In vitro and in vivo Evaluation of Moringa Gum As a Carrier for Buccal Drug Delivery

Bukkal Yoldan İlaç Verilmesinde bir Taşıyıcı Olarak Moringa Reçinesinin in vivo ve in vitro Koşularda İncelenmesi

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Abstract
Purpose: The objective of the study was to evaluate the naturally available Moringa gum as drug carrier and mucoadhesive component in buccal delivery and to compare the bioavailability of Propranolol Hydrochloride buccal tablet with the oral tablet in healthy human volunteers.
Material and Methods: The buccal tablets containing various concentration (Formulation1: 10, F2: 20, F3: 30 and F4: 40 mg) of Moringa gum were prepared and coated with 5% (w/v) ethyl cellulose on one face and oral tablet (F5) without polymer were formulated using a direct compression technique. The muco-adhesion of the polymer was evaluated using porcine buccal mucosa as a model tissue under simulated buccal conditions. The tablets were subjected to *in vitro* drug release studies at pH 6.8 phosphate buffer and the bioavailability study was conducted with the 16 healthy human volunteers.
Results: The forces of detachment for the tablets were 10.21, 12.12, 14.31 and 15.42 (From F1 formulation to F4 formulation, respectively). The cumulative percentage release of propranolol in pH 6.8 phosphate buffer were found to be 97.l3, 98.12 and 100.1 (F3, F4 and F5, respectively). The bio-availability of buccal tablet (F2, F3 and F4) and oral (F5) tablet was found to be 2491.69, 4292.17, 4244.9 and 2196 ng.hr/ml., respectively.
Conclusion: The study indicates that the Moringa gum in the concentrations of 30 (F3) and 40 mg (F4) not only gives higher bioavailability but also have sufficient mucoadhesive property for clinical application.

Keywords : **Buccal Administration; Drug Delivery Systems; Moringa Oleifera; Propranolol.**

Özet
Amaç: Sunulan çalışmanın amacı, bukkal yoldan ilaç verilmesinde doğada hazır olarak bulunan Moringa reçinesini ilaç taşıyıcı ve mukoadeziv bileşen olarak değerlendirmek ve sağlıklı gönüllülerde propranolol hidrokloridin bukkal tabletlerinin biyo-yararlanımını oral tabletler ile karşılaştırmaktır.
Gereç ve Yöntem: Değişik derişimlerde (Formulasyon1: 10; F2: 20; F3: 30 ve F4: 40 mg) Moringa reçinesi içeren bukkal tabletler hazırlandı ve bir yüzleri %5 (a/h) etil sellüloz ile kaplandı; polimersiz oral tablet (F5) doğrudan baskı tekniği ile hazırlandı. Polimerin mukoadezyonu, bukkal koşullara benzerlik gösteren bir model doku olarak, domuz bukkal mukozası kullanılarak değerlendirildi. Tabletler 6.8 pH fosfat tamponu ortamında *in vitro* ilaç salınımı çalışmalarına maruz bırakıldı ve biyo-yararlanım çalışmaları 16 sağlıklı gönüllü üzerinde yapıldı.
Bulgular: Tabletler için ayırma kuvveti 10,21, 12,12, 14,31 ve 15,42 (sırasıyla F1 formülasyonundan F5 formülasyonuna) olarak bulundu. 6,8 pH fosfat tamponunda propranolol'ün birikimli yüzde salımı 97,13, 98,12 ve 100,1 (sırasıyla F3, F4 ve F5) olarak bulundu. Bukkal tabletin (F2, F3 ve F4)) ve oral tabletin (F5) biyo-yararlanımı sırasıyla 2491,69, 4292,17, 4244,9 ve 2196 ng.hr/ml. olarak bulundu.
Sonuç: Çalışma bulguları 30 (F3) ve 40 mg (F4) Moringa reçinesi içeren tabletlerin sadece yüksek biyo-yararlanım göstermekle kalmadığını aynı zamanda klinik uygulamalar için yeterli bir mukoadeziv özelliğe de sahip olduğunu göstermektedir.

