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Development and *In-vitro* Evaluation of Mucoadhesive Buccal Patches of Sertraline HCL

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ABSTRACT

In the present study, an attempt was made to formulate mucoadhesive buccal patches of antidepressant drug Sertraline hydrochloride inorder to bypass the first pass metabolism. Buccal patches were prepared by solvent casting technique using polymers like Eudragit and HPMC E15LV.The prepared patches were evaluated for their weight variation, thickness, folding endurance, surface pH, swelling index, moisture uptake study, moisture absorbance study, drug content uniformity and *in- vitro* drug release and FTIR studies were conducted for Drug – Excipient compatibility testing. The optimized patches showed that the drug release indicates non- fickian release kinetics and diffusion as chain relaxation mechanism. Formulation F3 showed the highest release rate of 83.412% and concluded that all the prepared patches were effective and showed excellent sustained drug release.

Keywords: Sertraline, Mucoadhesion, buccal patch**.**

INTRODUCTION

Sertraline Hcl is a selective serotonin reuptake inhibitor (SSRI) antidepressant and anxiolytic agent[1].The oral bioavailability of Sertraline is about 45% because of extensive first pass metabolism in liver and gut wall. Buccal routes of drug delivery offer distinct advantages over oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract, these factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery[2]. Moreover buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage from the buccal cavity therefore mucoadhesive drug delivery devices such as patches[3], tablets[4], films, gels ointments and discs[5] were suggested. Thus sertraline Hcl was selected as a model drug for investigation because of its suitable properties like dose strength (10mg), half

life (6hrs) and molecular weight (342.69 g/mol). In the present study, the mucoadhesive buccal patches were developed using polymers such as sodium alginate, HPMC E15LV, Eudragit at different proportions to get the controlled release rate from the buccal patches.

MATERIALS AND METHODS

Materials

Sertraline HCL was obtained from Glukempharmaceuticals, Hyderabad, India. Sodium alginate and Eudragit were obatined from lobachem pvt ltd, Mumbai. HPMC E15LV obtained from Molychem pvt ltd, Badlapur, Mumbai. Other solvents and materials used for the study were of analytical grade.

Method of Prepatation

Patches were prepared by solvent casting technique. Patches composed of sodium alginate, HPMC and Eudragit were prepared by taking weighed quantity of polymer and gradually added it with constant stirring to onethird of the required volume of distilled water (60◦C) and the final volume is made up by adding cold water. Glycerin was added in the polymeric solution as a plasticizer. The homogenously prepared gel was left overnight at room temperature to obtain a bubble free film. The gel was then poured into the plastic rings which were stuck to the floor of Petri dish and allowed to dry at 40◦C in an oven. The prepared patches were cut in to $1\times1cm^2$ packed in a suitable wax paper for further evaluations[5].

EVALUATION

Preformulation Studies

Drug–excipient compatibility study

Potassium bromide pellet method was employed to record the FT-IR spectra of pure drug, drug with mixtures of sodium alginate,HPMC,Eudragit in 1:1 ratio on Shimadzu FT IR – 8400 spectropho-tometer (Shimadzu Corporation, Kyoto, Japan). Each spectrum derived from single average scans collected in the region 400 – $4000cm^{-1}$ at spectral resolution of $2cm^{-2}$ and ratio against background interferogram[6].

Melting point Determination

Fusion technique was used in which the drug was filled in the fine capillary tube whose end was closed by fusion and Placed the tube in to the electrical melting point apparatus.The temperature at which the drug starts melting was recorded as melting point. The mean of the three readings was recorded.

Formulation studies

Weight uniformity of patches

Five patches of size $1\times1cm^2$ were weighed and the weight variation was calculated[7].

Thickness uniformity of the films

The thickness of each film was measured by using digital vernier calipers at five different positions of the patch and the average was calculated[8].

Folding Endurance

The folding endurance of each patch was determined by repeatedly folding the patch at the same place till it was broken or folded up to 300 times, which is considered satisfactory to reveal good film properties[9].

Surface pH

The prepared buccal patches were left to swell for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warmed phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature4.The surface pH was determined

by pH paper placed on the surface of the swollen patch. The mean of three readings was recorded[10].

