ORIGINAL ARTICLE

Formulation and evaluation of bioadhesive buccal drug delivery of repaglinide tablets

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The purpose of this research was to formulate and evaluate bioadhesive buccal tablets of repaglinide using HPMC K15M as a sustained release polymer, chitosan as a bioadhesive polymer and ethyl cellulose as an impermeable backing layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, *in vitro* drug release, *ex vivo* mucoadhesion time and *ex vivo* drug permeation. A 3^2 full factorial design was used in present study for optimization. Tablets containing HPMC K15M and chitosan in the ratio of 1:1 and lactose as a filler (F2) had the maximum percentage of *in vitro* drug release. The swelling index, friability and *in vitro* drug release was affected by type of filler as dicalcium phosphate (DCP) had good binding ability compared to lactose. The surface pH of all tablets was found to be satisfactory (between 6.26 and 7.01), close to neutral pH; hence buccal cavity irritation should not occur with these tablets. F2 batch was considered optimum based on good bioadhesive strength (17.83±0.51 gm) and maximum similarity factor (64.43). The drug release from optimum batch followed zero order kinetics with non-Fickian diffusion. Drug-excipients compatibility study showed no interaction between drug and excipients. Stability study of optimized formulation showed that tablets were stable at accelerated environment condition. Thus, buccal adhesive tablet of repaglinide could be an alternative route to bypass hepatic first pass metabolism and to improve bioavailability of repaglinide.

Key words: *Bioadhesion, buccal drug delivery, chitosan, full factorial design, repaglinide*

INTRODUCTION

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time.[1-4] The buccal route is considered as the most preferred route in case of bioadhesive drug delivery system. Drug delivery through the buccal mucosa has gained significant attention due to its convenient accessibility. The buccal mucosa offers a relatively permeable barrier for drug transport.[5] Drug delivery through the buccal mucosa has proven particularly useful and offers several advantages over other drug delivery systems including bypassing hepatic first-pass metabolism, increasing the bioavailability of drugs, improved patient compliance, excellent accessibility, unidirectional drug flux, and improved barrier permeability compared, for example, with intact skin.[6,7] Attempts have been made to formulate different buccal mucoadhesive dosage forms, including tablets,[8] gels,[9] ointments,[10] films,[11] patches [12] and disks.[13]

Repaglinide is a novel, fast-acting, oral prandial glucose regulator for the treatment of type-2 diabetes. It is the 1st member of the carbamoylmethylbenzoic acid chemical family to be used in a clinical setting, representing a new chemical class of insulin secretagogues.[14] Repaglinide is subjected to an extensive and highly variable hepatic first pass metabolism following oral administration, with a reported systemic availability of 62.5%. Although repaglinide is completely absorbed from gastrointestinal tract, it is degraded in intestine and poorly absorbed from upper intestinal tract.[15] Moreover, it is reported that it is expected to enable control of both PBG (Post-Prandial Blood Glucose) and FBG (Fasting Blood Glucose)

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for moderate and severe diabetes patients with a controlled release formulation containing a short-acting type oral blood glucose regulator (repaglinide, meglitinide, etc.).[16,17] The physicochemical properties of repaglinide, its half life of 1 hour, and its low dose(2–16 mg), make it suitable candidate for administration by the buccal route.[18]

The present study examined mucoadhesive bilayer buccal tablets of repaglinide using Hydroxy Propyl Methyl Cellulose K15M (HPMC K15M) as a sustained release polymer, Chitosan as a bioadhesive polymer, and Ethyl Cellulose (EC) as an impermeable backing layer. The buccal tablets were characterized by measuring weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, *in vitro* drug release, *ex vivo* mucoadhesion time, and *ex vivo* drug permeation.

MATERIALS AND METHODS

Materials

Repaglinide was gifted from Torrent Pharmaceutical Ltd., Ahmedabad, India. HPMC K15M and chitosan were purchased from Yarrow Chemicals (Mumbai, India). Lactose was obtained from Chemdyes Corporation (Ahmedabad, India). Microcrystallinecellulose (MCC) was purchased from Loba Chemie Pvt. Ltd (Mumbai, India). Di-Calcium Phosphate (DCP) was obtained from Finar Chemical Ltd (Ahmedabad, India). Ethyl Cellulose was purchased from SD Fine chem. Ltd (Mumbai, India).

