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RESEARCH ARTICLE

Computer Aided Formulation and Characterization of Propranolol Hcl Buccal Tablet Using Polymeric Blend

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Abstract: The current study was aimed to formulate a continuous release mucoadhesive buccal tablet containing propranolol HCl. The type and quantities of polymers as well as method of compression were set in a preliminary study (F1-F13). Direct compression method was employed in the main study (F14-F24) using Carbopol® 934P (CP), ethylcellulose (EC), sodium alginate (SA), hydroxypropyl methylcellulose (HPMC k4M) and carboxymethylcellulose (CMC) as mucoadhesive polymers and were tested for physicochemical tests *i.e.* swellability, surface pH, mucoadhesive time, mucoadhesive strength, *in vitro* release *etc*. Results obtained from the study were optimized using NeuralPower® 3.1, an artificial intelligence approach. Against the desirability of physico-chemical parameters, the software optimized the ingredients as HPMC (150mg), CMC (25mg), CP (20mg) and EC (20mg). Outcome revealed that HPMC primarily contributed to the physicochemical properties of mucoadhesive formulation. To compare prediction, optimized ingredients were formulated (F25) and tested. The swellability index of confirmation formulation (F25) was 102% at 6 h. As predicted, similar release pattern was of F25 was obtained as 26% (0.5h), 34% (1h), 40% (2h), 45% (3h), 50% (4h), 62% (5h), 76% (6h), 85% (7h) and 97% (8h) respectively. For release kinetics, DD solver® suggested the release of the drug to be non-Fickian.

Keywords: Mucoadhesive buccal tablet, Optimization, propranolol buccal tablet, HPMC, Cellulose.

1. INTRODUCTION

The oral route of drug administration is preferred over other routes because of diverse benefits [1]. The harsh environment to which an oral delivery system is exposed to after administration is a major drawback for drug delivery system *e.g.* acidity, enzymatic action *etc*. These drawbacks are the extreme pH variations, gastrointestinal enzymes and others [2 - 4]. Such effects can be avoided by using sublingual or buccal route [5]. Buccal cavity presents a milder environment for drug, devoid of the acid hydrolysis and hepatic first pass effect [6] improved drug delivery and bioavailability [7]. Moreover, it has been reported to improve drug delivery through buccal route and dosage form can be removed mechanically by hand in case of toxicity. The ideal polymeric combination provides both excellent release and better mucoadhesion with easy processing and lower cost [8].

Propranolol HCl, a non-selective therapeutic beta blocker and possesses beneficial effects in hypertension [9], angina [10], cardiomyopathy, cardiac arrhythmia [11], anxiety [12], hyperthyroidism [13], myocardial infarction [14], migraine prophylaxis [15], anti-angiogenesis [16] *etc*. The normal route of drug delivery is oral route. The drug has to undergo severe first pass metabolism effect as well as bioavailability range between 15 to 23% [17, 18] and relatively short half life *i.e.* 3-5 hours [21]. It is untoward the therapy goals as a continuous effective concentration is mandatory

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at the receptor site. The drug is a suitable contender to be delivered through buccal route as buccal route offers relative availability into direct system absorption bypassing first pass effect.

The aim of the current research was to deliver a continuous release of propranolol HCl as mucoadhesive buccal tablet. For this, mucoadhesive buccal tablet was formulated using mucoadhesive polymers *i.e.* CMC, EC, HPMC and CP. All such polymers have been extensively studied and showed good mucoadhesion, swellability and effect on drug releasing properties in the present study [19, 20]. The current work was carried out to formulate and evaluate the mucoadhesive buccal tablet in terms of physicochemical properties so as to release propranolol HCl in a continuous manner.

2. MATERIALS AND METHODS

2.1. Materials

Propranolol HCl was received as a gift from Munawar Pharmaceuticals Pvt. Limited Lahore (Pakistan). Carbopol® 934P, CMC high viscosity grade 500-2500 mPa and EC-100 were purchased from Glow Scientific Traders, Lahore.

2.2. Methods

The study was completed in three stages, preliminary, main study and confirmation study. The preliminary study was undertaken to select the method of preparation and an estimation of polymers for the delivery of the drug. In the main study, the selected factors were changed within some range of mucoadhesive ingredients in each formulation employing computer-aided approach, artificial neural network on different formula to find the optimized factors for quality attributes for propranolol buccal mucoadhesive tablet formulation. The dose of propranolol HCl was kept fixed throughout the study. The weight of the tablet was kept at 500 mg in each formulation except for preliminary study. All formulations in the study were punched by single punch automatic machine by applying a force of 2 tons for 20 seconds.