Anahtar Kelimeler: **Uygulama, Bukkal; İlaç Verme Sistemleri; Moringa Oleifera; Propranolol.**

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Introduction

In recent years, there has been increasing interest on the use of bioadhesive polymers to control the delivery of biologically active agents systematically or locally (1). Buccal bioadhesive system appears to be attractive because it avoids significant limitations of traditional routes of drug administration such as poor absorption, enzymatic degradation and first – pass metabolism. A variety of drug substance has been administered by the buccal route. Examples include peptides like TRH (thyrotropin – releasing hormone), calcitonin (2), buserelin (3) and oxytocin (4); analgesics such as morphine (5) and vasodilators such as nitroglycerin (6). Oral mucosal dosage form has been investigated for the systemic administration of insulin (7) and for the local delivery of lidocaine (8). Buccal delivery necessitates the use of mucoadhesive polymers as these dosage forms should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period of time. Examples of mucoadhesive polymers include sodium carboxy methylcellulose, carbopol 934, hydroxyl propyl cellulose, hydroxyl porpyl methylcellulose, acacia, gelatin etc.

Moringa gum is a natural polymer derived from bark of Moringa oleifera (Family: Moringaceae). The root yields an essential oil, which is very pungent and has a very offensive order. The bark contains a white crystalline alkaloid, two resins, an organic acid, mucilage and ash. The moringa gum contains about galactose 41.5%, arabinose 26.9%, xylose 25.9%, rhamnose 5.6% and trace amount of uronic acid (9).

Propranolol hydrochloride (PL) was selected as a drug for preparing buccal tablet (F1 to F4) and oral tablet (F5), oral dose starts with 10 mg BD to 160 mg QID (average 40 to 160 mg/day), i.v. – 2 to 5 mg injected over 10 mins (10).

The present investigation was aimed at using the inexpensive, naturally and abundantly available moringa gum as a mucoadhesive component in buccal tablets and to quantitate the plasma concentrations of propranolol hydrochloride following administration of mucoadhesvie buccal tablet and oral tablet in human volunteers and subsequently estimate the bioavailability. In addition the bioadhesive strength was reflected by the force of detachment of these buccal tablets was quantitated by in vitro study using a $TA.XT_2$ (Stable Micro System, Haslemere, Surrey, U.K.) texture analyzer equipment (11) porcine buccal mucosa (12) as a model tissue under simulated buccal conditions. The overall goal associated with the present study was not to determine that a conventional drug substance could be administered via the buccal route but to demonstrate the utility of a new, heretofore untested natural polymer to serve as a mucoadhesive tablet excipient.

Materials and Methods

Propranolol hydrochloride was obtained from Unichem Laboratories Ltd. Mumbai, India. Moringa gum was obtained from Archana Chemicals, Coimbatore, India. Microcrystalline cellulose and Ethyl cellulose was obtained from Loba Chemie Pvt. Ltd., India. Magnesium stearate was obtained from SD Fine Chem. Ltd. Mumbai. India. The bioavailability study was conducted with 16 healthy human volunteers and the purpose of the study was fully explained and each volunteer had given his written consent and was approved by the ethical committee of the institution.

Preparation of bilayered buccal tablets (13)
Preparation of mucoadhesive layer. The mucoadhesive layer was prepared by using the drug and natural polymers. The composition of the different formulations was represented in Table I. The various components of each formula were weighed, mixed and passed through mesh (250 micrometer) to ensure complete mixing. The average weight of about 150 mg were separately weighed and compressed using a 13 mm diameter of a die on an infrared hydraulic pellet press (Kimaya Engineers, India) using a force of 8 tons for 60 seconds. The prepared adhesive tablets were 13.32 mm in diameter and 1mm thickness (14, 15).

Table I. Composition of mucoadhesive buccal tablet.

Formulation	Composition (mg)				
	Propranolol HCl	Moringa gum	MCC	Magnesium stearate	Total
F1	10	10	129	1	150
F2	10	20	119	1	150
F3	10	30	109	1	150
F4	10	40	99	1	150

MCC: Micro crystalline cellulose

Formation of backing layer to the mucoadhesive layer The backing layer was made up of ethyl cellulose. The solution was prepared by dissolving 5% w/v of ethyl cellulose in chloroform. The prepared solution was sprayed on to one surface of the mucoadhesive layer leaving the other side free and both sides of the tablets coated with the ethyl cellulose layer solutions. Then it was air dried at room temperature. The double layered structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa. It avoids loss of drug due to wash out of saliva and the swelling profile of the buccal tablet can be changed dramatically by the amount of backing material and those changes could alter drug release profile. The resulting bilayered tablets were 13.32 mm in diameter and 1.4 mm in thickness (16).

