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Design and characterization of bilayer buccoadhesive tablets of venlafaxine using natural resins as mucoadhesive release retardants

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ABSTRACT

Venlafaxine is a serotonin norepinephrine reuptake inhibitor used for treating depression. Due to extensive first pass metabolism, its oral bioavailability is around 45%. The aim of the present study is to develop and evaluate buccoadhesive tablets of venlafaxine using natural resins like olibanum and colophony as mucoadhesive release retarding agents with an objective to bypass first-pass effect, to improve the bioavailability of the drug, to minimize the dose dependent side effects as well as to improve patient compliance. Buccoadhesive tablets were prepared by wet granulation technique and ethyl cellulose employed as a backing laminate for the preparation of unidirectional drug release of buccoadhesive tablets. The prepared granules of different batches were of good flow properties. The physicochemical interactions for pure drug and optimized formulation were investigated by Infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. The formulation F9 was found to be the optimized formulation based on drug dissolution studies. Mucoadhesive properties of resins employed were increased with increase in the concentration of polymer which was proved from ex-vivo residence time and detachment force measurement. The drug release was found to be following Fickian diffusion. It was concluded that resin based buccoadhesive tablets of venlafaxine exhibiting good controlled release characteristics and were proved as efficient mucoadhesive agents.

Keywords: Buccoadhesive drug delivery; Venlafaxine; Olibanum; Colophony; Resin.

INTRODUCTION

Novel drug delivery systems like buccoadhesive drug delivery system present an opportunity for the formulation scientists to overcome many challenges associated with oral conventional dosage forms in order to enhance the stability, bioavailability of the drug, targeting the drugs to a particular site for an extended period of time, maintaining the steady state plasma concentration etc. Buccoadhesive delivery is the administration of active pharmaceutical ingredients through the buccoadhesive mucosa [1, 2]. The thin film of mucin that exists on the surface of oral mucosa provides an opportunity to retain the drug delivery system in contact with mucosa for prolonged period [3]. Buccoadhesive drug delivery is one of the promising routes for administration of drugs undergoing first pass metabolism thereby enhancing the oral bioavailability of drugs. Also major advantage of this route is certain macromolecular drugs like steroids, proteins and peptides which are susceptible to acidic pH can be administered by this route [4]. Buccoadhesive drug delivery systems are the potential candidates for controlled or

sustained, targeted drug delivery because these drug delivery systems utilizes certain mucoadhesive resins such that they ensures close contact with the absorbing membrane upon hydration and thus optimizing the drug concentration gradient across the biological membrane [5]. Natural biodegradable resins were often more likely used as mucoadhesive release retarding agents, even though several synthetic resins were available; because of their biocompatibility, readily available, non-toxic, inexpensive, can undergoes chemical modifications etc [6]. In the present study olibanum and colophony were used as mucoadhesive release retarding agents. Olibanum is an oleo-gum resin obtained from incised trunk of the tree *Boswellia serrata* belonging to the family burseraceae and colophony (rosin) is an oleo resin obtained from the trees of the pinus species, *Pinus palustris* [7, 8]. An ideal buccoadhesive dosage forms must have three considerations; it must retain its position inside the mouth for a few hours, should control the release of the drug and release should be in unidirectional way towards buccoadhesive mucosa [9].

Depression is one of the serious threats to the global burden of disease and affecting people in all the communities across the world. More than 90% of people who kill themselves are due to depressive disorder [10]. Venlafaxine is a representative of a new class of antidepressant comes under serotonin norepinephrine reuptake inhibitors [11]. It acts by selectively blocking the reuptake of certain neurotransmitters like serotonin and nor epinephrine in the brain. This is similar to tricyclic antidepressants but lack of adverse effects like anticholinergic, sedative and cardiovascular effects [12]. The main limitation for therapeutic effectiveness of venlafaxine is its low oral bioavailability of around 45% and short biological half life of 5hrs, neccesating its frequent administration i.e., more than once a day in order to maintain adequate drug-plasma levels [13]. Moreover, it is an antidepressant, neccesating longer period of administration. The recommended daily dose of venlafaxine is around 75 to 450 mg. These obligations led to the development of an alternate drug delivery system that permits direct access of active constituents to the systemic circulation there by overcoming first pass effect. Also when compared with oral conventional formulations, the extended release formulations have less nausea and dizziness at the initiation of the therapy [14].

The current research endeavor aims at designing buccoadhesive venlafaxine tablets by using certain natural resins like olibanum and colophony as bioadhesive devices to bypass the first pass effect, improve the bioavailability, increase the duration of action, release the drug in a controlled manner and reduce the side effects.

EXPERIMENTAL SECTION

2.1. Materials

Venlafaxine was obtained as a gift sample from (Aurobindo Pharma Ltd, Hyderabad); Olibanum gum was procured from (Girijan Corporation, Vishakapatnam). Colophony resin, Microcrystalline cellulose, Magnesium stearate, Talc, Ethyl cellulose were procured from (Yarrow chemicals and products, Mumbai); Sheep buccoadhesive mucosa was procured from local slaughter house (Vizianagaram, India) for determining mucoadhesion strength and *ex-vivo* permeation studies.