2.3. Preliminary Study

The formulation F1 was prepared using the wet granulation method while all others were punched by the direct compression method. The composition of propranolol HCl was 40 mg/tablet. The weight for each tablet designed in preliminary study was 400 mg as depicted in Table **1**.

Table 1. Composition and amount of ingredients used in preliminary study.

Ingredients (mg)	Formulations Codes												
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
Propranolol HCl	40	40	40	40	40	40	40	40	40	40	40	40	40
CP	100	6	4	10	16	4	12	14	16	18	16	20	60
CMC	100	20	20	40	80	-	-	-	-	-	-	-	-
EC	-	-	-	-	-	12	40	30	20	10	30	20	60
Mg stearate	10	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	125	-	-	-	-	-	-	-	-	-	-	-	
Sucrose	25	25	25	25	25	25	25	25	25	25	25	25	25
Mannitol	-	304	306	280	234	314	278	286	294	302	284	0	210

2.4. Evaluation Buccal Tablets in the Preliminary Study (F1-F14)

2.4.1. Physical Evaluation

About 400mg per tablet was compressed to a thickness of about 3 mm with a 12 mm diameter. Compressed tablets were tested for physical evaluation.

2.4.1.1. Surface pH

Surface pH of the tablet was examined by compact Inolab pH/ cond 720 (WTW). The tablets were kept in contact with distilled water for 2 h. and pH was observed by bringing the electrode in contact with the surface of tablet [22]. The reading was taken when the pH of the system was stable. The procedure was repeated for different designated formulations.

2.4.1.2. Friability Test

Friability test on different formulations was performed using the Roche friabilitor according to USP [23]. Results were expressed as the percentage loss as shown by Equation 1.

$$\text{Friability (\%)} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100 \quad \textbf{(1)}$$

2.4.1.3. Mucoadhesive Time

A set up similar to Syed *et al.* [24] was developed for the measurement of mucoadhesion time. For this purpose, pH of the testing solution was adjusted to pH 6.8 by Compact Inolab pH/ cond 720 (WTW). One face of the tablet was moistened with 50 µL phosphate buffer (pH 6.8) and forced gently against rabbit's buccal mucosa which was stuck on the surface of the flat glass piece for 20 seconds. It was then positioned in a beaker containing 800 ml of buffer at 45^{o} horizontally and stirred magnetically at 150 rpm (maintained at 37^{o}C). The time of detachment of tablet was considered as *in vitro* mucoadhesive time [25].

2.5. Main study (F14-F24)

Based on the preliminary study, composition of ingredients and method of tableting for the main study was decided. The composition of formulation, F3 (Table **1**) was taken as formulation which could be manipulated further for the main study. The reason for the selection of F3 was its meetings of maximum specifications for a buccal dosage form. The formulations in preliminary study released the drug much earlier than the desired time due to which HPMC was added in the recipe. Since HPMC retards the release of the drug and has good mucoadhesion [26]. It has been extensively used in the literature [26]. For that reason, it was added in the formulations in the main study (F14-F24). In the main study, the amounts of HPMC, CP, CMC, Na-alginate and EC had been changed to study its effect on formulation. A further aim of study was to find the optimized levels of the above factors to produce an optimized formulation. For this purpose, 11 different formulations (F14- F24) were prepared in the main study (Table **2**).

Table 2. Amount of ingredients used in the main study (F14-F24).

Ingredients (mg)	Formulation Code										
	F14	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**
Propranolol HCl	40	40	40	40	40	40	40	40	40	40	40
CP	5	5	20	15	20	20	20	20	20	20	20
CMC	15	15	5	-	25	15	15	15	25	25	25
HPMC	-	-	-	-	-	-	-	-	50	100	150
EC	-	-	-	40	25	50	100	25	25	25	25
SA	-	-	-	-	-	-	-	15	-	-	-
Sucrose	25	25	25	25	25	25	25	25	25	25	25
Mg stearate	5	5	5	5	5	5	5	5	5	5	5
Lactose	410	410	405	375	360	345	295	355	310	260	210

2.6. Evaluation of Tablets in Main Study and Optimized Study

The formulations in the main study were evaluated with all the tests listed in the preliminary study. Additionally, in-vitro release, Swellability index and mucoadhesive strength were also performed on the formulations.

2.6.1. Mucoadhesive Strength

To quantify mucoadhesive strength of buccal tablet, a modified instrument was developed as shown in Fig. (**1**). One arm of the balance was replaced with thread with the help of which two glass slides were tide. The tablet was sandwiched between the slides as shown in Fig. (**1**). One glass slide was fixed while the other moveable glass slide the attached with arm of the balance to access the degree of mucoadhesion. Between glass slides, both surfaces of tablet were wetted with phosphate buffer solution (pH 6.8).

