

# FORMULATION AND EVALUATION OF SUBLINGUAL FILM OF PRAZOSIN HYDROCHLORIDE

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## ABSTRACT

**Objective:** The aim of present research work is formulate and evaluate sublingual films of Prazosin HCl.

**Materials and Methods :**Formulation of sublingual films were done using solvent casting method. Various polymers and plasticizers are screened for initial trials. Aspartame was used as sweetener and citric acid as saliva stimulation agent.

**Results:** Acceptable mechanical properties were obtained for optimized batch with *in-vitro* disintegration time of 33 secs. On the basis of data obtained from *in-vitro* dissolution study that O1 is promising formulation suitable for the immediate release of Carvedilol for the systemic use since they exhibited maximum drug release. Batch O1 found stable for 1 month during stability study. Hence, O1 is the optimized batch.

**Conclusion:**The results of the present study indicated that Pullulan could be used as a film forming polymer and PEG 400 as a plasticizer for formulation of fast dissolving sublingual films containing Prazosin HCl.

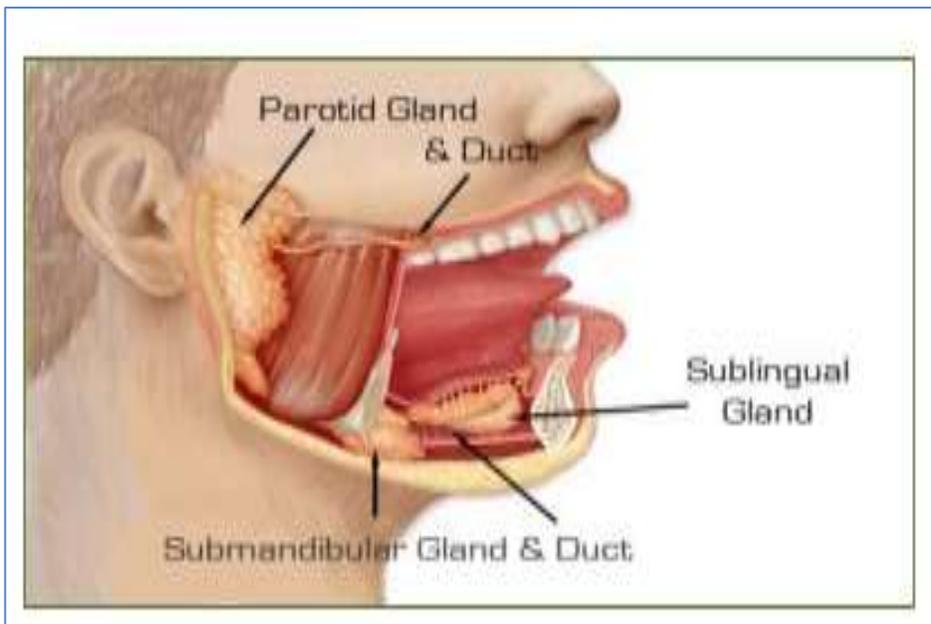
**Key Words:**Prazosin HCl, Sublingual film.

## • INTRODUCTION

Salivary organs are available in the floor of the mouth under underneath the tongue. They are otherwise called sublingual organs. They deliver mucine thusly creates salivation. The inside territory of the mouth stays lubed because of generation of the spit by the organs, which is important for biting and sustenance gulping. The liquid which is created by the organs gets blend with the nourishment, so the sustenance gets effortlessly bit. Because of low discharge of the spit it can make issue in gulping the sustenance and potential for nourishment hold up in the throat increments.

The assimilation is exchange of the medication from its site of organization into fundamental dissemination, so it tends to be said that retention is specifically relative layer thickness. The ingestion of the medication following along these lines Sublingual >Buccal> Gingival >Palatal.Due to high penetrability and rich blood

supply, the sublingual course can create quick beginning of activity so the medication with short conveyance period can be conveyed and portion regimen is visit. The medication gets weakened in the salivation and from that point the medication is adsorbed over the oral cavity.