Methods

Calculation for the dose of drug in the sustained release Tablets

The total dose of repaglinide for a sustained release formulation was calculated by following four equations[19] using available pharmacokinetic data from a design of one compartment model with simultaneous release of loading dose and a zero order release maintenance dose, as described by Robison and Eriksen.[20]

$$k_0 = D_i k_e \quad (1)$$
$$D_m = k_0 T \quad (2)$$
$$D_l = Di\text{-}k_0 T_p \quad (3)$$
$$D_t = D_l + D_m \quad (4)$$

Where, k_0 = zero order drug release; ke = $0.693/t_{1/2}$; D_i = initial dose/conventional dose; D_l = loading dose; D_m = maintenance dose; T = time for sustained action; T_p = time to reach peak plasma concentration; D_t = total dose of drug.

The conventional doses available in the market are 0.5 mg, 1 mg, and 2 mg. Hence, the conventional dose of repaglinide was taken 1.125 mg, i.e. average of three conventional doses.

Therefore the total dose of the drug is calculated using the equations.

$$k_0 = Dik_e = 1.125 \times 0.693/1 = 0.7796 \text{ mg} \quad (5)$$
$$Dm = k_0 T = 0.7796 \times 12 = 9.35 \text{ mg} \quad (6)$$
$$D_l = Di\text{-}k_0 Tp = 1.125\text{-}(0.7796 \times 1) = 0.3454 \text{ mg} \quad (7)$$
$$Dt = D_l + Dm = 0.3454 + 9.35 = 9.70 \equiv 10 \text{ mg} \quad (8)$$

Hence the matrix tablet should contain a total dose of 10 mg for 12 h. sustained release dosage form and it should release 0.3454 + 0.7796 = 1.125 (11.25%) mg in 1st hour like conventional dosage form and remaining dose (10 – 1.125 mg) in remaining 11 hours, i.e. 0.8068 (8.07%) mg per hour up to 12 h. Hence, the theoretical drug release profile can be generated using above value, which is shown in Table 1.

Preliminary screening

Optimization of bioadhesive polymer

Preliminary screening for optimization of bioadhesive polymer was carried out using five different bioadhesive polymers for selection of good bioadhesive polymer. The formulas of batch B_1 to B_5 are shown in Table 2. Tablets prepared using different bioadhesive polymers were evaluated for *ex vivo* bioadhesive strength and hardness.

Optimization of sustained release polymer

Sustained release polymer is necessary for sustained drug release for prolonged time. For optimization of sustained release polymer, different concentrations and different grades of HPMC were selected. Compositions of formulation for optimization are shown in Table 3. Formulations were evaluated for *in vitro* drug release for optimization.

Optimization using full factorial design

A 3^2 randomized full factorial design was used in present study. In this design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. Ratio of HPMC K15M to chitosan (2:1, 1:1 and 1:2) (X_1) and type of filler (lactose, MCC and DCP) (X_2) were chosen as two factors. The formulation layout for the factorial design batches (F1–F9) is shown in Table 4. Prepared tablets were evaluated for content uniformity, *ex vivo* mucoadhesion

Table 1: Theoretical drug release profile

Time (hours)	Total amount release from tablet containing 10 mg drug (mg)	%CPR
1	1.125	11.25
2	1.931	19.31
3	2.738	27.38
4	3.545	35.45
5	4.352	43.52
6	5.159	51.59
7	5.965	59.65
8	6.771	67.71
9	7.579	75.79
10	8.385	83.85
11	9.192	91.92
12	10.00	100

strength, thickness, hardness, weight variation, friability, *ex vivo* mucoadhesion time, swelling study, Surface pH, and *in vitro* drug release. *Ex vivo* permeation study was carried out for optimized batch.

Preparation of bilayer buccal tablets of repaglinide

Bilayer buccal tablets were prepared by a direct compression procedure involving two steps. Various batches were prepared by (1) varying the ratio of HPMC K15M and Chitosan (2:1, 1:1 and 1:2) and (2) changing the diluents (lactose, MCC, and DCP). The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug with HPMC K15M, chitosan, and diluents in a mortar for 15 min. The mixture (100 mg) was then compressed using 8 mm diameter die in a single stroke multistation tablet machine (Karnavati Engineering Pvt. Ltd., Ahmedabad, India). Then, core tablet was taken and put it in the center of 12 mm lower punch. The backing layer of EC was placed around and over the above tablet; the two layers were then compressed into a mucoadhesive bilayer tablet. Each tablet weighed ~200 mg with a thickness of 1.6 to 1.8 mm.

