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Research Article

FORMULATION AND EVALUATION OF BUCCOADHESIVE BILAYERED TABLETS OF ATOMOXETINE HYDROCHLORIDE

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ABSTRACT

The purpose of this research work was to establish mucoadhesive bilayered buccal tablets of Atomoxetine hydrochloride. The tablets were prepared by direct compression technique using HPMC-K4M, HPMC-K15M, SCMC, carbopol934P as mucoadhesive polymers and ethyl cellulose is used as a impermeable backing layer. These buccal tablets were evaluated by different parameters such as weight variation, friability, content uniformity, assay, hardness, thickness, surface pH, swelling index, exvivo mucoadhesion strength, exvivo mucoadhesion time, exvivo permeation studies, invitro drug release. The F6 formulation (containingK4M:934P 1:1) is optimized on the basis of invitro drug release and exvivo permeation studies. The F6 formulation follows the zero order kinetics.

Keywords: bilayered buccal tablet, buccoadhesive drug delivery, atomoxetine hydrochloride.

INTRODUCTION

Conventional routes of drug administration such as oral, intramuscular, intravenous have been supplanted by the advent of new, novel drug delivery systems[1]. The drug delivery via buccal route is an attractive route for both systemic as well as local effect. It has number of advantages when compared with oral route. These advantages include avoidance of first pass metabolism, additionally this route provides accessibility, reasonable patient acceptance and compliance and dosage form can be removed at any time[2]. The human buccal mucosa consists of series of, an outer most layer of stratified squamous epithelium, a basement membrane, a lamina propria and submucosa. The epithelium is the important permeable barrier for hydrophilic and polar permeants[5].Aatomoxetine Hcl is a potent inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other monoamine transporters or receptors and is the first non-stimulant medication approved for the management of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents and adults[3]. Atomoxetine Hcl is well absorbed after oral administration with peak plasma concentration in 1 to 2 hours after a dose. Bioavailability is about 63% in extensive metabolisers and 94% in poor metabolisers[4]. The half life of drug is 5.2 hr in extensive metabolisers and 21.6 hr poor metabolisers. The logP value of the drug is 3.95 which is sufficient to cross the oral mucosa. It has low therapeutic dose (10-100mg) and first pass effect by considering above points it is an ideal candidate for design and development of buccal drug delivery systems.

Materials and methods

Atomoxetine hydrochloride (99.85% purity), were gift samples from Aurobindo pharma limited. hyd., Carbopol 934P (Maruti chemicals Ltd, hyd, India), Methocel K15M, K4M (Colorncon Asia Pvt ltd, Goa, India), Sodium CMC (S.D.Fine chemicals Mumbai.India), D-mannitol (S.D.Fine chemicals Mumbai. India),

Magnesium Stearate (S.D.Fine chemicals Mumbai. India), all other reagents and chemicals used were of analytical reagent grade.

Preparation of mucoadhesive bilayered tablets[6]

The tablets were prepared by direct compression technique involving two consecutive steps.

Step1

The mucoadhesive drug and polymer mixture was mixed homogenously in a glass motor for 15 minutes. The mixture (100mg) was then compressed using 9-mm round shaped flat punches on multi station tablet machine.

Step2

The upper punch was raised and the backing layer of EC (50mg) was added to the above compact and two layers were compressed to from a bilayered tablets[6]. The tablets were prepared using various mucoadhesive polymers like sodium carboxy methyl cellulose, carbopol 934P, HPMC K4M, HPMC K15M. The composition given in table 1.

Table 1: The composition of bilayered tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
A-HCl	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4	11.4
SCMC	85.6	42.8	28.5	57.06	-	-	-	-	-	-	-	-
934P	-	42.8	57.06	28.5	-	42.8	57.06	28.5	-	42.8	57.06	28.5
K4M	-	-	-	-	85.6	42.8	28.5	57.06	-	-	-	-
K15M	-	-	-	-	-	-	-	-	85.6	42.8	28.5	57.06
D-mannitol	2	2	2	2	2	2	2	2	2	2	2	2
Mg.stearate	1	1	1	1	1	1	1	1	1	1	1	1
EC(N-50)	50	50	50	50	50	50	50	50	50	50	50	50

Evaluation

Swelling Study[7]

Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37-C ± 1-C. At regular 1-hour time intervals until 12 hours, the tablet was removed from the Petri dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the following formula:

$$SI = (W2-W1)/W1 *100$$

Surface pH[8]

The surface pH of the buccal tablets 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. Buccal tablets were left to swell for 2hours on the surface of an agar plate, prepared by dissolving 2%(w/v) in warmed isotonic phosphate buffer solution of pH6.8 under stirring and then pouring the solution into a petriplate till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen tablet. The mean of three readings was recorded.

