

DESIGN AND EVALUATION OF CHITOSAN CONTAINING MUCOADHESIVE BUCCAL PATCH OF FLUXOTINE HCL

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Abstract- The main objective of present study was to design and evaluate the Muco adhesive buccal patch. The buccal region is an attractive route of administration for systemic drug delivery. To provide prolonged desire state concentration of Fluxotine Hydrochloride with minimal fluctuation and improved bioavailability, a mucoadhesive buccal patch is designed in the present study that Fluxotine hydrochloride is an antidepressant with selective serotonin reuptake inhibitor, its oral bioavailability is 80% because of first pass metabolism.

In this study Mucoadhesive buccal patches were prepared with chitosan dissolved in glacial acetic acid and glycerol as plasticizer. Mucoadhesive patch containing 20mg of Fluxotine Hcl were evaluated with respect to their *invitro* drug permeation through goat buccal mucosa in 3 hr by using Franz diffusion cell, weight variation, uniformity of film, Area of the film, determination of % yield of buccal patch, percentage moisture loss, Mucoadhesive strength, folding endurance, drug content uniformity, swelling behaviour and surface pH were obtained. The physicochemical interaction between drug and polymer were investigated by FTIR spectroscopy revealed that there is no interaction.

Then the formula could be promising for the fabrication of buccal patches.

Index Terms- Fluxotine Hcl, buccal patches, invitro release, evaluation

I. INTRODUCTION

Recent years have seen an increasing interest in the development of novel mucoadhesive buccal dosage forms. These are useful for the systemic delivery of drug as well as for local targeting of drug to a particular region of the body. Buccal delivery for the transmucosal absorption of the drug into the systemic circulation offers number of advantages for those drugs that suffer from first pass metabolism in the liver, poor oral bioavailability. Conceivably buccal delivery systems provide easy administration, thereby increasing patient compliance.[1],[2]. FLUXOTINE HCL is an SSRI (selective serotonin reuptake inhibitor) used mainly as an antidepressant to treat major depression, bipolar disorder, obsessive compulsive disorder, bulimia nervosa, panic disorder and premenstrual dysphoric disorder. Fluxotine hydrochloride was selected as the model drug for the investigation because it has got certain characteristics that a drug should possess to get absorbed through

buccal route viz., biphasic solubility and low molecular weight (309.33 g/mol). Moreover it undergoes first-pass metabolism, so its bioavailability may be improved when delivered through buccal route.[3]

The main aim was to prepare mucoadhesive buccal patches by using different concentration of mucoadhesive polymer to drug ratio in order to obtain desired concentration of the drug when compared to conventional dosage forms. As the bioavailability of conventional dosage form is less than 80%

II. MATERIALS AND METHODS

Materials

FLUXOTINE HCL was obtained as a gift sample from NATCO PHARMA LTD. Hyderabad. Chitosan was provided from Hi Media Laboratories Pvt. Ltd Mumbai.PVP K-30, glycerol, glacial acetic acid were obtained from S.D. Fine Chemicals, India. All other reagent and chemicals were of analytical grade.

Methods

SOLVENT CASTING METHOD: *Preparation of mucoadhesive buccal patches:*

1%,2%(m/V) of chitosan was dissolved in 10 mL 1.5% (V/V) acetic acid under occasional stirring for 12 hr. The resulting viscous chitosan solution was filtered through nylon gauze to remove debris and suspended particles. To improve patch performance and release characteristics, a water-soluble hydrophilic additive, PVP K-30, was added in different concentrations. The drug and PVP K-30 were added into the chitosan solution under constant stirring. PEG 6000 was added into the solution as plasticizer under constant stirring. This viscous solution was left overnight at room temperature to ensure a clear, bubble-free solution. The solution was poured into a glass Petri dish (16 cm diameter) and allowed to dry at ambient temperature till a flexible film was formed. Dried films were carefully removed, checked for any imperfections or air bubbles and cut into patches of 16 mm in diameter, containing 20 mg of drug per patch.[4],[5]. The patches were packed in aluminum foil and stored in an airtight glass container to maintain the integrity and elasticity of the patches. **TABLE 1** contains the compositions of different formulations.