Table 2: Preliminary trial for selection of bioadhesive polymer

Ingredient	Quantity per tablet in mg				
	B1	B2	B3	B4	B5
Formulation of core tablet					
Repaglinide	10	10	10	10	10
HPMC K4M	15	15	15	15	15
Carbopol	15	-	-	-	-
Sodium Alginate	-	15	-	-	-
Sodium CMC	-	-	15	-	-
Chitosan	-	-	-	15	-
Xanthan gum	-	-	-	-	15
Lactose	60	60	60	60	60
Formulation of backing layer					
Ethyl cellulose	100	100	100	100	100
Total	200	200	200	200	200

Table 3: Compositions of formulation for optimization of sustained release polymer

Ingredient	Quantity per tablet in mg			
	S1	S2	S3	S4
Formulation of core tablet				
Repaglinide	10	10	10	10
HPMC K4M	15	20	-	-
HPMC K15M	-	-	20	-
HPMC K100M	-	-	-	20
Chitosan	15	20	20	20
Lactose	60	50	50	50
Formulation of backing layer				
Ethyl cellulose	100	100	100	100
Total weight	200	200	200	200

Determination of physicochemical parameters

Drug excipient compatibility study

Fourier transform infrared (FTIR) technique was used to study the physical and chemical interaction between drug and excipient used. FTIR spectra of pure drug, tablet containing DCP (F1 batch), tablet containing lactose (F2 batch), and tablet containing MCC (F3 batch) were recorded using KBr mixing method on FTIR instrument available at central instrument laboratory of the institute (FTIR-1700, Shimadzu, Kyoto, Japan).

Weight variation

Ten tablets were weighed individually and then collectively, average weight of the tablets was calculated.

Hardness

Hardness test was conducted for three tablets from each batch using Monsanto hardness tester and average values were calculated.

Friability

The tablets were tested for friability testing using Roche friabilator. For this test, six tablets were weighed and subjected to combined effect of abrasion and shock in the plastic chamber of friabilator revolving at 25 rpm for 4 min, and the tablets were then dusted and reweighed.

Table 4: Compositions of formulations of 3^2 full factorial design

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet (amount in mg)									
Repaglinide	10	10	10	10	10	10	10	10	10
HPMC K15M	26.67	26.67	26.67	20	20	20	13.33	13.33	13.33
Chitosan	13.33	13.33	13.33	20	20	20	26.67	26.67	26.67
Di-calcium phosphate	50	-	-	50	-	-	50	-	-
Lactose	-	50	-	-	50	-	-	50	-
Microcrystalline cellulose	-	-	50	-	-	50	-	-	50
Backing Layer									
Ethyl cellulose	100	100	100	100	100	100	100	100	100
Total weight	200	200	200	200	200	200	200	200	200

Thickness

The thicknesses of buccal tablets were determined using micrometer screw gauge. Ten individual tablets from each batch were used and the average thickness was calculated.

Content uniformity

Five tablets were selected at random and were powdered in a mortar; and amount of powder equivalent to single dose was dissolved in methanol[21] by sonication for 15 min and filtered through Whatmann filter (0.45 μm) paper. The drug content was analyzed spectrophotometrically at 281 nm using a UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

Ex vivo mucoadhesive strength

A modified balance method was used for determining the *ex vivo* mucoadhesion strength.[22] Goat buccal mucosa was used as the model substrate and phosphate buffer pH 6.8 was used as the moistening fluid. Freshly excised goat buccal mucosa was obtained from the local slaughter house used within 3 h of slaughter. The tablet was laid onto the model membrane under manual pressure of 5 min. Bioadhesive strength was measured in terms of weight in grams of water required to detach the tablet from the goat buccal mucosa. The addition of water was stopped when tablet was detached from porcine buccal mucosa. The weight of water required to detach the tablet from buccal mucosa was noted as *ex vivo* mucoadhesive strength. Mucoadhesive strength was performed in duplicate and average mucoadhesive strength was determined.

Swelling study

Buccal tablets were weighed individually; initial weight was considered as W1 and placed separately in Petri dishes containing 10 mL of phosphate buffer (pH 6.8) solution in such a way that the side of tablet, which attaches to the buccal membrane was positioned to the bottom of the Petri dishes with the backing membrane being viewable from the top. Tablets were soaked in such a way that the core tablet completely immersed in the buffer solution. At time intervals of 1 h, 6 h, and 12 h, the buccal tablets were removed from the Petri dishes using coverslips and excess surface water was removed carefully using the Whatmann filter paper. The swollen tablets were then reweighed (W2).[23,24] This experiment was performed in triplicate. The degree of swelling (water uptake) was calculated according to the following formula

$$\text{Degree of swelling} = [(W2 - W1)/W1] \times 100 \quad (9)$$

Surface pH study

The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg *et al*.[25] was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 mL of phosphate buffer (pH 6.8) for 2 h at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1 min.

