

Development of an ANN optimized mucoadhesive buccal tablet containing flurbiprofen and lidocaine for dental pain

AMJAD HUSSAIN¹
MUHAMMAD ALI SYED¹
NASIR ABBAS^{1*}
SANA HANIF¹
MUHAMMAD SOHAIL ARSHAD²
NADEEM IRFAN BUKHARI¹
KHALID HUSSAIN¹
MUHAMMAD AKHLAQ³
ZEESHAN AHMAD⁴

¹ University College of Pharmacy
University of the Punjab, Lahore
Pakistan

² Department of Pharmacy, Bahauddin
Zakariya University, Multan, Pakistan

³ Department of Pharmacy
Gomal University, Dera Ismail Khan
Pakistan

⁴ Leicester School of Pharmacy
De Montfort University, Leicester
LE1 9BH, UK

Accepted December 21, 2015
Published online May 20, 2016

A novel mucoadhesive buccal tablet containing flurbiprofen (FLB) and lidocaine HCl (LID) was prepared to relieve dental pain. Tablet formulations (F1-F9) were prepared using variable quantities of mucoadhesive agents, hydroxypropyl methyl cellulose (HPMC) and sodium alginate (SA). The formulations were evaluated for their physicochemical properties, mucoadhesive strength and mucoadhesion time, swellability index and *in vitro* release of active agents. Release of both drugs depended on the relative ratio of HPMC:SA. However, mucoadhesive strength and mucoadhesion time were better in formulations, containing higher proportions of HPMC compared to SA. An artificial neural network (ANN) approach was applied to optimise formulations based on known effective parameters (*i.e.*, mucoadhesive strength, mucoadhesion time and drug release), which proved valuable. This study indicates that an effective buccal tablet formulation of flurbiprofen and lidocaine can be prepared *via* an optimized ANN approach.

Keywords: dental pain, mucoadhesion time, mucoadhesive strength, buccal tablet, artificial neural network

Dental pathologies/disorders are usually associated with inflammation and moderate to severe pain (1). These are managed using analgesics alone or in combination with a variety of other drugs, *e.g.*, antibiotics, local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors (2, 3). Among analgesics, opioids and NSAIDs are commonly used to control acute dental pain. Opioids work by blocking nociceptors and are considered superior to NSAIDs. However, due to adverse drug reactions and psychological adherence, opioids require professional supervision, which restricts their use (4). NSAIDs, at higher doses, are usually considered the drugs of choice in dental pain (5). Among NSAIDs, flurbiprofen (FLB), a propionic acid derivative, is a drug used to treat acute pain associated with dental pathology (6, 7). For FLB, the recommended maximum daily dose is 300 mg; however, a single dose of 100 mg can be effective in treating dental pain (8).

* Correspondence; e-mail: nasirabbas77@gmail.com

An analgesic drug can also be combined with a local anaesthetic for the effective control of dental pain (9). Lidocaine (LID), an amide derivative, is a safer anaesthetic agent that possesses a mild local analgesic effect (10). The efficacy of combinatorial FLB and LID therapy has already been established for the propofol injection induced pain (11).

Local administration of these drugs, as a buccal dosage, can provide an effective route for treating dental pain (12). Over the last decade, extensive progress has been made in the development of buccal dosage forms (1). The buccal dosage form can be an attractive option to deliver drug locally with further advantages including fewer systemic adverse effects compared to conventional dosage forms, avoiding the first pass effect and oral enzymatic degradation (13, 14). The present study aims to formulate a mucoadhesive buccal dosage form to deliver FLB and LID concomitantly. This is achieved by using different proportions of mucoadhesive agents such as HPMC and SA. The formulation was optimized using an artificial neural network (ANN) approach based on mucoadhesive strength, mucoadhesion time and drug release as desired attributes.

EXPERIMENTAL

LID and FLB were obtained on an *in-kind* basis from Gufic Biosciences Limited, Lahore, Pakistan, and Sun Pharmaceuticals, Lahore, Pakistan, respectively. HPMC, Carbopol (CP), sodium alginate (SA) and mannitol were obtained from Glow Scientific Traders, Lahore, Pakistan. HPLC grade methanol and acetonitrile from Merck were obtained at the local market.