In-vitro Swelling Studies

The swelling rate of Buccoadhesive patch was evaluated by placing the film in phosphate buffer solution pH 6.8 at 37±0.5^{0}C. Intial weight of Buccal patch when placed in a 2% (w/v) agar gel plate and incubated at 37 ±1^{0}C was (W1). At regular intervals (upto 1 h), the patch was removed from the petridish and excess surface water was removed carefully using the filter paper. The swollen patch was then reweighed (W2) again and the swelling index was calculated[11] by the formula

$$\text{Swelling index} = \frac{W2 - W1}{W1}$$

Moisture Content and moisture absorption

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed[12]. The moisture content (%) was determined by calculating moisture loss (%) using the formula 1.

$$\text{Moisture content (\%)} = \frac{\text{Initial weight - final weight} \times 100}{\text{Initial weight}}$$

The Buccal patches were weighed accurately and placed in a deccicators containing100ml of saturated solution of aluminum chloride, which maintains 76% and 86% humidity (RH). After 3 days, films were taken out and weighed. The moisture absorption was calculated using the formula.

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight - initial weight} \times 100}{\text{Initial weight}}$$

Drug content uniformity

The patches were tested for the content uniformity by dissolving 1×1cm^2 patches in 100ml distilled water with simultaneously shaking for 6hrs. The absorbance of the solution was measured by UV spectrophotometrically at 224nm using corresponding blank solution[13].

In-vitro drug release

The in vitro drug release study was carried out using a modified dissolution test apparatus using commercially available dialysis membrane , and the effective diffusion area was 1.8cm^2. The receptor compartment was filled with 200ml of pH 6.8. Phosphate buffer saline. The patches were applied under occlusion on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37 ± 0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of drug released into the receptor medium was quantified by using UV–Visible spectrophotometer at 224 nm against a blank. The drug release data of the *in vitro* dissolution study was analyzed with various kinetics equations like zero order, first order, matrix, Peppas and Hixon crowell model. Coefficient of correlation (r) values were calculated for linear curves obtained by regression analysis of the plots.

RESULTS -INFERENCE

Drug – Excipient compatibility study

FT-IR spectrum results were shown in figure1 (a)-1(c). It indicates that there were no interaction between the drug and polymers used.

Melting point

248^{0}C.

Weight and thickness uniformity of patches

Results shown in Table 2 indicates uniform thickness.

Folding Endurance

No cracks - shows excellent folding endurance having good strength to withstand all environment variations as depicted in Table 2 and Figure 2.

Surface pH

All the five prepared patches show slightly acidic pH as depicted in table 2.

In-vitro Swelling Studies of Buccoadhesive patch

Results showed that all the patches shows good swelling index as shown in table 3. The order of percentage swelling was found to be $F_1>F_2>F_4>F_3>F_5$. Results concluded that VF_1 formulation shows more swelling index as shown in figure 3 due to the presence of more concentration of sodium alginate in the formulation.

Moisture Content and moisture absorption

The moisture content and uptake (%) study was done at high relative humidity like 76% of 3 days were shown in table 3. Increasing the concentration of hydrophilic polymer in the formulation shows moisture uptake. Low moisture content data shows that the patches were capable to protect from the microbial growth.

Drug content uniformity

Results indicated that drug was distributed uniformly in all the preparations and the percentage drug content value ranges from 99.36 – 98.15 as shown in table 3.

In-vitro drug release and release kinetics

Dissolution profiles of all five formulated patches were done by using modified dissolution test apparatus as shown in figure 4 in presence of pH 6.8 Phosphate Buffer Solution. For better comparison of dissolution profiles, dissolution data up to 8hrs was plotted in Figures 5 and dissolution efficiency was calculated. According to the results, the dissolution rates of F3 are remarkably faster than all other formulation as indicated in table 4. Release kinetics were performed using dissolution data and it was found to be all the formulated patches following peppas model as depicted in table 5 having the release exponent (n> 0.45) and the r^2 value is near to 1 for all the patches thus following non– fickian diffusion mechanism (case II transport).

DISCUSSION

The average weights of formulated patches range from 41.6mg to 56.20mg found tobe satisfactory.The film thickness was observed in the range 0.29 to 0.44mm. The folding endurance values were found to be optimum., highest for formulation F2 while the lowest for F3.All the patches exhibited good physical and mechanical properties. The surface pH values of all the five formulations were found to be 6.2 to 6.4 indicates no risk of mucosal damage or irritation. Swelling index increased as the weight gain by the patches increased proportionally with the rate of hydration due to sodium alginate as shown in Table3. All the formulations passes test for drug content uniformity and show acceptable results of 98.15% to 99.36%. This indicates that the drug dispersed uniformly throughout the polymeric surface. *In- vitro* drug release studies revealed that Sertraline HCL from different formulations varies with composition of polymers. The release rate decreased with increasing concentration of sodium alginate which acts as a release retardant main polymer. The Buccal patch prepared with sodium alginate and co polymer HPMC E15LV (F3) has good release profile of 83.412% for 8hrs when compare to other formulations. This was due to the fact that by increasing the density of the polymer