2.2. Methods

2.2.1. Formulation of buccoadhesive bilayered tablets

Venlafaxine buccoadhesive bilayered tablets were prepared by wet granulation technique. The formulations were prepared as according to table1. The buccoadhesive tablets were prepared by using olibanum gum, colophony resin, microcrystalline cellulose and ethyl cellulose as a backing layer. All the ingredients were initially passed through the sieve #60 and were blended in motar and pestle with geometric dilution method for 15 min except magnesium stearate, talc and ethyl cellulose. The blend of all the ingredients was granulated by using 3:7 ratios of methanol and water respectively to obtain wet masses. These wet mass was passed through sieve #12 and the resulting granules were dried at 40 ^{0}C. Finally, just before compression lubricants were added. Then the dried granules were pre-compressed on a rotary tablet punching machine (Rimek mini press, India) at a pressure of 0.5 ton and turret speed of 2 rpm to form single layered flat faced tablet of 8mm diameter. Then 40 mg of ethyl cellulose powder was added; final compression was done at a pressure of 3.5 tons and turret speed of 2 rpm to obtain flat faced tablets with ethyl cellulose layer as backing laminate [15].

Table 1: Composition of buccoadhesive tablets of venlafaxine

Ingredients (mg)	Formulation Codes											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Core layer												
Venlafaxine	25	25	25	25	25	25	25	25	25	25	25	25
Olibanum gum	60	-	30	40	-	20	35	-	17.5	15	-	7.5
Colophony	-	60	30	-	40	20	-	35	17.5	-	15	7.5
Microcrystalline cellulose	71	71	71	71	71	71	71	71	71	71	71	71
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Backing layer Ethyl cellulose	40	40	40	40	40	40	40	40	40	40	40	40
Total	200	200	200	200	200	200	200	200	200	200	200	200

2.2.2. Evaluation of Precompression parameters of buccoadhesive tablets

Flow properties like bulk density, angle of repose, tapped density; Hausner's ratio, compressibility index etc. were evaluated for different batches of granules. Angle of repose was determined by fixed funnel method. Loose and tapped density was determined by cylinder method from which Carr's Index (CI) and Hausner's ratio was calculated to define the flow property [16].

$$\%\ \text{Compressibility index} = \frac{\text{loose bulk volume } (v_0) - \text{tapped bulk volume}(v_t)}{\text{loose bulk volume } (v_0)} \times 100$$

2.2.3. Evaluation of post compression parameters of buccoadhesive tablets

The prepared buccoadhesive tables of different batches were evaluated for different physicochemical tests such as weight variation, hardness, thickness, friability, drug content study, surface pH, *ex-vivo* residence time, buccoadhesive strength, *ex-vivo* permeation studies, *in-vitro* dissolution studies and release kinetics.

2.2.3.1. Weight variation test

This test was performed by taking twenty tablets randomly from each batch and weighed individually using electronic balance (Infra Instruments Pvt Ltd, Chennai, India). From the total weight of tablets average weight was calculated and individual weight of each tablet was compared with average weight as per USP specifications [17].

$$\%\ \text{deviation} = \frac{\text{individual weight (W1)} - \text{average weight (W2)}}{\text{averageweight (W2)}} \times 100$$

2.2.3.2. Hardness

This test was conducted by randomly selecting three tablets from each batch and tested using Monsanto hardness tester (Shiv Scientific Stores). The average values were calculated [18].

2.2.3.3. Thickness

The thickness of tablets was determined by selecting ten tablets from each batch at random and average thickness was determined using vernier calipers (Linkar, Mumbai, India) [18].

2.2.3.4. Friability test

This test was performed in order to check the capability of a tablet to withstand the mechanical stress during handling, processing, transportation and shipment. Roche friabilator (DBK Instruments) was used to determine the friability. From each batch, ten preweighed (W) tablets were selected at random and placed in the apparatus revolving at 25 rpm for 4 min. Finally, at the end of the test the tablets were reweighed (W*) and compared with the initial tablet weight.

$$\%\ \text{friability} = \left(1 - \frac{W}{W^*}\right) \times 100$$

Where W is the original weight of the tablet, W* is the final weight of the tablet.
Acceptance Limits: 0.5-1% [19].

2.2.3.4. Drug content study
Five tablets were selected at random from each batch, triturated. The amount of powder equivalent to 25 mg was dissolved in pH 6.8 phosphate buffer and filtered using Whatmann filter paper. The drug content was analyzed spectrophotometrically using UV spectrophotometer. The test was carried out in triplicate [20].

2.2.3.5. Surface pH
Surface pH of buccoadhesive tablet was determined by using pH meter electrode (Cyber Lab, Hyderabad India). One tablet from each batch was placed in contact with 1 ml of phosphate buffer pH 6.8 for two hours at room temperature. Electrode of the pH meter was passed towards the surface of the tablet for 1 min to equilibrate [21].

