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School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Preparation and characterization of a sustained release buccoadhesive system for delivery of terbutaline sulfate

J. Emami*, M.A. ShetabBoushehri, J. Varshosaz and A. Eisaei

Department of Pharmaceutics and Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.

Abstract

Terbutaline sulfate exhibits extensive first pass metabolism and a short elimination half life which makes frequent oral administration of the drug inevitable. A novel buccoadhesive controlled delivery system of the drug can easily overcome the problem. A two-layered core tablet composed of a fast release layer made of mannitol, lactose, PEG and the drug attached to a sustained release layer composed of drug, varying ratios of HPMC, Carbomer 934 (CP), and lactose capped with a buccoadhesive cup coated with an impermeable backing layer was developed. Buccoadhesive cup initially optimized for bioadhesion strength using HPMC and CP with various ratios. Drug transport through buccal membrane indicated a high permeability coefficient (0.00105 cm/sec). All tablets were acceptable with regard to drug contents, thickness, weight variations, hardness and drug content uniformity. The CP:HPMC 2:1 mixture showed the best mucoadhesion properties and was selected as excipient for the cup layer. Swelling index was higher for formulations containing greater amount of lactose and lower percentage of polymers. Fast release layer released its entire content within 15 min while sustained release layer lasted for 12 h. Drug release controlled by a combination of diffusion and chain relaxation mechanism.

Keywords: Terbutaline sulfate; Buccoadhessive; Controlled-release; Fast release

INTRODUCTION

Terbutaline sulfate is a specific β_2-agonist affecting mostly the smooth and skeletal muscles (1) and slightly the α-adrenergic receptors (2). Administration of the drug mostly results in bronchodilatation, vasodilatation, and the relaxation of the uterine muscles. The drug is administered for the treatment of bronchial asthma, chronic bronchitis, amphism, and indicated for the prevention of the preterm labor in pregnancy (1). Furthermore, terbutaline sulfate as an auxiliary treatment to control the uterine inversion can also decrease the need for general anesthesia (3).

The absorption of terbutaline sulfate form the gastrointestinal (GI) tract is variable, although 33-50% of the total administered oral dose is believed to be absorbed (2) of which 60% is metabolized by the liver under the first pass effect (1). The first pass effect, therefore, decreases the bioavailability of the drug to 15% (1). To overcome this problem, other alternative administration routes should be considered. Disadvantages such as the first pass effect and the enzymatic degradation within the GI tract highlights the need for other alternative routes (4). Trans-mucosal routes have been long proved to be advantageous alternative routes, amongst which buccal delivery is of utmost importance.

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining the oral cavity (5). It offers unique advantages including an expanse of smooth muscle, relatively immobile mucosa, richness of vascularization, direct access to the systemic circulation through the internal jugular vein which bypasses drugs from the hepatic first pass metabolism leading to a higher bioavailability, low enzymatic activity, non-invasiveness, facility to include excipients such as permeation enhancers, enzyme inhibitors, and pH modifiers in the formulation,

*Corresponding author: J.Emami, this paper is extracted from the Pharm.D thesis No. 385297
Tel. 0098 311 7922586, Fax. 0098 311 6680011
Email: emami@pharm.mui.ac.ir

and versatility in designing multidirectional or unidirectional delivery systems (6). Furthermore, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa are amongst the other advantages offered by this delivery route(5).

Another inconvenience concerning terbutaline sulfate is its short elimination half-life, 3-4 h, which makes a thrice daily dosing pattern inevitable (1). A sustained release formulation of the drug can overcome the mentioned problem not only to increase the patients compliance, but also to bring about other advantages such as the reduction of the administered dose, the maintenance of the drug level for longer than the drug's biological half-life, the generation of fixed pharmacological effects due to the fixed blood concentration of the drug, and the reduction of the total drug doses required for the treatment of the disease (7). To achieve therapeutic level at a faster rate, at the same time, a two-layered core tablet composed of a fast release layer attached to a sustained release layer capped with a buccoadhesive cup coated with an impermeable backing layer seems to be an ideal candidate for the controlled delivery of terbutaline sulfate. Although other researchers reported preparation of buccoadhesive matrix tablet formulation of terbutaline sulfate (8,9), however, *in vitro* systematic membrane permeability studies and the development and optimization of such a novel fast and sustained release buccoadhesive system of this drug has not yet been reported.

MATERIALS AND METHODS

Materials

Terbutaline sulfate was kindly donated by Iran Hormone Pharmaceutical Company (Tehran, Iran), while Carbopol 934 (CP), Hydroxypropyl methylcellulose (HPMC,K4M) and ethyl cellulose were purchased from BF Goodrich (Germany), Colorcon (England) and Aldrich (USA), respectively. Other materials including magnesium stearate, glucose, monobasic potassium phosphate, lactose, manitol, sodium chloride, calcium chloride, potassium chloride and sodium bicarbonate were supplied by Merck (Germany).

Methods

Solubility measurement

Solubility of terbutaline sulfate was determined in phosphate buffer at pH=6.8. Excess amount of drug was added to 0.4 ml of phosphate buffer. The sample was stirred in a conical tube for 15 min, stored at room temperature and dark place for 24 h and then was stirred for 15 min. The solution was centrifuged at 1500 rpm for 15 min. The concentration of terbutaline sulfate in supernatant was determined spectrophotometrically at 207 nm.

Permeation kinetics through bovine buccal mucosa

To investigate the drug permeation kinetics and permeability coefficient from the bovine mucosa, pieces of bovine buccal mucosa were excised, and subsequently separated from the underlying tissues, fats, and muscles. These pieces were then fixed on the Franz diffusion cell, in a way that the mucosa surface faced the donor chamber. The experiment was thus conducted with 2 ml of the drug solution (1.5 mg/ml) within the donor chamber, 28 ml of Krebs buffer within the receiver chamber, a temperature set at 37°C, and on a magnet stirring device. Samples were taken after 5, 15, 30, 45, and 60 min and then every h up to 5 h, replaced by fresh buffer. Having diluted the samples with 2 ml of Krebs buffer, each was centrifuged in 1500 rpm for 10 min. The absorbance of the supernatant was then measured spectrophotometrically at 207 nm. The amount of the drug crossed the bovine buccal mucosa could be thus easily calculated.