Ex vivo mucoadhesion time

The *ex vivo* mucoadhesion time was examined ($n = 3$) after application of the buccal tablet on freshly cut goat buccal mucosa.[26] The fresh goat buccal mucosa was tied on the glass side, and a mucoadhesive core side of each tablet was wetted with 2 drops of phosphate buffer pH 6.8 and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 s. The glass slide was then put in the beaker, which was filled with 200 mL of the phosphate buffer pH 6.8 and kept at 37°C ± 1°C. After 2 min, a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 h. The time for detach from the goat buccal mucosa was recorded as the mucoadhesion time.

In vitro drug release

The US Pharmacopeia XXIII rotating paddle method was used to study the drug release from the bilayer tablet. The dissolution medium consisted of 250 mL of phosphate buffer pH 6.8. The experiment was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed at the bottom of the dissolution vessel. Samples (10 mL) were withdrawn at predetermined time intervals and equivalent amount was replaced with fresh medium. The samples were filtered through Whatmann filter (0.45 μm) paper and analyzed by UV spectrophotometer at 281 nm.

Ex vivo permeation of buccal tablets

The *ex vivo* buccal permeation was carried out for optimized batch of full factorial design. The permeation study of repaglinide through the goat buccal mucosa was performed using Franz diffusion cell at 37 ± 0.5°C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 mL of phosphate buffer pH 6.8. The receptor compartment (45 mL capacity) was filled with phosphate buffer pH 6.8 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. Five-mL samples were withdrawn at predetermined time intervals and analyzed for drug content by UV spectrophotometer at 281 nm.

Comparison of dissolution profiles for selection of optimum batch

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profiles. The dissolution profiles are considered

to be similar when f_2 is between 50 and 100. The dissolution profile of products were compared using a f_2 which is calculated from following formula,

$$f_2 = 50 \times \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \times 100\right\} \quad (10)$$

Where, n is the dissolution time and R_t and T_t are the reference (here this is the theoretical dissolution profile of repaglinide) and test dissolution value at time t.[27]

Kinetic modeling of dissolution data

The dissolution profile of all factorial batches were fitted to various models such as zero order, first order, Higuchi,[28] Hixon Crowell,[29] Korsemeyer and Peppas,[30] to ascertain the kinetic of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release.

Short-term stability study

To determine change in bioadhesive strength and *in vitro* release profile on storage, a short-term stability study of the optimal batch was performed at 40°C in humidity jar with 75% relative humidity (RH). Samples were withdrawn at 1-month intervals and evaluated for any change in bioadhesive strength and *in vitro* drug release pattern.

RESULTS AND DISCUSSION

Results of preliminary screening

Optimization of bioadhesive polymer

The evaluation results for different batches showed that batch B4, which contained chitosan as a bioadhesive polymer gave maximum bioadhesive strength and optimum hardness [Table 5]. Hence, chitosan was selected as a bioadhesive polymer for further study.

Optimization of sustained release polymer

From the results, it was shown that S1 and S2 batch (containing HPMC K4M) wasn't able to sustain the drug release up to 12 h. S3 batch (containing HPMC K15M) showed the complete drug release at 12 h, which was necessary for our research. S4 batch (containing HPMC K100M) sustained the drug release and gave only 63.16% drug release at 12 h. Hence, S3 batch was optimized as it gave complete drug release at 12 h. Results are shown in Table 6.

Table 5: Evaluation of preliminary batches for selection of bioadhesive polymer

Batches	Evaluation parameter	
	Bioadhesive strength (Gram force)	Hardness (kg/cm²)
B1 (Carbopol)	21.07±0.45	7.3±0.2
B2 (Na Alginate)	11.33±0.37	6.37±0.32
B3 (Na CMC)	8.5±0.26	7.23±0.21
B4 (Chitosan)	22.64±0.97	7.33±0.12
B5 (Xanthan gum)	18.72 ±2.51	8.43±0.12

All values are mean ± SD (*n* = 3)

Results of full factorial design

Drug excipient compatibility study

Drug excipient compatibility study was carried out using FTIR 1700 (Shimadzu, Kyoto, Japan). Drug–excipient interaction plays a vital role in the release of drug from formulation. The drug exhibits carbonyl peak (C = O) at 1628 cm^{-1} and hydroxyl peak (O-H) at 3305 cm^{-1}. It was observed that there were no changes in these main peaks in the IR spectra of a mixture of drug and excipient [Figures 1–4]. Hence, it was concluded that there is no interaction between drug and excipients.