Fig. (1). Tablet mucoadhesive strength testing apparatus.

On the left pan, drops of water were used in terms of weight to measure the force of detachment. When apparatus was in static equilibrium, water was added [27] until the slide detaches. The force was then accessed for mucoadhesion [28]. Weight in grams was converted to Newton using Equation 2.

$$\text{Mucoadhesive Force (N)} = \text{Weight of water gm} \times \left(\frac{9.8}{1000}\right) \quad \textbf{(2)}$$

2.6.2. Swellability Index

The water uptake by the mucoadhesive tablet was checked by calculating swellability index. Tablet was dipped in a Petri dish containing phosphate buffer (pH 6.8). The weight of the tablet was measured initially (W1) and then at every hour interval up to 6 h. The extent of increase in weight was related to water absorbed (W2) for each time. The percentage swellability was calculated by using Equation 3 [28].

$$\text{Swelling index} = \frac{W2-W1}{W1} \times 100 \quad \textbf{(3)}$$

2.6.3. In-vitro Drug Release

The *in vitro* release study was conducted in USP 28 Type 2 dissolution apparatus (ERWEKA DT-700) with a rotation of paddles at 50 rpm. 500 ml of phosphate buffer (pH 6.8) as dissolution medium was maintained at 37±0.5°C throughout the experiment. Samples were taken at 0.25, 0.5, 1, 2, 3, 4, 5 and 6 hour and measured against a calibration curve for the quantitative determination of propranolol HCl [29].

2.7. Data Analysis by Artificial Neural Network (ANN)

Change in the quantity of polymers in formulations was considered as factors for varied response in properties such as hardness, weight variation, friability, diameter, thickness, surface pH, mucoadhesive time, mucoadhesive strength and in-vitro drug release through artificial intelligence using Neural power 3.1 [30]. Desirability through optimization was generated using the approach "what if command" to predict concentration of polymers and a confirmation formulation was evaluated accordingly. For data analysis Incremental Back Propagation (IBP) method was used as learning algorithm. The connection type used for learning the trend in data was multilayer normal feed forward. The

number of total layers and input layers were 3 and 6 respectively. The number of nodes in output layer were 10 using tanh as a non-linear transfer function.

The desirable values of different physicochemical parameters for the optimization of mucoadhesive tablet has been listed in Table **3**. Note that the physiological pH of buccal cavity is around 6.5 so the desirability value would not damaging to the buccal mucosa. The tablet should be reasonably hard that it could release drug in a sustained manner. Similarly, the release of the drug was designed to be more than 65% till 6 hr.

Table 3. The desired parameters for optimization of ingredients.

Properties	Hardness (Kg/cm^2)	pH	Mucoadhesive time (h)	% Drug Release					
				1h	2h	3h	4h	5h	6h
Desired Value	6.5	6.5	4	15	25	35	45	55	65

2.8. Confirmation Study

The predicted levels (amounts) of factors, such as HPMC, EC, CMC, CP, Na-alginate and lactose generated by Neural Power 3.1 in the main study were tested experimentally by formulating the confirmation formulation based on prediction. Such formulation was tested for all the physicochemical tests as listed above.

2.9. Release Kinetics of Propranolol HCl

In vitro release kinetic model was studied on the release of propranolol HCl using software DD Solver®. The release data were fitted to zero order, 1st order Higuchi and Korsmeyer-Peppas release models. The best model was selected based on the highest R^2 value [31] and results were interpreted. It was applied only to confirmation formulation.

3. RESULTS AND DISCUSSION

In preliminary study, CP and EC were used as mucoadhesive polymers and release retardant which has been used in different studies. The aim of the preliminary study was to find the appropriate method and an estimation of the appropriate ingredients of the buccal tablet of propranolol HCl. While formulating, F1 was prepared with wet granulation (Table **1**) but it was dislodged immediately from the rabbit mucosa after its application in mucoadhesive time test. Thus wet granulation was not employed further rather all formulations including F1 were re-tableted by the direct compression method, the results of which have been expressed.

3.1. Physicochemical Characterization of Buccal Tablets in the Preliminary Study

A significant mucoadhesion time is required for the attachment of polymers to buccal mucosa so that drug can be released from matrix over time locally. For buccal tablet, the neutral pH is required to avoid irritation.