Nine tablet formulations (assigned as F1 to F9) were prepared using standard doses of LID (20 mg) and FLB (100 mg) and varying quantities of mucoadhesive agents (HPMC, SA), as given in Table I. Other excipients such as magnesium stearate (lubricant), CP (gelling

Table I. Composition by mass of different tablet formulations

Formulation	LID (mg)	FLB (mg)	Mg-stearate (mg)	Sucralose (mg)	CP (mg)	HPMC (mg)	SA (mg)	Mannitol (mg)
F1	20	100	2	5	7	10	60	296
F2	20	100	2	5	7	20	55	291
F3	20	100	2	5	7	30	50	286
F4	20	100	2	5	7	40	45	281
F5	20	100	2	5	7	50	40	276
F6	20	100	2	5	7	60	35	271
F7	20	100	2	5	7	70	30	266
F8	20	100	2	5	7	75	25	266
F9	20	100	2	5	7	80	20	266
F10 ^a	20	100	2	5	7	90	10	266

^a ANN predicted optimized formulation

agent) (15) and sucralose (sweetener) (16) were used in fixed quantities. Mannitol was used as a filler (17) to contribute towards the desired mass. All ingredients were mixed using a mortar and pestle, and tablets were prepared by the direct compression method using a single punch tablet machine (Okeda Chem. Co. Ltd.) applying a force of 2 tons for 20 s.

Physicochemical investigation of tablet formulations

Tablet formulations were tested for hardness, mass variation, friability, surface pH, mucoadhesive strength, mucoadhesion time, swellability index and *in vitro* release of both drugs. The hardness, mass variation and friability of tablet formulations were tested by the standard methods described in the BP (2011).

Surface pH

Surface pH was assessed by placing a tablet from each formulation in a petri dish containing 0.1 mol L⁻¹ phosphate buffer (pH 6.8) for 2 h. The pH was measured using a digital pH meter electrode on the tablet surface (18).

In vitro mucoadhesion time

An apparatus was devised for the measurement of *in vitro* mucoadhesion time. One face of formulated tablets was wetted with 50 µL phosphate buffer solution (pH 6.8) and pressed gently for 20 seconds on freshly cut rabbit mucosa supported by a glass slide. The slide was then placed, at an angle of about 45°, in a beaker containing 800 mL of phosphate buffer (pH 6.8), maintained at 37 °C. The solution was mechanically stirred at a speed of 150 rpm. The time taken for tablet detachment or for complete disappearance from the mucosa was considered as the mucoadhesion period (19).

In vitro mucoadhesive strength

The mucoadhesive strength was determined using a modified physical balance that measures the force of tablet detachment from the mucosal surface. Briefly, one arm of the balance was used to hold the tablet between 2 rabbit mucosa pasted on glass slides. Both faces of the tablet were wetted with a drop of phosphate buffer (pH 6.8) and pressed gently for 10 seconds before placing it between the mucosae. One glass slide was stationary and was fixed to the base, while the other was mobile and attached to the threaded arm of the pan. The minimum weight required to detach the tablet from the mucosa was considered as the mucoadhesive strength (20). The values for mucoadhesive strength were expressed in terms of Force (N) using Eq. 1.

$$\text{Mucoadhesive strength (N)} = \text{observed mass (g)} \times \frac{9.8 \frac{m}{s^2}}{1000} \quad \text{Eq. 1}$$

Swelling index

The swelling index was measured by placing weighed tablets in a Petri dish containing 10 mL of phosphate buffer (pH 6.8). The mass gain of an individual tablet was mea-

sured at different time intervals, initially at 0.5 h and then after each hour up to 4 h and then at 10 h. Swelling indices were measured using Eq. 2.

$$\text{Swellability index} = \frac{\text{swelled mass} - \text{dry mass}}{\text{dry mass}} \times 100 \quad \text{Eq. 2}$$

In vitro drugs release

Drug release studies were carried out using a USP type II (paddle) apparatus (ERWEKA DT-700) according to the method previously described in the literature (21). Experimental conditions adopted for dissolution studies include phosphate buffer (pH 6.8) (500 mL) maintained at 37 ± 5 °C with a paddle rotating speed of 50 rpm. Aliquots of 5 mL were withdrawn at selected time intervals (0.5, 1.0 and 3.0 h) and replaced with fresh dissolution medium to maintain the sink condition. The quantity of drug release over time was determined by the HPLC method. Since the solubility of lidocaine hydrochloride and flurbiprofen is 4.1 and 0.0249 mg mL⁻¹, respectively, 500 mL of dissolution media was enough to maintain the sink conditions.