Physicochemical parameters

The average weight of the tablet was found to be between

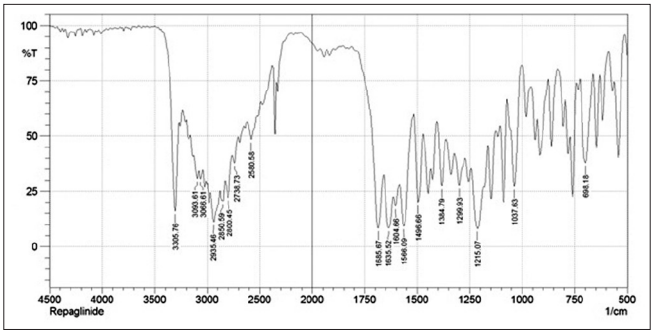

Figure 1: FTIR spectra of pure drug

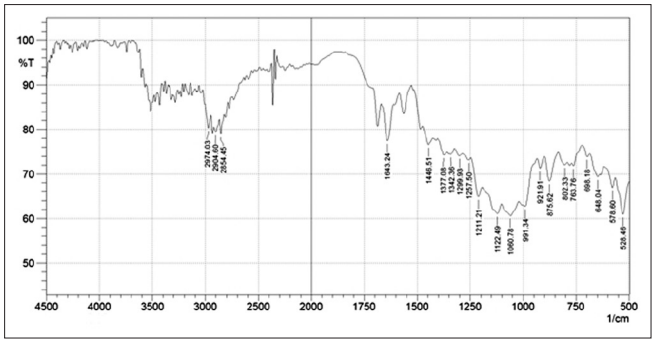

Figure 2: FTIR spectra of tablet containing DCP (F1 Batch)

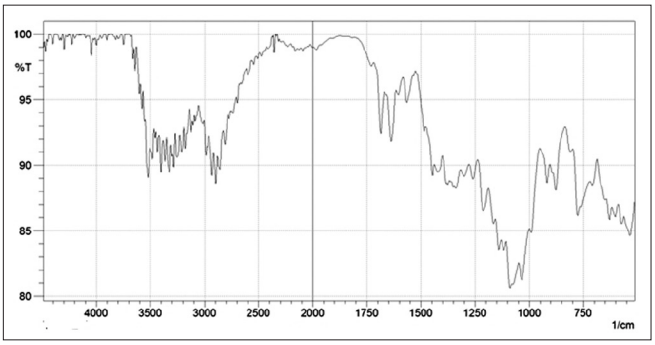

Figure 3: FTIR spectra of tablet containing lactose (F2 Batch)

200.4 to 201.8 mg. The maximum variation from average was found to be ±2.30% from all the formulations. Hardness of the tablets for all the formulations was found to be between 6.47 to 7.47 kg/cm^2 with an average of 6.99 kg/cm^2. The percentage deviation in hardness was 0.058 to 0.265.

Percentage friability for all formulations was found to be between 0.04 and 0.91 with an average of 0.48. From the friability test, it was shown that batch containing DCP (F1, F4 and F7) gave minimum percentage loss in weight whereas batch containing lactose (F2, F5 and F8) gave maximum percentage loss in weight [Table 7]. Hence, it was concluded that compressibility of DCP was maximum whereas compressibility of lactose was minimum.

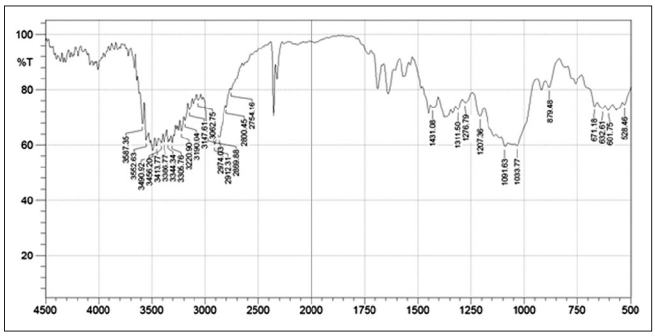

Figure 4: FTIR spectra of tablet containing MCC (F3 Batch)

Percentage drug content for all formulations was found to be between 99.39% and 101.94%. Thickness of buccal tablets of all the formulations was found to be between 1.63 and 1.89. Surface pH of all the formulations was found to be between 6.26 and 7.01, which were within the acceptable salivary pH range (5.5-7.0). It was concluded that the tablets would produce no local irritation to the mucosal surface. All these results are shown in Table 7.