Sublingual gland

- **Advantages:-**

- ✓ Drug given by sublingual route can easily absorbed by sublingual mucosa so it can directly come to the blood circulation and it will provide quick onset of action.
- ✓ As the drug comes in direct contact with large oral mucosa low dose give high efficacy.
- ✓ The formulation can bypass hepatic first pass metabolism so it will reduce hepatotoxicity and other GI side effect.
- ✓ In emergency condition like asthma attack, angina attack the sublingual formulation is highly recommended for quick response.
- ✓ As the drug comes in direct contact with large oral mucosa low dose give high efficacy.
- ✓ There is no need of water to engulf the formulation. It is a painless, highly accurate drug formulation gives more patient compliance compare to other formulation.
- ✓ As the drug bypass the GI tract side effect of drug regarding GIT is overcome.

- **Disadvantage**

- ✓ High dose cannot be administered
- ✓ Not suitable for bitter and irritating drugs
- ✓ Less patient compliance
- ✓ Eating and drinking, smoking is not allowed.
- ✓ Highly ionic drug cannot be administered.

- **Sublingual formulations**

- A. Bioadhesive sublingual tablet
- B. Fast-disintegrating sublingual tablets
- C. Thin film drug delivery
- D. Lipid matrix sublingual tablet
- E. Sublingual immunotherapy
- F. Sublingual vitamin tablet

- **Ideal Characteristics of A Drug to be Selected**

- ✓ Should have pleasant taste.
- ✓ Low dose of drug up to 40mg.
- ✓ Low molecular weight.
- ✓ Good stability and solubility in water/ saliva.
- ✓ Unionized at the pH of oral cavity.
- ✓ Ability to permeate the oral mucosal tissue.

### **Solvent casting method**

In this method, firstly the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size

### **. FTIR Study**

The Fourier transform infrared spectrum of moisture free powdered sample of Drug and final formulation was recorded on IR spectrophotometer by potassium bromide (KBr) pellet method. The range of spectra was found to be 400 to 4000  $\text{cm}^{-1}$ . The characteristics peaks of different functional group were compared with reported standard peak.

### **Pre-Formulation Studies**

#### **1) Bulk density and tapped density**

An accurately weighed quantity of the API (W), was carefully poured into the graduated cylinder and the volume ( $V_0$ ) was measured. Then the graduated cylinder was set for 100 taps and after that the volume ( $V_f$ )

was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas.

