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# Formulation and evaluation of mucoadhesive buccal patches of Tramadol hydrochloride

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## ABSTRACT

The goal of present investigation highlights the formulation and evaluation of mucoadhesive buccal patches of Tramadol hydrochloride. The mucoadhesive buccal patches of Tramadol hydrochloride were prepared by solvent casting technique using various concentrations of Chitosan polymer. The formulated patches were evaluated for their physicochemical parameters like thickness, weight variation, surface pH, content uniformity, folding endurance swelling percentage studies and *in vitro* residence time. *In vitro* release studies were performed with pH 6.8 phosphate buffer solution. Good results were obtained both in physicochemical and in vitro studies. The films were exhibited controlled release more than six hours. The in-vitro release datas were fit to different equation and kinetic models to explain release profiles. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation R6. The formulation was found be right and suitable candidate for the formulation of Tramadol HCL mucoadhesive buccal patches for therapeutic use.

**Key words**: Tramadol HCL, Chitosan, Mucoadhesive buccal patches, PVP K-30.

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## INTRODUCTION:

There is always increasing demand for the patient convenience, compliance related research and novel methods of drug delivery systems which gives the better results than the conventional formulations. Buccal delivery is considered to be a major alternative to the oral and parenteral routes of systemic drug delivery[1]. The buccal mucosa provides readily accessible route for transmucosal delivery[2]. Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastro intestinal tract, avoids active drug loss due to presystemic metabolism, acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved[3]. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane[4]. The work on buccoadhesive patch containing Tramadol HCl, yet not found, hence this is an area of our interest. Being a non-toxic, biocompatible and biodegradable polymer, chitosan has been widely used for pharmaceutical and biomedical applications and sustained release of formulations[5]. It has also been used as a pharmaceutical excipient in conventional dosage forms as well as in novel applications involving bioadhesion and transmucosal drug transport[6].

Tramadol HCL is a central acting analgesic used in management of chronic pain, recommended as second line treatment of neuropathic pain[7]and also used in the treatment of osteoarthritis to produce inadequate pain relief. The half-life of a drug is about 5.5 hrs and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hrs with a maximum dosage of 400 mg/day[8]. To reduce the frequency of administration and to improve patient compliance, a mucoadhesive patch formulation of Tramadol is developed. The buccal patches were prepared by solvent casting method using chitosan, PVP K-30 and evaluated for different physiochemical parameters.

## MATERIAL AND METHODS

Tramadol Hydrochloride was obtained as gift sample from B&T Pharmaceuticals, Hyderabad; Chitosan, Polyvinyl Pyrrolidone K-30 and Propylene glycol were obtained from SD fine chemicals, Bangalore. The other chemicals were used are of analytical grade.

### Preparation of Mucoadhesive Buccal Patch[9, 10]

The buccal mucoadhesive patches from chitosan polymer were prepared by solvent casting technique using various proportions of chitosan and PVP K-30 as mentioned in Table.1. The polymeric solution of chitosan was prepared using 1.5% (V/V) acetic acid in distilled water under occasional stirring for 48 h. To enhance the drug release character a water-soluble

hydrophilic additive polyvinyl Pyrrolidone (PVP K-30) was added into the chitosan solution under constant stirring. Propylene glycol (5%, V/V) was added as plasticizer under constant stirring. The resultant solution was left overnight at room temperature to ensure a clear, bubble-free solution. The solution was poured into a glass petri dish having 9.5 cm diameter. The weighed quantity of Tramadol HCl was added to polymeric solution and stirred well to get clear solution. The dummy patch without drug was also prepared. The Petri dishes were kept on flat surface and covered by inverted funnel to allow controlled evaporation of solvent at 40$^{o}$C till a flexible film was formed. Dried films were carefully removed, checked for any imperfections or air bubbles and cut into patches of 10mm in diameter. The patch containing Tramadol HCl drug was packed in aluminium foil and stored in an airtight glass container to maintain the integrity and elasticity of the patches.

**Table 1: Composition of Tramadol HCl buccal mucoadhesive patches**

| Formulation code | Chitosan[a] (50 ml) | PVP K-30 (mg) | Propylene Glycol | Drug[b] (mg/70.84cm2 area) |
|---|---|---|---|---|
| Placebo | 1 % | 50 | 5 % | - |
| R1 | 1 % | 50 | 5 % | 902 |
| R2 | 1 % | 100 | 5 % | 902 |
| R3 | 1 % | 150 | 5 % | 902 |
| R4 | 1.5 % | 50 | 5 % | 902 |
| R5 | 1.5 % | 100 | 5 % | 902 |
| R6 | 1.5 % | 150 | 5 % | 902 |
| R7 | 2 % | 50 | 5 % | 902 |
| R8 | 2 % | 100 | 5 % | 902 |
| R9 | 2 % | 150 | 5 % | 902 |

a Chitosan solution has been made in 1.5 % acetic acid.

b 10 mg drug per 1x1 cm2 patch.