Evaluation of Tablets. Ten tablets from each batch were evaluated for uniformity of weight and medicament content. Six tablets from each batch were examined for friability using a Roche- type friabilator. (Tropical Equipment Pvt. Ltd., Mumbai, India) and hardness using a Monsanto-type hardness tester (Camp bell, Mumbai, India).

Swelling Study. The swelling index of the tablets was evaluated for six tablets of each formulation. These were weighted and placed separately in a pre-weighed basket made of stainless steel mesh. The total weight was recorded (W_1). This basket was placed in a plastic vessel containing 4 ml of demineralized water, and placed in an incubator at 37°±5°C. At various time intervals 0.5, 1, 2, 3 and 4 h, excess water was carefully removed, and the swollen tablets were weighed (W_2). The swelling index was determined from the formula: Swelling index = (W_2 – W_1) / W_1 (17).

Surface pH of the tablet. The surface pH of the tablet was determined to investigate the effect of pH on the bioadhesion and possible side effect of the tablet *in vivo*. This was determined by allowing the tablet to swell in 1.0 ml. of demineralized water (pH 6.3 ± 0.06) for 2 hours. A combined glass pH electrode was brought into contact of the swollen tablet and pH was measured after 1 min. equilibration (18).

In vitro **bioadhesion study** (19). Satisfactory bioadhesion is essential for the successful application of a buccal bioadhesive drug delivery system. It implied the strength of attachment of the dosage form to the biological tissue. Several techniques for *in vitro* determination of bioadhesion have been reported, which included tensile testing (20), shear stress testing (21), adhesion weight method (22), fluorescent probe method (23), flow channel techniques (24), and colloidal gold staining method (25).

In vitro **drug release studies**. Release of propranolol HCl from the buccal tablets was studied in phosphate buffer (250ml.) of pH 6.8(26,27) using an USP XXII/XXII dissolution rate test apparatus, with a paddle rotating at a rate of 75 rpm and at 37°±0.5°C. A specially designed glass cylinder closed at one end and opened at other end was placed inside the dissolution apparatus and it allows the tablets to dissolve from the fixed place without any movement (since the tablet should release the drug from a fixed area in the buccal region). Samples were withdrawn through a filter (0.45m) at different time interval and were assayed at 290 nm for propranolol hydrochloride using Jasco V 530 1400 UV visible double beam spectrophotometer. The drug release experiments were conducted for concurrent results (12).

Drug Release Kinetics. To examine the release mechanism of propranolol HCl from the prepared bio-adhesive tablets, the results were analyzed according to the following equation.

$$\frac{Mt}{M\alpha} = Kt^n$$

Where $Mt/M\alpha$ is the fractional drug released at time t, K is the kinetic constant incorporating structural and geometrical characteristics of drug / polymer system (device) and n is the diffusional exponent that characterizes the mechanism of drug release. For non-Fickian release, the n value falls between 0.5 and 1.0 ($0.5<n<1.0$), whereas in the case of Fickian diffusion, n = 0.5, for zero order release (case II transport) n = 1 and for supercase II transport, n>1. The values of n as estimated by linear regression of log $Mt/ M\infty$ vs. log (t) of different formulations (28).

In vivo **bio-availability study in healthy human volunteers Protocol.** Each study was carried out in 16 healthy male volunteers of 20-23 years of age and 55-70 kg weight was selected. A complete crossover design is employed in which each subject receives the test product and the reference product. Their liver and kidney functions were assessed to be normal by clinical and standard biochemical investigation. None of the subjects used alcohol or tobacco or had not taken any medication for a

week prior to study. Volunteers were fasted overnight and zero hour blood samples were collected early in the morning from each volunteer. For oral administration one tablet containing the drug (10 mg propranolol HCl) was administered at 8 hours along with 200 ml of water. The mouth was rinsed with an additional 100 ml of water that was also swallowed. Food was withheld for a period of 2 hours. The samples of blood were collected at various time intervals. Blood samples obtained were immediately centrifuged and the plasma was separated and stored at -20°C for analysis. For buccal administration, buccal tablet was placed in the buccal cavity, while the subjects were in a sitting position. Samples of blood (5ml) were collected at various time intervals (1, 2, 3, 4, 5, 6, 8 and 9 hr). Blood samples obtained were immediately centrifuged and the plasma was separated and stored at -20°C until analysis.