To study the transport kinetics of terbutaline through buccal mucosa, two kinetic equations including zero-order (Equation 1) and first order (Equation 2) were used as follows:

$$W_R = K_0 t \qquad \text{(Equation 1)}$$

$$(W_o - W_R) = W_o e^{-k1t} \qquad \text{(Equation 2)}$$

where, W_0 is the initial amount of drug in the donor chamber, W_R is the amount of drug transfered to receiver chamber at time t. When the permeation kinetics conformed best to zero order kinetics, the permeability coefficient was calculated using Equation 3. Once the permeation kinetics, however, could be better fitted within the first order model, the

permeability coefficient was calculated on the basis of Equation 4 (10,11).

$P = K. V_r / S$ (Equation 3)

where, S is the bovine buccal mucosa surface, V_r is the receiver chamber volume, K is the zero order constant, and P is the permeability coefficient.

$P = J/S.C_d$ (Equation 4)

where, J is the slope of the line, C_d is the drug concentration within the receiver chamber, S is the bovine buccal mucosa surface, and P is the permeability coefficient.

Preparation of the sustained release buccoadhesive tablets

Fig. 1 shows a simple scheme of the prepared sustained release, buccoadhesive tablets. The tablet is composed of four different layers, including an immediate release layer, a sustained release layer, a mucoadhesive cup, and an ethyl cellulose coating (12). Table 1 tabulates the name and amount of the substances used for the preparation of each layer.

The required weight of the terbutaline sulfate within the immediate release and sustained release layers were calculated on the basis of Equations 5 and 6, respectively.

$Q_i = C_{ss} \times V_d \times (M_{ws} / M_{wb})$ (Equation 5)

$Q_s = C_{ss} \times K_E \times V_d \times M_{ws} \times T_d / 1000 \times F \times M_{wb}$ (Equation 6)

where, C_{ss} is the required balanced concentration of terbutaline sulfate within the blood.(3.6 µg/L) (13), V_d is the distribution volume of the drug for a 70kg adult (112.l), M_{ws} is the mass molar weight of terbutaline sulfate (548.65), M_{wb} is the molecular weight of terbutaline itself as a free base (225.28) (13), F is the bioavailability of the buccoadhesive dosage form (~100%), T_d is the intended duration of action in which the therapeutic concentration should be maintained within the body till the next dose is administered. Considering all the mentioned values, the required weight of terbutaline sulfate within the immediate release and sustained release layers are calculated to be 1 mg and 2 mg, respectively.

The preparation process of the mucoadhesive tablets mainly involves formation of the core (immediate and sustained-release layers) and formation of the buccoadhesive cup. A 7-mm flat-faced punch and die was used for the fabrication of the core, while an 11-mm one was used to locate the adhesive cup around the core. The immediate release layer of the tablets was prepared through the wet granulation method, using the 10% starch paste as the granulating agent, and 1% magnesium stearate as the lubricating agent. The required weight of manitol, lactose, and terbutaline sulfate was determined based on Table 1. Polyethylene glycol (PEG) was used to enhance the drug dissolution rate from the immediate release layer. The compression process was accomplished on a 9-mm punch and using a single-punch machine (GMBH-KS Kilian, Germany).

The sustained release layer was prepared through the direct compaction method, using 1% magnesium stearate as the lubricating agent in a way that the final hardness of the prepared tablets would range from 20 to 30 N. The required weight for the other excipients was determined on the basis of Table 1.

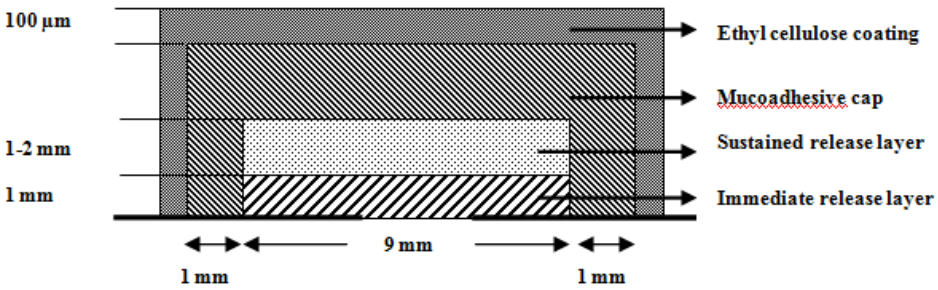

Fig. 1. General scheme of the prepared sustained release buccoadhesive tablets

Table 1. The amount of materials used for the preparation of the terbutaline sulfate sustained released buccoadhesive tablets