2.2.3.6. *Ex-Vivo* residence time
Ex-Vivo residence time of buccoadhesive tablets was measured using modified USP disintegration apparatus (Cintex Industrial Corporation, Dadar, Mumbai) by removing the baskets from the shaft. The fresh buccoadhesive mucosa of sheep was collected from local slaughter house, defatted and washed with the buffer. Then it was attached to a glass slide using cyanoacrylate adhesive in such a way that mucosal side facing outwards. Glass slide was attached to the shaft of disintegration apparatus with the help of a stainless steel rod. 500 ml of pH 6.8 Phosphate buffer was taken as medium and maintained at 37 ^{0}C. Buccoadhesive tablet was wetted with pH 6.8 phosphate buffer prior fixing on to the mucosa, with light pressure to get the initial contact. The apparatus was modified to immerse the tablet completely at the lowest point and out at the highest point. The time required for detachment of tablet from the mucosal surface was recorded. The test was done in triplicate and finally the mean value was determined [22].

2.2.3.7. Measurement of bioadhesion strength
Mucoadhesion strength of the tablet was determined by measuring the detachment force i.e., the force required to detach the tablet from the surface of mucosa. The detachment force was measured on a modified physical balance, in which the right pan was removed completely. A plastic beaker was kept on the left pan and both the pans were balanced by adjusting with weights. Fresh buccoadhesive tissue membrane collected from the local slaughter house was washed with pH 6.8 phosphate buffer. This buccoadhesive mucosa was attached to a glass slide using cyanoacrylate adhesive in such a way that the mucosal side facing towards (top) viewable side. Glass slide was fixed on to the petri dish and kept on the right side of physical balance. Tablet was then attached to another glass slide using cyanoacrylate adhesive facing the core outwards. Glass slide was suspended from right side of the balance by means of non elastic thread and the heights were adjusted. Both mucosal membrane and tablet were wetted with pH 6.8 phosphate buffer before fixing the tablet on to the mucosal membrane with little thumb pressure. This was undisturbed for 5 min and to the left pan containing plastic beaker, water was added with the help of a burette until the tablet just separates from the mucosal surface. Weight of the water required to detach the tablet (g) was determined and the detachment force was measured in milli Newton's which corresponds to mucoadhesive strength of the tablet. Experiment was performed for triplicate and the mean value was measured [23].

$$\text{Detachment Force (F)} = \text{W (Kg)} \times 9.8\ \text{m/s}^2$$

2.2.3.8. *Ex-Vivo* permeation study
This study was performed by using dissolution cell and a membrane assembly. From the local slaughter house fresh sheep buccoadhesive mucosa was collected as a model membrane. Buccoadhesive mucosa was washed thoroughly with the Kreb's solution and the epithelium was separated from the underlying connective tissues using scissors. Then it was tied to the open end of the tube (donor chamber) in such a way that mucosal side facing upwards. The end with mucosal membrane was dipped into the beaker comprising 50 ml of pH 6.8 phosphate buffer (receiver chamber). Then the buccoadhesive tablet was attached to the mucosal membrane with light pressure. Further this beaker was kept on a magnetic stirrer with a heating plate. Simulated temperature and buccoadhesive movements were maintained by using water bath with thermometer attached to it and by using magnetic stirrer respectively. At predetermined intervals 5ml of samples were withdrawn, filtered through Whatmann filter paper and analyzed by UV spectrophotometer at 225 nm. At each time of withdrawal equal amount of buffer was replaced into the receiver chamber. The whole experiment was carried out for triplicate, finally the flux and permeation coefficient were determined.

$$J = (dq/dt)/A$$

$$P = J/\Delta C$$

Where, J refers to flux ($mg.hrs^{-1}cm^{-2}$); (dq/dt) is the slope; A is the area of diffusion (cm^2); P is the permeability coefficient (cm/hr^{-1}); C is the concentration gradient across the mucosa [24].

2.2.3.9. *In-Vitro* drug release study

Rotating paddle type dissolution apparatus USP XXIII (Electro lab, Mumbai, India) was used for determining the percentage of drug release from buccoadhesive tablets employing 200 ml of pH 6.8 Phosphate buffer as the dissolution medium. Temperature was maintained at 37 ± 0.2 ^{0}C, with 50 rpm rotation speed. The tablet was placed in the dissolution vessel in such a way that the backing layer of buccoadhesive tablet was attached to a glass slide using cyanoacrylate adhesive so that the core layer of tablet faces outwards i.e., towards the dissolution media. At predetermine intervals 5 ml of samples were withdrawn and filtered through Whatman filter paper. At 225 nm, the samples were analyzed by using UV spectrophotometer (Agilent technologies). At each time of withdrawals, equal amount of buffer was replaced in order to maintain sink condition [25, 26].

2.2.4. Release Kinetics

The *in-vitro* drug release data of different batches of buccoadhesive venlafaxine tablets was subjected to different kinetic models like first order, zero order, Hixon-Crowell, Higuchi, and Korsemeyer-Peppas. A criterion for selecting most appropriate model was based on goodness of fit and high regression coefficient [27].

2.2.5. Characterization of buccoadhesive tablets

2.2.5.1 FTIR study

Interactions between drug and resin were studied by FTIR spectroscopy using the instrument Shimadzu, Japan, FTIR-8400S. Samples were prepared by KBr pellet method in which 2 mg of sample was mixed with 200 mg of KBr with a hydrostatic press at a force of 5.2 N/m^2 for 3 min. The spectra were recorded for pure drug venlafaxine and buccoadhesive tablets containing drug. The spectra were scanned over a wave number range of 400–4000 cm^{-1} [28].