**Evaluation of Buccal Patches**

**Thickness and weight uniformity[10]**

The thickness of three randomly selected buccal patches from each batch was determined using a standard screw gauge. Weight uniformity of patch was tested by taking weight of five patches of sizes 10 mm diameter from each batch and weigh individually on electronic balance and the average weight was calculated.

**Content uniformity[5]**

Drug content uniformity was determined by dissolving the buccal patch (10 mm in diameter) from each batch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 6 h under occasional shaking. The 5 ml of resulting solution was diluted to 20ml with buffer and

filtered through a Whattman filter paper. The drug content was then determined after proper dilution and measured the absorbance at 271 nm using a UV-visible spectrophotometer.

**Folding endurance**[2]

Folding endurance of the patches were determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three patches from each batch.

**Surface pH**[11, 12]

Buccal patches were left to swell for 1 hr on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then poured the solution into the petridish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

**Swelling percentage study**[13]

Swelling study of prepared buccal patch was calculated by function of weight and area increase due to swelling, which was measured for each formulation as follows.

**a) Weight increase due to swelling**: Patches of 10 mm size (1 x 1 $cm^2$) diameter from each batch were weighed on a pre weighed cover slip. It was kept in a petri dish and 10 ml of phosphate buffer, pH 6.8 was added. After one hour, the cover slip was removed and weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

**b) Area increase due to swelling**: The prepared buccal patch was allowed to swell on the surface of the agar plate kept in an incubator maintained at 37± $0.5^0$C. Measurement of the diameter of the swollen patch was done at hourly intervals of 5 h. Radial swelling was calculated from the following equation:

$$\%S = \frac{X_t - X_o}{X_o} \times 100$$

Where %S is the percent change in radial swelling of patches, $X_t$ is the diameter of the swollen patch after time t, $X_o$ is the original diameter i.e., at time zero.

***In vitro* residence time**[14]

The *in vitro* residence time was determined employing a modified USP disintegration apparatus. The disintegration medium was composed of 800 ml isotonic phosphate buffer of pH 6.8 (IPB)

maintained at 37± 0.5$^0$C. A piece of porcine buccal tissue, 3 cm length was used for this study. The tissue was attached to a rectangular glass piece using cyanoacrylate adhesive from non-mucosal surface. The mucoadhesive patch was hydrated from one surface using pH 6.8 IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was observed and recorded (n=3).

***In vitro* release study**[14]

This was carried out in a USP dissolution apparatus type 1 (eight-station dissolution apparatus, TDT 08L, Electro lab, India), with a modification in order to take care of the small volume of dissolution medium. The dissolution medium, 50 ml IPB, pH 6.8, maintained at 37± 0.5$^0$C was kept in a glass beaker placed inside the dissolution flask. The patch was attached to end of the shaft (without basket) with the help of cyanoacrylate adhesive, which was rotated at 50 rpm. Samples (2 ml) were withdrawn at intervals of 1, 2, 3, 4, 5, 6 and 7 hrs and filtered using Whattman filter paper. The withdrawals were compensated using equal volumes of IPB kept at the same temperature. The concentration of drug released in the medium was assayed spectrophotometrically at 271 nm after suitable dilution with the dissolution medium whenever necessary. The experiment was carried out three times.

## RESULTS AND DISCUSSION

Buccal films of Tramadol hydrochloride were prepared by solvent casting technique employing a glass petri dish lined with aluminium foil having diameter of 9.5 cm with mucoadhesive polymers of Chitosan and PVP K-30. Propylene glycol was used as the plasticizer as well as penetration enhancer. The drug delivery system was formulated as a matrix controlled drug delivery. The prepared buccal patches were evaluated or characterized based upon their physicochemical properties like thickness, weight variation, surface pH, content uniformity, folding endurance,swelling percentage studies and In-vitro residence time. The results were shown in Table.2 & 3. In-vitro release studies were performed by using USP dissolution apparatus type 1 (eight-station dissolution apparatus, TDT 08L, Electro lab, India), with a modification in order to take care of the small volume of dissolution medium. The dissolution medium, 50 ml IPB, pH 6.8, was thermostated at 37± 0.5$^0$C was kept in a glass beaker, placed

inside the dissolution flask. The patch was attached to end of the shaft (without basket) with the help of cyanoacrylate adhesive so that the drug released only from one side.