Immediate release layer (50 mg)				
Formulation code	**Manitol (mg)**	**Lactose (mg)**	**Polyethylene glycol (mg)**	**Terbutaline sulfate (mg)**
$M_{10}L_{40}$	10	40	0	1
$M_{20}L_{30}$	20	30	0	1
$M_{30}L_{20}$	30	20	0	1
$M_{40}L_{10}$	40	10	0	1
$M_{18}L_{12}P_{20}$	18	12	20	1
$M_{24}L_{16}P_{10}$	24	16	10	1
$M_{27}L_{18}P_{5}$	27	18	5	1
Sustained release layaer (50 mg)				
Formulation code	**Carbapol (mg)**	**Hydroxypropyl methylcellulose (mg)**	**Polyethylene glycol (mg)**	**Terbutaline sulfate (mg)**
$C_9H_9L_{30}$	9	9	30	2
$C_9H_{18}L_{21}$	9	18	21	2
$C_9H_{27}L_{12}$	9	27	12	2
$C_{18}H_9L_{21}$	18	9	21	2
$C_{18}H_{18}L_{12}$	18	18	12	2
$C_{18}H_{27}L_3$	18	27	3	2
$C_{27}H_9L_{12}$	27	9	12	2
$C_{27}H_{18}L_3$	27	18	3	2
$C_{25}H_{25}L_0$	25	25	0	2
Mucoadhesive cup (150 mg)				
Formulation code	**Carbapol (mg)**	**Hydroxypropyl methylcellulose (mg)**		**Terbutaline sulfate (mg)**
C_0H_{150}	0	150		0
$C_{50}H_{100}$	50	100		0
$C_{75}H_{75}$	75	75		0
$C_{100}H_{50}$	100	50		0
$C_{150}H_0$	150	0		0

The mixture was transferred on top of the immediate release layer already pressed very moderately and compression process of both layers was fulfilled using the same single-punch machine.

To prepare the mucoadhesive cup, all the excipients required for this purpose were accurately weighed based on Table 1 and mixed with 1% magnesium stearate as the lubricating agent. Cores were transferred to the middle of 11-mm cavity and filled with the mucoadhesive mixture. The tablets were compressed on the 11-mm punch of the single-punch machine, having a weight of 250 mg, a hardness equal to 50 N, and flat surfaces.

The dip coating method was subsequently applied to cover the tablets in three directions with ethyl cellulose. To fulfill this goal, a 5% solution of ethyl cellulose in acetone-ethanol mixture (2:8) was used.

Weight, thickness,and hardness uniformity

The weight of the prepared tablets was determined using a digital balance (Sartorius 2434, Germany), while their thickness and hardness were measured using a simple cullies and a TB324 hardness tester (Erweka, Germany), respectively.

Drug content uniformity

To evaluate the content uniformity of the prepared tablets, ten tablets were chosen randomly from each batch, weighed accurately and powdered separately. The powder related to each tablet was then transferred to a 100-ml volumetric flask containing 5 ml ethanol to dissolve the ethyl cellulose coating and 95 ml distilled water. After sonication of the sample for 30 min in a water bath sonicator, 2 ml of the attained solution was centrifuged at 1500 rpm for 15 min. The absorbance of the supernatant was then measured in 222nm using a UV-visible spectrophotometer (Shimadzu, Japan). The drug concentrations were determined based on the previously generated calibration curve, and the average values were calculated.

In vitro bioadhesion test

To determine the formulation with maximum bioadhesion, several tablets with the same immediate and sustained release layers

were prepared, which differed solely in polymer ratio within the mucoadhesive cup. The bioadhesion of the tablets was evaluated using DARTEC HC10 computer instrument and through "sheer and peel strength". For this purpose, the bovine buccal tissue was glued as 3×3 cm segments on a small tissue holder, and soaked using the Krebs buffer. Each tablet was kept on the tissue for 5 min using a 5-g weight. The plate was then fixed on the apparatus, and the lever caused a force parallel to the mucosa surface to the tablet, with a 2 mm/min velocity. The force was then increased until the tablet was completely detached from the mucosa. The relative force was subsequently noted (14).

Swelling properties

To investigate the swelling properties of the prepared tablets, 27 tablets from manufactured sustained-release formulations with similar formulations for the immediate release layer and the mucoadhesive cup were prepared and divided randomly in 9 groups of 3 members. The tablets in each group were then separately weighed (W_1), and marked using a colored sign. Having placed the tablets within the plates containing 3 ml of phosphate buffer (pH, 6.8), each was then taken out of the buffer solution after 0.5, 1,2,3,4,5,6,7, and 8 h, their surface water was carefully absorbed using a paper filter, and were weighed once more on the digital balance (W_2). The swelling index was then calculated using Equation 7.

Swelling Index = $W_2 - W_1 / W_1$ (Equation 7)

Dissolution rate

The dissolution test was performed for the immediate and sustained release layers separately.

Drug dissolution from the immediate release layer

When the immediate release core contained no PEG, it was glued to the end of a glass bar and placed within a flask containing 125 ml of phosphate buffer (pH, 6.8). This was to simulate the tablet while adhered to the buccal mucosa. The dissolution was performed in 37±0.2°C at a stirring rate of 150 rpm. Samples (1ml each) were withdrawn after 5, 10, 15, 20, and 30 min and replaced by fresh buffer. Having diluted each sample with 1 ml phosphate buffer of the same pH, and centrifuged each in 1500 rpm for 10 min, the UV absorbance of the supernatant was measured at 207 nm. The amount of free drug within the medium was thus calculated using the previously generated calibration curve.

Drug dissolution from the immediate and sustained release layers

To study the drug dissolution from the final tablets, each was glued to the end of a glass bar and placed within the dissolution medium (phosphate buffer, pH 6.8). The dissolution test was fulfilled at 37±0.2°C with a stirring rate of 150 rpm. Samples (1ml each) were withdrawn after 5, 10, 15, 20, 30, and 60 min and then every h up to 12 h and replaced by fresh buffer. Each sample was diluted with 1ml of phosphate buffer, and centrifuged at 1500 rpm for 10 min. The UV absorbance of the supernatant was then measured at 207 nm. The amount of the drug within the dissolution medium was calculated on the basis of the previously generated calibration curve. Considering the drug dissolution profile from the immediate release layer and the total drug weight loaded within it (1mg), the drug release profile from the sustained release layer could be easily depicted.

Determination of release parameters

Based on the acquired dissolution profiles, drug release kinetics from each layer was investigated. To fulfill this goal, release profiles were fitted into zero order kinetic, first order kinetic, higuchi model, and hixon-crawell model. The drug diffusion mechanism from the sustained release tablets was also investigated. In order to compare the dissolution profiles, mean dissolution time (MDT) and release percent (RP) for 8 and 12 h were calculated using the following equations.