$$\text{Bulk density} = W/ V_0, \text{ Tapped density} = W/ V_f$$

## 2) Compressibility index (CI) / Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

$$\% \text{ Carr's index} = (T.D. - B.D. \div T.D.) \times 100$$

## 3) Hausner's ratio

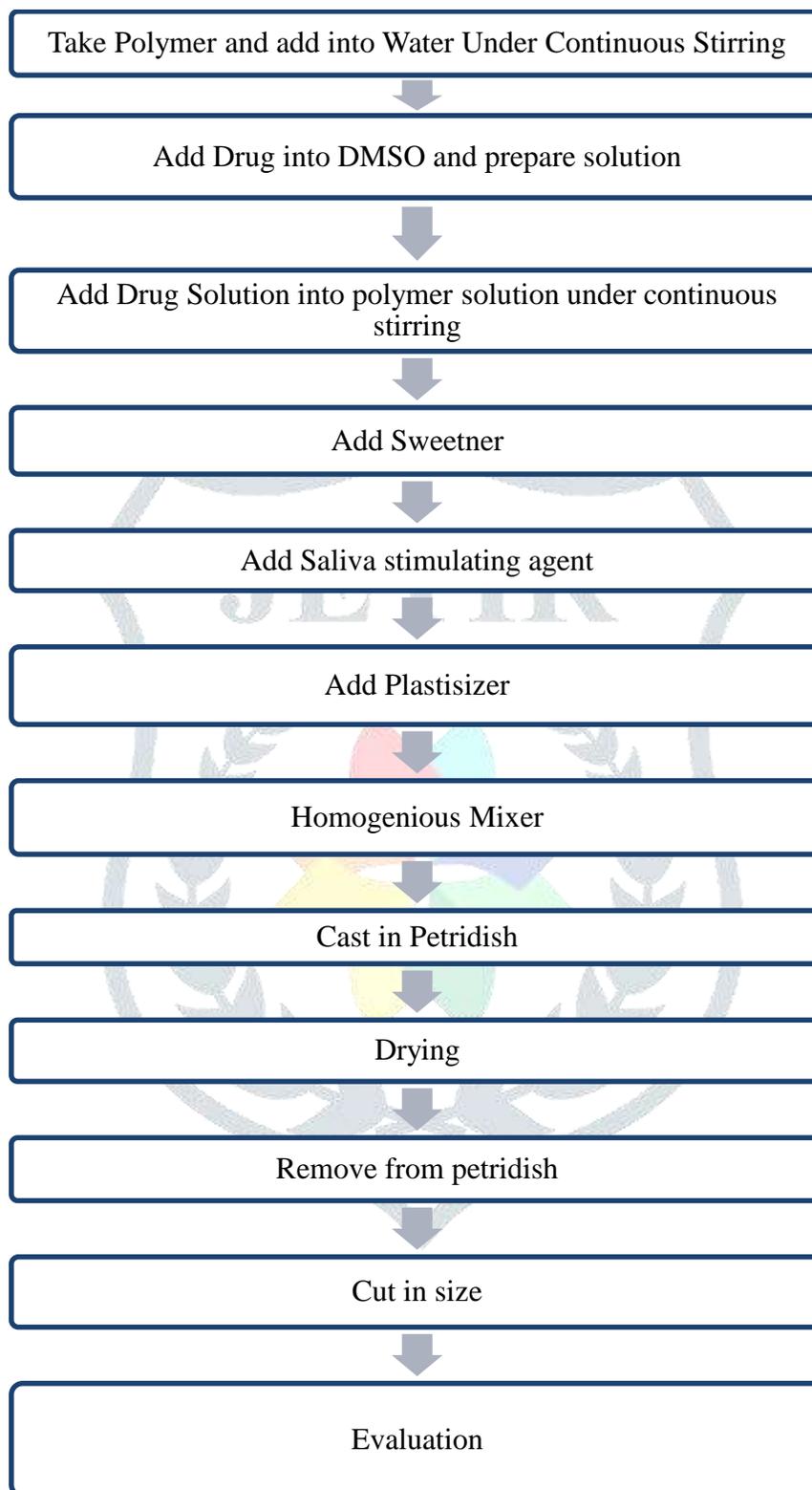
Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = (\text{Tapped density} \div \text{Bulk Density})$$

## 4) Angle of repose

Angle of repose of API powder was determined by the funnel method. Accurately weight powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r$$

**Preparation of Prazocin Hydrochloride Sublingual Films: -****Method: - “Solvent Casting Method”****Preliminary trial batches for selection of plasticizer and polymer**

<b>Ingredients</b>	<b>T1</b>	<b>T2</b>	<b>T3</b>	<b>T4</b>	<b>T5</b>	<b>T6</b>	<b>T7</b>	<b>T8</b>	<b>T9</b>
Prazocin Hydrochloride (mg)	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5

Pullulan (mg)	500	500	500	-	-	-	-	-	-
PVA (mg)	-	-	-	500	500	500	-	-	-
Pectin(mg)	-	-	-	-	-	-	500	500	500
PEG 400(ml)	0.5			0.5	-	-	0.5	-	-
Propylene Glycol (ml)	-	0.5	-	-	0.5	-	-	0.5	-
Glycerin(ml)	-	-	0.5	-	-	0.5	-	-	0.5
Aspartame (mg)	30	30	30	30	30	30	30	30	30
Citric acid (mg)	50	50	50	50	50	50	50	50	50
Water (ml)	10	10	10	10	10	10	10	10	10

### Evaluation of Sublingual Films of Prazocin Hydrochloride

- **Thickness**

The thickness of the films was measured using digital Vernier Caliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the films and average was taken and SD was calculated.

- **Weight Variation**

Four-centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

- **Folding Endurance**

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

- **Surface pH**

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported.

- **Disintegration Time**

In vitro disintegration time was determined visually in a petridish containing 25 ml of pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

- **Drug Content**

Drug content determination of the film was carried out by dissolving the film of 4 cm<sup>2</sup> in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at  $\lambda_{\max}$  of 246 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

- **In-vitro dissolution**

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 phosphate buffer maintained at  $37 \pm 0.5^{\circ}\text{C}$  at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at  $37 \pm 0.5^{\circ}\text{C}$ . Drug amount in the samples was then determined spectrophotometrically at  $\lambda_{\max}$  of 246 nm. The results were expressed as mean of three determinations.

