
Design and Evaluation of Propranolol Hydrochloride Buccal Films

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Propranolol hydrochloride buccal films were prepared using three different polymers in various proportions and combinations. The physicochemical parameters like weight variation, thickness, folding endurance, drug content, percentage moisture absorption and percentage moisture loss were evaluated. An *in vitro* study was designed and it was carried out using commercial semipermeable membrane. *In vitro* release profile for the formulation F₆ (drug reservoir with 6% ethyl cellulose (EC) + 0.5% polyvinyl pyrrolidone (PVP) and 8% EC as rate controlling membrane) showed sustained release upto 24 h. It also obeyed first order kinetics. The studies conducted in rabbits confirmed the sustained release.

Development of new drug delivery systems has been one of the major thrust area of pharmaceutical research these days. Buccal cavity has a wide variety of functions and it acts as an excellent site for the absorption of drugs¹. Film type dosage forms can be used for transdermal and also for buccal or sublingual use². In the present investigation, focus was given to design propranolol buccal films with different polymers. Propranolol is a beta blocker widely used in the treatment of hypertension³. Although it is well absorbed from the gastrointestinal tract, its bioavailability is low due to extensive first pass metabolism⁴ by CYP2C19 and CYP2D6⁵. Since the buccal route bypasses the hepatic first pass effect, the dose of propranolol hydrochloride could be reduced. The physicochemical properties of propranolol, its suitable half life (3-5 h) and low molecular weight 295.81⁶ make it a suitable candidate for administration by the buccal route.

MATERIALS AND METHODS

Propranolol hydrochloride (IP) was a generous gift by Tablets India (P) Ltd., Chennai. The polymers hydroxypropylmethylcellulose-15 cps (HPMC 15 cps),

hydroxy ethyl cellulose-10 cps (HEC 10 cps), ethyl cellulose-20 cps (20 cps) and polyvinyl pyrrolidone (PVP K 30) were procured from S. D. Fine Chem., Boisar, Gujarat. Other chemicals and plasticizers used were of A.R. grade.

Preparation of reservoir films:

A series of buccal films containing 20 mg of propranolol hydrochloride (PHY) in an area of 1 cm² were prepared by solvent casting technique^{7,8}. PEG-600, castor oil, glycerol in a concentration 30% w/w of polymer was incorporated as plasticizer in HPMC, HEC and EC films respectively. A film of 1 cm² area was punched out from the total film area by a specially fabricated mould.

Rate controlling membrane:

A rate controlling membrane was cast on a glass plate using the polymer EC (8%)⁹ by incorporating glycerol (30% w/w of polymer) as plasticizer. A membrane of 1.44 cm² area was cut and both sides of the drug reservoir was sealed using this membrane to control the release¹⁰.

Measurement of folding endurance¹¹:

The folding endurance was measured manually for the prepared films without rate controlling membrane. A

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small strip of film (2 cm x 2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Drug content determination:

Buccal films of propranolol hydrochloride (1 cm²) were prepared with the polymers HPMC and HEC. Hydroxy ethyl cellulose was dissolved in small amount of water, shaken vigorously for 5 min and then diluted to 10 ml with water. Buccal films of PHY prepared with EC was dissolved in small amount of chloroform (3 ml), shaken vigorously for 5 min and then diluted to 10 ml with water. Both the solutions were filtered through Whatman filter paper (No. 42). The drug content was then determined after proper dilution and the absorbance was measured spectrophotometrically at 290 nm⁶ against a blank. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0-10 µg/ml ($r=0.998$). When a standard drug solution was repeatedly assayed ($n=6$), the relative error and co-efficient of variation were found to be 1.25% and 1.6%, respectively. No interference by the excipients used in the study was observed. The experiments were carried out in triplicate and average values were reported.

