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Research Article

Development and Evaluation of Buccoadhesive Controlled Release Tablets of Lercanidipine

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Abstract. The purpose of this research was to develop and evaluate buccal mucoadhesive controlled release tablets of lercanidipine hydrochloride using polyethylene oxide and different viscosity grades of hydroxypropyl methylcellulose individually and in combination. Effect of polymer type, proportion and combination was studied on the drug release rate, release mechanism and mucoadhesive strength of the prepared formulations. Buccal mucoadhesive tablets were made by direct compression and were characterized for content uniformity, weight variation, friability, surface pH, thickness and mechanism of release. In order to estimate the relative enhancement in bioavailability one optimized formulation was evaluated in rabbits. Further, placebo tablets were also evaluated for acceptability in human subjects. Results indicated acceptable physical characteristics of designed tablets with good content uniformity and minimum weight variation. Drug release and mucoadhesive strength were found to depend upon polymer type, proportion and viscosity. The formulations prepared using poly ethylene oxide gave maximum mucoadhesion. The release mechanism of most formulations was found to be of anomalous non-Fickian type. *In vivo* studies of selected formulation in rabbits demonstrated significant enhancement in bioavailability of lercanidipine hydrochloride relative to orally administered drug. Moreover, in human acceptability studies of placebo formulations, the designed tablets adhered well to the buccal mucosa for more than 4 h without causing any discomfort. It may be concluded that the designed buccoadhesive controlled release tablets have the potential to overcome the disadvantage of poor and erratic oral bioavailability associated with the presently marketed formulations of lercanidipine hydrochloride.

KEY WORDS: buccal; hydroxypropyl methylcellulose; lercanidipine; mucoadhesive; poly ethylene oxide.

INTRODUCTION

The buccal route has long been advocated as possible route of delivery of drugs having poor oral bioavailability because of high first pass metabolism or degradation in the gastrointestinal tract (1). This route is well vascularized, with venous blood draining the buccal mucosa reaching the heart directly via the internal jugular vein (2). Although, the drug fluxes via this route are less than that obtained with sublingual mucosa due to permeability barrier (2), the relative immobility of buccal musculature, as compared to that of sublingual route, makes this site ideally suited for sustained delivery of drugs (1). Thus, adhesive delivery systems like tablets (3), gels (4), and patches (5), have been recommended for buccal drug delivery.

Lercanidipine hydrochloride (LER) is chemically 2-[(3,3-diphenylpropyl) methylamine]-1,1-dimethylethylmethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5 pyridine carboxylic ester hydrochloride. LER is used in treatment of hypertension, because of its selectivity and specificity on the smooth vascular cells (6, 7). The drug is administered orally in a dose of 10–20 mg daily as its hydrochloride salt, reducing significantly the diastolic blood pressure (7). After oral administration, LER is completely and erratically absorbed from the gastrointestinal tract (8). However, absolute bioavailability is reduced to approximately 10% because of extensive first pass metabolism to inactive metabolites (7). Literature suggests mean half-lives of 2.8 and 4.4 h in humans after single dose of 10 and 20 mg of LER, respectively (8). These pharmacokinetic parameters make LER a suitable candidate for buccal delivery.

In this context, few formulations of LER have been reported that serve to overcome drawback of poor oral bioavailability and erratic oral absorption. Modified release acrylic acid ester beads have been reported for reducing erratic oral absorption of LER (9). A capsule formulation of LER to maintain therapeutically active levels of LER for 24 h has also been reported using polyethylene glycol esters (10). Modified release delivery systems of LER like pH dependent pulsatile delivery systems (11), and controlled release osmotic devices have also been described in literature for increasing oral bioavailability (12, 13).

Extensive survey of literature and patent databases did not reveal any buccal dosage form of LER for improving

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bioavailability. Hence, the objective of present investigation was to develop and evaluate buccal mucoadhesive controlled release tablets of LER using polyethylene oxide (PEO) or different viscosity grades of hydroxypropyl methylcellulose (HPMC) individually and their combination. Effect of polymer type, proportion and combination was studied on drug release rate, release mechanism and mucoadhesive strength of the prepared formulations. *In vivo* bioavailability and acceptability studies were carried out in rabbits and healthy human volunteers respectively.

MATERIALS AND METHODS

Materials

LER, HPMC of various viscosity grades and PEO (Polyox WSR 1105 of 900 KDa) were obtained as gift samples from Glenmark Pharmaceuticals Ltd., India; IPCA Laboratories, India; and Ranbaxy Laboratories Ltd., India respectively. All other chemicals and reagents used were of analytical grade.

Methods

Analytical Methods

An in-house developed and validated HPLC (Shimadzu, Japan) method was used for estimation of drug in formulations, stability, and bio samples. Mobile phase consisted of an aqueous phase (10 mM potassium dihydrogen phosphate buffer, pH 4.0) and acetonitrile (40:60 *v/v*). Chromatographic separation of LER was achieved using an endcapped C18 reverse phase column (Lichrospher®, 125 mm long, particle size 5 μm, E. Merck, Germany). The injection volume was 100 μL and LER was monitored at wavelength of 240 nm with flow rate of 1 mL/min.