**Table 2: Physicochemical characteristics of prepared buccal patches of Tramadol HCl**

| Formulation Code | Thickness[a] (mm) | Weight[b] Uniformity(mg) | Surface pHa | Content Uniformity(%) | Folding Endurance |
|---|---|---|---|---|---|
| **Placebo** | 0.23 ± 0.01 | 21.4 ± 1.59 | 6.12 ± 0.47 | -------- | 234 |
| **R1** | 0.27 ± 0.04 | 37.6 ± 1.63 | 5.42 ± 0.28 | 96.66 | 223 |
| **R2** | 0.30 ± 0.03 | 39.6 ± 1.53 | 5.50 ± 0.16 | 98.14 | 248 |
| **R3** | 0.32 ± 0.03 | 41.1 ± 1.64 | 5.47 ± 0.09 | 95.51 | 256 |
| **R4** | 0.35 ± 0.02 | 40.7 ± 1.61 | 5.59 ± 0.12 | 94.82 | 253 |
| **R5** | 0.56 ± 0.04 | 41.5 ± 1.31 | 5.72 ± 0.21 | 96.94 | 266 |
| **R6** | 0.59 ± 0.06 | 46.2 ± 1.38 | 5.62 ± 0.44 | 90.58 | 272 |
| **R7** | 0.61 ± 0.01 | 43.2 ± 1.38 | 5.98 ± 0.53 | 92.94 | 245 |
| **R8** | 0.64 ± 0.02 | 50.3 ± 1.33 | 6.43 ± 0.23 | 99.87 | 287 |
| **R9** | 0.73 ± 0.03 | 53.1 ± 1.25 | 6.65 ± 0.33 | 95.82 | 290 |

a n=3; standard deviation for three determinations.

b n=10; standard deviation for ten determinations.

**Table 3: Physical and mucoadhesive characteristics of prepared buccal patches**

| Formulation Code | swelling index[a] | | In-vitro[a] Residence Time (hour) |
|---|---|---|---|
| | % Weight Increase After 1 Hour | % Area Increase After 6 Hour | |
| **Placebo** | 11.64 ± 0.25 | 17.40 ± 0.28 | 3.00 ± 0.25 |
| **R1** | 12.15 ± 2.84 | 18.33 ± 1.04 | 3.10 ± 0.30 |
| **R2** | 14.45 ± 1.35 | 20.66 ± 1.50 | 2.55 ± 0.20 |
| **R3** | 20.23 ± 1.26 | 24.33 ± 1.61 | 2.13 ± 0.30 |
| **R4** | 13.82 ± 1.21 | 19.33 ± 1.25 | 3.25 ± 0.25 |
| **R5** | 16.73 ± 2.56 | 22.11 ± 1.08 | 3.45 ± 0.35 |
| **R6** | 26.56 ± 1.93 | 23.66 ± 1.12 | 3.15 ± 0.10 |
| **R7** | 18.27 ± 1.26 | 17.98 ± 1.04 | 3.50 ± 0.20 |
| **R8** | 21.56 ± 3.04 | 19.55 ± 1.35 | 3.30 ± 0.30 |
| **R9** | 25.36 ± 3.86 | 21.66 ± 1.52 | 3.15 ± 0.10 |

a n=3; standard deviation for three determinations

The thickness (Table 2) of formulated patches was ranges from 0.27 ± 0.04 to 0.73 ± 0.03 mm, while the average weight of patch from each batch ranges from 37.6 ± 1.63 to 53.1 ± 1.25 mg. The surface pH of patches was ranges from 5.42 ± 0.28 to 6.65 ± 0.33 were found around neutral pH. The content uniformity recovery was possible to the tune of 90.58 to 99.87 %. Films did not show any cracks even after folding for around 250 for all batches. The placebo chitosan base matrix shows less swelling index. The weight increasing order of swelling percentage of batches are R6 >R9 >R8 >R3 >R7 >R5 >R2 >R4>R1> Placebo. The area after 6 hour increased in ordered of R3 >R6 >R5 >R9 >R2 >R8 >R4 >R1 >R7 > Placebo. Time requires for the complete erosion or detachment of buccal patches from the mucosa was found satisfactory. Table 3 had shown in results of the residence time. In general, mucoadhesion is considered to

occur in three major stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors such as molecular mass of polymers, contact time with mucus, swelling rate of the polymer and the biological membrane used in the study Thus, residence time of batch R2 from 1% chitosan, R6 from 1.5% chitosan and R7 from 2% chitosan was found to be 3.10 ± 0.30h, 3.15 ± 0.10h and 3.50 ± 0.20h respectively, had shown good bioadhesion properties. The cumulative percentage of drug dissolved in buffer pH 6.8 for the period of 6 h at temperature 37± 0.5 $^{o}$C are analyzed by using UV-Spectrophotometer at 271 nm wavelength. The drug release increased linearly with the increasing concentration of PVP K-30 from batches R1 to R3, R4 to R6, and R7 to R9 containing 1%, 1.5 %, and 2 % Chitosan base respectively. The maximum *in vitro* release was found to be 82.60 % over a period of 6 h in batch R6, containing 20 ml of 1.5% chitosan base and high concentration of PVP K-30 (Fig. 1). The films also subjected to FTIR studies showed no interaction between the polymer and the drug, Tramadol Hydrochloride.