In vitro release:

Commercial dialysis membrane (obtained from Sigma Chemicals) was employed for the study. The membrane used was transparent and a regenerated cellulose type, which was permeable to low molecular weight substances. The semipermeable membrane was tied to one end of open ended cylinder made up of glass (15 mm x 75 mm) which acted as a donor compartment. A buccal film containing 20 mg equivalent of PHY was placed inside the compartment. This set up was placed over a beaker containing 100 ml distilled water which acted as a receptor compartment. The temperature in the receptor compartment was maintained at $37 \pm 1^\circ$ and its contents were continuously stirred using a magnetic stirrer. Five milliliter samples were withdrawn from the receptor compartment at every 1 h time interval, up to 24 h. The quantity withdrawn was replaced with distilled water immediately. The collected samples were analysed spectrophotometrically at 290 nm against a blank. The experiment was carried out in triplicate and average values were reported.

In vivo release:

Among the six formulations prepared and tested, the

best formulation F₆ (DR with 6% EC + 0.5% PVP and 8% EC as rate controlling membrane) was chosen for animal studies. Male healthy rabbits (*Orytolagus cuniculus*) weighing 1.5 to 2 kg were chosen for this study. Rabbits were fasted overnight and were divided into four groups of four rabbits each. The rabbits were kept in cages with husk bedding.

To the group I, a tablet containing 20 mg of PHY was given orally with the help of plastic tube. To group II, a capsule containing 20 mg of PHY was given. To group III, buccal film was placed in the cheek pouch of the rabbit with the help of a clip. To group IV, buccal film without drug (placebo) was placed in the cheek pouch, which acted as a control. Blood samples (0.5 ml) were withdrawn from the marginal ear vein of the rabbit at hourly intervals using a syringe containing 3.8% sodium citrate to prevent clotting.

To the above sample 0.5 ml of 0.5 N NaOH and 0.5 ml of 10% ZnSO₄ was added to precipitate blood protein. Then it was filtered through a Whatman filter paper and the samples were analysed at 290 nm against a blank. This process was continued up to 8 h.

RESULTS AND DISCUSSION

In the present study efforts were made to prepare buccal films of PHY using polymers like HPMC, HEC, EC and PVP¹². The drug delivery system was designed as a matrix and the release was controlled by using polymeric rate controlling membrane. The physicochemical evaluation¹³ (Table 1) indicates the thickness of film varies between 0.18 ± 0.01 mm to 0.22 ± 0.02 mm. The thinnest being the formulation F₁ (4% HPMC) and thickest being the formulation F₆ (6% EC + 0.5% PVP). Buccal films prepared with different plasticizers were transparent, dry and flexible. The folding endurance was measured manually, films were folded 250 times and if the films did not show any cracks, it was taken as the endpoint. The weight of the films varied between 0.016 to 0.019 mg Table 1. The percentage of moisture absorption was more in formulation F₄ (6% HEC) (Table 1) due to hydrophilic nature of the polymer. The % moisture loss was also very high in formulation F₄ but there were no change in integrity at high humid and dry conditions.

Drug content in the formulations was uniform with a maximum variation of 0.35% (Table 1). This indicates that the drug is dispersed uniformly throughout the film. The amount of drug entrapped in the matrix type of buccal film was found to be in the range of 95.8% to 97.4%.

TABLE 1: PHYSIOCHEMICAL EVALUATION AND DRUG RELEASE OF FORMULATIONS.

FC	DRFC	PL (%w/w p)	WV* (mg)	T [±] S.D. (mm)	%MA* ±S.D	%ML* ±S.D	DC ±S.D (mg)
F ₁	4% HPMC	PEG-600 (30%)	0.017	0.18 ±0.01	0.54 ±0.62	0.53 ±0.02	19.16 ±0.28
F ₂	6% HPMC	PEG-600 (30%)	0.018	0.19 ±0.02	0.56 ±0.51	0.48 ±0.01	19.33 ±0.25
F ₃	4% HEC	Castor oil (30%)	0.016	0.20 ±0.01	1.11 ±0.12	0.91 ±0.01	19.19 ±0.24
F ₄	6% HEC	Castor oil (30%)	0.018	0.21 ±0.01	1.17 ±0.21	0.98 ±0.02	19.23 ±0.30
F ₅	4%EC+ 0.5% PVP	Glycerol (30%)	0.016	0.19 ±0.02	0.31 ±0.04	0.28 ±0.12	19.33 ±0.26
F ₆	6%EC+ 0.5%PVP	Glycerol (30%)	0.019	0.22 ±0.02	0.34 ±0.02	0.30 ±0.24	19.48 ±0.21