$MDT = \sum_{i=1}^{n} tmid\,\Delta Mt / \sum_{i=1}^{n} \Delta Mt$ (Equation 8)

where, *i*is the sampling number, n is the number of dissolution samplingtime, $t_{mid}$is the time at midpoint between t_i and t_{i-1} easily calculated with expression $(t_i+t_{i-1})/2$ and ΔM_i is the additional amount of drug dissolved between t_i and t_{i-1}.

RP = amount of drug released/ amount of drug loaded (Equation 9)

DSC analyses

DSC thermograms were obtained using Mettler DSC system (Mettler, Germany), to investigate the drug-polymer and the polymer-polymer interactions. The system was first calibrated using indium, while the previously dried samples were heated from 25°C to 300°C at a heating rate of 10°C/min.

Statistical analyses

Statistical comparisons of differences between bioadhesive force of tablets with different polymer mixing ratios, different polymers, swelling indices, correlation coefficients of different release kinetic studies, and dissolution rate constants were performed by analysis of variance (ANOVA) based on Fisher's PLSD test. In all cases, $P<0.05$ was consideredas significant.

RESULTS

Solubility evaluation and permeation through buccal mucosa

Solubility of terbutaline sulfate in phosphate buffer solution (pH 6.8) was found to be 631.75 ± 33.7 mg/ml. *In vitro* permeation studies of terbutaline sulfate through bovine buccal mucosa indicated that the transport of the drug follows first order kinetics with a rate constant of 0.88 h^{-1}. The calculation of the bovine buccal mucosa permeability coefficient to terbutaline sulfate revealed a high permeability (0.001 cm/sec) to the drug.

Weight, thickness, hardness, content uniformity and swelling properties

Results concerning the weight, thickness, hardness, and content uniformity of the prepared tablets are tabulated in Table 2. These results clearly demonstrate that all the prepared tablets are uniform in terms of weight, thickness and hardness. The content uniformity of the tablets also meets the USP standards.

Bioadhesion

Table 3 shows the bioadhesionforces of the prepared tablets. An increase in CP content lead to the increment of the bioadhesion force, while increasing HPMC reversely affects it. Therefore, tablets containing only the latter possess the least bioadhesion forces, while those with a 2:1 (CP:HPMC) are the most bioadhesive. Fig. 2 pictures the swelling index of the prepared terbutaline sulfate tablets versus time.

Table 2. Weight, thickness, hardness, and content uniformity of the buccoadhesive sustained release terbutaline sulfate tablets

Formulation code	Thickness (mm)	Weight (g)	Hardness (N)	Content uniformity (mg)
$C_9H_9L_{30}(M_{27}L_{18}P_5)$	2.45±0.108	0.263±0.004	55.00±5.000	3.023±0.071
$C_9H_{18}L_{21}(M_{27}L_{18}P_5)$	2.47±0.095	0.264±0.004	56.67±7.638	3.022±0.061
$C_9H_{27}L_{12}(M_{27}L_{18}P_5)$	2.49±0.099	0.271±0.002	53.33±12.58	3.003±0.072
$C_{18}H_9L_{21}(M_{27}L_{18}P_5)$	2.46±0.107	0.265±0.012	58.33±7.638	3.113±0.194
$C_{18}H_{18}L_1(M_{27}L_{18}P_5)_2$	2.47±0.116	0.270±0.003	63.33±7.638	3.109±0.179
$C_{18}H_{27}L_3(M_{27}L_{18}P_5)$	2.50±0.133	0.267±0.001	56.67±7.638	3.135±0.130
$C_{27}H_9L_{12}(M_{27}L_{18}P_5)$	2.48±0.103	0.261±0.014	45.00±5.000	3.092±0.007
$C_{27}H_{18}L_3(M_{27}L_{18}P_5)$	2.51±0.120	0.274±0.004	55.00±10.00	3.049±0.198
$C_{25}H_{25}L_0(M_{27}L_{18}P_5)$	2.55±0.127	0.269±0.005	61.67±10.41	3.085±0.203

M; Manitol, L; Lactose, P; Polyethylen glycol, C; Carbapol, H; Hydroxypropyl methylcellulose

Table 3. Bioadhesion forces of the buccoadhesive sustained released terbutaline sulfate tablets

Formulation code of the bioadhesive cup	Bioadhesion average force (N)
C_0H_{150}	3.761±0.541
$C_{50}H_{100}$	4.922±0.443
$C_{75}H_{75}$	7.521±0.311
$C_{100}H_{50}$	11.20±0.367
$C_{150}H_0$	7.301±0.681

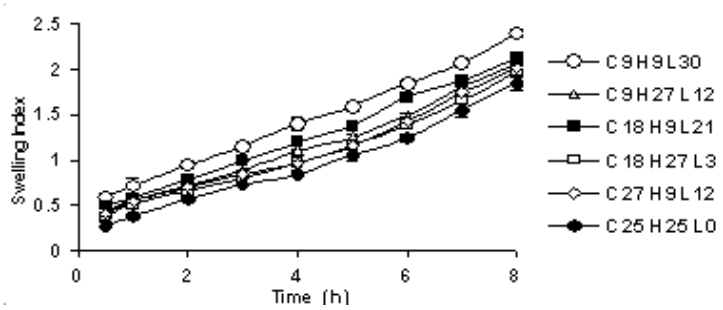

Fig. 2. Swelling index of the buccoadhesive sustained release terbutaline sulfate tablets