TISSUE ISOLATION:

Buccal tissue was taken from goat at a slaughter-house. It was collected within 10 minutes after slaughter of the goat and tissue was kept in **Krebs buffer solution**. It was transported immediately to the laboratory and was mounted within 2 hours of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffer saline to remove any adherent material. The

buccal membrane from the tissue was isolated using surgical procedure. Buccal membrane was isolated and buccal epithelium was carefully separated from the underlying connective tissue. Sufficient care was taken to prevent any damage to the buccal epithelium.[6]

TABLE 1: Composition of chitosan buccal patches of fluxotine hydrochloride

COMPONENTS	F1	F2	F3	F4
FLUXOTINE(mg)	20	20	20	20
CHITOSAN	0.1	0.1	0.2	0.2
PEG200(ml)	1		1	-
PEG6000(ml)	-	1	-	1
PVP (gm)	0.01	0.01	0.01	0.01
VANILLIN(gm)	0.02	0.02	0.02	0.02
DISTILLED WATER(ml)	5	5	5	5

EVALUATION OF PATCHES:

Mass uniformity and patch thickness. – Assessment of mass and thickness was done on ten patches. The mean and standard deviation were calculated.

Content uniformity:

The drug loaded patch was allowed to dissolved in 100mL phosphate buffer, pH 6.8 The amount of fluxotine in the patch was measured spectrophotometrically at λ_{max} of 226 nm (n = 3).

Surface pH. – Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (m/V) agar in warmed isotonic phosphate buffer of pH 6.75 under stirring and then pouring the solution into a Petridish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of three readings was recorded.

Folding endurance test. –The folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties.

The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Radial swelling:

Radial swelling was determined by diameter method. After determination of the original patch diameter, the patch was

allowed to swell on the surface of an agar plate kept in an incubator maintained at 37°C. Measurement of the diameter of the swollen patch was done at one hour intervals for 6 h. Radial swelling was calculated from the following equation:

$$SD (\%) = [(Dt - Do) / Do] \times 100$$

Where SD (%) is the percent swelling, Dt is the diameter of the swollen patch after time t, and Do is the original diameter of the patch at time zero.

Drug content uniformity:

The amount of drug contained in the patch was determined by dissolving the patch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 8 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml, and the resulting solution was filtered through a 0.45 μ m Whatman filter paper. The drug content was then determined after proper dilution by UV spectrophotometer (Shimadzu-1700 Japan) at λ_{max} of 226 nm. The experiments were carried out in triplicate

In vitro Swelling Studies of Buccoadhesive patch: The degree of swelling of bioadhesive polymer is important factor affecting adhesion. Upon application of the bioadhesive material to a tissue a process of swelling may occur. The swelling rate of buccoadhesive patch was evaluated by placing the film in phosphate buffer solution pH 6.8 at 37±0.5 oC. Buccal patch was weighed (W1), placed in a 2% (w/v) agar gel plate and incubated at 37 ±10C. At regular one-hour time intervals (upto 3 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]

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

Bioadhesion force:

The tensile strength required to detach the bioadhesion patch from the mucosal surface was applied as a measure of the bioadhesion performance. The apparatus was locally assembled and mainly composed of two-arm balance. The left arm of the balance was replaced by a small platinum lamina vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the mucosal membrane. For determination of bioadhesion force, the mucoadhesive patch was fixed to the platinum lamina using cyanoacrylate adhesive. A piece of rabbit intestinal mucosa was also glued to the platform. The patch surface was moistened with 10 µL of phosphate buffer and left for 20 s for initial hydration. On the right pan, a constant weight of 5 g was added at 2 min interval, until the hydrated patch was brought into contact with the mucosal surface. The total weight required for complete detachment of the patch was recorded and the bioadhesion force was calculated per unit area of the patch as follows:

$$F = \frac{(Ww \times g)}{A}$$

where F is the bioadhesion force (kg m⁻¹ S⁻²), Ww is the mass applied (g), g is the acceleration due to gravity (cm s⁻²), A is the surface of the patch (cm²). The bioadhesion force data reported represent the mean of three determinations.[7],[8]

In vitro drug release study:

For in vitro release study, goat buccal mucosa membrane was used as a barrier membrane with Phosphate buffer (pH 7.4) as a medium. The patches were evaluated for drug release using franz diffusion cells. Buccal mucosa membrane was mounted between the donor and receptors compartments. The patch was placed on the mucosal membrane. The diffusion cell was placed in a **simulated saliva** maintained at 37±2°C. The receptor compartment was filled with 50 mL phosphate buffer (pH 7.4) and hydrodynamics was maintained by stirring with a magnetic bead at 300 rpm. Five mL sample was withdrawn and replaced with 5 mL fresh medium to maintain the sink condition. The samples were analyzed in U.V. spectrophotometer at 226 nm.[9],[10]

Fig.1: *in vitro* Buccal Permeations studies:



COMPOSITION OF SIMULATED SALIVA: 2.38 g Na₂HPO₄, 0.19 g KH₂PO₄ and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.75[12]

DRUG RELEASE PROFILE:

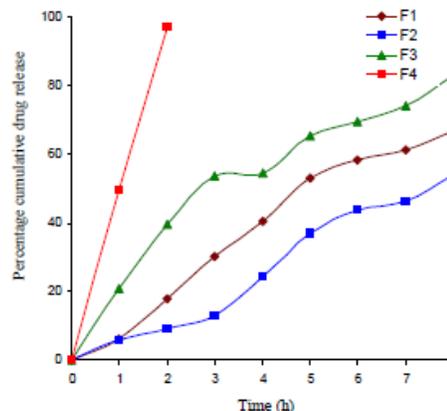


FIG: 1 In vitro drug release profiles of different formulations through buccal membrane

TABLE NO: 2 Characteristics of mucoadhesive buccal patch of fluxotine hcl:

s.no	characteristics	F1	F2	F3	F4
1	Content uniformity(%)	95.44	95.68	98.75	97.20
2	Patch weight(mg)	117	124	156	148
3	Patch thickness(mm)	1.02	1.01	1.04	1.03
4	Surface ph	7	7	7	7
5	Folding endurance	>300	>300	>300	>300
6	Radial swelling(h)	7.28	7.43	9.54	9.14
7	Swelling index	128.4	129.8	143.5	138.4
8	Bioadhesive force kg/m/s ²	45.34	50.7	65.60	58.46
9	% drug release	85.65	88.45	98.45	92.33

FTIR STUDIES:



FIG: 2 FTIR spectra of chitosan

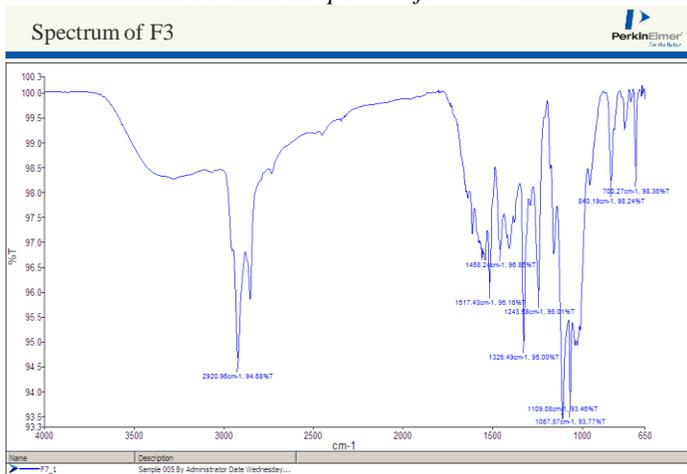


FIG: 3 FTIR spectra of optimizes formulation

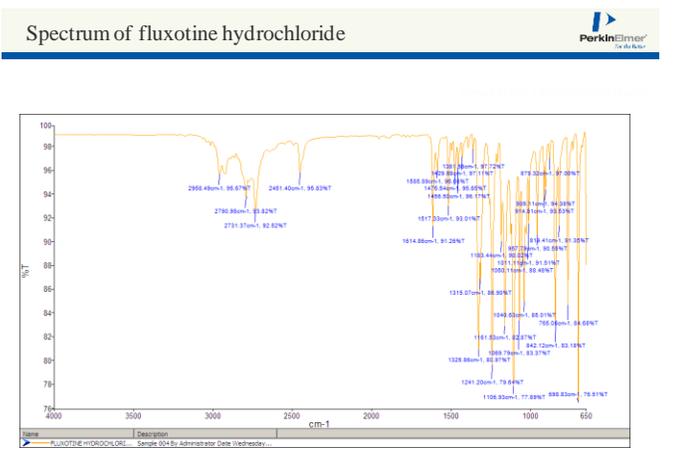


FIG: 4 FTIR spectra of drug (fluxotine HCL)