Estimation of propranolol HCl in plasma. The frozen samples were thawed at room temperature and 1 ml was pipetted into a clean borosilicate, graduated centrifuge tube. A 6 ml of methanol was added and vortexed for 1 min and then centrifuged at 5000 rpm for 15 minutes. One ml of the supernatant was then diluted with 1.0 ml. of distilled deionized water. The fluorescence of the samples was observed at λ_{emi} 340 nm and λ_{exi} 317 nm. The plasma concentration of the drug was calculated from standard plot (30).

Data analysis. Data was generated by assuming first order absorption and one compartment model with first order elimination. Maximum plasma concentration (C_{max}), time required to reach maximum concentration (T_{max}), elimination rate constant (K_{el}), biological half life ($t_{½}$), area under the plasma concentration time curve from 0-t hrs (AUC_{0-t}) or from 0-α hrs ($AUC_{0-\alpha}$), area under first moment curve from 0-t hrs (AUMC0-t) or from 0-α hrs (AUC0-α) and mean residence time (MRT) were determined from the data of drug concentration in plasma following buccal administration of 10 mg propranolol prepared with different concentrations of moringa gum (31).

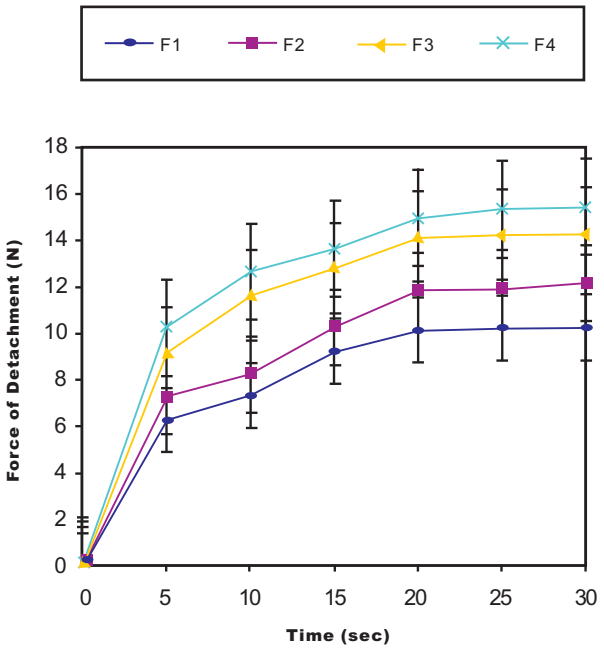
Statistical Analysis. The results obtained for *in vivo* studies were subjected to statistical analysis using a computer program Instat (Graph Pad) for one way analysis of variance ($p<0.01$) followed by Dunnett's test.

Results

Evaluation of tablets. Tablet hardness varied between 4.4 and 5.0 kg/cm^2 and friability ranged between 0.62 and 0.74%. Tablet weight varied between 148.4 and 150.6 mg and the assay content of propranolol hydrochloride varied between 98.4 and 99.2%.

Bioadhesion study. A profile showing the mean values of the force of detachment of propranolol HCl buccal tablets following their application to excised pigs buccal membrane is shown in Figure 1.

Figure 1. The force of detachment from pig buccal membrane for directly compressed buccal tablets containing 10 (F1), 20 (F2), 30 (F3) and 40 (F4) mg of Moringa gum. All data points represent the mean value ± standart deviation of three experiments.



Swelling study. The swelling index for the various formulations is shown in Table II. These profiles indicate the uptake of water into the tablet matrix producing an increase in weight.

Table II. Index of swelling in water of the prepared buccal tablets containing 10 (F1), 20 (F2), 30 (F3) and 40mg (F4) of Moringa gum.

