~ 104.0	0.0006*	< 0.0001*
$T_{1/2}$ (h)	90.2 ~ 105.0	0.0006*	< 0.0001*

*$p < 0.05$ shows the statistical significant different.

two one-sided test were all less than 0.05 (Table 4). These results further supported that the extremely low dose procaterol HCl preparation produced in this paper, i.e., procaterol HCl pellets capsule, was bioequivalent to Meptin®-mini tablet, the commercial product of the same dosage.

CONCLUSION

The results of this paper suggested that the proposed fluidized-bed coating method is feasible and reliable to prepare an extremely low dose procaterol HCl oral dosage form within a relative short operation time. The prepared procaterol HCl pellets capsule is not only pharmaceutical equivalent but also bioequivalent to Meptin®-mini tablet, a commercial product of procaterol HCl with the same dosage.

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