- **Tensile strength**

Tensile testing was conducted using a texture analyzer equipped with a 5 N load cell. The film was cut into 30 × 20 mm strips. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each test strip was placed in tensile grips on the texture analyzer. Initial grip separation was 20 mm and crosshead speed were 1 inch/min. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross-sectional area to evaluate tensile properties of the films. Tensile strength (TS) Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa)

$$\text{Tensile Strength} = \text{Force at break (N)} / \text{Cross sectional area (mm}^2\text{)}$$

- **Percentage elongation**

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the formula given below: -

$$\%E = (D_f - D_0) / D_0 \times 100$$

Where: -

%E = Percentage elongation

D<sub>0</sub> = Distance between the tensile grips before the fracture of the film.

D<sub>f</sub> = Distance between the tensile grips after the fracture of the film

- **Ex-vivo permeation studies**

Ex vivo permeation studies through porcine oral mucosa (ventral surface of tongue) was carried out using the Franz diffusion cell of internal diameter of 2.5 cm. The buccal mucosa was excised and trimmed evenly from the sides, washed in isotonic phosphate buffer of pH 6.8 and used immediately. The membrane was stabilized

before mounting to remove the soluble components. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 15 ml of isotonic phosphate buffer of pH 7.4 which was maintained at  $37 \pm 0.2^\circ\text{C}$  and hydrodynamics were maintained using magnetic stirrer. One film of dimension  $2\text{ cm} \times 2\text{ cm}$  was previously moistened with a few drops of pH 6.8 phosphate buffer and placed in donor compartment. The donor compartment was filled with 1 ml of pH 6.8 phosphate buffer. 1 ml samples from receptor compartment were withdrawn at suitable time interval which was then replaced with 1 ml of pH 7.4 phosphate buffer. The percentage of drug permeated was determined by measuring the absorbance in UVVisible spectrophotometer at  $\lambda_{\text{max}}$  of 246 nm.

- **Stability study**

Stability study was carried out at  $40^\circ\text{C}/75\% \text{RH}$  for 1 month. Each piece of the film of optimized formulation was packed in butter paper followed by aluminum foil and plastic tape. After 1 month, the films were evaluated for the physical appearance, surface pH, drug content and in vitro drug release.

#### Preliminary trial batches evaluation of plasticizer and polymer

Batch	Weight variation (mg)	Thickness (mm)	Surface pH
T1	$40.3 \pm 2.8$	$0.18 \pm 0.03$	$6.8 \pm 0.2$
T2	$40.4 \pm 3.1$	$0.20 \pm 0.01$	$7.1 \pm 0.1$
T3	$40.9 \pm 2.6$	$0.21 \pm 0.04$	$6.9 \pm 0.3$
T4	$49.1 \pm 2.3$	$0.23 \pm 0.02$	$6.8 \pm 0.2$
T5	$49.9 \pm 2.5$	$0.25 \pm 0.01$	$6.7 \pm 0.3$
T6	$50.0 \pm 2.9$	$0.25 \pm 0.04$	$7.0 \pm 0.1$
T7	$57.6 \pm 1.8$	$0.26 \pm 0.03$	$6.9 \pm 0.1$
T8	$58.3 \pm 2.4$	$0.27 \pm 0.02$	$7.1 \pm 0.2$
T9	$58.9 \pm 2.6$	$0.27 \pm 0.03$	$6.9 \pm 0.1$

