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Formulation and Evaluation of Buccal Patches of Prazosin Hydrochloride

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Abstract

Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. Prazosin hydrochloride patches were prepared by using hydroxy propyl methyl Cellulose E-15, Ethyl cellulose 20 cps, Poly vinyl alcohol and Poly Vinyl Pyrrolidone K-30. IR and UV spectroscopic methods revealed that there is no interaction between Prazosin HCl and polymers. The patches were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength, and surface pH. *In vitro* release studies of Prazosin HCl-loaded patches in phosphate buffer (pH, 6.8) exhibited drug release in the range of 55.32 % to 97.49 % in 6 Hrs. Data of *in vitro* release from patches were fit in to different equations and kinetic models to explain release kinetics. The models used were zero and first-order equations, Higuchi and Korsmeyer-Peppas models. Good correlation among *in vitro* release and *ex-vivo* absorption of Prazosin Hydrochloride was observed.

Key words: Buccal Patch, Hypertension, Mucoadhesive polymers, HPMC

Introduction

Cosmetics are substances used to enhance or protect the appearance or odor of the human skin [1]. Among all cosmetics, hair cosmetics has a large market today. Shampoos are based on soap or synthetic detergents used to cleanse, glossify and leave the hair lustrous [2,3]. The present work was aimed to formulate and evaluate herbal shampoo containing natural ingredients like Chamomile, Rose flower and orange peel using sodium lauryl sulphate as detergent. Transmucosal route of drug delivery offers distinct advantages over per oral administration for systemic drug delivery.

These advantages include possible bypass of the first pass effect, avoidance of presystemic elimination within the GI tract, within the oral mucosal cavity the buccal region offers an attractive route of administration for systemic drug delivery. Buccal mucosa has rich blood supply and it is relatively permeable.¹ Buccal drug delivery has become an important route of administration. Prazosin Hydrochloride, a selective α -Adrenergic antagonist, which is widely used in treating hypertension and congestive heart failure. It was the first of a new class of direct-acting vasodilators acting by α -adrenoreceptor blockade. Prazosin Hydrochloride is a BSC class-II having short biological half-life (2 to 3 hours).

Main objective of study is to enhance the bioavailability of Anti-hypertensive drug: Prazosin HCl, to achieve quick onset of action and sustain the release of drug into blood circulation. Prazosin hydrochloride has various side effects related to the GIT eg. Vomiting, feeling discomfort, gastric irritation etc. By formulating buccal patch of this drug we overcome to these problems. Prazosin Hydrochloride is a very potent drug which may give side effects in even a low dose by formulating the buccal patch of this drug discontinuation of the dose is possible which is not possible by another route like oral tablets. In context of the above principles, a strong need was recognized for the development of a dosage form to deliver Prazosin hydrochloride by a buccal patch formulation and to increase the efficiency of the drug, providing sustained action. The present investigation applied a systematic approach to the development of mucoadhesive buccal patch of Prazosin Hydrochloride^{2,3}.

Material and Method

Prazosin Hydrochloride was a gift sample from Intas Pharmaceuticals Private Ltd. India, Hydroxypropyl methyl cellulose E-15, Ethyl Cellulose 10cps, Polyvinyl Pyrrolidone K-30 (PVP K-30), Dichloromethane, Methanol, Glycerol and Polyethylene Glycol were purchased from (Chemdyes corporation Pvt Ltd. Rajkot Gujrat).

Preparation of Mucoadhesive Buccal Patches

Buccoadhesive patches of Prazosin HCl were prepared by solvent casting technique using film forming polymers mentioned in table 1. HPMC E-15, PVP K-30 and EC 10 cps polymers were weighed accurately and dissolved in 5 ml of methanol:DCM solvent. The beaker containing polymer and solvent was kept aside for 5 min for swell. After that the drug is dissolved by adding further 5 ml of solvent. All polymers and drug solution stirred in the magnetic stirrer to dissolve perfectly. Pour the solution in petridish for drying for 24 Hrs. Formulated patches were subjected to the evaluation tests. Patches with any imperfections, entrapped air, differing in thickness, or weight (or) content uniformity were excluded from further studies.

Table 1: Formulation & Design of buccal patches Patch of Prazosin Hcl

Batch Code	F1	F2	F3	F4	F5	F6	F7
Prazosin HCl (mg)	222.75	222.75	222.75	222.75	222.75	222.75	222.75
HPMC E-15 (mg)	450	500	550	600	650	700	450
EC 10 cps (mg)	300	250	250	150	200	-	350
PVP K-30 (mg)	50	50	-	50	-	50	-
DCM:Methanol(4:1) (ml)	10	10	10	10	10	10	10
Glycerol (ml)	3	3	-	-	-	3	3
Peg-400 (ml)	-	-	3	3	3	-	-
Total Weight (mg)	1035	1035	1035	1035	1035	1035	1035

Evaluation of the patches

1. Surface pH

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.