Estimation of LER in *in vitro* release samples was achieved using in-house developed and validated UV spectrophotometric (Jasco, Japan) method employing dissolution media (pH 6.8 phosphate buffer with 2.5% *v/v* polysorbate 80) as a solvent system at 354 nm.

Drug Excipient Compatibility Studies

Stability of LER in presence of excipients like PEO, HPMC, lactose, mannitol, talc and magnesium stearate was studied. Compatibility study was carried out for pure LER, individual excipient and combination of LER with excipients in 1:1 ratio. Mixed samples of drug and excipient were analyzed by HPLC method for content uniformity. Differential scanning calorimetry (DSC) (Shimadzu, Japan) study was carried out over a temperature range of 35 to 225 °C with a heating rate of 10 °C per min in an inert environment of nitrogen gas. Fourier transform infra red (FTIR) spectroscopic (Shimadzu, Japan) studies were carried out by appropriately diluting the sample with dried potassium bromide and acquiring infra red (IR) spectrum in the range of 400 to 4,000 cm^{-1}. All samples were stored at accelerated (40±2 °C/75±5% RH) and ambient (25±2 °C and 60±5% RH) conditions protected from light for 6 and 12 months respectively and DSC and FTIR studies were repeated.

Formulation of Buccal Mucoadhesive Controlled Release Formulations

Matrix embedded buccoadhesive controlled release tablets containing LER (10 mg) were prepared using varying proportions of PEO, HPMC (4,000, 15,000, 100,000 cPs) and combination of HPMC and PEO. Tablets were prepared by direct compression technique. Drug (100#), polymer (100#) and other excipients (80#) were carefully mixed using geometrical technique and compressed (Cadmach, India) using 10 mm punches at a compression force of 5,000 kg. The prepared tablets were packed into airtight cellophane packets and stored at ambient condition (25±2 °C and 60± 5% RH) protected from light.

Physical Characterization of the Designed Formulations

For each batch, 20 tablets were weighed (Afcoset, India) for assessing weight variation. Thickness was determined using vernier caliper. Friability was determined by subjecting 20 tablets to falling shocks in friabilator (Campbell Electronics, India) for 4 min at 25 rpm. Drug content of each batch was determined by weighing and finely powdering 20 tablets. An aliquot of this powder equivalent to 10 mg of drug was accurately weighed, dissolved in acetonitrile and analyzed using HPLC method.

Crushing strength (hardness) of the tablets was determined using texture analyzer (Stable Micro Systems, UK) fitted with a 30 kg load cell using a 3 mm diameter stainless steel cylindrical probe. Hardness of the tablet was recorded as the maximum force required (N) to break the tablet.

The designed tablets were first allowed to swell in contact with 5 mL of triple distilled water (pH 7.2) for 2 h in petriplates. The surface pH was measured by bringing glass electrode of pH meter (Eutech Instruments, Singapore) in contact with the surface of tablets and allowing it to equilibrate for 1 min. The surface pH of the tablets was determined in order to investigate the possibility of any discomfort in oral cavity as acidic or alkaline pH may lead to irritation (14).

Mucoadhesion Studies

Mucoadhesion studies of designed formulations were carried out using texture analyzer. Freshly excised porcine buccal mucosa was obtained from the local slaughterhouse. The tissue was placed in simulated salivary fluid (15), and stored at −20 °C till further usage. The thawed mucosal tissue was held using clips on a holder immersed in simulated salivary fluid maintained at 37 °C, so that the fluid is just in contact with the surface of the mucosal tissue. The designed tablet was attached to the probe (stainless steel cylindrical probe with 10 mm diameter) using glue. The probe was lowered at a speed of 0.1 mm/s until the tablet made contact with mucosal tissue. A constant force of 0.4 N was applied for 30 s, after which the probe was withdrawn at a speed of 0.5 mm/s. Peak detachment force and area under the force-

time curve were used to establish mucoadhesive strength and work of adhesion respectively.

Release Rate Studies

In vitro release studies were carried out using USP Type I dissolution test apparatus (Electrolab, India) with minor modifications. The jars of standard dissolution apparatus were replaced with in-house fabricated perplex plates with a cavity in centre to accommodate 60 mL glass beakers concentric with shaft of the dissolution apparatus. The tablets were placed in baskets of dissolution apparatus with both the sides exposed to dissolution media for drug release. Phosphate buffer, 50 mL, pH 6.8, with 2.5% *v/v* polysorbate 80 maintained at 37±1 °C was used as dissolution media at a stirring rate of 25 rpm. Samples (5 mL) were collected and replaced with fresh dissolution media at predetermined time intervals. The samples collected were diluted suitably and analyzed using UV spectrophotometric method.