Results for hardness, thickness, diameter, surface, pH, mucoadhesive time and friability of the tablets prepared in the preliminary study are summarized in Table **4**. Though F1 was prepared using wet as well as direct compression method, the results for F1 prepared by the direct compression method have been enlisted (Table **4**). All the formulations from F1 to F13 demonstrated 4 to 7.5 kg/cm^2 hardness, thickness 3 to 3.2 mm, diameter 12 to 12.3mm whereas friability was 0.5 to 0.7%. The mucoadhesive time ranges from 2 to 4 h. The average weight for all formulations in preliminary studies was ranged between 391.6 to 407.4 mg. The deviation of weight of the tablets was within the compendia limits according to USP 32. Surface pH in between 5.8 to 7.0 was considered to be in the physiological range of pH. The surface pH of all formulations was from 5 to7. Only formulations F1, F5, F6 were more acidic and outside the physiological pH range which might be due to the greater concentrations of CMC and CP used as shown in Table **4**.

Table 4. Physicochemical response of the formulations in the preliminary study.

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Surface pH	Mucoadhesive time (h)
F1	404.6±2.34	7.0	3.0±0.05	12.0±0.14	5.5	4.0
F2	398.2±2.1	7.2	3.0±0.01	12.0±0.10	6.5	2.5
F3	405.1±3.4	6.4	3.0±0.03	12.1±0.04	6.2	2.5
F4	391.6±1.86	6.1	3.0±0.03	12.3±0.03	6.4	2.0
F5	392.2±5.78	6.3	3.0±0.03	12.0±0.03	5.0	2.0
F6	404.5±3.36	7.3	3.0±0.1	12.0±0.03	5.5	2.0

(Table 4) contd.....

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Surface pH	Mucoadhesive time (h)
F7	401.8±3.55	5.5	3.2±0.03	12.0±0.11	6.5	3.0
F8	407.4±1.91	5.6	3.2±0.1	12.3±0.03	7.2	3.0
F9	390.7±4.46	4.1	3.2±0.03	12.3±0.05	6.0	3.0
F10	390.3±3.79	4.7	3.2±0.03	12.0±0.12	7.0	4.0
F11	392.4±4.21	5.2	3.2±0.1	12.1±0.05	7.0	4.0
F12	397.8±4.49	5.2	3.0±0.03	12.0±0.04	6.0	4.0
F13	402.3±4.06	7.4	3.1±0.02	12.0±0.08	6.0	4.0

Thickness and diameter were calculated as mean ± SD of 10 determinants whereas weight variation was performed on 20. (SD = standard deviation).

The required pH for propranolol HCl is 6.5 ± 0.05 [32]. In the main study, HPMC was added so as to increase the mucoadhesion properties. Sucrose acted as a diluents, binder and sweetener, thus was kept in further formulation design in the main study

3.2. Physicochemical Characterization of Buccal Tablets in the Main Study

The aim of the main study was to find the levels of CP, EC, HPMC, SA and CMC for the production of an optimized buccal tablet of propranolol HCl. HPMC as a release retardant and mucoadhesive agent was additionally added in the study. Because the mucoadhesive time for tablet in the preliminary study was comparatively lower than the desired criteria due to which HPMC was predicted to increase mucoadhesion. It has been extensively used in buccal drug delivery and has proven satisfactory results [8]. The results from the main study are summarized in Table **5**. As shown, the average weight and friability of all the formulations were within the USP limit of not more than 0.8%. The average weight of all formulations in the main study was also within in ±5% USP allowed deviation. The pH should be such that it should not disturb the local physiological functions because the buccal tablet has to reside a longer period of time. It should not convert the lining of mucosa into any pathological form being more acidic or so. As in Table **5**, the pH of all formulations was within the physiological limit (5.8-7.0) except three [33], F16, F18 and F19 which was 5.5 for all. The hardness of formulations was designed to be around 6-8 Kg/cm^2 [34]. A greater value of hardness would alter the release and patterns of swelling of the tablets. The diameter and thickness of the tablets showed a deviation than 5%.

Table 5. Physiochemical properties of buccal tablets in main study.

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Diameter (mm)	Surface pH	Friability (%)	Mucoadhesive time (h)
F14	7.2	3.0±0.32	503.0±2.14	12.1±0.01	6.5	0.6	4.3
F15	7.1	3.5±0.09	493.5±1.84	12±0.05	6.0	0.4	3.6
F16	7.4	3.2±0.09	490.8±1.56	12±0.03	5.5	0.6	4.3
F17	8.0	3.2±0.23	495.4±2.11	11.5±0.01	7.0	0.4	2.7
F18	7.3	3.2±0.08	497.1±1.23	12.1±0.01	5.5	0.5	2.9
F19	7.7	3.1±0.09	492.6±0.98	12.2±0.01	5.5	0.6	4.8
F20	8.1	3.0±0.04	491.4±3.12	12±0.01	6.0	0.7	2.7
F21	6.8	3.0±0.03	500.5±1.87	12±0.03	5.2	0.2	4.0
F22	8.0	3.0±0.04	492.3±1.19	12±0.03	6.0	0.6	4.0
F23	8.0	3.0±0.008	493.3±2.21	11±0.01	6.2	0.6	4.7
F24	8.1	3.2±0.08	496.2±3.26	11±0.01	6.0	0.4	2.3

Thickness and diameter were calculated as mean ± SD of 10 tablets whereas weight variation was performed on 20. (SD = standard deviation).