***Ex vivo* Mucoadhesive strength[6, 10]**

A modified balance method was used for determining the *ex vivo* mucoadhesive strength. Fresh buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter .The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 saliva solutions at 37^0C. The porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH6.8 at 37^oC+1^0C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanocarylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g weight on the right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

$$\text{Force adhesion (N)} = \frac{\text{Bioadhesive strength X 9.81}}{1000}$$

$$\text{bond strength (Nm}^{-2}\text{)} = \frac{\text{force of adhesion}}{\text{disk surface area}}$$

Ex Vivo Mucoadhesion Time[6]

The ex vivo mucoadhesion time was examined (n = 3) after application of the buccal tablet on freshly cut porcine buccal mucosa. The fresh porcine buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the porcine buccal mucosa by applying a light force with a fingertip for 30 seconds. 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 minutes, a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the porcine buccal mucosa was recorded as the mucoadhesion time.

In Vitro Drug Release[6]

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the bilayered tablets. The dissolution medium consisted of 200 mL of phosphate buffer pH 6.8. The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium .The samples were filtered through 0.2-μm Whatman filter paper and analyzed by UV spectrophotometry at 270 nm.

Exvivo Drug Permeation[6, 9]

The Exvivo buccal drug permeation study of atomoxetine hydrochloride through the porcine buccal mucosa was performed using Keshary-Chien type glass diffusion cell at 37°C ± 0.2°C. With the diffusional area of 3.14cm$^{2.}$ Fresh porcine buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment was filled with 1 mL of phosphate buffer pH 6.8. The receptor compartment (12-mL capacity) was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. A 1-mL sample was withdrawn at predetermined time intervals and analyzed for drug content at 270 nm using a UV-spectrophotometer.

Table 2: Physico chemical properties of bilayered buccal tablets of Atomoxetine hydrochloride

Formulation Code	Friability Mean±SD	Thickness (mm) mean± S.D	Hardness (kg/cm^2) Mean±SD	%drug content (Mean±SD)	Surface pH (Mean±SD)	Swelling index at 12hrs
F1	0.96±0.057	2.66±0.057	3.5±.0.54	99.39±0.105	7±0.5	231.08
F2	0.483±0.028	2.23±0.057	2.66 ± 0.814	98.23±0.25	7±0.5	161.74
F3	0.8±0.1	2.1±0.1	2.33±0.516	99.2±0.26	5.83±0.288	140.25
F4	0.533±0.057	2.36±0.058	2.33±0.516	100±1	7.5±0.5	161.4
F5	0.2±0.02	2.22±0.111	6.58 ±0.548	100.46±0.838	7.666±0.288	100
F6	0.316±0.763	2.15±0.041	8.33±0.288	101.53±0.472	6.5±0.5	145.09
F7	0.4±0.05	2.35±0.051	8.33±0.76	101.5±0.5	5.66±0.288	189.35
F8	0.37±0.03	2.19±0.040	7.833±0.288	98.41±0.381	7.5±0.5	108.05
F9	0.288±0.03	2.25±0.07	4.33±0.288	99.16±1.607	6.33±0.577	98.03
F10	0.186±0.005	2.29±0.115	7.16±0.288	99.00±0.500	7.5±0.5	121.51
F11	0.26±0.02	2.23±0.075	7.16±0.288	99.11±0.682	6.5±0.5	173.58
F12	0.344±0.01	2.1±0.02	7.6±0.114	101.5±0.500	7.5±0.5	164.23

Table 3: Exvivo parametes of bilayered buccal tablets of Atomoxetine hydrochloride

Formulation Code	Bioadhesive strength (gm) (Mean± S. D.)	Force of adhesion (N)	Bond strength (NM^{-2})	Exvivo mucoadhesion Time (hrs)
F1	11.53±0.503	0.113	1782.33	>12
F2	24.41±0.381	0.239	3769.71	>12
F3	33.88±1.019	0.332	5296.59	>12
F4	12.41±0.381	0.121	1908.51	>12
F5	14.27±0.254	0.139	2192.42	>12
F6	17.83±0.288	0.174	2744.47	>12
F7	25.88±0.835	0.253	3990.53	>12
F8	14.38±0.344	0.141	2223.97	>12
F9	12.33±0.288	0.120	1892.74	>12
F10	14.94±0.417	0.146	2302.83	>12
F11	22.38±0.344	0.219	3454.25	>12
F12	19.41±0.381	0.190	2839.11	>12