The release data was mathematically treated using Peppas power equation to investigate the mechanism of drug release from the formulations. The values of release rate constant (K), diffusion exponent (n) and time required for 50% drug release ($t_{50\%}$) were calculated for all the formulations (16). Furthermore, the kinetics of drug release from the formulations was inferred based on regression coefficient (R^2) obtained from the plots for zero order, first order and Higuchi's square root kinetics. The values of K and $t_{50\%}$ were also calculated using the equation of the kinetic model showing the best R^2 value.

Swelling Studies

The swelling behavior of the formulations (HK4/10, HK15/10, HK100/10, PEO/10) was investigated using texture analyzer. The formulations were placed in glass beakers under conditions identical to those for *in vitro* drug release. The hydrated tablets were removed at predetermined time intervals and subjected to texture profiling after soaking the excessive water using a tissue paper. The force–displacement–time profile associated with the penetration of a 3 mm round-tipped probe into the swollen matrices was monitored (17). The probe was lowered at a speed of 0.1 mm/s till a trigger force of 5 g was detected, after which the probe advanced into the sample at a speed of 0.1 mm/s. The probe was withdrawn at a speed of 0.5 mm/sec after maximum force of 30 g was reached. Swollen thickness was determined by measuring the total probe penetration value recorded. Percent axial swelling was calculated using previously reported formula given in equation 1 (17). Original thickness of the tablets was determined using vernier caliper.

$$\text{Axial Swelling}(\%) = \frac{[\text{Swollen Thickness} - \text{Original Thickness}]}{[\text{Original Thickness}]} \times 100 \quad (1)$$

Batch Reproducibility and Stability Studies

Three batches of each formulation were prepared and their quality and release characters were evaluated using the methodology previously described to check batch reproducibility. To study the effect of storage on stability and release profile of formulations, formulations were stored at accelerated (40±2 °C/ 75±5% RH) and ambient (25±2 °C/ 60±5% RH) conditions for 6 and 24 months respectively. All the quality control tests were again carried out on aged samples at predetermined time intervals to assess stability of formulations.

Human Acceptability Studies

Freshly prepared placebo tablets of selected batches (HK4/10, HK15/10, HK100/10, PEO/10) were used for human studies. Placebo tablets were prepared by replacing LER in all formulations with lactose. A clearance was obtained from Institutional Human Ethics Committee (Protocol approval number: IHEC-02/05-06) before conducting the studies. Informed consent was obtained from volunteers selected for the study. The procedures followed were in accordance with the ethical standards of the Institutional Human Ethics Committee and the Helsinki Declaration. The study was conducted on ten healthy human male volunteers (aged 20 to 25 years). Volunteers were asked to wash the oral cavity using around 100 mL of distilled water. Volunteers were instructed to press the placebo tablets against the mucosal lining of cheek for 1 min. Food and water were not allowed for first 60 and 30 min respectively after application of tablets. Volunteers were asked to record time of tablet placement and time and circumstances at end of adhesion (erosion or dislodgement of tablets). Volunteers were given a questionnaire to assess the acceptability of the tablets (18). The study was designed in a cross over pattern, so that each volunteer received each of the test formulations. Volunteers were instructed to place successive tablet at a location opposite to the site of placement of the previous tablet. The percentage response of volunteers for various parameters listed in questionnaire was calculated.

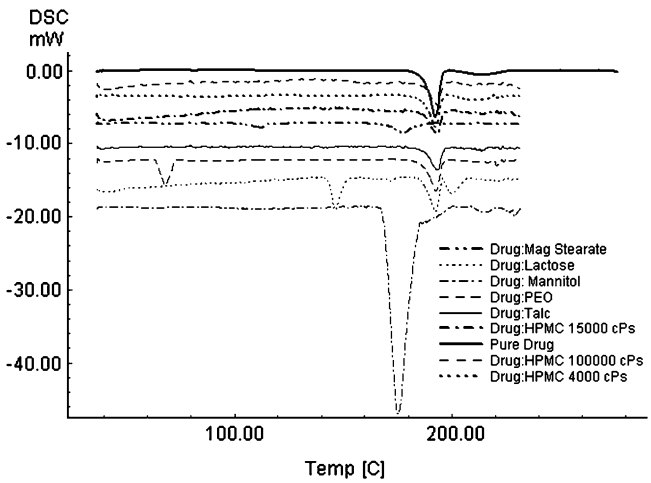

Fig. 1. DSC thermogram of drug and physical mixtures of drug and excipients (1:1)

Table I. Thermal Properties of Drug Alone, Excipient Alone and Physical Mixtures (1:1)