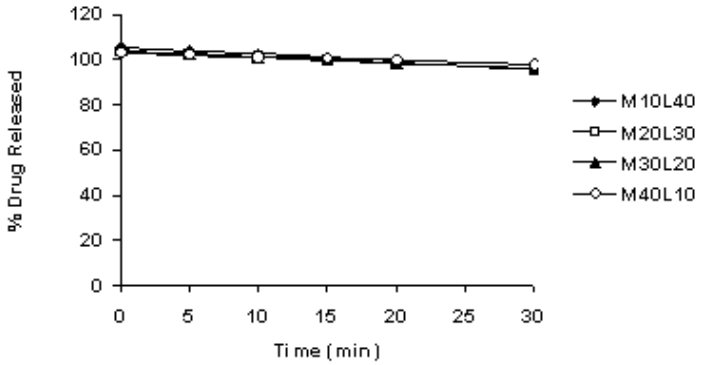

Fig. 3. Drug release from the immediate release core (not coated by the other layers)

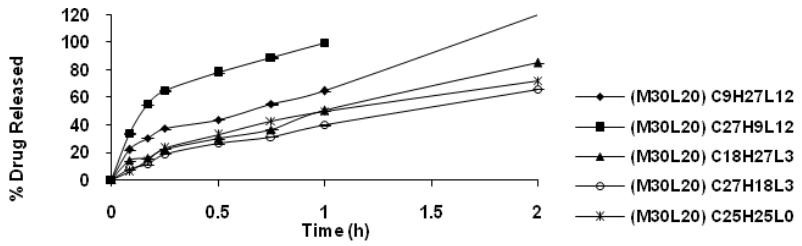

Fig. 4. Drug release from the immediate release layer (coated by the other layers)

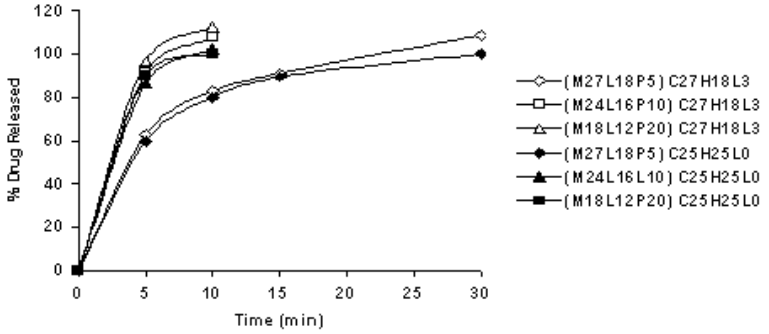

Fig.5. Drug release from the immediate release layer (coated with the other layers) after the addition of PEG

Dissolution test

Drug dissolution from the immediate release layer

All the immediate release cores made of lactose and mannitol released their drug within 5 min (Fig. 3). When covered with the sustained release layer, the mucoadhesive cup and the ethyl cellulose layer,the loaded drug was released at a much slower rate, and during a one h period (Fig,. 4). In order to enhance the drug release rate from the immediate release core, PEG4000 was added. Following the addition of different PEG ratios, the loaded drug was released within 15 min from the final tablets (Fig. 5).

Drug dissolution from the sustained release layer

The release profiles of the sustained release layers of the final tablets are pictured in Figs. 6 and 7, while Table 4 tabulates the related release kinetics, drug diffusion mechanism,and

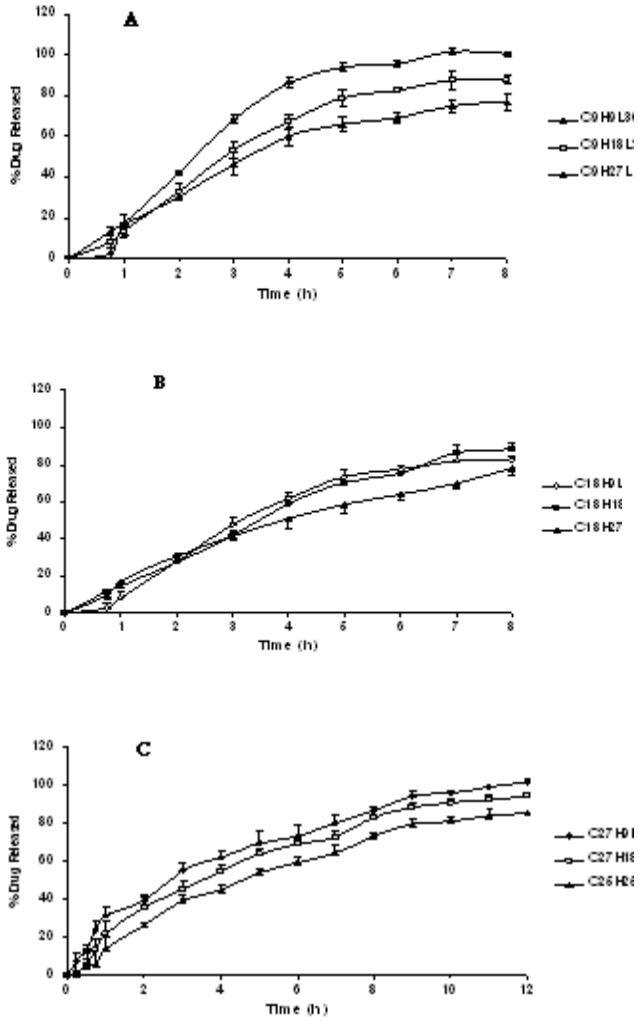

Fig. 6. Drug release profile from the sustained release layer of the final terbutaline sulfate tablets (comprised of an immediate release layer, a sustained release layer, a mucoadhesive cup, and an ethyl cellulose coating). A: Formulations made of 9 mg CP and various amounts of HPMC and lactose, B: Formulations made of 18 mg CP and various amounts of HPMC and lactose C: Formulations made of 27 mg of CP and various amounts of HPMC and lactose

