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Formulation and Characterization of Bioadhesive Buccal Drug Delivery System of Testosterone

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***Abstract* — The objective of present study was to formulate and evaluate mucoadhesive buccal drug delivery system of testosterone. The system was prepared by solvent evaporation method using natural biodegradable mucoadhesive film forming chitosan polymer. The formulations were then characterized for various physicochemical parameters viz, thickness, folding endurance, surface pH, drug content, swelling index, moisture absorption and in vitro drug release study. The in vitro drug release from different formulations was studied using USP XXIV six station dissolution test apparatus type-1. The results of various physicochemical properties were in the range of acceptable limit. The drug release profile from these films followed nonfickian diffusion as the value of diffusion release exponent (η) is in the range of 0.712 to 0.858.**

***Keywords* — Novel Drug Delivery, Bioadhesive, Chitosan, Steroidal Drug.**

1. INTRODUCTION

In current years, considerable attention has been focused on the development of novel drug delivery system (NDDS) in place of developing new drug molecule. This approach is adopted owing to relatively low development cost and time required for introducing new NDDS product [1]. Pharmaceutical compound in a form of NDDS product gets another life as well as increases its market value, competitiveness and patent life. Among the various NDDS buccal drug delivery system is one of the most extensively studied system [2]. The buccal route offers several advantages over conventional route [3]. Researchers have tried to deliver a drug through the buccal cavity including antihypertensive, antimicrobials [4], [5], topical corticosteroids [6], and polypeptides [7]. Buccal film should be compatible to the buccal cavity like bioadhesive, non toxic, non irritating, non immunogenic, soft yet adequately strong to withstand breakage due to stress from intra mouth activities [8].

Testosterone is androgen and anabolic hormone and it is clinically used as a supplement therapy in men and women for androgen deficiency. Since testosterone undergoes extensive first-pass metabolism after oral administration [9], conventional treatment for testosterone consist of periodic intramuscular injections of chemically modified testosterone or oral administration of methyl testosterone. Recently, many alternative formulations have been developed for testosterone administration including the transdermal drug delivery system [10]. Among these, buccal patch is considered to be safer and cost effective than other preparations.

The purpose of proposed work was to prepare and evaluate buccoadhesive film containing testosterone for androgen deficiency in man and women that can be use to the buccal mucosa to deliver testosterone at a desired rate for 8 hour. The buccal route is an advantageous alternative for systemic drug delivery. It is also helpful in avoiding parenteral medication. The buccal route has high bioavailability and has no first pass effect. Thus, it is suitable for testosterone administration. There is considerable literature available for mucoadhesive polymers as carriers for steroids [11], [12]. Chitosan is most preferred polymer to be used for buccal delivery because it is inert, non toxic, non irritant, inactive, compatible polymer and moreover it has mucoadhesive property, that allow it to stay in the oral cavity for longer period of time and release the drug in a controlled release manner towards the mucosa [13]. Chitosan polymer serves as an absorption enhancer by transient opening of the tight junctions in the buccal mucus membranes to allow permeation transmucosally. Chitosan showed penetration enhancement properties towards monostratified epithelia. It is able to enhance absorption of drug molecules through across buccal mucosa [14]. Therefore proposed, bioadhesive testosterone film would also be able to overcome all the drawbacks of the presently available replacement therapy of testosterone. Buccal films as compared to tablet take less space and adhere properly on the mucus membrane, thereby overcoming the side effects of buccal tablet.

2. MATERIALS AND METHODS

2.1. MATERIALS

The sample of testosterone USP was supplied generously by M/s Sun Pharma Advance Research Centre, Varodara, India. Chitosan (purified viscosity grade: 50 cps, molecular weight: 150 KDa, deacetylation degree: 85%) was purchased from (Sigma Chem. Co., St. Louis. MO). The other chemicals used were either analytical reagent or laboratory reagent grade.