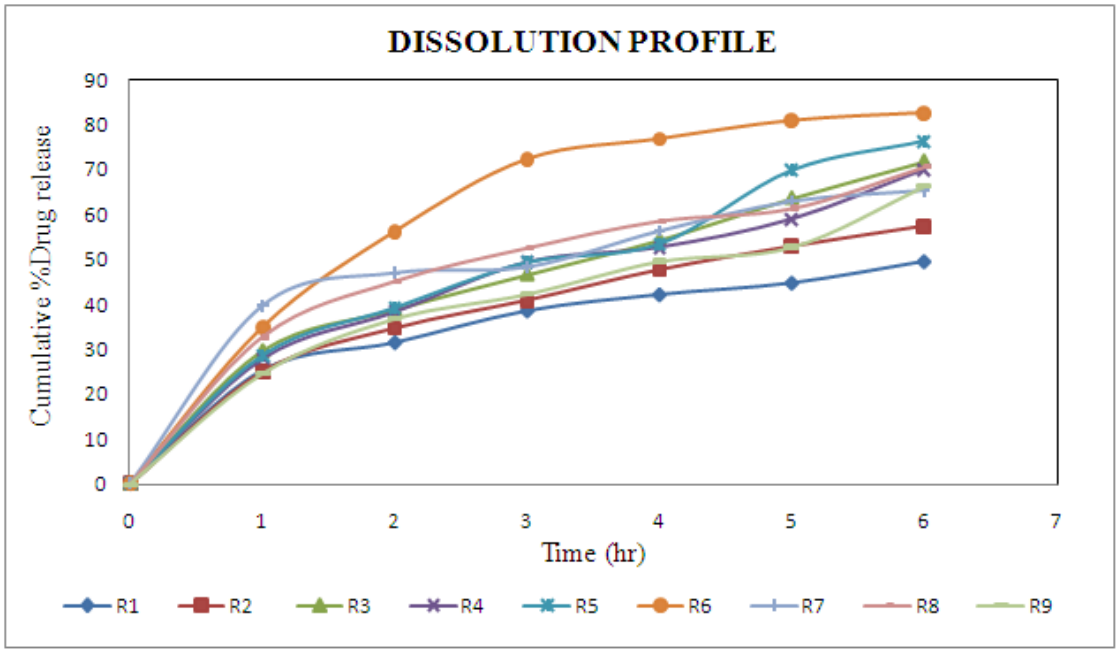


**Figure 1:Dissolution profile of Tramadol Hydrochloride buccal patch**

The thickness and weight variation might be due to increasing concentration of chitosan and PVP K-30. The surface pH study indicates no mucosal irritation was expected between the pH reported in table 2 for each batch. Folding endurance did not vary when the comparison was made between plain films and drug loaded patches (Table 2). Due to poor aqueous solubility of chitosan, the placebo of chitosan base matrix shown less swelling index. The results mentioned cleared that; the increasing concentration of PVP K-30 increases the swelling percentage. Also

the swelling percentage of placebo batch was found less, might be due to absence of water soluble drug. PVP K-30 increased the surface wettability and consequently water penetration within the matrix, hence increased weight and area. In residence time, the increasing concentrations of PVP-K30 allow swelling the buccal patch and made hydrogen bonding weaker. The buccal patch R7 has highest 3.50 ± 0.20 hour and batch R1 has less 3.10 ± 0.30 hour residence time. From the obtained data, we conclude that the Chitosan base has good bioadhesion properties in appropriate concentration, and good bond strength forming capacity with mucin. But as the concentration of PVP K-30 increases, the bioadhesion was found very less, may be due to hydrophilic natures which loosen the bond strength with mucosal area. So patch might be detached as it absorbed water molecule. Mean while some formulation batches had shown less mucoadhesion. The reason might be due to increasing concentration of both Chitosan and PVP K-30[5], The drug release finding was also supported by the reported swelling studies where the highest swelling index was also exhibited by batch R6, indicating that the increase in water-soluble polymer PVP K-30 content result in faster swelling and release from patches.

## CONCLUSION

A new buccoadhesive patches for sustained released of Tramadol hydrochloride was developed by chitosan in appropriate ratio. Chitosan has not only film forming but also good bioadhesion properties with drug Tramadol hydrochloride. The drug release rate increases on inclusion of PVP K-30 into the chitosan base matrix system and can be modifying for kinetic study. So lastly we conclude that, chitosan with PVP K-30 can meet the ideal requirement for buccal devices, which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability. The prepared formulation was found to be right and suitable candidate for the formulation of Tramadol HCl buccal patches for therapeutic use.

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