Swelling index

Appropriate swelling behavior of a buccal adhesive system is essential for uniform and prolonged release of the drug and effective mucoadhesion.[31] The swelling study indicated that batch having DCP as filler gave minimum swelling, whereas batch having lactose as filler gave maximum swelling index. This finding may have been because of the good compressibility of DCP compared with lactose. The comparison of degree of swelling of all formulations was shown in Figure 5.

Table 6: Evaluation of preliminary batches for optimization of sustained release polymer

Time (Hour)	Cumulative percentage release			
	S1	S2	S3	S4
0.5	49.38±2.36	51.45±3.29	14.95±1.26	2.41±0.42
1	60.10±3.87	56.80±2.47	15.93±1.84	5.69±1.12
2	72.53±2.15	64.30±4.14	36.8±2.61	8.81±1.37
3	79.01±4.56	67.56±3.24	58.19±2.43	15.8±1.06
4	83.03±3.68	74.24±5.51	62.44±3.67	19.11±3.17
5	87.52±1.16	78.44±2.26	68.31±5.26	25.32±2.21
6	94.05±2.54	83.13±2.78	77.7±5.32	28.38±3.69
7	99.16±1.03	86.63±3.91	81.68±4.93	38.56±2.32
8	-	92.70±2.68	88.12±3.61	44.67±2.67
9	-	97.10±3.72	92.77±3.94	52.61±1.63
10	-	-	96.34±2.24	55.59±2.34
11	-	-	98.97±1.96	58.72±1.95
12	-	-	100.81±1.63	63.16±2.23

Table 7: Physicochemical properties of mucoadhesive buccal tablets of repaglinide

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm.)	% Drug content	Surface pH	Friability (%)
F1	200.4±2.30	7.30±0.17	1.81±0.012	100.71±0.99	6.32±0.015	0.04
F2	201.2±1.79	6.70±0.20	1.86±0.010	99.39±2.08	6.44±0.017	0.89
F3	201.4±1.14	7.03±0.15	1.80±0.015	101.94±0.86	6.58±0.015	0.48
F4	200.4±1.52	7.43±0.15	1.66±0.021	99.48±2.39	6.26±0.030	0.05
F5	201.0±2.12	6.57±0.20	1.77±0.015	101.65±1.56	6.70±0.015	0.88
F6	200.2±1.64	7.03±0.32	1.89±0.012	101.35±3.20	6.47±0.015	0.51
F7	201.2±1.92	7.47±0.21	1.65±0.015	99.82±3.00	6.33±0.005	0.04
F8	201.0±1.87	6.47±0.06	1.72±0.015	99.72±2.18	6.98±0.025	0.91
F9	201.8±1.30	6.90±0.27	1.63±0.015	100.10±1.88	7.01±0.035	0.49

All values are mean ± SD (n = 3)

Ex vivo mucoadhesion strength and time

The *ex vivo* mucoadhesion strength and time of the tablets was determined for all formulations using goat buccal mucosa. Tablets containing equal polymer ratio (1:1) showed higher bioadhesive strength as well as higher bioadhesion time [Table 8]. This finding is owing to optimum concentration of mucoadhesive polymer; when concentration of mucoadhesive polymer was increased or decreased compared with optimum concentration, mucoadhesive strength was decreased. At optimum concentration, mucoadhesion strength was maximum. The maximum bioadhesive strength was found in F8 batch (21.66 ± 0.79 gm) and the lowest in F9 batch (11.19 ± 2.11 gm).

In vitro drug release

In vitro drug release studies indicated that the drug release was higher in case of lactose as filler and lower in case of DCP as filler [Figure 6]. DCP has good compressibility compared with lactose. Batch F5 showed maximum drug release at 12 h, whereas batch F1 showed minimum drug release at 12 h.

Kinetic modeling of dissolution data

The dissolution profile of all factorial batches were fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsemeyer and Peppas, to ascertain the kinetic of drug release [Table 9]. For batches F1 to F6, the values of n ranged from 0.5059 to 0.8019, indicating non-Fickian release; whereas for batches F7 to F9, the values of n ranged from 0.3522 to 0.4407, indicating Fickian release.

Comparison of dissolution profiles for selection of optimum batch

Dissolution data of all batches was subjected to find f_2 similarity for selection of optimum batch. Theoretical profile of repaglinide was taken as reference. F2 batch showed maximum similarity (64.43) compared with other batches [Table 10]. Hence formulation F2 was optimized based on highest f_2 similarity (64.43), swelling index (102.86 ± 2.24 at 12 hours) and *ex vivo* mucoadhesive strength (17.83 ± 0.51 gm); it showed zero order drug release with sufficient mucoadhesion.