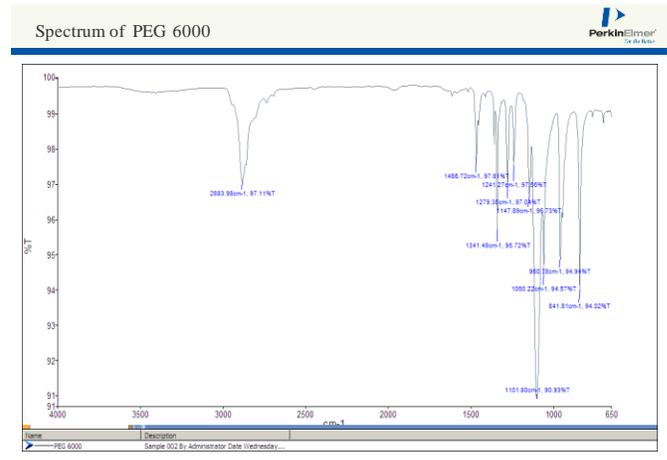


FIG: 5 FTIR spectra of PEG 6000

III. RESULTS AND DISCUSSION

The results of Physical Characteristics of patches containing individual concentration of polymer are shown in Table 2. The patches were 10 mm in diameter, and 1.01±0.01 to 1.07±0.02 mm in thickness. The weight ranged from 117±0.15 to 123±0.22 mg.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa. The surface pH of the buccal films was determined to optimize both drug permeation and muco adhesion. Attempts were made to keep the surface pH as close as to salivary pH. The pH values of all the formulations were within the range of salivary pH. No significant difference was observed in surface pH for different formulations. The surface pH of all formulations was nearer to neutral (≈7) and hence no mucosal irritation was expected. The folding endurance was measured manually, by folding the film repeatedly at a point till they were broken. The breaking time was considered as the end point. The recorded folding endurance of the patch was > 300 times. The patch exhibited good physical and mechanical properties. Assessment of the swelling behavior was done by measuring radial swelling. F3 patches showed high radial swelling, followed by f4 and then f2 ; All the formulations showed good mucoadhesive strength. Among the formulations F3 showed maximum mucoadhesive strength while formulation F1 showed less mucoadhesive strength. Maximum bioadhesion was recorded for f3 (65.60 x 102 kg m-1s-2), followed by the f4 (58.46 x 102 kg m-1s-2), then f-2 (50.7 x 102 kgm-1s-2).

Drug content in all formulations was found to be uniform ranging from 95.2% to 97.9%. This indicates that the drug was dispersed uniformly throughout the patches. The *in vitro* drug release a study was performed using cellophane membrane.

The release profile of mucoadhesive buccal patches is shown in Fig.1. The extent of fluxotine release within 1h from f-1, f-2 and f-3 and f-4 patches was 85.65%, 88.45% , 98.45% and 92.33% respectively. FTIR studies were performed and has been showed and clearly shows that there is no interactions between drug and selected polymers. Chitosan patches containing 10 mg fluxotine were subjected to 2- months storage at 37± 0.5o C and 75± 0.5 RH and found that they exhibit excellent drug content over the

storage period. The folding endurance test revealed good flexibility and elastic properties. The formulation F4 did not control the release and it releases the fluxotine as immediate release formulation, but F3 offers promising drug release pattern and good swelling index.

IV. CONCLUSION

It may be concluded that adhesion of buccal drug delivery device to mucosal membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug. Mucoadhesive patches

are a promising drug delivery system for fluxotine in maintaining drug level in blood. The mucoadhesive polymer chitosan showed good mucoadhesive and swelling characteristics.

From the present investigation, one can conclude that the optimized Bucco-adhesive patches of Fluxotine hydrochloride with the combination of chitosan PEG 200, PEG 6000 and PVP K-30 can meet the ideal requirements for buccal devices, which can be a good way to bypass the extensive hepatic first pass metabolism

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