2.2. PREPARATION OF THE TESTOSTERONE BUCCAL FILMS

Buccal films containing testosterone were prepared by solvent evaporation technique by taking aluminium foil cups (placed on glass mould) as the substrate. Compositions of various formulations are given in Table

1. Chitosan was dissolved in 50 mL of 0.5% (v/v) acetic acid under constant stirring using a magnetic stirrer (Remi Pvt. Ltd, India) for 2 hours. The resultant viscous solution was filtered through a muslin cloth and the filtrate was sonicated in bath sonicator (PCI Ltd., Mumbai, India) for 30 min to remove air bubbles. Testosterone was dissolved in minimum quantity of the absolute alcohol and mixed well with the above polymer solution and again sonicated. Polyethylene glycol 400 and tween 80 was also added before sonication. This polymer mixture (20 mL) was poured on the aluminium foil placed on plain glass mould. These moulds were placed in the oven (Yorko India Pvt. Ltd) and dried the film in oven at 40± 5^{o}C for 6 hours. After drying, the films were carefully removed checked for any defect like wrinkles and air bubbles and then cut into pieces of 1x1 cm^2 size. These films were wrapped in aluminium foil, placed in self sealable polyethylene bags, and then stored in tightly closed container.

3. Evaluation of Testosterone Buccal Films

3.1. DETERMINATION OF THICKNESS AND FOLDING ENDURANCE

Films thickness was measured at six different places using a Screw gauge (Nisco Ltd., India). The mean thickness of the buccal films was calculated. The Folding endurance of the films was determined by repeatedly folding the film. The number of times the film could be folded at the same place without breaking was noted as the value of the folding endurance [15].

3.2. MEASUREMENT OF SURFACE PH

Surface pH of the film was determined by keeping the film to swell for 1 hour on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warmed phosphate buffer saline (PBS) pH 6.8 under stirring and then pouring the solution into a petridish till gelling at room temperature. Surface pH of the film was measured with the help of a pH paper. After 60 seconds, the developed color was compared with the standard color chart [16].

3.3. DETERMINATION OF DRUG CONTENT

Films (1x1 cm^2 size) were weighed accurately and transferred into a separate 100 ml volumetric flask. Initially 10 ml double distilled water was added to dissolve the film and then about 90 ml absolute alcohol added to dissolve remaining ingredients. The solution was filtered, and the amount of drug was determined by spectrophotometrically at 241 nm [17].

3.4. DETERMINATION OF SWELLING INDEX OF THE FILMS

Swelling index of the film was determined by taking difference in initial weight and weight at time t of the buccal films. Three films of each formulation were allowed to swell on the surface of agar plate by keeping in an incubator (JSGW Pvt. Ltd, India) maintained at 35±5 ^{o}C. Increase in weight of the films (n=3) was determined at every one hour interval for 8 hour. The percent swelling was calculated using the following equation.

$$\% \text{ Swelling Index} = (Wt - Wo / Wt)\ 100$$

Where Wt is the weight of swollen film after time t, Wo is the initial weight of film at zero time.

3.5. DETERMINATION OF MOISTURE ABSORPTION OF THE FILMS

The films were dried in oven at 35±5 ^{o}C till a constant weight. Then these dried films were placed in a desiccator maintained at 75±5% RH (containing saturated solution of sodium nitrite). After 3 days, the weight of films was determined and percentage moisture absorption was calculated using following formula [18].

% Moisture absorption = (Wt. of exposed film - Wt. of dry film/ Wt. of dry film) X 100

3.6. IN VITRO DRUG RELEASE STUDY

In vitro drug release study from buccal films was determined by using USP XXIV six station dissolution test apparatus type-1 (Labindia, India). Each formulation was fixed to the central rotating shaft of dissolution test apparatus using adhesive. The dissolution medium phosphate buffer (pH 6.8) 40% PEG 400, 200 ml was filled in the vessel and the release study was carried out at 37±02^{o}C with a rotation speed of 50 rpm. After every 1 hour, 10 ml samples were withdrawn from each station and immediately replaced with fresh medium, the release study was performed for 8 hours. The samples were analyzed by spectrophotometrically at 241 nm.

The kinetics of drug release from the buccal films was determined using the formula given by Peppas, and used to study the drug release behavior from the polymeric drug delivery systems. The drug release kinetic parameters from buccal films were calculated as follows [19].

$$M_t/M_\omega = K\ t^{\eta}$$

Where M_t/M_ω is the fractional release of the drug, t denotes the release time. K is a constant incorporating structural and geometric characteristic of the controlled release device and η is the diffusion release exponent, indicative of the drug release.

The value of η was calculated from the slope of log (M_t/M_ω) Vs log (t) plot of different formulations of buccal films.