Each sample was analysed for drug content using an HPLC system (Shimadzu, LC10 ATVP). The elution was carried out using the mobile phase (aqueous solution of sodium heptane sulphonate anhydrous, sodium phosphate dibasic and EDTA/acetonitrile (6:4, V/V)). The flow rate under ambient conditions was 1.2 mL min⁻¹. Drug concentration was determined by calculating the area under the curve of two absorption peaks ($\lambda = 210$ nm) obtained at the retention time at 1.5 min and 5.8 min for LID and FLB, respectively (Fig. 1).

A calibration curve of both drugs in phosphate buffer solution (pH 6.8) was constructed by recording the absorption peaks of standard solutions containing 1, 5, 10, 20, 40, 60, 80 and 100 µg mL⁻¹ of each drug. Calibration curves for both drugs showed linearity over a range of 1 to 100 µg mL⁻¹ ($R^2 = 0.999$). The regression equation for flurbiprofen was found to be $y = 42516x + 27660$ while that for lidocaine HCl was $y = 20231x + 26075$. The calibration curves manifest a limit of quantitation of 0.12 and 1.11 µg mL⁻¹ and limit of detection of

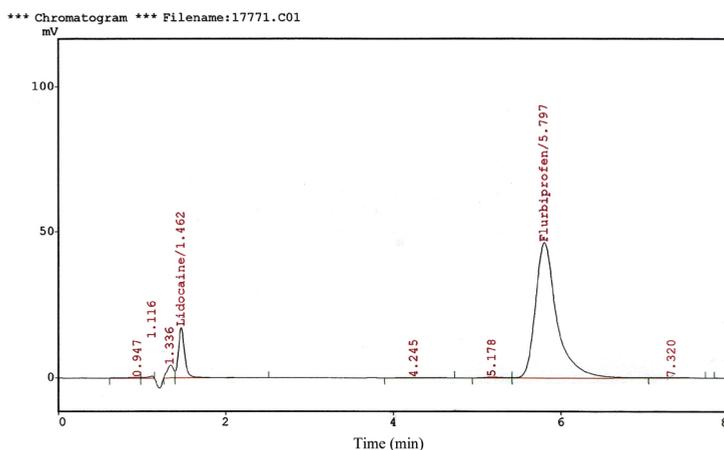


Fig. 1. Representative HPLC chromatogram for flurbiprofen and lidocaine hydrochloride.

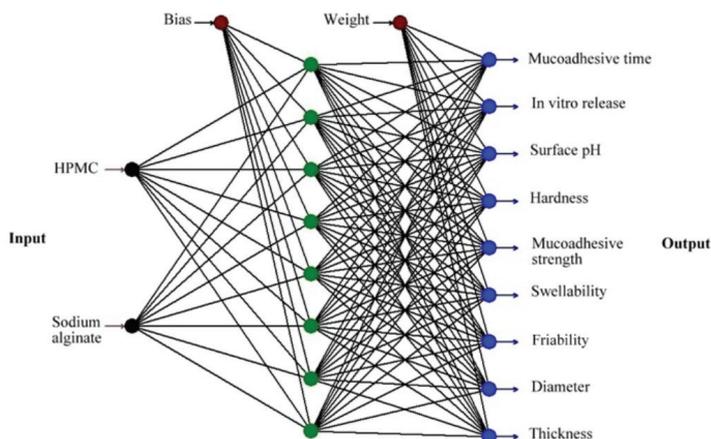


Fig. 2. Structure of ANN employed in this study.

0.03 and 0.33 $\mu\text{g mL}^{-1}$ for LID and FLB, respectively. The coefficient of variation for intra-assay and inter-assay precision was less than or equal to 5.42 % and the accuracy was between 95 and 101 %.

Optimization of mucoadhesive formulation by the artificial neural network approach

To study relative effects of HPMC and SA on physicochemical parameters, ANN, *i.e.*, the NeuralPower[®] version 3.1, was employed using a „what if” command. Quick propagation (QP) method was used for the learning algorithm with Tanh as transfer function. Multilayer perceptron (MLP) structure was used in the study where the class of structure was feed forward. The total number of input, output and hidden layers was 2, 9 and 1, respectively (Fig. 2). Surface responses were generated for relative excipient importance towards physicochemical parameters.