Time required by the tablet to detach from the oral mucosa is the mucoadhesive time [21]. The mucoadhesive time of the tablet should be such that it should neither detach instantly from the mucosa due to slight pressure or may not as much strong in mucoadhesion that it may damage the mucosal layer due to sticking action. Highest mucoadhesive time was obtained with the formulations F19 (4.8 h) which was containing 10% of EC only. Higher time was also observed with formulation (F23) containing 5% each of CMC and EC; and 20% percent of HPMC.

In general, swelling behaviour for formulations F17, F18 and F19 was faster compared with the others. Formulations containing HPMC *i.e.* F22-F24 showed least expansion of the gel. Formulations containing low concentrations of CP exhibited greater fragmentation of the gel from the peripheries compared with formulations containing higher concentrations of CP [24].

The data obtained from the main Study was used as input to optimize ingredient's output. For this purpose, NeuralPower® version 3.1, artificial neural network (ANN) software was used for prediction of the optimized levels of above polymers [35]. In this study, 11 tablet formulations, F14-F24 were prepared and buccal tablet formulation F25 was the confirmation formulation. The tests accomplished in addition to that performed in preliminary study included dissolution test, mucoadhesive strength. Results of different tests are summarized in Table **5**. For in-vitro release, standard calibration curve was drawn for propranolol HCl in phosphate buffer (pH 6.8) at concentrations from 0.5 to 40 µg/ml and a regression value of 0.9998 was obtained at 289 nm.

3.3. Critical Factors Affecting the Physical Properties of Tablets

Relative importance generated by software of the factors affecting the overall properties of the buccal tablet formulations as shown in Fig. (**2**). The two factors, viz, HPMC and EC exhibited more importance for the overall properties of the buccal tablet. The relative importance of CMC, lactose was equal to that of SA and CP showed little importance. Thus to achieve an optimized formulation, by manipulating the HPMC and EC, an optimized buccal table was achieved.

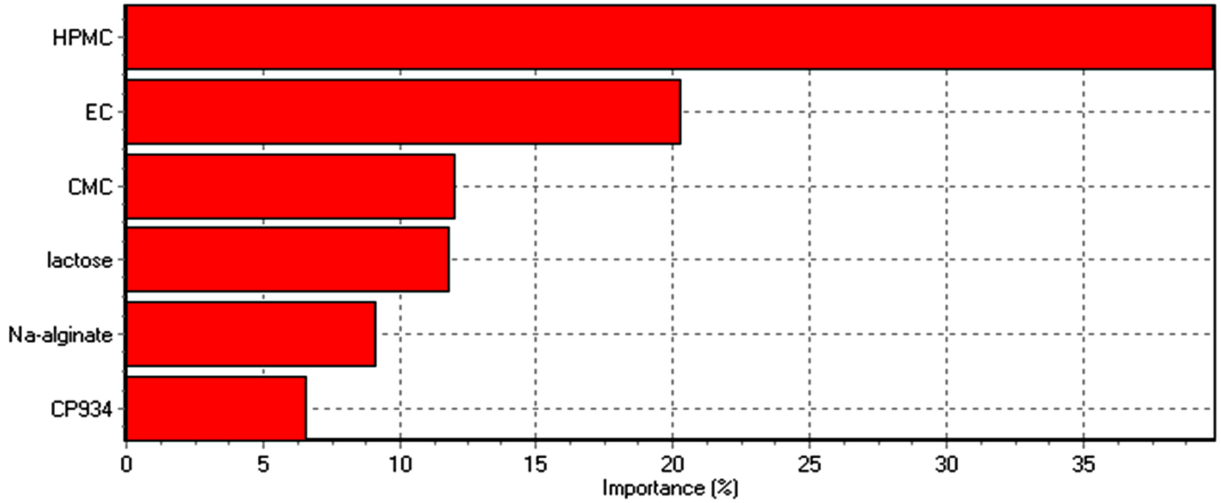

Fig. (2). Relative importance of HPMC, EC, CMC, lactose, Na-alginate and CP934 for different physicochemical properties of propranolol HCl generated by the optimization software, NeuralPower 3.1.