Formulation	Swelling index				
	0.5 Hr	I Hr	2 Hr	3 Hr	4 Hr
Fl	0.261±0.04	0.568±0.07	0.691±0.04	0.420±0.01	0.316±0.02
F2	0.346±0.01	0.671±0.08	0.796±0.01	0.821±0.02	0.862±0.03
F3	0.391±0.03	0.596±0.01	0.821±0.03	0.861±0.04	0.881±0.02
F4	0.486±0.04	0.712±0.04	0.861±0.04	0.910±0.03	0.926±0.02

Surface pH. An acidic or alkaline pH may cause irritation to buccal mucosa. The surface pH of the tablets was determined in order to investigate the possibility of any side effects, in vivo (shown in Table III).

Table III. Surface pH of the buccal tablets containing 10, 20, 30 and 40 mg of moringa gum

Formulation	Surface pH
F1	6.25±0.01
F2	6.70±0.04
F3	6.99±0.06
F4	6.28±0.14

Drug release characteristics. The drug release profiles from the prepared buccal propranolol HCl tablets containing 10, 20, 30, and 40 mg of moringa gum are shown in Figure 2. Propranolol was more rapidly released from F1 when compared with F2, F3 and F4. However increasing concentration of moringa gum decreased the release of propranolol. Some fitting parameters of release data are shown in Table IV.

Figure 2. Cumulative mean (± S.D.) percentage release of propranollol hydrochloride from directly compressed buccal tablets containing 10 (F1), 20 (F2), 30 (F3) and 40 (F4) mg of Moringa gum and oral tablets (F5) in phosphate buffer pH: 6.8.

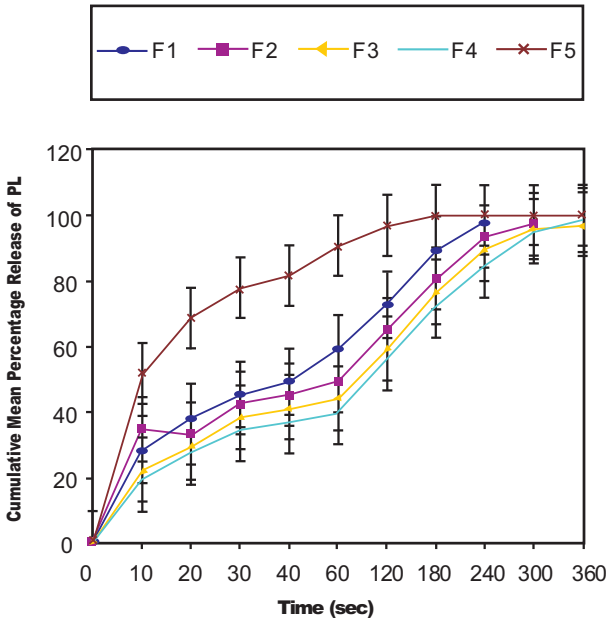


Table IV. Linear correlation coefficient (r), determination coefficient (r^2), kinetic release constants (K), and diffusion exponents (n) after fitting the release data to the simple power law (Log Mt / M∞ Vs Log t).

Formulation	r	r^2	$K(h^{-n})$	N
F1	0.999	0.999	2.388	0.367
F2	0.997	0.998	2.083	0.571
F3	0.996	0.998	1.789	0.536
F4	0.990	0.998	1.535	0.517

$T_{50\%}$ and $T_{90\%}$ release of propranolol hydrochloride. The time for 50% ($T_{50\%}$) and 90% ($T_{90\%}$) release of propranolol from the prepared buccal tablets were estimated by linear regression of log (Mt/Mα) vs. log (t) of different formulations are shown in Table V.

Table V. Time (h) for 50% and 90% propranolol HCl release from the prepared buccal tablets containing moringa gum.

Formulation code	$T_{50\%}$	$T_{90\%}$
F1	0.7 5	3.24
F2	1.15	3.44
F3	1.42	4.15
F4	1.38	4.30

***In vivo* bioavailability study.** The mean plasma profiles and pharmacokinetic parameters of propranolol form the prepared buccal tablets in comparison with the formulated oral tablets are shown in Figure 3 and Table VI, and statistics in Table VII.