Results from the physicochemical parameters of initial nine formulations were the basis for using a ‘what if’ approach in ANN for the prediction of the best levels of polymers to achieve an optimized buccoadhesive formulation. Surface responses were then generated for relative excipient importance towards physicochemical parameters as followed in a similar study (21). ANN predicted results were validated by preparing a confirmation formulation (F10) using the quantity of ingredients as described in Table I. Tablets were then prepared by the same method as above, *i.e.*, by the direct compression method. Tablets were tested for hardness, weight variation, friability, surface pH, mucoadhesive strength, mucoadhesion time, swellability index and *in vitro* release of both drugs.

RESULTS AND DISCUSSION

Results of the physical parameters such as weight variation, hardness, friability, mucoadhesive strength and time are shown in Table II. All the tablet formulations showed acceptable values of these parameters, based on BP (2011) specification.

Table II. Mass variation, hardness, friability, mucoadhesive strength, mucoadhesion time and surface pH of the tablet formulations

Formulation	Average mass (mg)	Hardness (kg/cm ²)	Friability (%)	Mucoadhesive strength (N)	Surface pH	Mucoadhesive time (h)
F1	495.6 ± 3.69	6.0	0.455	0.11	5.02	4.21
F2	495.4 ± 4.17	6.2	0.397	0.14	4.35	4.62
F3	499.0 ± 3.82	6.7	0.578	0.13	4.41	6.33
F4	496.0 ± 4.60	6.6	0.688	0.14	6.98	5.81
F5	496.2 ± 4.84	6.9	0.447	0.15	6.76	6.94
F6	497.4 ± 3.90	6.3	0.621	0.16	4.25	6.40
F7	497.2 ± 4.34	6.6	0.63	0.22	5.64	7.52
F8	497.1 ± 4.06	6.5	0.572	0.21	5.02	9.50
F9	497.7 ± 3.77	7.0	0.402	0.17	4.92	9.00

Average mass was calculated as mean ± SD of 10 determinants.

The surface pH of the buccal tablet should not disturb the micro-environment of buccal mucosa, body functions and physiological features of the mucosa. Low pH can damage the mucous membrane, so an acceptable range of 5.8–7.0 is ideal (22). All formulations demonstrated slight variations in surface pH and were generally acidic (Table II). The surface pH of formulations F4 and F5 were within the acceptable range (pH 5.8–7.0). The acidic nature of the majority of formulations is ascribed to the release of LID HCl.

The mucoadhesive strength and mucoadhesion time of each formulation are measures of capability to adhere to the buccal cavity and also relate to drug release (for localised effect). Both parameters depend upon the type and concentration of polymers used in the formulation (19). In general, greater values are deemed favourable for tablet attachment to the mucosa (21). The results show that formulations containing greater quantities of HPMC (F7 to F9) exhibit higher mucoadhesive strength (~0.2 N) and mucoadhesive time (~9 h) compared to those containing reduced quantities of these excipients (F1 to F6, see Table III). Formulations demonstrating mucoadhesive strength > 0.15 N (F5 to F9) were selected for *in vitro* release studies.

Swelling index is a quantitative determination of the degree of water uptake by the tablet. In general, the swellability index for F1-F4 decreased over time (up to 10 h) relative to the initial dry tablet weight (Table III). The decrease in swellability index is explained by LID solubility in water, which causes it to diffuse out of the matrix, thereby decreasing the tablet mass over time.

The release of both FLB and LID from different formulations is given in Fig. 3. Among formulations F5 to F9, the release of FLB in the first 0.5 h was highest from formulation F6 (~85 %) while it was lowest from formulation F9 (~40 %). However, after 1 h, all five formulations exhibited almost complete release of FLB (Fig. 3a).

In contrast, the release of LID was slow (compared to FLB), with all formulations except F6 releasing from 10–30 % within 0.5 h. The release of LID from formulation F6 over

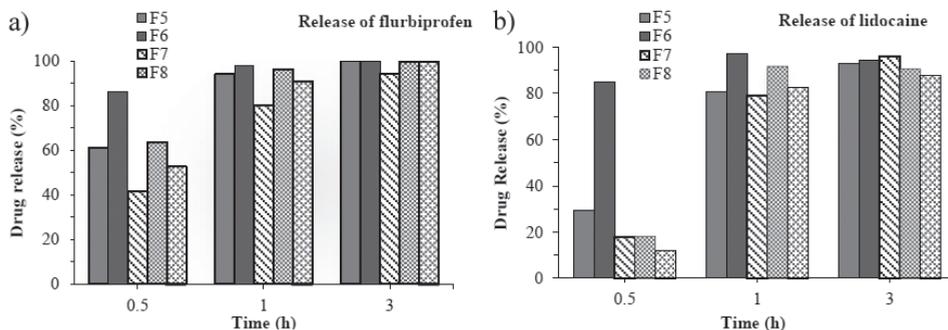


Fig. 3. Plot showing *in vitro* release of: a) flurbiprofen and b) lidocaine hydrochloride from various formulations at different time intervals. Formulations in the preliminary study (F1-F4) were not tested for *in vitro* release.