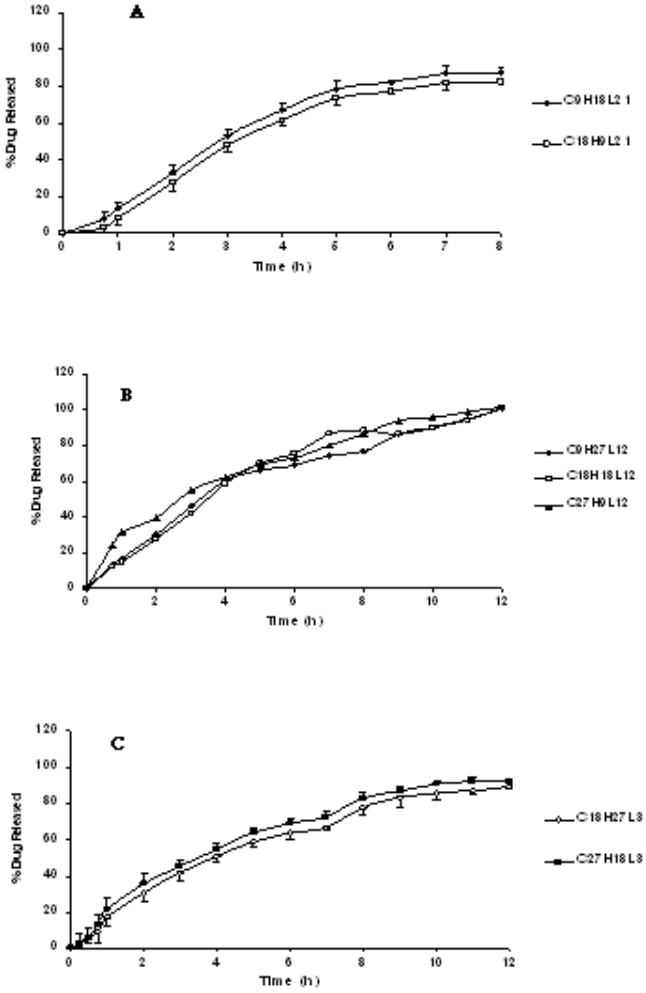

Fig. 7. Drug release profile from the sustained release layer of the final terbutaline sulfate tablets (comprised of an immediate release layer, a sustained release layer, a mucoadhesive cup, and an ethyl cellulose coating). A: Formulations made of 21 mg lactose and various amounts of HPMC and CP, B: Formulations made of 12 mg lactose and various amounts of HPMC and CP C: Formulations made of 3 mg of lactose and various amounts of HPMC and CP

MDT and RP values for 8 and 12 h.The release profiles clearly indicate that tablets with the highest amount of lactose and the lowest amounts of polymers ($C_9H_9L_{30}$) possessed the fastest dissolution rate, i.e. the whole loaded drug was released within 8 h. This formulation owned the highest swelling properties, and had an MDT value equal to 2.5±0.1h (Table 4). On the contrary, tablets made of CP and HPMC but no lactose ($C_{25}H_{25}L_0$) owned the slowest dissolution rates, i.e. only 85% of the total loaded drug was released after 12 h, and the lowest swelling properties. The related MDT value was equal to 4.25±0.28 h. Other formulations had dissolution rates between these two extremes. Formulations with 3 mg lactose ($C_{27}H_{18}L_3$ and $C_{18}H_{27}L_3$) released 80% of the loaded drug in 12 h, and had MDT values equal to 3.99±0.29 and 3.85±0.16, respectively. These figures clearly demonstrate that the dissolution rate from the tablets with the same amount of polymers is quite similar. Thus, what really affects the dissolution rate is the total amount of the polymers used. Such formulations possessed average swelling properties. It was also observed that formulations with 12 mg lactose ($C_{27}H_9L_{12}$, $C_{18}H_{18}L_{12}$, and $C_9H_{27}L_{12}$) released around 90% of the loaded drug in 8 h, and indicated MDT values equal to 3.64±0.06, 3.2±0.09 and 4.3±0.22 h. In addition, these formulations showed very high swelling properties. The same dissolution rate and swelling properties were observed for the formulations with 21 mg lactose ($C_{18}H_9L_{21}$ and $C_9H_{18}L_{21}$). The calculated MDT values for these formulations were equal to 2.8±0.09 and 2.72±0.07, respectively. The MDT values related to the formulations with 12 mg lactose were greater than those of the formulations containing 21 mg of this disaccharide ($P \leq 0.05$). The results also suggested that a linear correlation exists between the amount of lactose used within the tablets and the resulted MDT value. This correlation is shown in Fig. 8.

Kinetics and mechanism of drug release

The linear nature of curves obtained for zero order, first order, Higuchi model and Hixson-Crowell model as demonstrated by very close and higher r squared values suggested that the release from the formulations may follow any one of these models. The results obtained from the equation of Korsmeyer-Peppasaaare shown in Table 4.

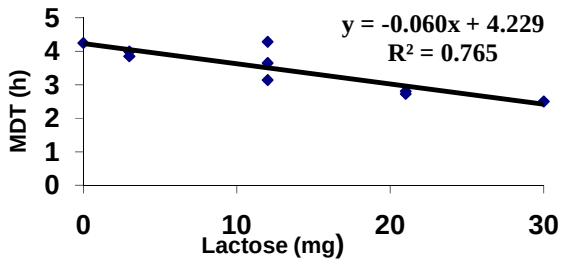

Fig. 8. The existing correlation between the amounts of lactose used in the formulation and the resulted MDT values

Table 4. Release kinetics, diffusion mechanism, MDT, and RP for 8 and 12 h of the prepared tablets