matrix at high concentration results in an increase in diffusion path length. This may finally results in decrease the drug release from the polymer matrix. To study the release mechanism of Sertraline HCL the drug release data was fit in to several kinetics and release models. From the data of drug release, it was found that, the maximum percent release of Sertraline HCl from the formulation F3 was 83.412% as promote dissolution and hence the release, of the highly water soluble drug. From the peppas equation the obtained values of 'n' lie between 0.5 to 1.0 in the optimized formulations for release of Sertraline HCL indicates non- fickian release kinetics, which indicates the drug release mechanism involves diffusion as chain relaxation as shown in table 5. Finally it was concluded that all the hydrophilic co polymers which were used for the study provides the sustained release of Sertraline HCL as per the limits according to USP. Thus it was concluded that formulation F3 could be used to release Sertraline HCL uni-directionally in buccal cavity for extended period of time without the risk of mucosal irritation.

CONCLUSION

This study clearly demonstrated that Sertraline can be successfully delivered through buccal route. The patches were non-irritating with favorable film properties and showed sufficient mucoadhesive potential until the drug is absorbed from the formulation. The *in-vitro* study is considered a useful methodology for screening Sertraline buccal patches formulations to be considered for further studies such as clinical evaluation. Further, it is also proved that the combination of sodium alginate: HPMC E15LV meets the ideal pre-requisites for a buccal delivery of Sertraline to avoid the disadvantages of parenteral and oral routes.

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Table 1. Composition of Sertraline HCL mucoadhesive Buccal patches

Patch code	Sertraline Hcl (mg)	Sodium alginate(mg)	HPMC E15LV (mg)	Eudragit (mg)	Glycerine (mg)	Water (ml)
F1	10	200	-	100	211	8
F2	10	200	-	200	211	8
F3	10	200	100	-	211	8
F4	10	200	200	-	211	8
F5	10	200	-	-	211	8

Table 2. Characteristics of mucoadhesive Buccal patches containing Sertraline HCL

Patch code	Weight Uniformity (mg)	Thickness (mm)	Folding endurance	Surface pH
F1	11 ± 0.05	0.244 ± 0.003	312	6.2 ± 0.05
F2	11 ± 0.04	0.23 ± 0.002	320	6.4 ± 0.03
F3	12 ± 0.05	0.241 ± 0.002	306	6.3 ± 0.03
F4	12 ± 0.06	0.238 ± 0.003	319	6.4 ± 0.03
F5	12 ± 0.05	0.229 ± 0.002	317	6.3 ±0.03

Table 3. Moisture Content, Moisture Absorption, Swelling Study and mucoadhesive strength for the Prepared Formulations

Patch code	Moisture content (%)	Moisture absorption (%)	Swelling index (%)	Drug content (%)
F1	20	81.81	95	98.15
F2	36.36	45.45	93.21	99.36
F3	27.27	54.54	87.69	99.15
F4	33.33	36.36	90.44	99.29
F5	36.36	54.54	84.96	99.22

Table 4. Drug content uniformity and *In- vitro* drug release data for the prepared formulations

Time (hrs)	F1	F2	F3	F4	F5
0	0.000	0.000	0.000	0.000	0.000
1	19.491	22.089	23.820	30.574	21.483
2	32.933	33.034	34.775	41.480	27.490
3	37.445	37.459	39.210	45.346	42.620
4	48.647	49.008	49.903	47.413	52.466
5	55.927	57.503	59.614	55.033	57.516
6	64.286	64.051	65.828	66.762	66.663
7	72.403	73.146	78.396	74.832	75.079
8	75.248	80.471	83.412	78.875	79.124

Table 5. Release kinetics exhibited by the prepared formulations

Patch code	Mathematical models					
	Zero order	First order	Higuchi	Hixson	Peppas model	
	r^2	r^2	r^2	r^2	n	r^2
F1	0.9605	0.9957	0.9865	0.9937	0.6083	0.9963
F2	0.9647	0.9879	0.9846	0.9934	0.6083	0.9934
F3	0.9632	0.9806	0.9831	0.9906	0.5065	0.9905
F4	0.9696	0.9940	0.9809	0.9951	0.4261	0.9969
F5	0.9622	0.9898	0.9853	0.9926	0.5774	0.9947