Table VI. Pharmacokinetic parameters of propanolol hydrochloride directly compressed buccal tablets obtained from in vivo studies carried out in healthy human volunteers.

Parameters	F2 20 mg Moringa Gum	F3 30 mg Moringa Gum	F4 40 mg Moringa Gum	F5 Oral tablet
C_{max} (ng/ml)	612.62±64	560.82±10	550.84±28	473.74±2.4
T_{max} (h)	1±0.0	2±0.0	2±0.0	2±0.0
K_{el} (h)	0.2951±0.01	0.0675±0.01	0.079±0.04	0.293±0.013
$T_{½}$ (h)	2.34±0.61	10.26±1.61	8.71±0.56	2.36±0.40
AUC_{0-t} (ng. h/ ml)	2014.5±210	2890.1±220	2920.3 ±215	1647.73 ± 96
$AUC_{0-\alpha}$ (ng.h/ml)	2491.69±240	4292.17±29	4244.9 ±310	2196 ± 8.88
$AUMC_{0-t}$ ($ng.h^2/ml$)	8837.58±340	15313.3±41	19799±512	4156.4±61
MRT	5.45±0.21	12.38±0.36	12.33±0.34	2.95 ± 0.14

C_{max}:maximum plasma concentration; T_{max}:time required to reach maximum concentration; K_{el}:elimination rate constant; $t_{½}$:biological half life, AUC_{0-t} or $AUC_{0-\alpha}$:area under the plasma concentration time curve from 0-t hrs or 0-α hrs; $AUMC_{0-t}$:area under first moment curve from 0-t hrs MRT:mean residence time.

Figure 3. Plasma profiles of Propranolol hydrochloride in healthy human volunteers from directly compressed buccal tablets containing 20 (F2), 30 (F3) and 40 (F4) mg of Moringa gum and oral tablet (F5).

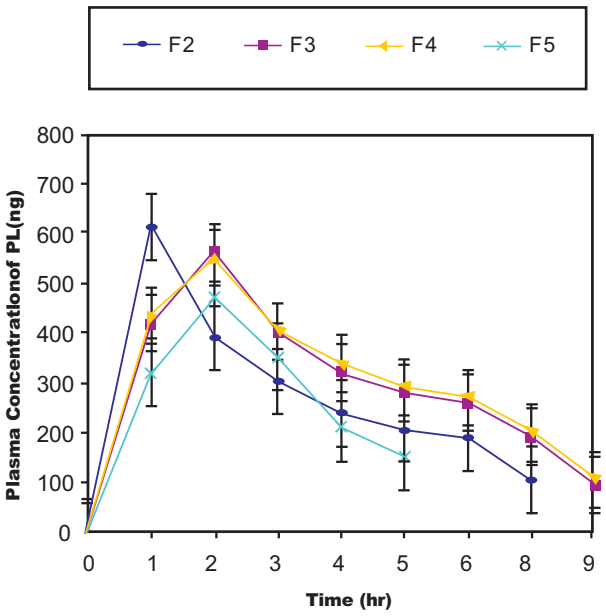


Table VII. Instat (Graph Pad) one- way analysis of variance of the in vivo characteristics of buccal tablets (F2, F3, and F4) contain moringa gum and oral tablets (F5). *P< 0.01 vs oral tablets.

Formulation	Pharmacokinetic parameter(mean ± SEM)		
	N	C_{max}	AUC $_{O-t*}$
F2	16	612.62 ± 2.10*	2014.5 ±49.50*
F3	16	560.82 ± 6.56*	2890.1 ± 52.56*
F4	16	550.84 ± 2.75*	2820.3 ± 49.91*
F5	16	473.74 ± 13.74	1647.73 ± 21.40

Discussion

Evaluation of tablets. The microcrystalline cellulose is added in the formulation as a direct compression adjuvant, since the moringa gum alone do not produce sufficient hardness. Thus all the parameters of the compressed tablets were practically within control.

Bioadhesion study. It can be noted that the mean values of the force of detachment increased with time and reached a plateau at later time points. The mean values of the force of detachment were significantly greater at each time point for tablet containing 10, 20, 30 and 40 mg of Moringa gum. In the present study, the amount of Moringa gum incorporated into the buccal tablets was observed to be a critical factor in defining the resulting bioadhesive strength. The bioadhesive bond strength increases with increase in moringa gum.