2.2.5.2. Differential scanning calorimetry (DSC)

The thermal behavior of the buccoadhesive tablets were investigated by using differential scanning calorimeter (DSC 60, Shimadzu, Japan). 5 mg of Samples of were placed in perforated aluminium pans (50 μm) and were sealed. All the samples were run over a temperature range of around 5–300 ^{0}C and heating rate of 10 ^{0}C/min in atmosphere of nitrogen as purging gas at a flow rate of 25 ml/min [28].

2.2.5.3. X-ray diffraction study (XRD)

XRD is a powerful tool in recognizing crystalline behavior of tablets. Buccoadhesive tablets were subjected to X-ray diffraction analysis, using Philips PW 170 system (Philips USA) with Cu-Kα radiation (400 kV, 30 mA, and scan speed 1 ^{0}/min) to investigate the physical state of venlafaxine [28].

RESULTS AND DISCUSSION

3.1. Precompression parameters evaluation

Precompression parameters were evaluated as per USP specifications, where angle of repose was found to lie in between 27.34 ^{0} to 31.74 ^{0}, which indicates that the granules prepared by wet granulation technique showing good flow properties. A blend of 2% of magnesium stearate and talc was further added to improve the flow properties of granules in order to avoid the weight variation among various batches. Bulk density and Tapped density for different batches were determined and the results were obtained in the range of 0.3806-0.4223 g/ ml and 0.4464-0.4854 g/ml respectively. This indicates that there was no significant difference between bulk and tapped densities, confirming proper filling of the die cavity to avoid weight variation among various batches.

Carr's compressibility index was found to lie in the range 9.89 ± 1.56 to 14.64 ± 0.56 for all the formulations indicating good to fair flowability and compressibility. Hausner's ratio was found to lie in the range of 1.109 to 1.186, indicating good flow properties. Results were depicted in table 2.

Table 2: Physical characteristics of buccoadhesive tablets of venlafaxine

Formulation Codes	Angle of Repose (θ^0)*	Loose Bulk Density (g/ml)*	Tapped Bulk Density (g/ml)*	Hausner's Ratio	Carr's Index (%)*
F1	25.34±0.34	0.406±0.02	0.476±0.013	14.63±0.58	1.170
F2	30.64±0.27	0.403±0.01	0.462±0.011	12.89±1.58	1.140
F3	27.89±0.35	0.396±0.02	0.440±0.013	11.97±0.61	1.110
F4	25.45±0.23	0.413±0.01	0.485±0.018	14.88±1.41	1.170
F5	27.34±0.43	0.390±0.02	0.458±0.016	14.87±0.58	1.174
F6	26.79±1.12	0.409±0.02	0.454±0.018	9.83±1.41	1.109
F7	31.74±1.03	0.411±0.02	0.472±0.013	13.04±1.78	1.150
F8	27.47±0.56	0.418±0.02	0.474±0.016	11.75±0.61	1.133
F9	29.74±0.75	0.380±0.01	0.451±0.017	15.74±0.48	1.186
F10	28.24±0.88	0.422±0.03	0.490±0.015	13.851±0.67	1.160
F11	27.28±1.14	0.399±0.04	0.446±0.012	10.535±111	1.117
F12	28.58±0.27	0.417±0.024	0.474±0.018	12.058±0.23	1.137

**All the values are expressed as mean ±SE, n=3*

3.2. Post compression studies

Post compression studies were conducted for the prepared buccoadhesive tablets and results were depicted in table 3. The hardness and friability values indicate that the tablets were of good mechanical strength and can withstand possible wear and tear during handling and transportation. As the tablet weight was 200 mg, 7.5% of 200 mg of venlafaxine tablet can have weight variation of 15 mg. The result suggests that weight variation obtained was within the range and there was no significant variation in weight between different batches of tablet indicating that amount of glidant added was sufficient. The drug content of various formulations was in the range of 98.02 to 100.05 indicating a uniform distribution of drug among all the batches.

Table 3: Post compression parameters of buccoadhesive tablets

Formulation Codes	Weight Variation (%)*	Hardness (kg/cm^2)*	Thickness (mm)*	Friability (%)	Drug Content Estimation (%)
F1	2.25±0.026	0.012±0.020	202.06±0.45	7.45±0.21	98.42±0.206
F2	2.92±0.029	0.023±0.010	205.08±0.23	8.5±0.15	98.63±0.24
F3	2.71±0.011	0.09±0.036	195.78±1.55	8.34±0.21	98.17±0.25
F4	2.62±0.004	0.017±0.042	204.02±0.65	8.04±0.26	98.20±0.24
F5	2.73±0.01	0.17±0.025	200.14±0.49	8.27±0.15	99.27±0.16
F6	2.52±0.01	0.08±0.065	200.04±0.19	7.91±0.23	99.17±0.14
F7	2.54±0.02	0.42±0.031	201.38±1.12	8.49±0.38	98.02±0.27
F8	2.64±0.050	0.31±0.036	201.14±1.65	8.12±0.44	97.15±0.38
F9	2.26±0.025	0.30±0.021	204.43±0.98	7.75±0.12	100.05±0.305
F10	2.37±0.027	0.07±0.045	203.79±0.76	7.83±0.09	98.76±0.119
F11	2.56±0.011	0.08±0.020	202.29±1.56	7.97±0.27	100.12±0.314
F12	2.71±0.063	0.43±0.025	201.84±0.31	8.36±0.35	100.04±0.33