Sample	Peak Onset (°C)	Peak (°C)	Peak Endset (°C)	Heat (J/g)
Drug	188.2	192.6	195.6	−56.2
Lactose	144.7	146.8	151.9	−54.0
	211.9	217.5	221.6	−87.3
Drug + Lactose	187.2	192.6	195.5	−59.9
Mannitol	166.8	168.1	172.4	−207.3
Drug + Mannitol	179.3	184.4	187.2	−263.0
Talc	–	–	–	–
Drug + Talc	188.0	193.5	196.1	−52.8
HPMC 4,000 cPs	–	–	–	–
Drug + HPMC 4,000 cPs	187.6	192.7	195.8	−53.4
HPMC 15,000 cPs	–	–	–	–
Drug + HPMC 15,000 cPs	188.5	193.7	196.7	−57.0
HPMC 100,000 cPs	–	–	–	–
Drug + HPMC 100,000 cPs	188.5	193.7	197.5	−57.5
PEO	62.3	67.1	71.8	−100.6
Drug + PEO	184.3	190.5	195.2	−59.3
Magnesium stearate	106.2	112.9	115.6	−14.6
Drug + Magnesium Stearate	182.2	185.7	189.2	−54.0

In Vivo Bioavailability Studies in Rabbits

The Central Animal Facility of the Institute provided New Zealand white male rabbits with mean weight of 1.79± 0.24 kg. The study was conducted with the approval of (Protocol approval number: IAEC/RES/7/4) and as per guidelines prescribed by Institutional Animal Ethics Committee, under the supervision of registered veterinarian. Animals were issued 6 days prior to experimentation for acclimatization and were kept on standard pellet diet and water ad libitum. Food was stopped to all animals 8–10 h prior to experimentation. Food and water was not given to animals till 2 h after the start of the study.

To study the oral pharmacokinetics of LER, 2 mL of 5 mg/mL solution of LER in 40% *v*/*v* poly ethylene glycol 400 in water was administered to rabbits (n=3) using an oral catheter. The catheter was flushed with 5 mL of 40% *v*/*v* poly ethylene glycol 400 in water to ensure complete dosing.

The designed tablet containing 10 mg LER was pre-moistened by dipping the tablet in distilled water for 5 s. The mouth of rabbit (n=3) was opened using specially designed mouth restrainers and the pre-moistened tablet was pressed gently against mucosal lining of cheek using forceps for 1min to ensure adhesion. Each rabbit was dosed with specific dose of LER (10 mg) without taking weight of the rabbit into consideration.

For each study, blood samples (1 mL) were withdrawn from the marginal ear vein of rabbits using a 21 G needle. Samples were withdrawn before dosing and 0.5, 1.0, 2.0, 4.0, 6.0, 9.0, 12.0, 18.0, 24.0 h post dosing. The collected blood was harvested for 45 min at ambient temperature and centrifuged at 2000 rpm for 20 min. The clear supernatant serum layer was collected and stored at -20 °C until analysis.

Frozen serum samples were thawed at ambient temperature (25±2 °C) for at least 60 min. A simple and efficient one-step process was employed to isolate LER from rabbit serum. To aliquot of 500 μL of serum samples, 1.5 mL of acetonitrile was added and vortex mixed for 1 min to ensure complete precipitation. Samples were vortex mixed again for 1 min and centrifuged at 10,000 rpm at 4 °C for 20 min.

Table II. Wavelength Attribution of IR Spectrum of LER in Potassium Bromide

Wavelength (cm^{-1})	Attribution
3,182	NH stretching
3,100–2,800	Alkyl and phenyl stretching
2,531	N^+ stretching
1,668	C=O stretching
1,523, 1,346	Assymetric and symmetric stretching of NO_2 group
1,406, 1,384	Bending of geminal methyl group
795–696	Out of plane bending of 5 and 3 adjacent hydrogen on aromatic ring

Table III. Composition of Designed Buccal Mucoadhesive Controlled Release Tablets Containing 10 mg of LER per Tablet

	Formulation Composition (in mg/ tablet)[a]			
Formulation Code	PEO	HPMC 4,000 cPs	HPMC 15,000 cPs	HPMC 100,000 cPs
HK4/10	–	10	–	–
HK4/15	–	15	–	–
HK15/10	–	–	10	–
HK15/15	–	–	15	–
HK100/10	–	–	–	10
HK100/15	–	–	–	15
PEO/5	5	–	–	–
PEO/10	10	–	–	–
PEO/15	15	–	–	–
PHK4/5050	5	5	–	–
PHK15/5050	5	–	5	–
PHK100/5050	5	–	–	5

[a] Apart from these ingredients each formulation contained mannitol (80 mg/ tablet), lactose (80 mg/ tablet), talc (2 mg/ tablet) and magnesium stearate (2 mg/ tablet)

Table IV. Results of Quality Control Tests Carried out on Designed Buccal Mucoadhesive Tablets