FC: Formulation code, DRFC: Drug reservoir film composition, PL: Plasticizer, %w/w p: %w/w of polymer, WV: Weight variation, S.D: Standard deviation, T: Thickness, %MA: Moisture absorption, %ML: Moisture loss, DC: Drug content. In all the formulations from f₁ to f₆ 8% EC was used as the rate controlling membrane. *Average of three readings.

Drug release from the prepared films varied with respect to the proportion of polymer. Increase in polymer concentration decreases the diffusion of drug from the matrix. Among the six formulations, the formulation F₆ (DR 6% EC + 0.5% PVP and 8% EC as rate controlling membrane) shows the required drug release through an semipermeable membrane over an extended period of 24 h like reported in fig. 1.

The formulation F₆ followed first order release pattern like depicted in fig. 2. The regression value was found to be 0.9814. It fulfilled many requirements of an once a day delivery system. Next to the formulation F₆, the release from the formulation F₂ (DR with 6% HPMC and 8% EC as rate controlling membrane) showed good extended release for 24 h. The peak drug release for this formulation was at 21 h where as it was 23 h for formulation F₆ (DR with 6% EC + 0.5% PVP and 8% EC as rate controlling membrane). The release from HEC matrix films were not encouraging up to expected level.

In vivo evaluation of the formulation F₆ (DR with 6% EC + 0.5% PVP and 8% EC as rate controlling membrane) in rabbits showed that the drug permeated well across the

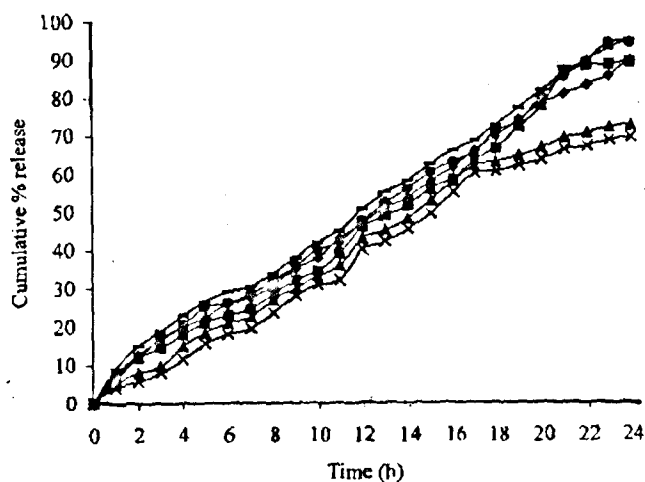


Fig. 1: Comparative *in vitro* release profiles of propranolol hydrochloride formulations.

(-●-) Formulation F₁, 4% HPMC (-■-) Formulation F₂, 6% HPMC, (-▲-) Formulation F₃, 4% HEC, (-x-) Formulation F₄, 6% HEC, (- — -) Formulation F₅, 4% EC + 0.5% PVP, (-●-) Formulation F₆, 6% EC + 0.5% PVP. In all the formulations from F₁ to F₆ 8% EC was used as the rate controlling membrane.