**All the values are expressed as mean ±SE, n=3*

The surface pH of all the formulations was determined in order to find out the possibility of any side effects in the buccoadhesive environment. The observed surface pH of all the formulations was in the range of 6.69 ± 0.040 to 6.81 ± 0.031. It indicates that the pH of the tablets lies within the range of salivary pH (6.5-6.8) thereby indicating that there was no cause of irritation at the site of administration.

Ex-Vivo residence time is the time necessary for complete detachment or erosion of tablet from mucosal surface without losing integrity. This test reflects adhesive property of resin in the formulation. All the prepared tablets showed residence time of 5-7 hrs. It was found that with increase in resin concentration residence time was also increased.

Mucoadhesion strength determination was conducted for all formulations by modified physical balance. The maximum mucoadhesion strength was observed for the formulation F2 containing colophony 30% with adhesion strength of 112.25 ± 0.5 mN and low mucoadhesion strength was observed for the formulation F10 containing olibanum 15% with less adhesion strength of 46.98 ± 0.3 mN. The results indicate that mucoadhesion strength of the prepared formulations increases with increase in resin concentration and colophony resin having more adhesiveness than that of olibanum resin. For the optimized batch F9 containing a blend of colophony (8.75%) and olibanum

(8.75%), good mucoadhesion strength was obtained (84.44 ± 0.6 mN). The results for all the formulations were shown in table 4.

Table 4: Results of Surface pH, *Ex-Vivo* residence time and Mucoadhesion strength for formulations F1-F12

Formulation Codes	Surface pH	*Ex-Vivo* Residence Time (hrs)	Mucoadhesion Strength (mN)
F1	6.72±0.061	7.4±0.24	103.25±0.6
F2	6.77±0.030	6.9±0.15	112.25±0.5
F3	6.69±0.040	6.4±0.61	105.64±0.8
F4	6.72±0.026	6.2±0.38	84.23±0.5
F5	6.8±0.066	6.8±0.15	98.25±0.2
F6	6.79±0.065	5.6±0.46	92.24±0.9
F7	6.73±0.030	5.4±0.54	77.21±0.5
F8	6.78±±0.026	5.1±0.65	90.52±0.6
F9	6.68±0.045	7.2±0.68	87.54±0.6
F10	6.81±0.031	6.5±0.74	46.98±0.3
F11	6.77±0.011	6.0±0.92	54.26±0.5
F12	6.66±0.029	5.8±0.87	53.24±0.7

**All the values are expressed as mean ±SE, n=3*

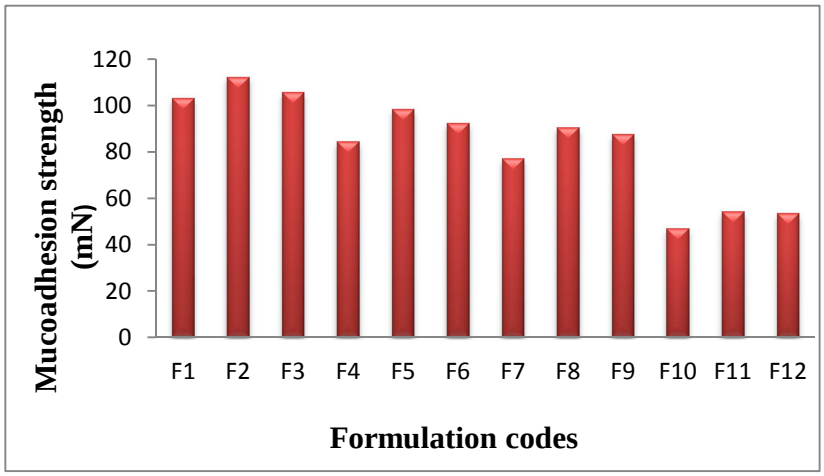

Figure 1: Mucoadhesion strength of formulations F1-F12

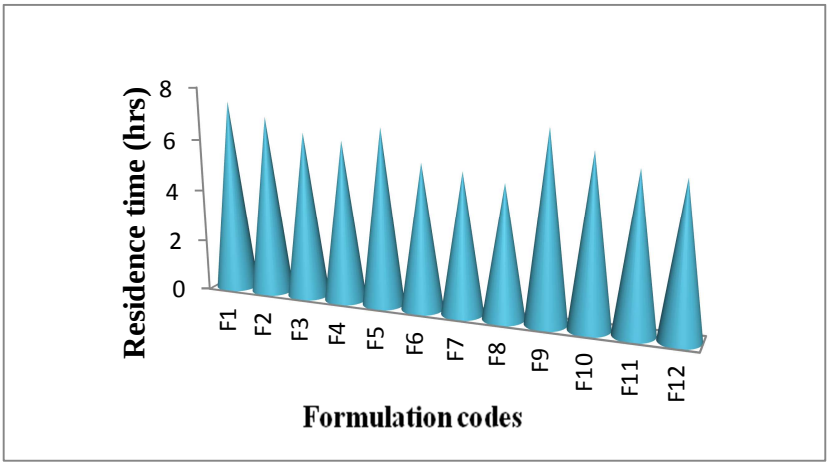

Figure 2: *Ex-Vivo* residence time for formulations F1-F12

In order to evaluate the performance of backing membrane (to find out the leakage of drug), permeation study was conducted. In the present investigation, this study was conducted for the optimized formulation F9 and the