Formulation code	Release kinetics	Diffusion mechanism	MDT (h)	RP (8h) (%)	RP (12h) (%)
$C_9H_9L_{30}$	First order	Super-case II	2.494±0.105	100.7±0.892	-
$C_9H_{18}L_{21}$	First order	Super-case II	2.725±0.073	87.68±2.038	-
$C_9H_{27}L_{12}$	Higuchi	Non-fickian	4.279±0.220	76.81±4.093	100.9±1.981
$C_{18}H_9L_{21}$	First order	Super-case II	2.801±0.089	82.43±1.869	-
$C_{18}H_9L_{12}$	Hixon-crawell	Case II	3.135±0.099	88.50±1.823	100.5±1.253
$C_{18}H_{27}L_3$	Hixon-crawell	Case II	3.850±0.161	77.94±4.091	89.51±1.553
$C_{27}H_9L_{12}$	Higuchi	Non-fickian	3.643±0.056	86.67±2.147	101.57±1.346
$C_{27}H_{18}L_3$	Hixon-crawell	Case II	3.994±0.299	83.05±3.343	94.56±2.566
$C_{25}H_{25}L_0$	First order	Super-case II	4.246±0.267	73.10±4.288	85.09±3.286

Table 5. Review of the DSC endothermic peaks of the drug and excipients used in the immediate release layer along with the optimized immediate release formulation

Material	Endothermic temperature (°C)	Peak shape
Terbutaline sulfate	276.4	sharp
Lactose monohydrate	220, 145	sharp
Manitol	168	sharp
PEG_{4000}	66	sharp
	276.4	very small related to terbutaline sulfate
$M_{27}L_{18}P_5D_1$	66	sharp related to PEG_{4000}
	168	sharp related to manitol
	220, 145	small related to lactose

Table 6. Review of the DSC endothermic peaks of the drug and excipients used in the sustained release layer along with the optimized sustained release formulations

Material	Endothermic temperature (°C)	Peak shape
Terbutaline sulfate	276.4	sharp
HPMC	No distinct endothermic peak	-
Carbopol	No distinct endothermic peak	-
Lactose monohydrate	145, 220	sharp
$C_9H_{12}L_{27}D_2$	276.4	very small related to terbutaline sulfate
	145,220	sharp related to lactose
$C_{27}H_9L_{12}D_2$	276.4	very small related to terbutaline sulfate
	145,220	sharp related to lactose

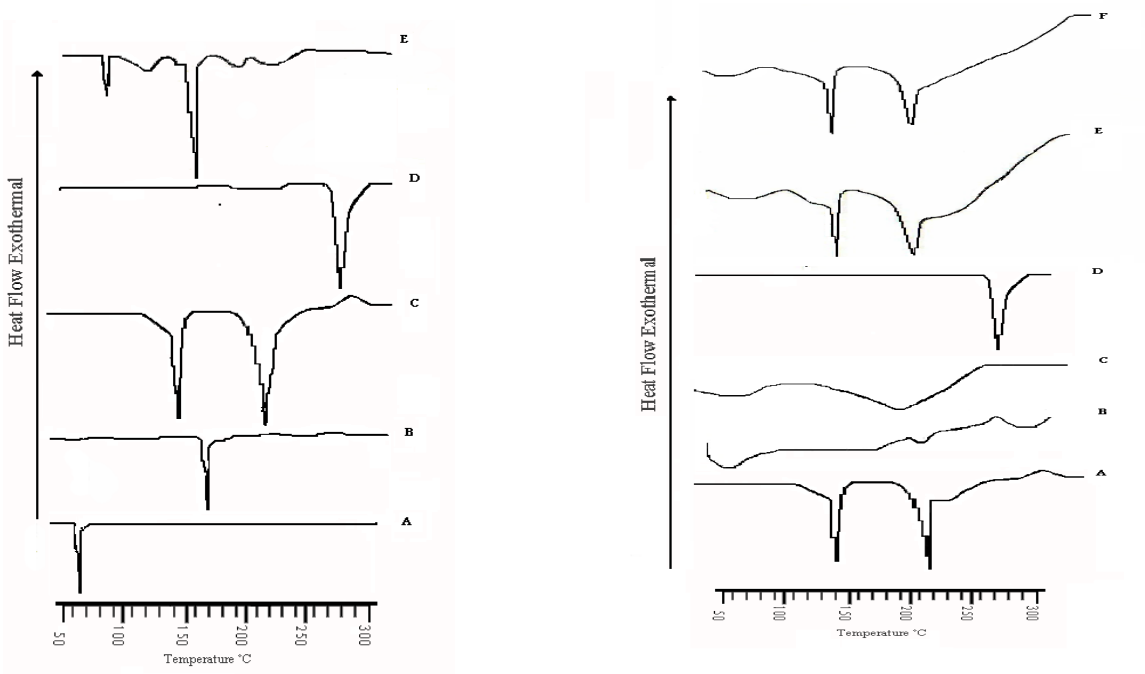

Fig. 9. Left: DSC thermograms of the drug and excipients used in the immediate release layer along with the optimized immediate release formulation: A) PEG_{4000}, B) manitol, C) lactose, D) terbutaline sulfate, and E) $C_{27}L_{18}P_5D_1$ (D = drug). Right: DSC thermograms of the drug and excipients used in the sustained release layer along with the optimized sustained release formulations: A) lactose, B) HPMC, C) CP, D) terbutaline sulfate, E) $C_{27}H_9L_{12}D_2$, and F) $C_9H_{27}L_{12}D_2$.

DCS analyses

A simple review of the peaks and their forms are shown in Tables 5 and 6.The DSC thermograms of the drug and the excipients used within the sustained release layer and the immediate release layer are shown in Fig. 9.

DISCUSSION

Solubility behavior of the drug in solution with pH value of oral cavity (pH 6.8) and its permeation kinetics via buccal mucosa provide useful information prior to the development of a mucoadhesive drug delivery system. High drug solubility in phosphate buffer solution (pH 6.8) indicates that solubility of the drug in saliva and buccal mucosa is not a rate limiting step for drug solution. Bovine buccal mucosa permeability coefficient to terbutaline sulfate (0.001 cm/sec) revealed a high permeability to the drug. It is estimated that if permeability coefficient is greater than 10^{-6} cm/sec, the drug shows a high permeation to the membrane.This justifies our attempts toward the preparation of a buccoadhesive system for terbutaline sulfate.