Swelling study. The Moringa gum formulations take up water over the first 1 hr, the rate depending on the concentration of the polymer present (lower concentrations swell more rapidly). Higher moringa gum polymer concentrations showed slower initial water uptake, but take longer to become fully hydrated. After one hour the formulation F1 containing 10 mg Moringa gum polymer displays loss of weight due to tablet disintegration. The formulation F2, F3 and F4 containing 20 mg, 30 mg and 40 mg Moringa gum continue to swell over the 4 hour test with the degree of swelling being dependent on the Moringa gum concentration, higher concentration display a greater hydration capacity. Formulation F2, F3 and F4 which contained higher amount of Moringa gum were found to observe more than the formulation F1, exhibited n value characteristic of non-Fickian release mechanism.

Surface pH. The surface pH of all the formulations was found to be within 1.5 units of the neutral pH and hence, these formulations would not produce cause any irritation in the buccal cavity.

Drug release characteristics. Propranolol was more rapidly released from F1 when compared with F2, F3 and F4. However increasing concentration of moringa gum decreased the release of propranolol.

Data analysis. The data obtained from dissolution kinetic studies were analyzed using PCP Disso V2.08 software. Dissolution profiles for Moringa gum in Figure 2 demonstrate the rapid release of propranolol from the 10 mg, Moringa gum formulations as a result of tablet erosion and disintegration. Formulation F2, F3 and F4 containing 20, 30 and 40 mg Moringa gum demonstrate slower propranolol hydrochloride release compared with formulation F1 is due to the combination of swelling and erosion in the matrix.

The obtained value for formulation F2, F3 and F4 of the diffusion release exponent (n) was 0.571, 0.535 and 0.517 respectively. This indicate the non-Fickian release kinetics, involving a combination of both diffusion and chain relaxation mechanism, while the other formulation F1 releases more than 50% of the drug within one hour. So formulation F1 cannot follow any of the release characteristics. The kinetic release constant, K decreases with an increase in the amount of polymer (shown in table 4). This may be attributed to the fact that with an increase in polymer concentration, the viscosity of the gel layer around the tablet tends to limit further the release of active ingredient.

$T_{50\%}$ and $T_{90\%}$ release of propranolol hydrochloride. For F1, F2, F3 and F4 the $T_{50\%}$ values were 0.75, 1.15, 1.42 and 1.38 hours respectively. These results clearly indicate increasing the half life ($T_{50\%}$) of propranolol release from the prepared tablets by increasing the concentration of moringa gum.

***In vivo* bio-availability study.** The plasma profiles exhibited a higher C_{max} with a faster decline in the plasma concentrations for the formulated buccal tablet F2 but exhibited a comparative slow release for buccal tablets, F3 and F4.

It has been observed that, by increasing the Moringa gum content C_{max} was decreased and T_{max} was increased (Table 6). This could be attributed to the slower in vitro release of the drug by increasing the Moringa gum concentration.

For F2, F3 and F4 the mean C_{max} values were 612.62 ± 64, 560.82 ± 10 and 550.84 ± 28 and the mean T_{max} values were 1 ± 0.0, 2 ± 0.0 and 2 ± 0.0 respectively . The higher the C_{max} and less T_{max} value for formulation F2 is due to the faster release of the drug from the polymer. The area under the curve (AUC) for the various formulations F2, F3 and F4 were found to be 2014.5 ± 210, 2890.1 ± 220 and 2920.3 ± 215 respectively. The higher AUC_{o-t} values or the prepared formulations F3 and F4 is due to the slow release of the drug by the polymer. All the formulated buccal tablets showed higher AUC than the formulated oral tablets. This could be attributed to the avoidance of first pass metabolism by the buccal dosage form. The mean residence time (MRT) for the various formulations increased from 5.45 ± 0.21 h to 12.33 ± 0.34 on increasing the concentration of the polymer.

Table VII presents the statistical analysis of the obtained pharmacokineitc parameters C_{max} and AUC_{0-t} were significantly ($P<0.01$) affected ($p<0.01$) by the type and composition of the prepared buccal tablets, which could be attributed to the difference in the *in vitro* release of the drug.

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