The response surface plot of hardness test between HPMC and EC showed that changing amount of HPMC showed inverse relation with hardness of the tablet in the current study. The desired hardness can be achieved if lower amounts of HPMC is used along with higher concentrations of EC used in the study as depicted in Fig. (**3a**).

The response surface plot showing the combined effect of HPMC and EC indicated the relative importance for physicochemical parameters. The surface pH of all buccal tablet formulations shown to be within the required pH, *i.e.*, 5-7±0.2 [36]. The response surface plot for surface pH showed that at higher level of HPMC and lower level of EC the pH was higher. The red region in Figs. (**3b,c**) depicted that pH and mucoadhesive time were mainly dependant on the concentration of HPMC in the formulations. It meant that the increase in the concentration of HPMC was associated with increasing values of pH and mucoadhesion time. The blue colour corresponds to the area where least values of such tests were observed in the curve. The *in vitro* release was dependent upon the concentration of both polymers *i.e.* HPMC and EC where the release of drug was dependent upon the lowest concentration of the polymers. At higher concentration, little or least effect was evident at times 1 h 2 h and 3 h according to the surface plots as shown in Figs. (**3d,e,f**). The release of drug at 4 h was mainly dependant on the concentration of EC where the increase in the concentration of polymer in the formulations was dependent upon the release of the drug as depicted in the red region in Fig. (**3g**). Conversely, the release of propranolol HCl at 5 h was dependent on the concentrations of both HPMC and EC. Where high impact of EC was found at 5 h and maximum release was relied on EC as shown in red region in Fig. (**3h**).

3.4. Confirmation Formulation

The composition provided by the ANN was confirmed by formulating the predicted amounts of the ingredients. The predicted composition is provided in Table **6**. The software also generated optimized values of the different physicochemical tests as provided in Table **7**.