4. Results and Discussion

Buccal films bearing testosterone were prepared by solvent evaporation method as composition shown in Table 1. The prepared films were characterized for various physicochemical parameters viz. thickness, folding endurance, surface pH, drug content, swelling index, moisture absorption and in vitro drug release study. The in vitro drug release from different formulations was studied using USP XXIV six station dissolution test apparatus type-1. The results of physicochemical parameters summarized in Table 2. Film thickness was in the range of 0.49±0.36 to 0.67±0.28 mm. The folding endurance of buccal films

was determined manually, and found to be as high as 249 and more than 200 for all the films. This indicates that all the films are good in term of mechanical strength and film Ts5 is better in terms of mechanical strength and flexibility. The folding endurance of the films mainly depends on the concentration of plasticizer.

The surface pH of the films was found to be in the range of 6.5±0.5 to 7.0±0.5 for all the formulations. Thus the surface pH of the films was close to the physiological pH (6.8) of the buccal mucosa. Hence, it may be expected that these films may not cause any irritation to the buccal mucosa after their application. Drug content of the prepared films was found to be uniform in a range of 5.63±0.16 to 5.81±0.24 mg per cm^2 for formulation Ts1 to Ts6. Swelling index and moisture absorption was determined. However, both the parameters are related to each other in some extent. Swelling index was in the range of 6.39% to 10.34% and moisture absorption was in the range of 7.56% to 12.42%. This deviation may be due to difference in percentage of polymer content and it increased on increasing polymer quantity. In vitro drug release study from buccal films was performed by using USP XXIV six station dissolution test apparatus type-1. All the sox formulations showed good release property; however formulation Ts5 showed better results (Figure 1) as it offered 83.31 cumulative percentage drug releases for 8 hours which may increase in some more extent during in vivo conditions. Formulation Ts1 showed highest and formulation Ts6 showed lowest percentage release. Therefore, formulation Ts5 considered as developed formulation. The release data were fitted for the determination of release mechanism with help of model fitting. The drug release profile from the films followed nonfickian diffusion as the value of diffusion release exponent (η) is in the range of 0.712 to 0.858 (Table 3).

5. Conclusion

In this work the developed formulation may be effective and convenient drug delivery system for testosterone replacement therapy. Mucoadhesive chitosan film can be adhere and deliver the drug at a controlled rate manner for an extended period of time. The system may be popular substitutes among the available testosterone dosages forms. Moreover, newly developed system would also likely to overcome all the drawbacks of the presently available dosages form of testosterone.

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TABLE 1. COMPOSITION OF FORMULATIONS OF BUCCAL FILMS

Ingredients	Formulation Code					
	Ts1	Ts2	Ts3	Ts4	Ts5	Ts6
Testosterone (mg)	50	50	50	50	50	50
Chitosan (%w/v)	0.5	1	1.5	2	2.5	3
Acetic acid (0.5%v/v) q.s. ml	20	20	20	20	20	20
Propylene glycol 400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Tween 80 (ml)	0.5	0.5	0.5	0.5	0.5	0.5

TABLE 2. EVALUATION OF TESTOSTERONE BUCCAL FILMS ON VARIOUS PARAMETERS

Film Code	Thickness (mm)	Folding Endurance	Surface pH	Drug Content (mg/cm^2)	% swelling Index	% Moisture Absorption
Ts1	0.49±0.36	248	7.0±0.5	5.71 ± 0.36	6.39	7.56
Ts2	0.52 ± 0.24	239	6.5 ± 0.5	5.63±0.16	7.26	8.98
Ts3	0.58 ± 0.23	233	6.5 ± 0.5	5.69 ± 0.23	8.31	10.24
Ts4	0.61 ± 0.26	228	6.8 ± 0.5	5.74 ± 0.45	9.14	10.93
Ts5	0.64 ± 0.13	230	6.5±0.5	5.81±0.24	9.87	11.68
Ts6	0.67±0.28	225	6.5 ± 0.5	5.66 ± 0.58	10.34	12.42

Values = mean ± S.E.M (n = 3)

TABLE 3. VALUES OF DIFFUSION RELEASE EXPONENT FROM IN VITRO RELEASE STUDY

S. No.	Formulation Code	Diffusion Release Exponent (η)
1.	Ts1	0.712
2.	Ts2	0.729
3.	Ts3	0.858
4.	Ts4	0.825
5.	Ts5	0.838
6.	Ts6	0.723

FIGURE 1: CUMULATIVE PERCENTAGE DRUG RELEASES VS TIME FROM BUCCAL FILMS