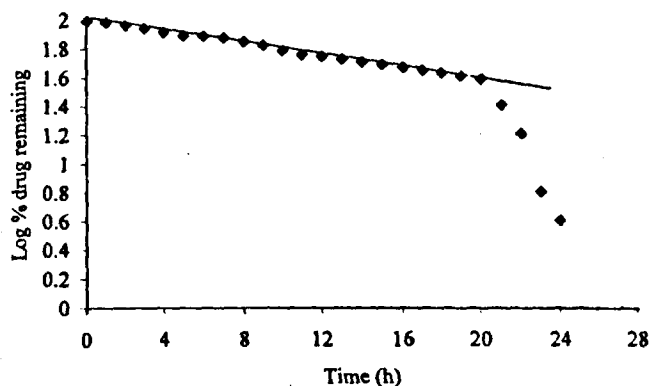


Fig. 2: Release pattern of propranolol hydrochloride Propranolol hydrochloride buccal film, F₈ (Drug reservoir with 6% EC + 0.5% PVP and 8% EC as rate controlling membrane) showing first order release.

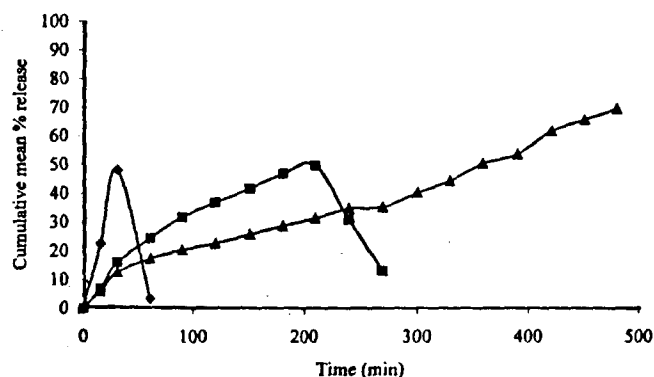


Fig. 3: Comparative *in vivo* release profiles of propranolol hydrochloride formulations.

Release profiles of propranolol from a commercial brand capsule containing 20 mg PHY (-◆-), a commercial brand tablet containing 20 mg PHY (-■-) and the buccal film, formulation F₈ containing 20 mg PHY (-▲-). Each point is an average of two determinations.

buccal mucosa. Drug concentration in blood after giving equivalent doses of PHY via buccal route to rabbits reveals that the drug release was in a sustained fashion for 8 h and the same pattern of release can be expected upto 24 h. Release from tablets and capsule was high during initial hours (3-4 h and 15-30 min respectively) followed by a sudden decline. The comparative drug release pattern from buccal films, tablets and capsules are presented in fig. 3. This release confirms the sustained released of drug from the buccal films and efficiency of buccal films over the tablets and capsules. To establish a correlation between *in*

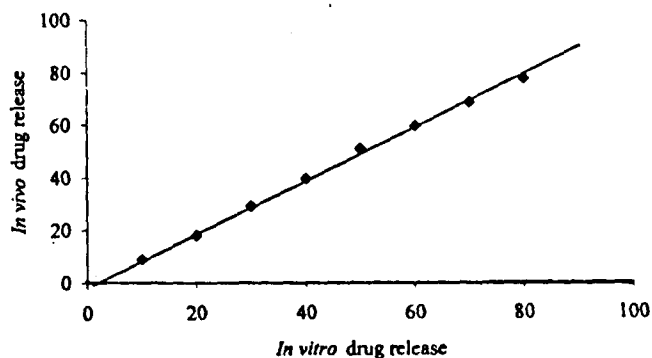


Fig. 4: *In vitro* - *In vivo* correlation of the release of propranolol hydrochloride from F₈.

Formulation F₈ was subjected to *in vitro* release studies using a bichambered donor - receiver compartment model and *in vivo* release studies using rabbits. The correlation coefficient was found to be 0.9912.

in vitro and *in vivo* release data, regression analysis was carried out. A correlation value 0.9912 obtained, shows the *in vitro* method carried out using a dialysis membrane simulates similar release characteristics like that of *in vivo* and the drug release was found to be in a concentration dependent manner (fig. 4).

In conclusion, these results indicate that formulation F₈ has a distinct advantage over the existing conventional dosage forms. Patient compliance can also be improved to a greater extent with the use of matrix type buccal films.

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