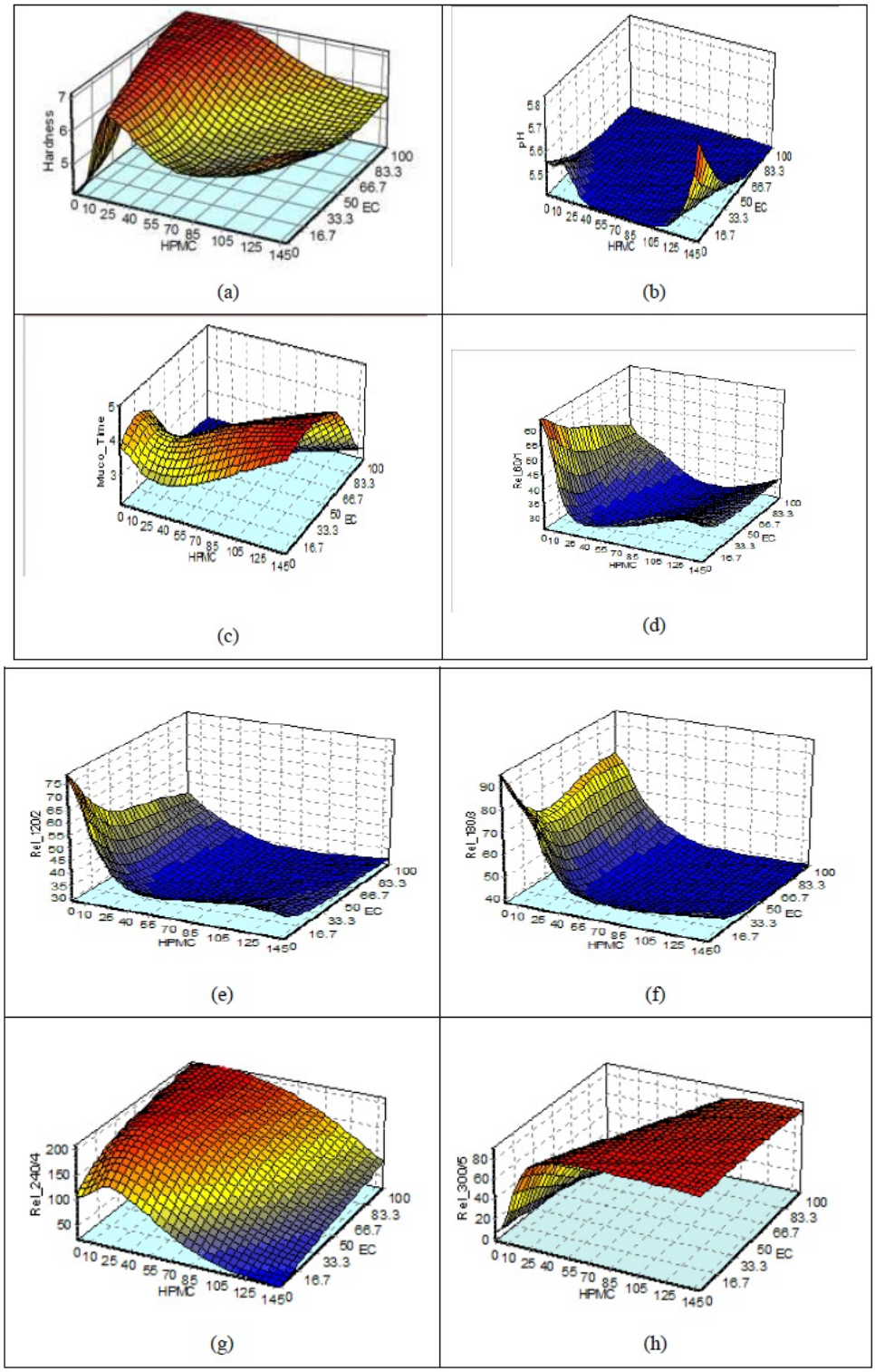

Fig. (3). Combined effect of HPMC and EC on (**a**)- hardness, (**b**)- pH, (**c**)- mucoadhesive time, (**d**)- *in vitro* release at 1 h, (**e**)- *in vitro* release at 2 h, (**f**)- *in vitro* release at 3 h, (**g**)- *in vitro* release at 4 h, (**h**)- *in vitro* release at 5 h of propranolol HCl buccal tablet.

Table 6. ANN-predicted composition of optimized mucoadhesive buccal tablet, F25.

Ingredients	CP	CMC	EC	HPMC	Na-alginate	Lactose
Amounts (mg)	20	25	20	150	0	210

Table 7. ANN-predicted physicochemical properties of buccal tablet.

Properties	**Hardness (Kg/cm^2)**	**pH**	**Mucoadhesive time (h)**	**% Drug Release**					
				1h	**2h**	**3h**	**4h**	**5h**	**6h**
Desirability	7.02	6.9	4.92	25.42	32.78	36.80	48.69	63.30	65.70

All the tests listed in method section were applied on the confirmation formulation. Additionally, swellability index and release kinetics were employed on the formulation. Results are summarized in Table **8**. The formulation F25 showed hardness 8 kg/cm^{2,} diameter 11.1 mm, thickness 3mm, surface pH 6.5, mucoadhesion time 3.9 h and release was 22% at 15 min, 26% at 30 min, 34% at1 h, 40% at 2 h, 45% at 3 h, 50% at 4 h, 62% at 5h, 76% at 6h, 85% at 7h and 97% at 8 h. However, a slight difference was noted in hardness, surface pH, mucoadhesive time and release profile compared with the predicted values generated by artificial intelligence.

Table 8. Physicochemical characterization of confirmation formulation (F25).

Formulation code	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Diameter (mm)**	**Surface pH**	**Mucoadhesive time (h)**	**Friability test**	**Mucoadhesive Strength (N)**
F25	8	3	11.1	6.5	3.9	0.7	0.033

A significant mucoadhesion is required or the attachment of tablet on to the mucosal membrane. Mucoadhesive strength of optimized formulation F25 was 0. 0338N which was comparable [21]. Swellability index is the direct measurement of sorption of water into the mucoadhesive matrix. The ability of water intake by the polymers used in the formulations makes them swell and creates a passage for drugs to release either by erosion of the matrix or by movement of drug out of the intact matrix [37]. Swelling index continuously increased from 42% to more than 100% during time 1 h to 6 h reaching a plateau at 6 h. Swellable weight equal to the dry weight was achieved at 5 h. The maximum swelling was observed at 6 h as observed in Fig. (**4**).

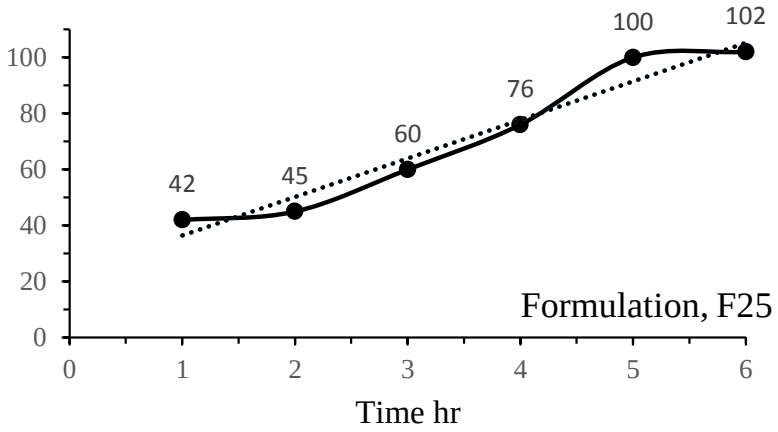

Fig. (4). Swellability index of Formulation, F25 with predicted trendline.