percentage of drug permeation was found to be 60% for 12 hrs. From the permeation data, different permeation parameters like amount of drug permeated for 12 hrs, flux (J) and permeation coefficient Kp were determined. The flux and permeation coefficient for the optimized formulation was found to be 7.289 $mg/h^1/cm^2$ and 0.40423 cmh^{-1} respectively.

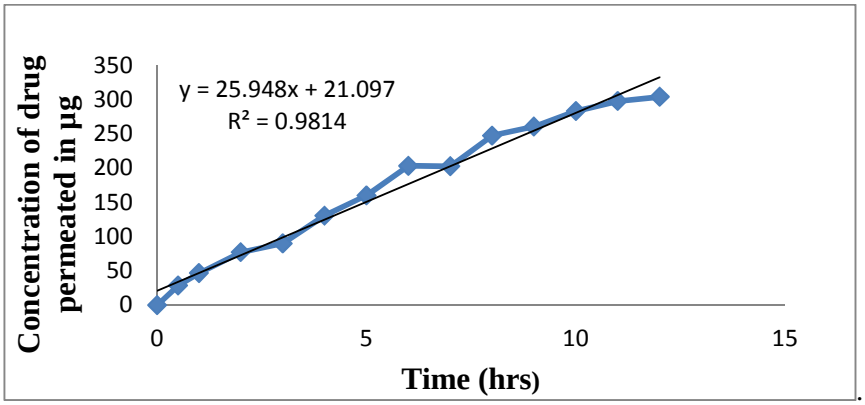

Figure 3: Permeation study of optimized formulation F9

3.2.1. *In-Vitro* Drug Release Study

The *In-Vitro* drug release study for different batches was conducted by using phosphate buffer pH 6.8. The formulations F1-F3 were prepared by using 30% w/w of olibanum, colophony alone and in combination respectively. The *In-Vitro* drug release was found to be 75% within 12 hrs, 64% in 12 hrs and 69% within 12 hrs respectively. From the release data, it was found that the employed concentration of the resin (30% w/w) retarded the release of the drug more than required and hence the concentration of the resins was reduced from the preceding concentration.

The formulations F4-F6 were prepared by using 20% w/w of olibanum, colophony alone and in combination respectively. The *in- vitro* drug release was found to be 82% within 12 hrs, 77% in 12 hrs and 84% within 12 hrs respectively. Formulations F4-F6 showed improved release rate when compared with formulations F1-F3, but not optimum within 12 hrs. This may be due to the fact that as resins are adhesive and highly hydrophobic in nature, decreasing the resin concentration decreases the ability of the matrix to confine the drug particles and increases the diffusion rate of the drug from the matrix. So, increasing the concentration of resin in the formulation increases the time taken for the drug to leave the matrix, thereby retarding the rate of release of the drug.

The formulations F10-F12 were prepared by using 15% w/w of olibanum, colophony alone and in combination respectively. The *in- vitro* drug release was found to be 94% within 9 hrs, 96% in 11 hrs and 96% within 8 hrs respectively. From the release data, it was clear that the resins employed in the concentration (15% w/w) were not sufficient to control the release of the drug from the formulations and hence the concentration of the resin was increased for further studies.

The formulations F7-F9 were prepared by using 17.5% w/w of olibanum, colophony alone and combination respectively. The *in- vitro* drug release was found to be 95% within 11 hrs, 85% within 12 hrs, 96% within 12 hrs respectively. It was observed that formulations F7-F9 provides optimum release of the drug up to a period of 12 hrs. From the release data, it was found that except F1and F2 batches, all the remaining formulations showing a biphasic release pattern, with an initial burst release of more than 30% within first two hours, confirming the concept of loading and maintenance dose.