the same time period was ~85 %. At 1 h, all formulations showed almost complete dissolution (Fig. 3b). The results for *in vitro* release suggest that drug release from formulations depended upon the ratio of HPMC to SA. The formulation with higher HPMC to SA ratio, *i.e.*, F6, showed higher release of FLB and LID compared the formulations with reverse ratio values (23). In this instance, formulation F6, due to its low mucoadhesive strength and mucoadhesion time, was not considered useful for providing analgesic and anaesthetic action locally. The ANN approach was applied to obtain a formulation with optimum drug release, mucoadhesive strength and mucoadhesion time.

Data for physicochemical properties, *in vitro* mucoadhesive strength, mucoadhesion time, surface pH (Table II), swellability index (Table III) and *in vitro* drug release (Fig. 1) were used to analyse the combined effect of HPMC and SA. ANN generated surface plots

Table III. Swelling indices (%) of tablet formulations at different time intervals

Formulation	Swelling index at different time intervals					
	Time (h)					
	0.5	1	2	3	4	10
F1	210.8	207.6	198.2	176.9	167.2	63.9
F2	165.1	152.2	145.1	139.6	132	132
F3	157.4	142.9	134.4	126.9	129.7	70.3
F4	127.3	106.4	109.8	100.4	96.2	107.6
F5	63.9	54.2	62.7	63.5	60.7	86.7
F6	66.3	60.1	55.8	55.2	59.4	102.5
F7	55.7	53.5	51.3	53.5	53.5	55.3
F8	51.7	50.6	48.8	50.6	52.9	59.4
F9	41.3	40.5	42.1	42.3	44.3	71.9

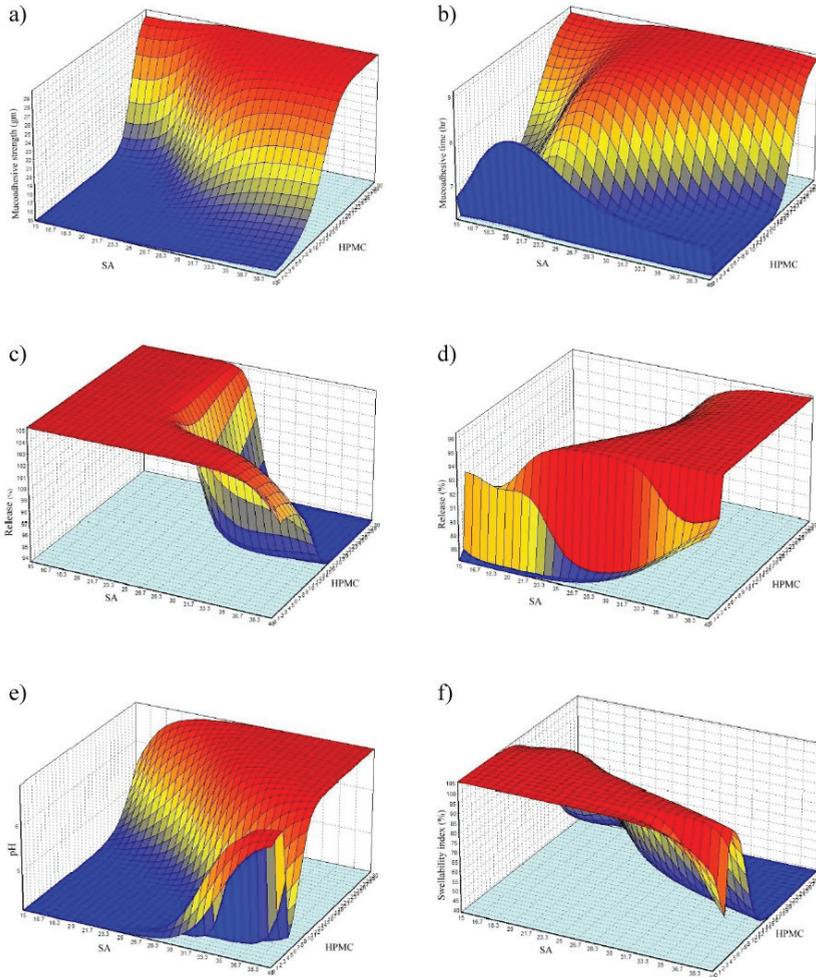


Fig. 4. ANN predicted relative importance of HPMC and SA for: a) mucoadhesive strength, b) mucoadhesion time, c) *in vitro* release FLB, d) *in vitro* release LID, e) surface pH and f) swellability index at 10 h.