2. Tensile Strength

A Tensile strength study of patch is total weight, which is necessary to break or rupture the Dosage form and this will be done by a device has rectangular frame with two plates. Tensile strength of the patch was determined with Digital Tensile Tester. The sensitivity range of the machine is 1 to 10 Newton's. It

consisted of two load cell grips. The lower one was fixed and upper one was movable. The test patch of size (2×2 cm²) will be fixed between these cell grips and force will gradually applied till the film broke. The tensile strength of the patch will be taken directly from the dial reading in Newton's, which will be converted into kilograms.

$$TS \text{ (g/cm}^2\text{)} = \text{Force at break (g)} / \text{Initial cross sectional area of patch}$$

3. Weight uniformity

Patches sizes of 1 × 1 cm² were cut. The weights of five patches were taken and the weight variation was calculated.

4. Thickness

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated

5. Folding endurance

Folding endurance of the patches was determined (Kevin et al., 2008) by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which is 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 all the patches for five times.

6. Swelling Index

Buccal patches are weighed individually (designated as W₁), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1- hour time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper. The swollen patches are then reweighed (W₂) and the swelling index (SI) is calculated using the following formula

$$SI = \frac{W_2 - W_1}{W_1} \times 100$$

Where W₁ = Dry weight of the film and W₂ = Wet weight of the film

7. Drug Content uniformity

The patches will be tested for the content uniformity. One patch will be cut and placed in a beaker. 10 ml of a phosphate buffer solution will be added. The contents will be stirred to dissolve the film. The contents will be transferred to a volumetric flask (10 ml). The absorbance of the solution will be measured.

8. % Moisture Content

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

$$\text{Moisture Content (\%)} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

9. % Moisture Uptake

The weighed patches were kept in desiccators at room temperature for 24 h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, the films were reweighed and determined the percentage moisture uptake from the below mentioned formula:

$$\text{Percentage moisture uptake} = \left[\frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \right] \times 100.$$

In Vitro Drug Release Study

In Vitro drug release study was performed by using a Franz diffusion cell. The egg membrane was used for the determination of drug from the prepared buccal matrix-type patches. The egg membrane was placed between the donor and receptor compartment of the diffusion cell. The prepared patch was placed on the egg membrane and cover with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 6.8. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead and the temperature was maintained at 37 ± 0.5°C. The samples withdrawn at different time intervals and analyzed for drug content by UV spectroscopy. The receptor phase refilled with an equal volume of phosphate buffer at each sample withdrawal.

Table 2: Evaluation of buccal patches of Prazosin Hydrochloride

Formulation code	Surface pH	Tensile Strength	Thickness (mm)	Folding endurance
F1	6.40 ± 0.032	5.345 ± 0.003	0.80 ± 0.10	313 ± 4
F2	6.35 ± 0.043	5.023 ± 0.120	0.82 ± 0.12	320 ± 6
F3	6.55 ± 0.011	4.084 ± 0.232	0.85 ± 0.08	329 ± 8
F4	6.81 ± 0.012	4.563 ± 0.132	0.81 ± 0.05	321 ± 5
F5	6.53 ± 0.021	6.432 ± 0.003	0.83 ± 0.13	342 ± 8
F6	6.78 ± 0.323	6.513 ± 0.102	0.80 ± 0.34	310 ± 4
F7	6.41 ± 0.351	8.612 ± 0.191	0.87 ± 0.13	318 ± 6

Table 3: Evaluation of buccal patches of Prazosin Hydrochloride

Formulation Code	Swelling Index (%)	Drug Content (mg)	% Moisture Content	% Moisture Uptake
F1	20 ± 0.004	3.40 ± 0.021	5.53 ± 0.192	4.68 ± 0.134
F2	25 ± 0.002	3.34 ± 0.121	4.87 ± 0.151	4.01 ± 0.201
F3	28 ± 0.011	4.12 ± 0.002	4.60 ± 0.142	3.93 ± 0.113
F4	36 ± 0.006	4.98 ± 0.011	4.37 ± 0.011	3.41 ± 0.191
F5	34 ± 0.020	4.34 ± 0.002	3.13 ± 0.121	3.95 ± 0.211
F6	31 ± 0.013	3.98 ± 0.005	5.48 ± 0.113	4.86 ± 0.156
F7	27 ± 0.007	3.56 ± 0.020	5.02 ± 0.134	4.10 ± 0.187

Comparison of Release Profile

From the result of In-vitro study it was observed that as the concentration of Ethyl cellulose along with PVP K-30 increases the drug release from the buccal patch decreases. The formulation F-1 showed minimum release of 55% in 6 hours. Hence the F1 was not considered as ideal formulation because it failed to release the drug in 6 hours. The formulation F2 showed more drug release than the F1. But this was not more than the best formulation F4. The formulation F3 and F5, F6 and F7 showed the maximum release of 76.32%, 89.8%, 82.52 and 79.32 in 6 hrs which is effecting by the concentration of all polymers used. Here, Ethyl Cellulose 10 cps and PVP K-30 seemed to be as viscosity enhancing polymers which were finally retarding the drug to release. The formulation F1, F2 and F7 also were not considered as ideal formulation because these failed to release the entire drug comprised within buccal Patch. Formulation F4 showed the maximum release of 92.16% of Prazosin Hydrochloride in 6 hours. Hence the F4 considered as ideal formulation it showed better release with sustained effect as compared to other formulations.