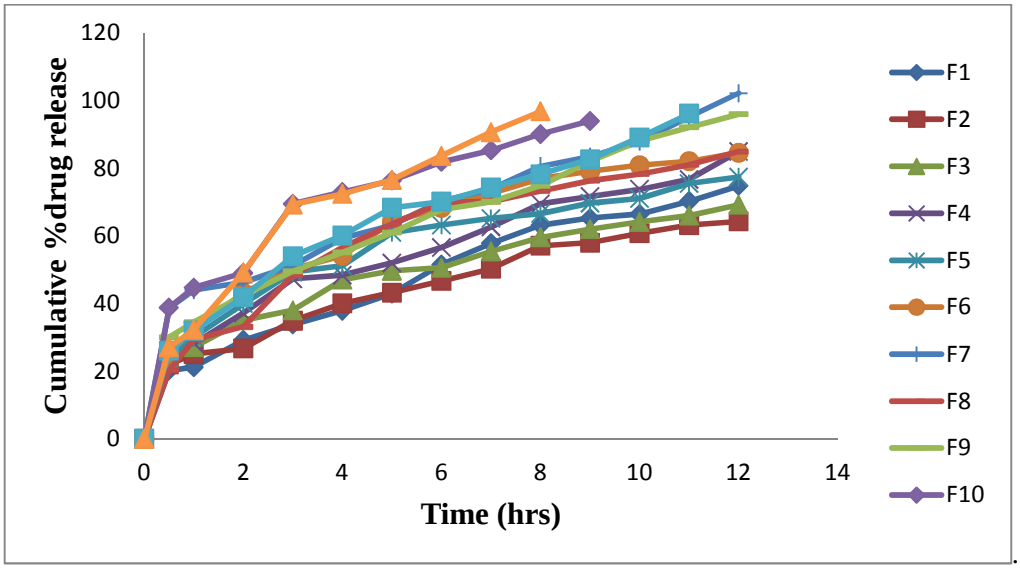

Figure 4: *In-Vitro* drug release profile for formulations F1-F12

Among different formulated batches, Formulations F9 was selected as optimized one as it releases around 96% of drug for a desired period of 12 hrs, with satisfactory mucoadhesion strength, residence time and good permeation coefficient.

3.3. Kinetic Analysis

When the release data were subjected to zero order and first order model high coefficient of determination (r^2) values observed for first order (0.902-0.985) rather than zero order (0.815-0.943), suggesting that drug release from different formulated batches following first order kinetics. The relative contributions of drug diffusion and matrix erosion were further confirmed by subjecting the data to Higuchi and Hixon-Crowell models. It was found that formulations made with olibanum in different ratios following Hixon-Crowell equation with high r^2 value of (0.977-0.990), suggesting that geometric shape of the tablet matrix diminishes proportionally over the time due to erosion of the resin. The formulations made with colophony in different ratios were following Higuchi model with high r^2 value of (0.982-0.988), suggesting that drug release from tablet followed matrix diffusion mechanism.

The formulations containing combination of olibanum and colophony in different ratios were following Higuchi model with high r^2 value (0.982-0.992) except formulation F3 (with 15% + 15% w/w ratio) following both Hixon-Crowell as well as Higuchi (r^2 value 0.982). So, in order to define a perfect model which will represent a better fit, the release data were subjected to Korsemeyer-Peppas equation to find out the diffusion coefficient (*n*) value.

Table 5: Release kinetics for formulations F1-F12

Formulation Codes	Zero Order		First Order		Higuchi		Korsemeyer's Peppas		Hixon-Crowell	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	*n*	r^2	K
F1	5.434	0.943	0.103	0.985	21.21	0.985	0.453	0.960	-0.122	0.990
F2	4.451	0.901	0.075	0.967	17.76	0.988	0.371	0.956	-0.09	0.982
F3	4.550	0.867	0.082	0.958	18.49	0.982	0.355	0.989	-0.094	0.982
F4	5.452	0.898	0.119	0.977	21.80	0.984	0.371	0.970	-0.130	0.990
F5	5.102	0.832	0.105	0.950	21.06	0.972	0.372	0.991	-0.114	0.957
F6	5.848	0.859	0.145	0.979	23.89	0.982	0.393	0.995	-0.149	0.976
F7	6.031	0.868	0.207	0.942	24.26	0.963	0.299	0.933	-0.191	0.977
F8	6.045	0.869	0.142	0.977	24.52	0.981	0.458	0.980	-0.152	0.964
F9	6.465	0.917	0.216	0.92	25.61	0.987	0.378	0.973	-0.204	0.967
F10	8.171	0.815	0.267	0.971	28.96	0.959	0.322	0.963	-0.241	0.982
F11	7.094	0.901	0.225	0.902	27.11	0.992	0.423	0.992	-0.214	0.958
F12	10.73	0.893	0.361	0.935	34.21	0.988	0.481	0.980	-0.334	0.974

The optimized formulation F9 containing blend of olibanum and colophony (8.75% + 8.75% w/w ratio) exhibited first order indicating that release of drug was concentration dependent. The mechanism of drug release for F9 formulation was found to be diffusion controlled, as F9 follows Higuchi model which was further supported by '*n*' value (0.378 i.e., < 0.5), so indicating Fickian diffusion. For, all the formulations F1-F12 value of '*n*' obtained is < 0.5, which indicates that all the formulations of different batches following Fickian diffusion.