describing the relative importance of HPMC and SA for physicochemical properties are shown in Fig. 3. Change in colour (24) from blue to red shows an increasing effect of these polymers. Here, red colour indicates a more prominent effect than blue colour. As shown in Fig. 4, HPMC imparted a stronger impact on the *in vitro* LID release, mucoadhesive strength, mucoadhesive time and pH compared to SA. Conversely, *in vitro* FLB release and swellability index parameters were more related to SA, Fig. 4c and f.

As predicted by ANN, formulation F10 (Table I) was prepared and evaluated (through experimentation and observed outcomes) (21) for all the physicochemical properties (Table IV).

Table IV. Comparison of the properties of predicted vs. experimental formulation

Parameters	Predicted	Observed
Mucoadhesive strength (N)	0.285	0.286
Surface pH	5.44	5.44
Mucoadhesion time (h)	8.99	9.2
Swellability at 30 min (%)	38.13	39.4
Swellability at 1 h (%)	37.66	38.8
Swellability at 2 h (%)	39.04	39
Swellability at 3 h (%)	40.63	41.6
Swellability at 4 h (%)	38.29	39.4
Swellability at 10 h (%)	41.66	42.4
<i>In vitro</i> % release at 0.5 h (Lidocaine HCl)	11.64	11.80
<i>In vitro</i> release at 1 h (%)	18.01	17.91
<i>In vitro</i> release at 3 h (%)	88.92	88.90
<i>In vitro</i> release at 0.5 h (%) (Flurbiprofen)	36.69	37.12
<i>In vitro</i> release at 1 h (%)	61.87	62.74
<i>In vitro</i> release at 3 h (%)	100.28	100.45

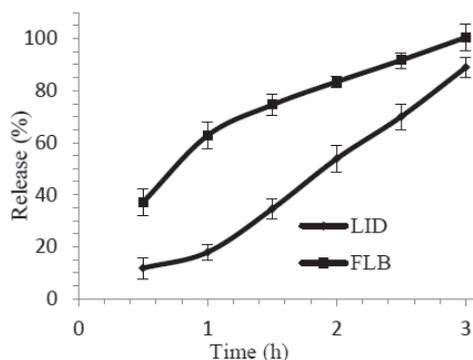


Fig. 5. The plot showing the release of flurbiprofen and lidocaine from optimized formulation, F10.

For formulation F10, predicted outcomes for mucoadhesive strength and mucoadhesion time were in close proximity to the actually observed outcomes. The release of FLB and LID from F10 (Fig. 5) was gradual over a 3 h period, suggesting prolonged action of the drug at the site of action (buccal cavity). Thus the prepared formulation can be used for the relief of dental pain for a longer period of time by acting locally.

Release kinetics of formulation F10 show that LID and FLB followed the Korsmeyer-Peppas model where $n = 1.340$, explicating a special type ($n > 0.89$), *i.e.*, super case II release.

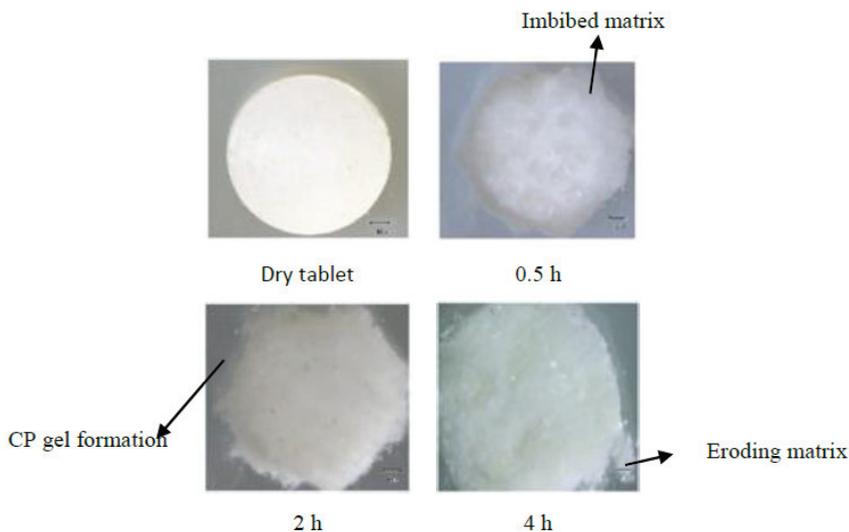


Fig. 6. Diagrammatic illustration of matrix and gel formation, breaking of small gel particles and matrix erosion during swelling of F10 at different time intervals when placed in 20 mL phosphate buffer solution, pH = 6.8 (taken with a Stereo zoom microscope).