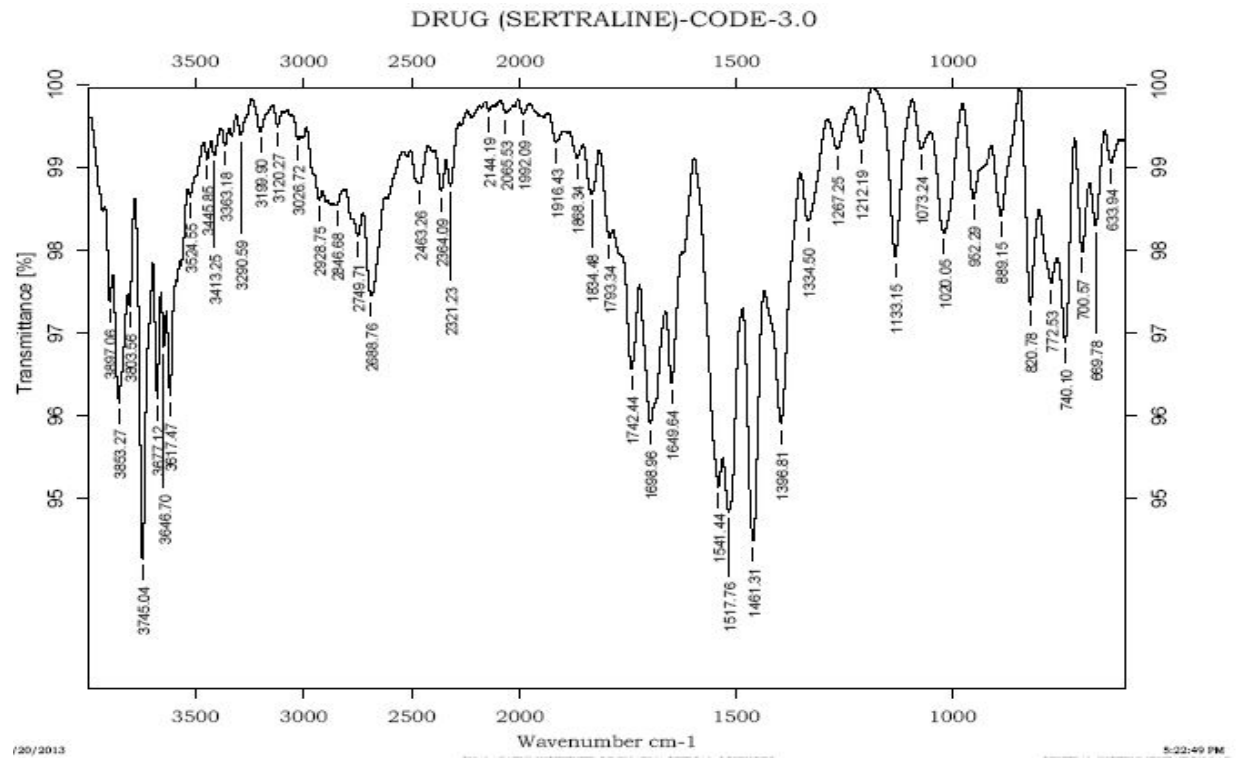

Figure.1(a) FT-IR spectra for pure drug

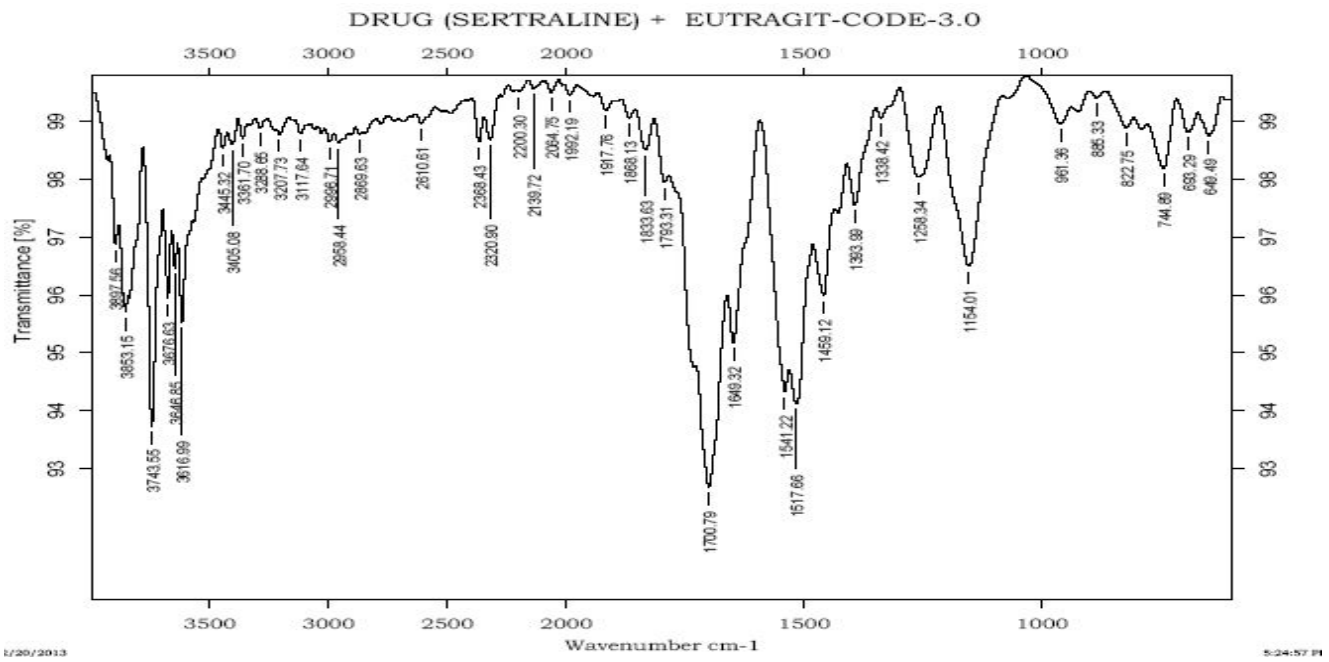

Figure. 1(b) F T-IR spectra for drug+Eudragit