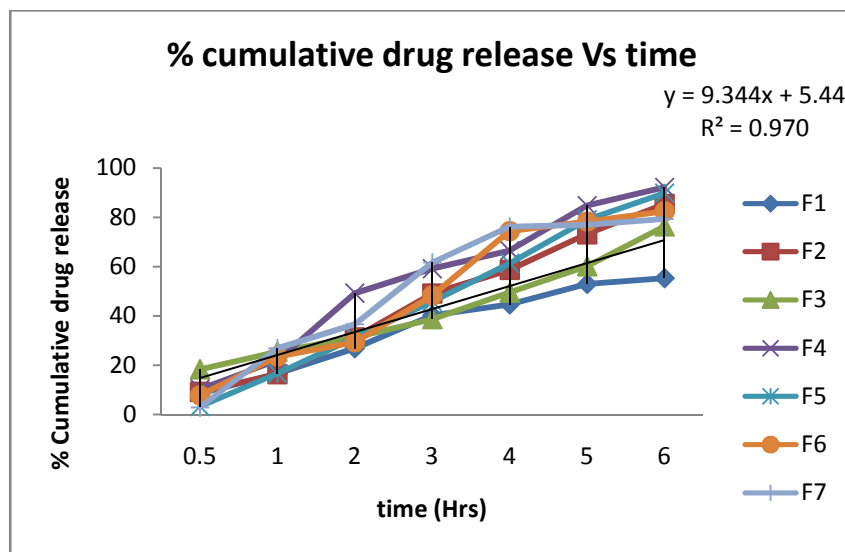


Figure 1: Comparative release profile of formulation F1-F7

This indicated that higher proportion of hydrophilic polymer was released the drug to greater extent but failed to sustain the release for long time and higher proportion of hydrophobic polymer sustained the drug release for greater extent but failed to release entire drug comprised in buccal patch. So the proportion of all types of polymers should be in a correct ratio which maintained the criteria of buccal drug delivery system.

Table 4: Curve fitting data of release profile for designed formulations

Formulation	Zero order (R^2)	First Order R^2	Higuchi Model (R^2)	Korsmeyer- Peppas Model	
				R^2	N
F-1	0.9856	0.8464	0.9911	0.9928	0.7927
F-2	0.9830	0.8538	0.9957	0.9973	0.6453
F-3	0.9819	0.8334	0.9976	0.9947	0.7161
F-4	0.9921	0.7866	0.9970	0.9882	0.7160
F-5	0.9659	0.7529	0.9913	0.9705	0.7041
F-6	0.9801	0.8632	0.9920	0.9971	0.6703
F-7	0.9912	0.8767	0.9736	0.9959	0.6597

The In-Vitro drug release data were subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and korsmeyer models in order to determine the mechanism of drug release. When the regression coefficient values of zero order and first order plots were compared, it was observed the 'r' value of zero order plots were in the range of 0.96 to 0.99 indicating drug release from most of the formulation was found to follow zero order kinetics. It is notable the 'r' values of the linear regression for Higuchi's plot were found to be 0.997 indicating that the data fits the Higuchi's model well and the drug release was found to be predominantly controlled by diffusion. When the In-Vitro release data was fitted to exponential model, the 'r' values were found to be in range of 0.97 to 0.99 in most of formulation, indicating the data fits the exponential model well. The slope 'n' values of exponential equation were found to be > 0.45 and < 0.89 indicating the drug release is governed by non-fickian diffusion mechanism.

Stability Study

Accelerated stability study was carried out for selected formulation F4 for 1 month by keeping at $40^\circ\text{C}/75\% \text{RH}$ and $30^\circ\text{C}/65\% \text{RH}$, the data showed no significant difference in the appearance, thickness, weight uniformity, folding endurance, % moisture content, % moisture uptake, tensile strength, and in- vitro release which confirms the stability of the product.

Conclusion

It may be concluded that mucoadhesive patches for oral cavity are a promising drug delivery system for Prazosin Hydrochloride. The combination of polymers HPMC E-15, EC 10 cps and PVP K-30 showed good mucoadhesive and swelling characteristics. Formulation F4 shown best release in concentration independent manner. Good correlation observed between the in-vitro and ex- vivo profile. Medicated patches and demonstrated non-Fickian release of the drug over a relatively long period (6 hrs.). Hence the best formulation F4 achieved the objective of present study such as reducing the dose, improving the bioavailability by avoiding first pass metabolism and it may have better patient compliance.

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