This is probably due to the influx of fluid into the tablet matrix causing the swelling and subsequent diffusion of the drug from the matrix into the dissolution medium (25, 26). These results are supported by the microscopic observation (Fig. 6) showing disintegration and subsequent cleavage of particles from the „swelled tablet” eliciting erosion of the matrix (27, 28).

CONCLUSIONS

Novel mucoadhesive dental analgesic tablets containing FLB and LID HCl were prepared using HPMC and SA as mucoadhesive agents. The release of both active ingredients was also found to be dependent on the relative ratio of HPMC to SA. The formulation containing a higher proportion of HPMC to SA showed an extended release profile. ANN assisted factor analysis showed that the HPMC imparted a stronger impact on the *in vitro* LID release, mucoadhesive strength, mucoadhesive time and pH compared to SA. Conversely, *in vitro* FLB release and swellability index parameters were more related to SA. ANN predicted optimized formulation provides appropriate *in vitro* mucoadhesive strength (0.286 N), mucoadhesion time (9.2 h) and drug release > 85 %, which supports the application of the *in silico* tool in formulation development.

Ethical approval for using mucosal membrane was obtained from the Animal Ethics Committee (Approval No. AEC/UCP/1031/4313, dated 15/09/2014), University College of Pharmacy, University of the Punjab, Lahore, Pakistan.

REFERENCES

1. N. Salamat-Miller, M. Chittchang and T. P. Johnston, The use of mucoadhesive polymers in buccal drug delivery, *Adv. Drug Deliv. Rev.* **57** (2005) 1666–1691; DOI: 10.1016/j.addr.2005.07.003.
2. R. A. Medve, J. Wang and R. Karim, Tramadol and acetaminophen tablets for dental pain, *Anesth. Prog.* **48** (2001) 79–81.
3. B. W. Morrison, S. Christensen, W. Yuan, J. Brown, S. Amlani and B. Seidenberg, Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomized, controlled trial, *Clin. Ther.* **21** (1999) 943–953; DOI: 10.1016/S0149-2918(99)80016-2.
4. J. M. Swegle and C. Logemann, Management of common opioid-induced adverse effects, *Am. Fam. Physician* **74** (2006) 1347–1354.
5. I. Bjarnason, J. Hayllar, A. J. Macpherson and A. Russell, Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans, *Gastroenterology* **104** (1993) 1832–1847.
6. A. Sultan, H. J. McQuay, R. A. Moore and S. Derry, Single dose oral flurbiprofen for acute postoperative pain in adults, *Cochrane Libr.* (2009); DOI: 10.1002/14651858.CD007358.
7. M. Takada, M. Fukusaki, Y. Terao, K. Yamashita, C. Inadomi, M. Takada and K. Sumikawa, Pre-administration of flurbiprofen suppresses prostaglandin production and postoperative pain in orthopedic patients undergoing tourniquet inflation, *J. Clin. Anesth.* **19** (2007) 97–100; DOI: 10.1016/j.jclinane.2006.05.028.
8. R. K. Flath, M. L. Hicks, R. A. Dionne and G. B. Pelleu Jr., Pain suppression after pulpectomy with preoperative flurbiprofen, *J. Endodont.* **13** (1987) 339–347; DOI: 10.1016/S0099-2399(87)80116-487.
9. Y. Fujii and Y. Shiga, Flurbiprofen axetil preceded by venous occlusion in the prevention of pain on propofol injection in the hand: a prospective, randomized, double-blind, vehicle-controlled, dose-finding study in Japanese adult surgical patients, *Clin. Ther.* **27** (2005) 588–593; 10.1016/j.clinthera.2005.05.003.
10. P.-L. Lin, S.-Z. Fan, C.-H. Huang, H.-H. Huang, M.-C. Tsai, C.-J. Lin and W.-Z. Sun, Analgesic effect of lidocaine patch 5 % in the treatment of acute herpes zoster: a double-blind and vehicle-controlled study, *Region. Anesth. Pain M.* **33** (2008) 320–325.
11. L. Perioli, V. Ambrogi, S. Giovagnoli, M. Ricci, P. Blasi and C. Rossi, Mucoadhesive bilayered tablets for buccal sustained release of flurbiprofen, *AAPS PharmSciTech.* **8** (2007) E20-E27; DOI: 10.1208/pt0803054.
12. H. Okamoto, H. Taguchi, K. Iida and K. Danjo, Development of polymer film dosage forms of lidocaine for buccal administration: I. Penetration rate and release rate, *J. Control. Release* **77** (2001) 253–260; DOI: 10.1016/s0168-3659(01)00509-001.
13. Y. Sudhakar, K. Kuotsu and A. Bandyopadhyay, Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs, *J. Control. Release* **114** (2006) 15–40; 10.1016/j.jconrel.2006.04.012.
14. V. F. Patel, F. Liu and M. B. Brown, Advances in oral transmucosal drug delivery, *J. Control. Release* **153** (2011) 106–116; DOI: 10.1016/j.jconrel.2011.01.027.
15. A. Bernkop-Schnürch and S. Steininger, Synthesis and characterisation of mucoadhesive thiolated polymers, *Int. J. Pharm.* **194** (2000) 239–247; 10.1016/s0378-5173(99)00387-799.
16. I. Knight, The development and applications of sucralose, a new high-intensity sweetener, *Can. J. Physiol. Pharmacol.* **72** (1994) 435–439; DOI: 10.1139/y94-063.
17. L. Allen, Featured excipient: capsule and tablet diluents, *Int. J. Pharm. Compd.* **4** (2000) 306–312.
18. V. M. Patel, B. G. Prajapati, H. V. Patel and K. M. Patel, Mucoadhesive bilayer tablets of propranolol hydrochloride, *AAPS PharmSciTech.* **8** (2007) E203-E208; 10.1208/pt0803077.
19. L. Perioli, V. Ambrogi, D. Rubini, S. Giovagnoli, M. Ricci, P. Blasi and C. Rossi, Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease, *J. Control. Release* **95** (2004) 521–533; DOI: 10.1016/j.jconrel.2003.12.018.