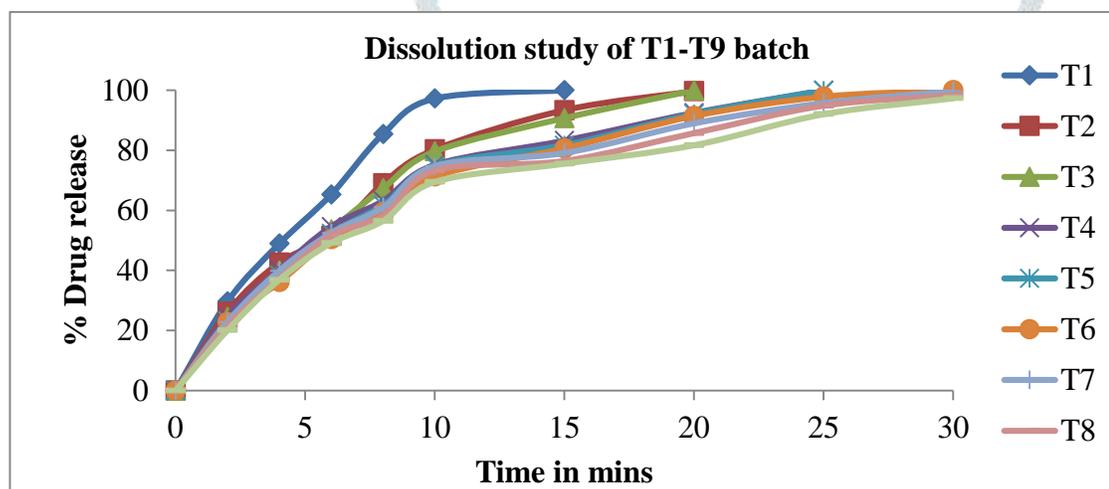
**Table Preliminary trial batches evaluation of plasticizer and polymer**

Batch	Drug Content (%)	Disintegrating time(sec)	Folding Endurance
<b>T1</b>	99.2± 1.5	25± 7	300± 12
<b>T2</b>	97.8± 2.7	38± 3	290± 17
<b>T3</b>	98.7± 2.0	43± 6	270± 14
<b>T4</b>	97.1± 2.5	50± 8	270± 19
<b>T5</b>	97.6± 3.2	47± 5	280± 10
<b>T6</b>	98.9± 2.8	50± 9	270± 15
<b>T7</b>	97.3± 2.2	45± 4	240± 11
<b>T8</b>	97.2± 2.9	58± 7	260± 18
<b>T9</b>	98.5± 2.1	40± 3	250± 16

Drug release study of all 9 batches were performed to identify the good polymer and plasticizer combination in a trial batch. Among all batches, T1 batch which contains pullulan and PEG 400 as polymer and plasticizer gives more than 85% drug release within 15 mins. None of other polymers give more than 65% in 15 mins. Hence the desired drug release was expected from pullulan and PEG combination. Fine tuning in formulation T1 gives better results. The results were recorded in below table and the comparison also showed in below figure.

## Dissolution profile of trial batch T1 –T9

% Cumulative drug release									
Time (min)	T1	T2	T3	T4	T5	T6	T7	T8	T9
2	29.64	26.13	24.46	24.72	23.18	22.79	22.80	21.55	20.06
4	48.90	42.55	39.89	40.31	38.42	36.07	39.87	37.30	36.89
6	65.27	51.50	53.57	54.60	52.34	50.46	52.40	51.67	49.14
8	85.42	68.95	67.32	63.14	61.69	59.47	60.96	58.11	56.48
10	97.25	80.25	79.62	75.17	74.81	71.33	74.71	73.27	69.50
15	99.96	93.37	90.71	83.23	81.70	80.66	79.08	76.46	75.56
20	-	99.65	99.94	92.46	92.10	91.44	88.93	85.72	81.70
25	-	-	-	99.98	99.90	97.86	95.68	94.86	92.05
30	-	-	-	-	-	99.98	99.71	98.38	97.34



## Dissolution of Trial Batches T1-T9

Based on trial batches results, factorial design was applied for formulation optimization by taking Pullulan and PEG 400 as independent factors.

## CONCLUSION

The results of the present study indicated that Pullulan could be used as a film forming polymer and PEG 400 as a plasticizer for formulation of fast dissolving sublingual films containing Prazocin Hydrochloride. Acceptable mechanical properties were obtained for trial batch with *in vitro* disintegration time. On the basis of data obtained from *in-vitro* dissolution study that T1 is promising formulation suitable for the immediate release of Prazocin Hydrochloride for the systemic use since they exhibited maximum drug release. On the basis of data obtained from *in-vitro* dissolution study that O1 is promising formulation suitable for the

immediate release of Prazosin HCl for the systemic use since they exhibited maximum drug release. Batch O1 found stable for 1 month during stability study. Hence, O1 is the optimized batch.

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