Invitro release and Exvivo permeation correlation

Table 4: comparison of Invitro drug release and Exvivo drug permeation of optimized formulation

Time(min)	%DR invitro	%drug permeated exvivo
30	13.19149	9.34
60	15.2234	11.50
120	20.2766	11.50
180	30.12766	17.44
240	36.38298	22.96
300	35.96809	31.44
360	38.15661	42.15
420	52.17021	52.39
480	58.89362	60.22
540	68.30851	65.66
600	80.05319	74.83
660	86.52128	80.15
720	99.58511	87.83

RESULTS AND DISCUSSION

EC has recently been reported to be an excellent backing material, given its low water permeability, hydrophobicity, and moderate flexibility, so it was chosen as an impermeable backing layer[7]. D-mannitol was used to any bitter taste; magnesium stearate was used to improve flow properties.

Tablets were found to be satisfactory when evaluated for weight variation (0.78%± 0.15%), thickness (2.23 ± 0.15mm), hardness (6.62± 2.41 kg/cm2), friability (0.428% ± 0.236%), and drug content (99.79% ± 0.62%). Table 2.

The formulations containing sodium CMC showed less hardness (2.33 to 3.5kg/cm^2) compared to other formulations.

The surface pH of all the tablets was within a range of 5.83 to 7.6which was with in 7+-1.5units of the neutral pH and hence these buccal tablets should not cause any irritation in the buccal cavity. Those formulations containing higher amount of carbopol showing acidic nature because acidic nature of carbopol. Appropriate swelling behavior of a buccal adhesive system is essential for uniform and prolonged release of the drug and effective mucoadhesion[7].the swelling index in formulation F1 to F4 is directly proportion to the SCMC content and inversely proportional to CP content. Formulations F5 to F12 swelling index directly proportion to CP content and inversely proportion to HPMC content. Highest swelling index (231.08%) was found to be F1 formulation containing SCMC alone, the high amount of water intake by SCMC at a faster rate might be the reason for highest swelling index[6]. Lowest swelling index (98.03%) was found to be F9 formulation containing HPMC K15M alone. The optimised formulation F6 showed swelling index of 149.05% at 12hrs. (Figure1).

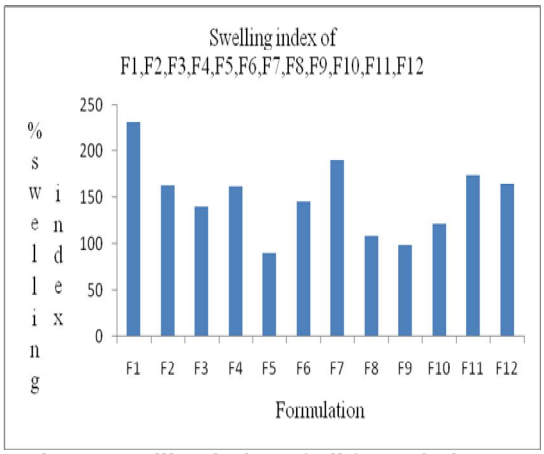

Fig. 1: swelling index of all formulations

Mucoadhesion may be defined as the adhesion between a polymer and mucus. In general, mucoadhesion is considered to occur in 3 major stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors such as molecular weight of polymers, contact time with mucus, swelling rate of the polymer, and biological membrane used in the studys[8]. In this study the porcine buccal mucosa was used as biological membrane for mucoadhesion. The formulations containing high amount of CP shows high bioadhesion strength, this is because formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region. F3 formulation shows highest bioadhesion strength (33.88%). All formulations exhibit good bioadhesion strength on the porcine mucosa. The optimised formulation F6 showed 17.83±0.288 gms mucoadhesion strength.
Exvivo mucoadhesion time for all formulations F1 to F12 was found to be greater than 12 hrs.87.83% drug permeated in 12 hours.