20. S. Mohammadi-Samani, R. Bahri-Najafi and G. Yousefi, Formulation and in vitro evaluation of prednisolone buccoadhesive tablets, *Farmaco* **60** (2005) 339–344; DOI: 10.1016/j.farmac.2005.01.009.
21. S. Edavalath and B. Rao, Design, development and optimization of buccal bioadhesive tablets of diclofenac sodium for the treatment of odontalgia, *Ars Pharm.* **52** (2011) 5–13.
22. M. S. Pendekal and P. K. Tegginamat, Formulation and evaluation of a bioadhesive patch for buccal delivery of tizanidine, *Acta Pharm. Sin. B* **2** (2012) 318–324; DOI: 10.1016/j.apsb.2011.12.012.
23. N. Shah, G. Zhang, V. Apelian, F. Zeng, M. H. Infeld and A. W. Malick, Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: effect of polymer concentration, *Pharm. Res.* **10** (1993) 1693–1695; DOI: 10.1023/a:1018901509855.
24. J. Malakar, A. K. Nayak and S. Goswami, Use of response surface methodology in the formulation and optimization of bisoprolol fumarate matrix tablets for sustained drug release, *ISRN Pharmaceutics* **2012** (2012), article ID 730624; DOI: 10.5402/2012/730624.
25. S. Dash, P. N. Murthy, L. Nath and P. Chowdhury, Kinetic modeling on drug release from controlled drug delivery systems, *Acta Pol. Pharm.* **67** (2010) 217–223; DOI: 10.1080/10717540490265379.
26. D. Jones, *Pharmaceutical Applications of Polymers for Drug Delivery*, Smithers Rapra Publishing, U.K. 2004. pp. 31–35.
27. J. Parojčić, Z. Đurić, M. Jovanović and S. Ibrić, An investigation into the factors influencing drug release from hydrophilic matrix tablets based on novel carbomer polymers, *Drug Deliv.* **11** (2004) 59–65.
28. X. Huang and C. S. Brazel, On the importance and mechanisms of burst release in matrix-controlled drug delivery systems, *J. Control. Release* **73** (2001) 121–136; DOI: 10.1016/s0168-3659(01)00248-601.