3.5. *In vitro* Drug Release and Release Kinetics

The desirability of buccal tablet was to release the drug in a continuous manner upto 8 hours. This design was to avoid fluctuation of concentration of drug at the serum. Propranolol HCl is a potent drug and slighter change in the

amounts of drug in plasma is associated with adverse effects [38]. So, a continuous release was preferred. The data was used for optimization of the ingredients. The release data for formulation F25 was taken up to 8 h based on the predicted release of at least 65.70% at 6 h, as given in Table **7**. The *in vitro* release data is presented in Table **9**. It revealed that the initial release was neither slow nor fast and at time 5 h, half of the drug was released from tablet matrix. The release of the drug was almost complete and at 8 h, more than 97% of propranolol HCl was released.

Table 9. *In vitro* release data propranolol HCl from the confirmation formulation, F25.

Time (h)	0.025	0.5	1	2	3	4	5	6	7	8
Release (%)	22.38	26.54	33.92	40.35	45	49.64	62.61	76.54	85.11	97.26

Kinetic behaviour of the confirmation formulation, F25 was studied using software "DD Solver. The coefficient of relationship (R^2) values of the models are given in Table **10**. Based on the highest R^2 value, the Korsmeyer-Peppas model (Fig. **5**) fitted the release data well and has been indicated in Fig. (**4**). The n value of the formulation F25 was found to be 0.534 (R^2 = 0.9235) which suggests the non-Fickian drug release [39]. Such a system shows that the rate of drug diffusion and the polymer erosion are same [40]. It suggests that drug is released by an "initial burst" and drug resides in the surrounding gel layer of the polymer. After that erosion of polymer will take place following the diffusion of drug into the dissolution medium [39]. The amount of the drug released depends upon the penetration of dissolution medium through the surrounding gel of CP into the HPMC matrix.

Table 10. The value of R^2 in different kinetic models to predict the release kinetics of optimized mucoadhesive formulation, F25.

Kinetic models	R^2 value	n value
Zero order	0.7387	-
First order	0.8187	-
Higuchi	0.9216	-
Korsmeyer-Peppas	0.9235	0.534

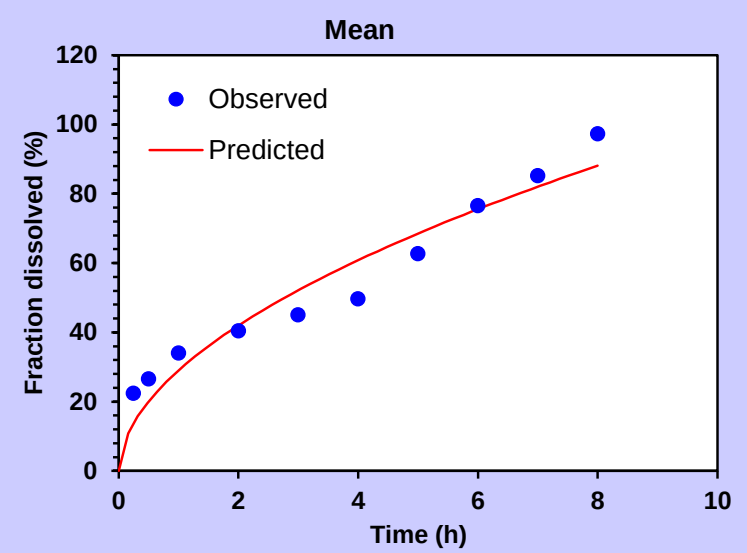

Fig. (5). Fitting of release of propranolol HCl in optimized formulation, F25 according to Korsmeyer-Peppas Model.

CONCLUSION

The buccal anti-hypertensive tablet of propranolol HCl was prepared by the direct compression using mucoadhesive polymeric combination of CP, EC, CMC and HPMC. It was concluded that drug release observed to be faster with the increase in concentration of HPMC. The swellability was controlled BY CP gel surrounding the HPMC matrix. The formulation was optimized for maximum release and physicochemical characters for desired period of time using NeuralPower 3.1. Results revealed that HPMC imparted greater importance on physicochemical parameters like *in vitro* drug release, swellability and mucoadhesion compared with the other. It can be concluded that buccal mucoadhesive tablet for the continuous release of propranolol HCl can be an effective option to deliver the drug through

mucoadhesive buccal route.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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