The results of the physical assessment of the tablets clearly demonstrated that all the prepared tablets were uniform and acceptable in terms of weight, thickness, hardness and content uniformity.

The bioadhesion characteristics are affected by the type and ratio of the bioadhesive polymers (15). An increase in CP content resulted in an increase in the bioadhesion force. Our findings are in agreement with the literature (15-18). Interestingly enough, tablets made of CP alone (containing no HPMC) have less bioadhesive forces than those made of CP and HPMC (2:1). This might happen due to the pH dependent bioadhesion of CP molecules. Since the pKa of the carboxyl group in CP is 4.75, the polymer is more hydrophilic at a pH greater than 6. This will, of course, lead to the reduction of the bioadhesion due to loss of hydrogen bonding (19). It is believed that when used along with HPMC, CP is much less touched by this phenomenon, and hence shows higher bioadhesion properties. The bioadhesion characteristics of the polymers also depend on the rate of swelling, pH, applied strength, initial contact time, and selection of the model substrate surface (20).

The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The swelling as well as the release of the drug from buccoadhesive tablets varied according to the type and ratio of the matrix forming polymers.

It has been shown that swelling of the CP is greatest at pH 6-7 as compared to acidic or alkaline pH. CP with the of 4.75 is almost completely ionized at pH 6.8 which gives rise to negative charges along the CP backbone whose repulsion induces CP molecule to uncoil into an elongated structure. Diffusion of counter-ion inside the gel generates an osmotic pressure difference across the gel that leads to higher water uptake which results in the substantial swelling of the polymer (21). Since HPMC is a non-ionic polymer, its swelling properties are smaller than CP. It is therefore believed that the increment of the CP ratio in a CP-HPMC matrix increases the swelling properties, while an increase in HPMC ratio enhances the drug release rate from the matrix (13,16). The present study, however, found that in formulations with fixed total amount of CP and HPMC ($C_{27}H_9L_{12}$, $C_9H_{27}L_{12}$, $C_{18}H_{18}L_{12}$) and ($C_{18}H_{27}L_3$, $C_{27}H_{18}L_3$) different ratios of the polymers do not bring about significant changes in swelling properties. However, when the total amount of CP and HPMC increases, or in other terms, the amount of lactose used within the formulation decreases, the swelling characteristics decline, and thus the formulation made of the maximum amount of lactose and the minimum amount of the bioadhesive polymers (CP and HPMC) has the highest swelling properties. This might be due to the ability of lactose to absorb water into the tablet. Evidently, as water enters a tablet in greater amount and at a faster rate, numerous pores will appear within the system which may enhance the swelling of the prepared tablets (21).

Immediate release cores released their drug within 5 min but when covered with the sustained release layer, the mucoadhesive cup and the ethyl cellulose layer, the loaded drug was released at a much slower rate. The main reason for this phenomenon is that the drug loaded within the immediate release core alone is subjected to the surrounding medium from three directions. Therefore, the buffer penetration into the core is much faster, and the dissolution rate increases. When the

immediate release core is coated by the other three layers, however, the loaded drug is subjected to the surrounding medium solely from one direction. This will, of course, lead to a slower dissolution rate. To enhance the drug release rate from the immediate release core, PEG4000 was added. Since the drug release rate increased acceptably following the addition of different PEG ratios, and the loaded drug was released within 15 min from the final tablets (Fig. 5), the formulation with the least amount of PEG, i.e. $M_{27}L_{18}P_5$, was chosen as the immediate release core of these multilayer tablets.

The results of drug dissolution from the sustained release layer are clear enough to reveal that the increment of lactose within the sustained release layer along with the reduction of the polymers enhances the dissolution rate remarkably, and when the amount of lactose is equal in formulations, different CP/HPMC ratios don't touch the dissolution rate significantly. It is also evident that the swelling properties and the dissolution rate are correlated, i.e. increasing the amount of lactose enhances the dissolution rate through the increment of the swelling properties. Khan and coworkers (22) reported that increasing of amount of lactose and decreasing amount of CP results increasing of dissolving rate.

The n values estimated from the equation of Korsmeyer-Peppas were found to be between 0.5 and 1.3 which indicated non-Fickian, Case II, or Super-case II drug release (Table 4). In swellable systems, factors affecting release kinetics are liquid diffusion rate and polymeric chain relaxation rate. When the liquid diffusion rate is slower than the relaxation rate of the polymeric chains, the diffusion is Fickian; whereas when the relaxation process is very slow compared with the diffusion, the case II transport occurs. When liquid diffusion rate and polymer relaxation rate are of the same order of magnitude, anomalous or non-Fickian diffusion is observed (16).

The DSC thermogram of terbutaline sulfate shows a sharp endothermic peak in 276.4°C which conforms to the other reports (8). Thermograms of all the excipients are also thoroughly in accordance with the other reports (23,24). This justifies the type and the purity of all the materials used in the experiment. Since the amount of drug used within the studied formulations was much less than the amount of the other excipients, and the end of lactose endothermic peak is broadened in 276°C, only a small endothermic peak related to terbutaline sulfate is observed within the formulations' thermograms. The sharp endothermic peaks in 145°C and 220°C pertain to lactose. This ensures that none of the materials used for the preparation of the tablets may have physicochemical interactions.

CONCLUSION

The present investigation established that the prepared buccoadhesive sustained released tablets are convenient systems for the delivery of terbutaline sulfate, remarkably increasing the bioavailability of the drug compared to the systems administered orally, and possessing all the advantages related to the sustained release systems.

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