Invitro drug release for formulations containing SCMC F1 toF4 shows immediate release this suggests that SCMC will not sustain the release of drug. The optimized formulation shows 99.59% of drug release at 12hrs. from formulation F5,F7,F8,F9 the drug release was 97.46, 97.54, 75.29,92.89, this indicates the drug release was not satisfactory compare to F6 formulation F10, F11 formulation release the drug 100% with in 9hrs,8hrs respectively ,78.17% drug is released from F12 formulation after 12th hour.(figure 4)

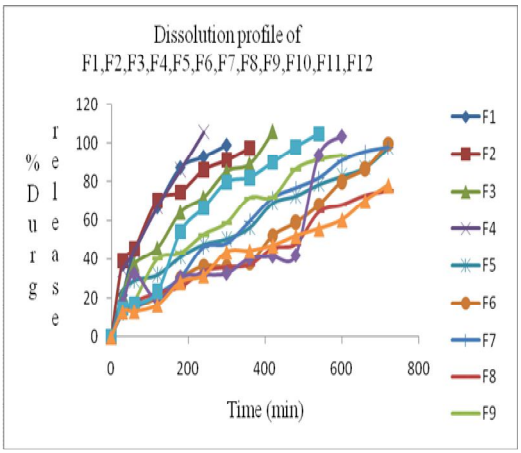

Fig. 2: invitro drug release profile of bilayered buccal tablets of formulatons F5 to F12

The optimized tablets (F6) subjected to exvivo permeation, this study showed that The correlation between the invitro drug release and exvivo drug permeation across the porcine mucosa was found to be positive with a correlation coefficient of 0.9647(figure5).

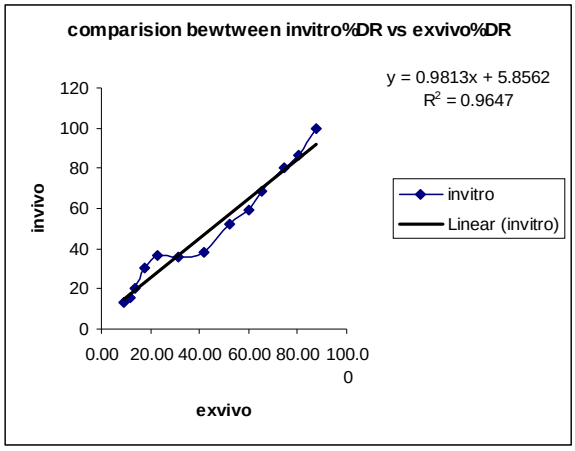

Fig. 5: comparison of invitro drug release and exvivo drug permeated

Table 5: release kinetics of optimized formulation

F6 (Invitro)	K	0.1203	-0.002	3.8677	0.5978
	R^2	0.9701	0.5684	0.8984	0.8856
F6 (Exvivo)	K	0.1192	-0.0011	3.8379	0.784
	R^2	0.9831	0.8894	0.9132	0.9148

From the above results it was concluded that the optimized formulation followed the zero order kinetics.

DSC studies revealed that there was no interaction between the drug and the polymers used (Fig3)

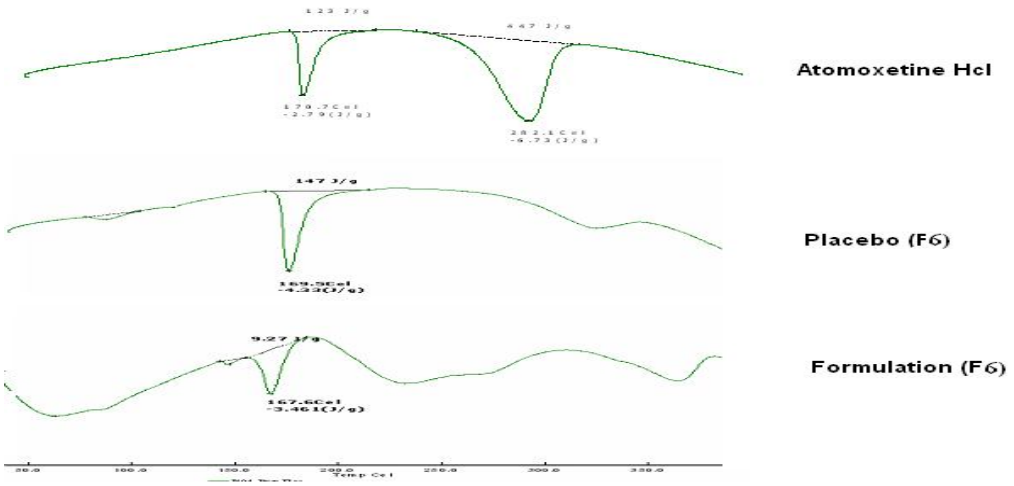

Fig. 3: DSC thermogram of pure drug, placebo, formulation

CONCLUSIONS

From the present investigation, one can conclude that the optimized formulation containing HPMC K4M: CP 934P in 1:1can meet the ideal requirements for buccal devices, which can be good way to bypass the extensive hepatic first pass metabolism and is also suitable for sustaining.

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