Formulation Code	Weight[a] (mg)	Thickness[b] (mm)	Assay[a] (%)	Crushing Strength[b] (*N*)	Detachment Force[b] (N/cm^2)	Work of Adhesion[b] (N s/cm^2)
HK4/10	184.3±1.1	2.51±0.04	99.5±1.7	35.3±1.8	1.48±0.06	0.97±0.03
HK4/15	188.5±1.4	2.45±0.04	98.3±1.7	37.8±1.8	1.62±0.04	1.35±0.05
HK15/10	183.6±1.5	2.50±0.10	100.4±1.5	36.9±1.2	1.70±0.03	1.05±0.04
HK15/15	188.7±1.7	2.33±0.05	102.1±1.2	35.3±1.5	2.00±0.03	1.43±0.03
HK100/10	182.7±2.1	2.43±0.09	99.7±1.9	35.9±1.5	2.01±0.02	1.71±0.03
HK100/15	187.7±2.3	2.41±0.03	99.6±1.3	36.8±1.1	2.53±0.03	2.23±0.04
PEO/5	178.4±1.0	2.49±0.04	101.2±1.3	29.4±1.2	2.22±0.04	1.85±0.03
PEO/10	183.2±1.5	2.53±0.04	98.8±1.3	30.3±1.7	2.66±0.06	2.20±0.09
PEO/15	190.3±1.3	2.55±0.10	101.3±1.5	31.0±1.7	3.19±0.03	2.78±0.08
PHK4/5050	184.1±1.5	2.52±0.01	98.8±1.5	33.3±1.1	2.34±0.07	1.60±0.04
PHK15/5050	184.2±1.7	2.53±0.01	100.3±0.9	35.3±1.5	2.38±0.06	1.66±0.06
PHK100/5050	184.9±1.6	2.51±0.05	100.5±2.0	35.3±0.8	2.58±0.06	2.29±0.06

[a] Mean (±SD) of 20 tablets
[b] Mean (± SD) of three independent determinations

Supernatant of the centrifuged samples was evaporated to dryness in vacuum concentrator maintained at 30 °C. Vacuum dried residue was reconstituted in 500 μL of mobile phase and analyzed using HPLC method.

The serum concentration versus time data of LER obtained during various sets of studies was subjected to non-compartmental analysis using WinNonlin Standard edition, Version 2.1 (WinNonlin Scientific Consultants, USA) to acquire various pharmacokinetic parameters. Results of in vivo studies were statistically evaluated using unpaired t-test at 5% level of significance.

RESULTS AND DISCUSSIONS

Drug Excipient Compatibility Studies

DSC study was carried out for pure LER, individual excipient and combination of LER with various excipients (mixed in 1:1 ratio). DSC thermogram of LER showed a distinct melting endotherm of drug at 192.64 °C (Fig. 1) with an enthalpy value of −56.16 J/g (Table I). Fig. 1 represent thermograms of pure LER and 1:1 physical mixtures of LER with different excipients selected for the study. Melting endotherm of drug was well preserved in most of the cases. However a slight change in peak shape with little broadening and shifting to higher or lower temperature was observed in some physical mixtures, which could be attributed to the mixing process that lowers the purity of each component of the mixture (19).

In DSC thermogram of pure mannitol, a sharp endothermic peak was observed at 168.13 °C very near to that of the drug with an enthalpy value of −207.31 J/g (Table I). In physical mixture a single, wide endothermic peak was observed which can be attributed to both drug and mannitol because of their similar melting points (Fig. 1). The enthalpy value of single peak observed in physical mixture of drug and mannitol was found to be −263.02 J/g, which is almost equal to summation of individual enthalpy values of drug (−56.16 J/g) and mannitol (−207.31 J/g; Table I). On basis of this observation it can be concluded that drug is stable in presence of mannitol (19). Similar results were obtained when the study was repeated on the samples stored at accelerated and ambient conditions.

In FTIR study, the IR bands that can be attributed to drug are presented in Table II. In all the drug-excipient mixtures studied, these bands were retained (data not shown). FTIR study further established absence of interaction between drug and excipients studied. Similar results were obtained when the study was repeated on the samples stored at accelerated and ambient conditions. The drug content of all

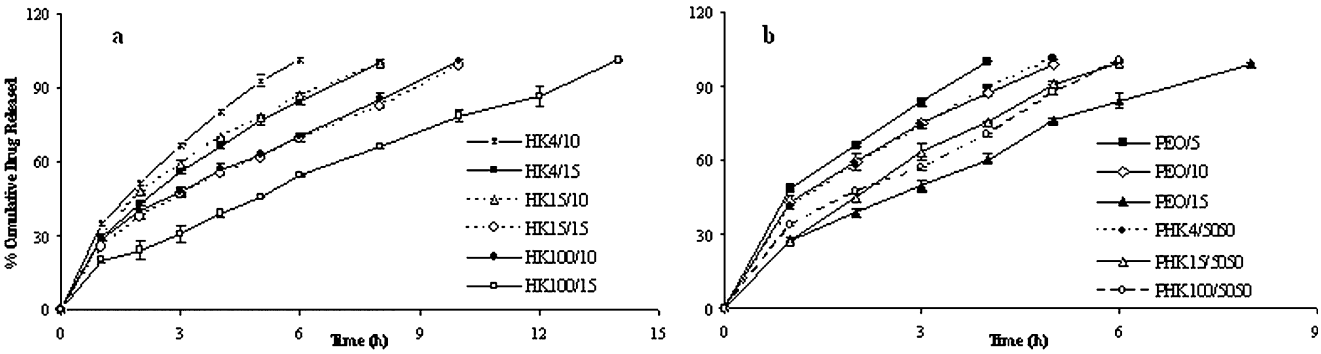

Fig. 2. Comparative percentage cumulative drug released from designed tablets (Mean±SD of three independent determinations) **a** For tablets prepared using different viscosity grades of HPMC; **b** For tablets prepared using PEO and combination of PEO and HPMC