Table 8: *In vitro* mucoadhesive study of bilayer buccal tablets of repaglinide

Batch code	Mucoadhesive strength (gram force)	*Ex vivo* mucoadhesion time (hrs)
F1	16.25±1.08	10.67±1.15
F2	17.83±0.51	12.67±0.58
F3	18.36±1.75	14.33±1.15
F4	16.30±0.47	11.33±0.58
F5	18.44±0.45	15.00±1.00
F6	16.47±0.44	11.67±0.58
F7	14.45±1.84	8.67±0.58
F8	21.66±0.79	16.67±1.15
F9	11.19±2.11	6.33±0.58

All values are mean ± SD (n = 3)

Ex vivo permeation of buccal tablets

Formulation F2 was subjected to an *ex vivo* buccal permeation study using a franz diffusion cell [Figure 7]. The results showed drug permeation of 84.43% ± 3.68% in 12 h. The correlation between *in vitro* drug release rate and *in vitro* drug permeation across the goat buccal mucosa was found to be positive, with a correlation coefficient (R^2) of 0.988.

Short-term stability study

Stability study was carried out by storing optimized formulation at 40 ± 2°C and 75 ± 5% RH for 1 month. At the end of studies, samples were analyzed for the drug content, *in vitro* drug release and bioadhesive strength. There was not any change in morphological condition during stability study and also not any measurable change in the remaining parameter as shown in Table 11. *In vitro* drug release was 97.44 ± 2.38 % after 12 h [Figure 8]. Mucoadhesive strength was increased slightly due to hydration of polymer. Similarity factor of the batch after stability study was 64.85 comparable to initial drug release profile.

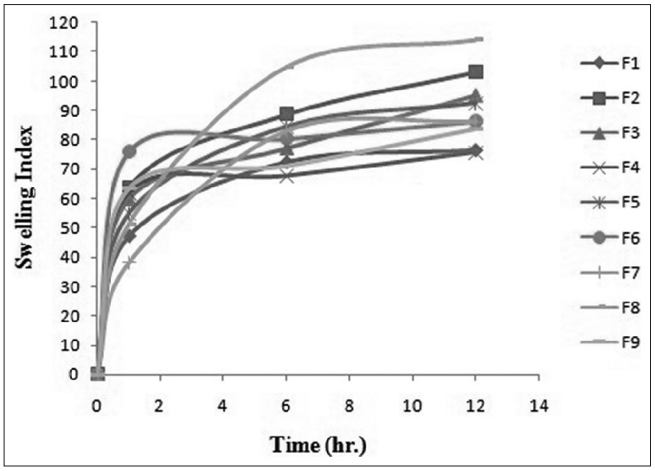

Figure 5: Plot of swelling index vs. time for all formulations

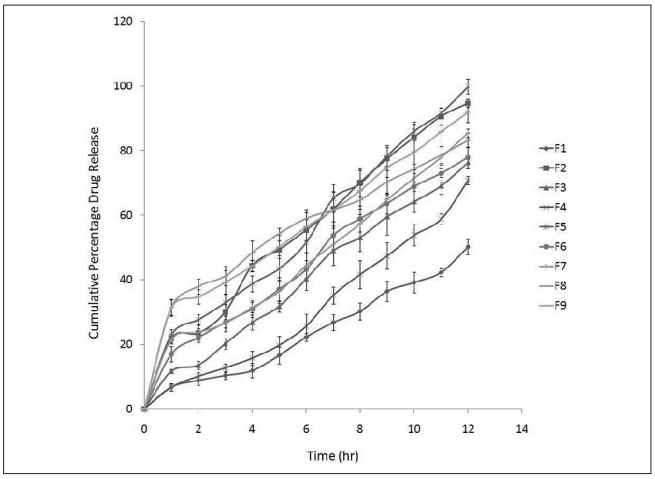

Figure 6: Plot of cumulative percentage drug release vs. time for all formulations