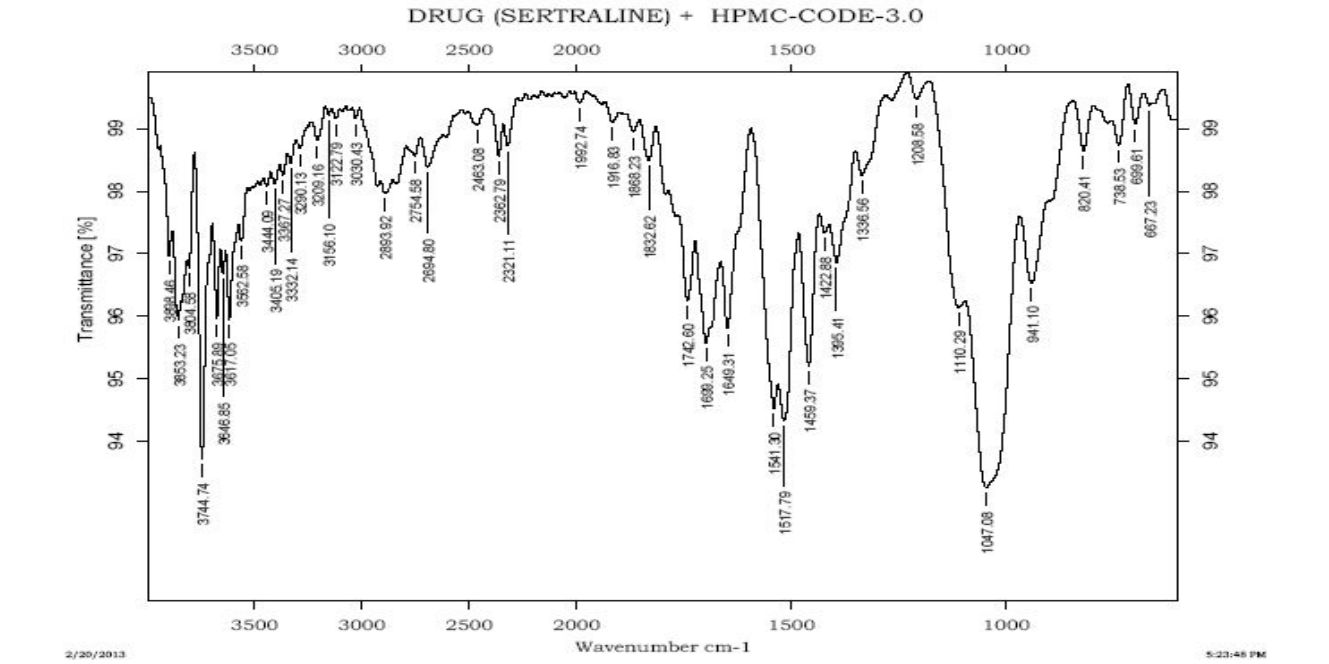

Figure. 1(c) F T-IR spectra for drug+HPMC

Figure.2. Surface pH Study for the formulated patches