Table V. Model Fitting of *In Vitro* Drug Release Data for Determination of Mechanism and Kinetics of Release

	Peppas Model			Release Kinetics			
Formulation Code	n^a	Release Rate Constant K (h^{-n})	$t_{50\%}{}^b$ (h)	Order	Release Rate Constant (h^{-1})	$t_{50\%}{}^b$ (h)	R^{2c}
HK4/10	0.6069	37.9×10^{-2}	1.62	First Order	48.6×10^{-2}	1.38	0.9914
HK4/15	0.5981	29.0×10^{-2}	2.48	First Order	30.2×10^{-2}	2.37	0.9932
HK15/10	0.5847	30.6×10^{-2}	2.30	First Order	32.5×10^{-2}	2.18	0.9964
HK15/15	0.5755	25.4×10^{-2}	3.24	First Order	20.8×10^{-2}	3.19	0.9895
HK100/10	0.5369	27.3×10^{-2}	3.08	First Order	21.2×10^{-2}	3.18	0.9898
HK100/15	0.6473	16.8×10^{-2}	5.40	First Order	15.3×10^{-2}	5.02	0.9751
PEO/5	0.5137	47.9×10^{-2}	1.08	First Order	58.2×10^{-2}	1.16	0.9941
PEO/10	0.5175	43.1×10^{-2}	1.33	First Order	52.0×10^{-2}	1.36	0.9924
PEO/15	0.6333	26.6×10^{-2}	2.70	First Order	30.5×10^{-2}	2.47	0.9706
PHK4/5050	0.5631	40.0×10^{-2}	1.48	First Order	51.4×10^{-2}	1.47	0.9955
PHK15/5050	0.7422	27.3×10^{-2}	2.26	Zero Order	16.4×10^{-2}	2.53	0.9765
PHK100/5050	0.5976	32.1×10^{-2}	2.09	First Order	36.7×10^{-2}	2.06	0.9743

[a] Diffusion exponent indicative of release mechanism
[b] Time required for 50% drug release
[c] Regression coefficient

the stored samples (accelerated and ambient condition) was found to be in range of 98.76 to 101.19% with maximum SD of 1.14 indicating stability of drug.

Physical Characterization of the Designed Tablets

The designed buccal mucoadhesive controlled release tablets (Table III) containing LER were found to possess very good physical properties and the results are presented in Table IV. The prepared tablets were smooth and pale yellow in color. Weight variation in case of all tablets was acceptable as indicated by the low SD values (maximum SD of 2.34 mg; Table IV). The weight variation in case of all the tablets was within ±1.5% of theoretical tablet weight. This falls well within the acceptance criteria. Friability in case of all the designed tablets was less than 1% *w*/*w* indicating suitability of the method used for manufacturing the tablets (data not shown). The prepared tablets showed maximum thickness of 2.55 mm with maximum SD of 0.10 mm (Table IV). The drug content of all the developed formulations was between 98 to 103% of the theoretical claim with maximum SD value of 2.00. This further indicated reliability and reproducibility of the manufacturing process. The designed buccal mucoadhesive controlled release tablets of LER were found to posses good hardness. The hardness for various formulations prepared using different polymers varied between 29.42 and 37.77 N. Surface pH of the prepared tablets was varying between 6.38 and 7.13 (data not shown). The near neutral surface pH of the tablets is essential for avoiding potential irritation to buccal mucosa due to continuous application of designed formulations.

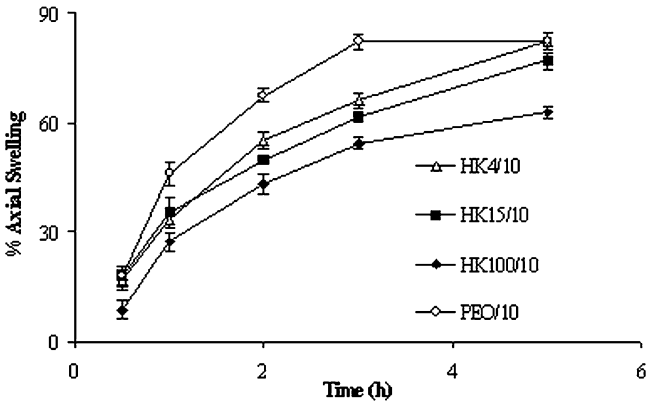

Fig. 3. Percentage axial thickness of prepared formulations at different time points (Mean ± SD of three independent determinations)

Mucoadhesion Studies

The work of adhesion and detachment force of designed formulations is presented in Table IV. Detachment force and work of adhesion were dependent upon polymer type, polymer concentration and polymer viscosity. When the concentration of polymer is low, the number of penetrating polymeric chains per unit volume of the mucus is low resulting in weaker interaction (20). Increase in adhesion with viscosity of polymer used can be attributed to higher strength of gel formed by HPMC 100,000 cPs as compared to that of HPMC 4,000 and 15,000 cPs resulting in stronger entanglement of polymeric chains with glycoprotein chains of mucus.