Table 9: Kinetic treatment of dissolution data

Model	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Zero order									
B	3.77	7.28	6.35	5.206	7.09	6.04	5.59	4.79	5.49
A	0.011	11.79	2.20	–2.180	12.33	8.977	11.62	28.15	23.67
R^2	0.9809	0.9932	0.9951	0.9798	0.9896	0.9940	0.9871	0.9933	0.9968
First order									
B	0.100	0.082	0.108	0.113	0.072	0.079	0.064	0.04	0.05
A	0.720	1.249	0.959	0.744	1.292	1.170	1.246	1.47	1.44
R^2	0.9936	0.9767	0.9933	0.9956	0.9971	0.9968	0.9951	0.9862	0.9991
Higuchi									
B	14.87	29.38	25.47	20.52	28.25	24.22	22.13	19.62	21.97
A	–13.03	–14.83	–20.67	–20.18	–12.79	–12.74	–7.88	10.02	3.97
R^2	0.9457	0.9798	0.9756	0.9445	0.9633	0.9732	0.9549	0.9943	0.9756
Hixon crowell									
B	–0.1849	–0.211	–0.2396	–0.219	–0.188	–0.191	–0.1590	–0.13	–0.13
A	2.987	2.097	2.654	2.972	2.006	2.248	2.086	1.57	1.64
R^2	0.9522	0.9773	0.9811	0.9425	0.9474	0.9738	0.9533	0.9933	0.9728
Korsemeyer and peppas									
A	–1.244	–0.7303	–1.014	–1.2276	–0.6863	–0.81	–0.7277	–0.5218	–0.5410
n	0.6921	0.5872	0.7629	0.8019	0.5059	0.5657	0.4407	0.3580	0.3522
R^2	0.9432	0.9546	0.9688	0.9724	0.9605	0.9757	0.9341	0.9854	0.9628

b= Slope, a= Intercept, R^2= Correlation coefficient, *n* = Diffusion exponent

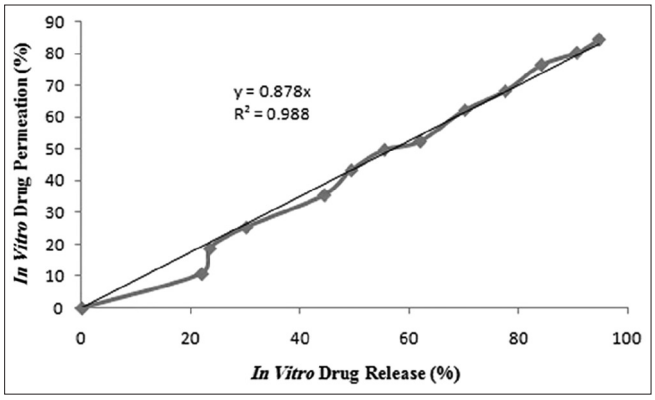

Figure 7: Correlation between *in vitro* drug release and *in vitro* drug permeation study

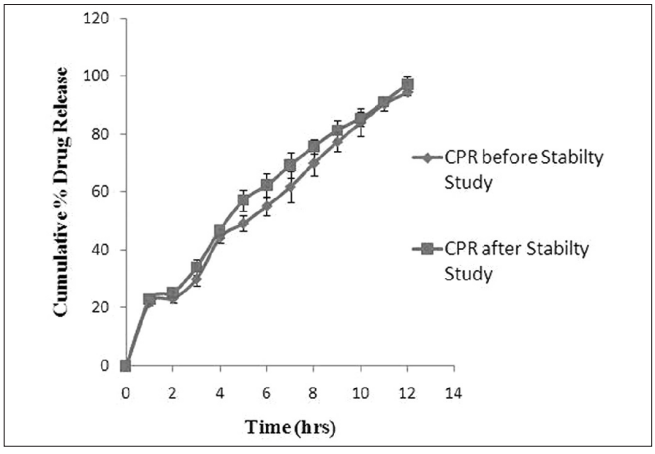

Figure 8: Comparison of drug release of optimized batch before stability study and after stability study

Table 10: f_2 similarity factor of bilayer buccal tablets of repaglinide

Batch code	f_2 Similarity factor
F1	24.92
F2	64.43
F3	43.83
F4	31.48
F5	63.01
F6	50.67
F7	51.94
F8	45.88
F9	51.07

Table 11: Evaluation of stability study of formulation F2

Batch F2	*In vitro* drug release	% Drug content	Bioadhesive strength (gram force)
Initial	94.63±1.24 % after 12 hours	99.39±2.08	17.83±0.51
After storage at 40±2°C and 75±5% RH	97.44±2.38 % after 12 hours	99.42±0.69	19.15±0.34

All values are mean ± SD (*n* = 3)

CONCLUSION

Development of bioadhesive buccal drug delivery of repaglinide tablets is one of the alternatives routes of administration to avoid first pass metabolism and provide prolonged release. In addition, these formulations reduce the need of frequent administration and enhance patient

compliance. A combination of HPMC K15M and Chitosan results in sustained release buccal drug delivery. The buccal bilayer tablet showed a mucoadhesion time of more than 12 h. Similarly, *in vitro* permeation studies showed 84.43% ± 3.68% drug release of the sustained dosage form, which can be used in once a day tablet.

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