3.4. Characterization of buccoadhesive tablets

3.4.1. FTIR analysis

Compatibility of excipients with the drug, as well as identification of drug was studied by FTIR studies (Shimadzu). FTIR of pure drug was characterized by O-H stretching at 3350 cm^{-1}, aromatic C-H stretching at 3076, aliphatic C-H stretching at 2833, C-O stretching at 1041 and asymmetric C-O-C stretching at 1033. Similar results were interpretated by Mitkare S *et al.*, confirming that the drug was venlafaxine [15]. The FTIR spectrum of different formulated batches was resulted in similar or slightly shifted in peak values when compared with the characteristic peak values of pure drug. The results of FTIR spectral studies showed that there were no significant interaction between the drug and resins. It was observed that there were no signs of major degenerative interactions to occur and hence the excipients could be used safely to formulate the buccoadhesive tablets**.**

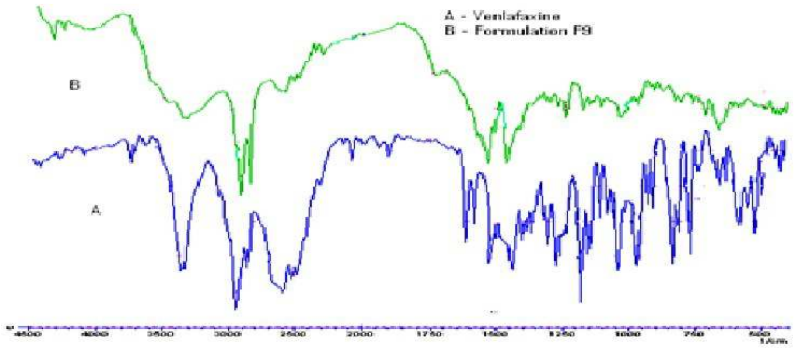

Figure 5: FTIR spectra of pure venlafaxine and formulation F9

3.4.2. DSC analysis

The thermal behavior of the drug as well as matrix tablets was investigated using differential scanning calorimeter (DSC 60, Shimadzu, Japan). The DSC thermogram for the drug gave a sharp melting endotherm at 215.38 ^{0}C. There was a slight decrease in the intensity of endothermic peak in case of formulation F9, indicating the partial physical transformation of the drug from crystalline to amorphous form in the matrix tablets. The comparative DSC thermo grams of the drug venlafaxine and optimized formulation (F9) were depicted in figure 6. The DSC study apparently revealed that the drug was compatible with the resin and neither drug decomposition nor drug-resin interactions occurred in the prepared buccoadhesive tablets.

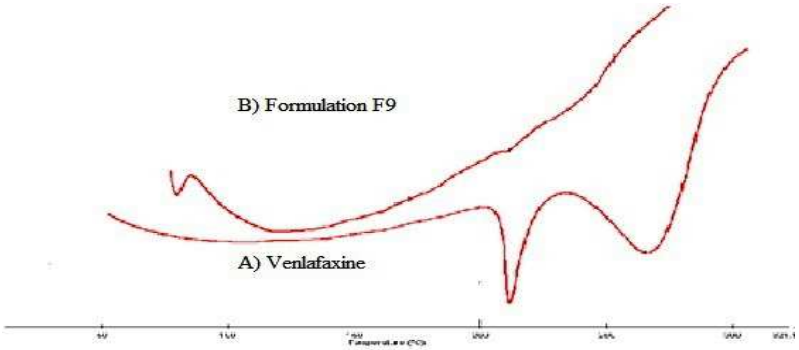

Figure 6: DSC spectra of pure venlafaxine and formulation F9

3.4.3. X-ray diffraction analysis

The thermal behavior coupled with the X-ray crystallographic data suggested that the diffractogram of pure venlafaxine indicates the crystalline structure of the drug. The diffractogram of pure drug and optimized formulation F9 shows a similar pattern with slight decrease in the intensity of the peaks, which suggests that the drug was able to disperse homogenously. This result confirms a partial transformation in the solid state of venlafaxine from crystalline to amorphous. Similar results were reported for other sustained release formulations had the same interpretation for venlafaxine [15].

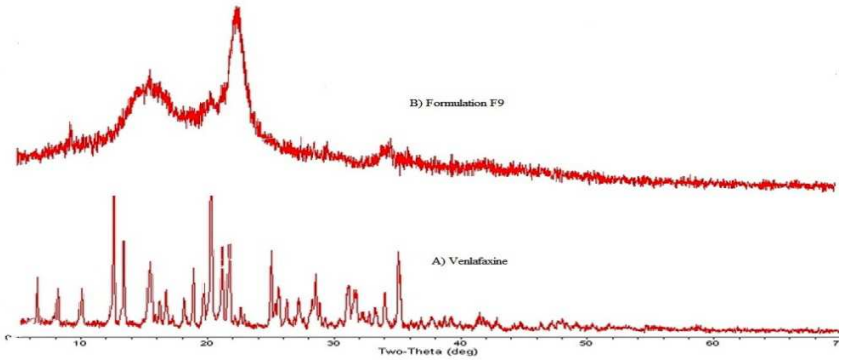

Figure 7: XRD spectra of pure venlafaxine and F9

CONCLUSION

The results suggested that, in an attempt to prepare buccoadhesive tablets of a drug like venlafaxine using olibanum and colophony resins was successful in enhancing the bioavailability and prolonging the therapeutic effect for the management of depression. In the present investigation, resins used are of natural origin, are non-toxic, biodegradable, readily available, inexpensive, ecofriendly when compared to synthetic polymers. The formulated tablets were can reduce the frequency of administration thereby reduces the chances of drawbacks that are associated with conventional venlafaxine tablets. The study conducted so far reveals a promising result suggesting scope for pharmcodynamic and pharmacokinetic evaluation.

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