Formulations containing PEO alone showed superior mucoadhesion when compared with other polymers like HPMC (4,000, 15,000, 100,000 cPs; Table IV). This can be attributed to quicker swelling and higher flexibility of polymeric chains of PEO resulting in better interaction with mucin. Reduction in mucoadhesive strength was observed, when a part of PEO in polymer matrix was replaced with HPMC 4,000 or HPMC 15,000 cPs. However, when higher viscosity grade (HPMC 100,000 cPs) was used in combination of PEO, almost identical detachment forces were obtained when compared to tablets prepared using PEO alone (Table IV) further indicating importance of polymer viscosity in mucoadhesive behavior.

Table VI. Percentage Response of Health Human Male Volunteers to Various Parameters

Criteria	Percentage Volunteer Response[a]			
	HK4/10	HK15/10	HK100/10	PEO/10
Irritation				
None	80	80	70	90
Slight	20	10	30	10
Moderate		10		
Severe				
Comfort				
Very Comfortable	60	80	60	50
Comfortable	40	20	40	50
Slightly Uncomfortable				
Severely Uncomfortable				
Taste				
Very Pleasant	10		20	50
Pleasant	50	60	30	40
Normal	40	40	50	10
Very Unpleasant				
Dryness of mouth				
None	80	70	60	90
Slight	20	30	40	10
Severe				
Heaviness of delivery system				
None	60	70	90	90
Slight	30	20	10	
Moderate	10	10		10
Severe				
Hindrance during drinking				
None	100	100	90	90
Slight			10	10
Severe				
Hindrance during eating				
None	70	70	70	90
Slight	30	30	30	10
Severe				
Mean time of adhesion±SD[a] (h)	4.3±0.3	5.0±0.7	5.3±0.4	4.6±0.4

[a] Each formulation was given to ten volunteers

Release Rate Studies

In vitro release study data indicate that duration of release of drug is dependent on the percentage of selected polymer used in the formulations. An increase in the polymer concentration not only causes increase in the viscosity of the gel but also leads to formation of gel layer with a longer diffusional path. This leads to a decrease in the diffusion of the drug and therefore a reduction in the drug release rate (16). Comparative cumulative percentage drug released profiles from tablets prepared using various polymers either alone or in combination are shown in Fig. 2. The results of release kinetic studies are presented in Table V.

For tablets prepared using different viscosity grades of HPMC, drug release extended from 6–10 h (Fig. 2a) when the viscosity of HPMC used was increased from 4,000 to 100,000 cPs keeping the total polymer proportion constant (100% *w*/*w* of drug weight). The release rate was faster with lower viscosity grades of HPMC probably due to lesser polymer entanglement, lesser gel strength and larger effective molecular diffusional area when compared to higher viscosity grades (21). All the formulations prepared with HPMC showed first order drug release kinetics with *n* value ranging between 0.5369 and 0.6473 indicating anomalous non-Fickian release mechanism of drug (Table V).

PEO being a water soluble polymer led to rapid drug release when used in smaller proportion. Increasing PEO from 50 to 150% *w*/*w* of drug weight resulted in extension of drug release from 4 to 8 h (Fig. 2b). The drug release was

Table VII. Summary of Pharmacokinetic Parameters of LER Following Administration of Single Dose of LER (10 mg) in Rabbits by Oral and Buccal Route (Mean±SD of Three Rabbits)

Parameter	Oral Solution	PEO/10
C_{max}[a] (µg/L)	148.3±12.9	180.0±10.6
T_{max}[b] (h)	1.0	2.0
$AUC_{(0-\infty)}$[c] (µg h/L)	1202.5±143.8	1997.4±261.0
MRT[d] (h)	6.8±0.3	7.8±1.0
Fr[e] (%)	100.0	166.1

[a] C_{max} Maximum serum concentration
[b] T_{max} Time to reach C_{max}
[c] $AUC_{(0-\infty)}$ Area under the serum concentration-time curve
[d] MRT Mean residence time
[e] Fr Relative bioavailability

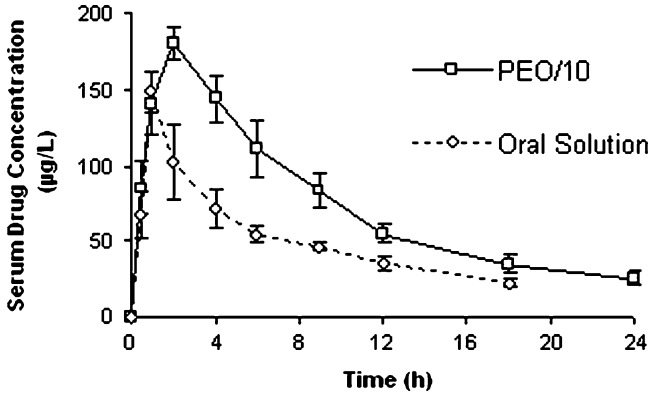

Fig. 4. Mean serum concentration of LER following administration of single dose of LER (10 mg) in rabbits by oral and buccal route (Mean±SD of three independent determinations)

rapid initially and slowly tapered off as the time progressed. The release data of all the formulations prepared using PEO fitted best in first order kinetic model. The release rate constants according to Peppas power equation for formulations containing 50, 100 and 150% *w/w* PEO of the drug weight were 47.92×10^{-2} $h^{-0.5137}$, 43.09×10^{-2} $h^{-0.5175}$ and 26.61×10^{-2} $h^{-0.6333}$ respectively with $t_{50\%}$ values of 1.08, 1.33, and 2.70 h respectively (Table V). When lower proportions of PEO (50 and 100% *w/w* of drug weight) were used n values close to 0.5 were obtained indicating Fickian diffusion as the mechanism of drug release. But in case of formulations containing higher proportions of PEO, the drug release mechanism was found to be anomalous non-Fickian (Table V). Use of HPMC (various viscosity grades) in combination with PEO in tablet formulations did not significantly affect the release mechanism of drug from formulations as indicated by similar values of n in case of formulations prepared with PEO or HPMC individually or in combination (Table V).

Swelling Studies

The profiles of percentage axial swelling of studied formulations at different time points are given in Fig. 3. Formulation prepared with PEO, HPMC 4,000 cPs and HPMC 15,000 cPs showed rapid swelling behavior with minimum 18% axial swelling within first 30 min of the study. This further explains rapid drug release from these formulations during *in vitro* drug release study. Formulations prepared using PEO showed maximum swelling behavior. Longer polymeric chains and quicker swelling of PEO based formulations, compared to that of HPMC (various viscosity grades), led to better interaction with glycoprotein chains of mucin and hence superior bioadhesion when compared with HPMC based formulations.

Batch Reproducibility and Stability Studies

No significant difference ($p>0.05$) was observed in the release and other quality characteristic when three different batches of each formulation were tested independently, indicating that the process of manufacturing was reliable and reproducible (data not shown). All the formulations were stable for entire duration of study when stored at accelerated (6 months) and ambient conditions (24 months) with no apparent change in physical characteristics and *in vitro* release and mucoadhesive behavior at 5% level of significance (data not shown).

Human Acceptability Studies

Acceptability of the designed delivery systems in buccal cavity is an important concern in buccal drug delivery. The percentage response of human volunteers to various parameters of questionnaire is presented in Table VI. All the formulations adhered to mucosal lining of cheek for at least 4 h indicating adequate adherence. The end of adhesion was due to dislodgement of designed formulations. The mean adhesion time of each of the selected formulations is given in Table VI. Based on these results it can be concluded that all the designed formulations were non-irritating and acceptable for human use.

In Vivo Bioavailability Studies in Rabbits

Buccal mucoadhesive controlled release matrix tablets prepared using PEO (PEO/10) were selected for *in vivo* bioavailability studies because of superior bioadhesive strength and desirable drug release profile. LER was not present in the samples taken prior to dosing. These samples served as negative control for the experiment. LER was detectable within 0.5 h of drug administration by both the routes. Drug was not detectable after 18 h when given orally.

Following oral administration of LER (10 mg) in solution form, average maximum serum concentration (C_{max}) of 148.29± 12.87 µg/L was achieved after 1.0 h (Table VII; Fig. 4). The area under the serum concentration-time curve ($AUC_{(0-\infty)}$) after oral dosing was found to be 1202.49±143.82 µg h/L with mean residence time of 6.75±0.33 h. After administration of designed formulation (PEO/10) drug levels in serum were detectable till 24 h with C_{max} of 179.99±10.64 achieved 2.0 h after dosing. The $AUC_{(0-\infty)}$ following buccal administration of LER was found to be 1,997.35±260.96 µg h/L with mean residence time of 7.78±0.99 h. The difference in C_{max} and $AUC_{(0-\infty)}$ values following oral and buccal administration was found to be statistically significant ($p<0.05$). Bioavailability of LER following buccal administration was found to be 166.10% relative to oral bioavailability. This higher relative bioavailability of LER can be attributed to reduced first pass metabolism of LER when administered via buccal route. The disadvantages of erratic oral absorption and interaction with food can also be potentially overcome by designed buccal drug delivery systems.

CONCLUSIONS

It can be concluded that the designed buccoadhesive controlled release tablets can overcome the disadvantage of poor and erratic oral bioavailability of LER associated with currently marketed formulations. This increased and predictable availability of LER from designed formulations may result in substantial dose reduction.

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