Int. J. Chem. Sci.: 6(2), 2008, 878-886

DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF PROPRANOLOL HYDROCHLORIDE BUCCAL FILMS

P. N. KRISHNAN[*], S. SANGEETHA[a], D. NAGASAMY VENKATESH[a] and R. SARASWATHI[b]

RVS College of Pharmacy, COIMBATORE – 641 402 (T. N.) INDIA
[a]JSS College of Pharmacy, OOTY (T. N.) INDIA
[b]PSG College of Pharmacy, COIMBATORE – 641 402 (T. N.), INDIA.

ABSTRACT

Mucoadhesive buccal films of propranolol hydrochloride were prepared using three different polymers by solvent casting technique using mercury as a substrate. The buccal films were evaluated for various physicochemical parameters such as weight variation, thickness, folding endurance, drug content and *in vitro* bioadhesive strength. Different media namely, distilled water and simulated saliva solution were used for swelling study. The *in vitro* dissolution study of buccoadhesive formulations were performed using dialysis membrane method and the release was found to obey first order following anomalous diffusion.

Key words: Propranolol hydrochloride, Buccal films, Swelling index and *in vitro* Dissolution study.

INTRODUCTION

Buccal delivery of drugs provides an alternative to the oral route of administration, especially in overcoming the problems associated with the later mode of dosing. The buccal route offers several advantages as compared to the traditional methods of systemic drug administration[1]. Problems such as first pass metabolism, drug degradation in gastro intestinal environment (GIT) can be circumvented by administering the drug via buccal route[2, 3]. In addition, the drug can be easily administered and, if necessary removed from the site of application, which is easily accessible for self medication. It is also possible to administer drugs to patients, who cannot be dosed orally via buccal route. Therefore, adhesive mucosal dosage forms were suggested for oral delivery, which includes buccoadhesive tablets, buccoadhesive gels, buccoadhesive patches and recently buccal films[4-9]. Buccal films may be preferred over adhesive tablets in terms of flexibility and

[*] Author for correspondence; E-mail: krisarascbe@rediffmail.com

comfort. In addition, they can circumvent the relatively short residence or oral gels on the mucosa, which is easily washed away and removed by saliva[10]. An ideal buccal film should be flexible, elastic, soft, yet adequately strong to withstand breakage due to stress from mouth activities. Moreover, it must possess good bioadhesive strength, so that it can be retained in the mouth for a desired action and swelling of films, if exists should not be two extensive to prevent discomfort[11]. Propranolol hydrochloride is a β-adrenergic blocking agent, which is used widely in the treatment of hypertension, angina pectoris and many other cardiovascular disorders. Although, it is well absorbed in the gastrointestinal tract, its bioavailability is low (15% to 23%) as a result of extensive first pass metabolism[12, 13]. So, its bioavailability may be improved when delivered through buccal route. The objective of the present study was to investigate the suitability of selected polymers such as hydroxylpropylmethylcellulose (HPMC), sodium carboxymethylcellulose (Na CMC), and hydroxyethylcellulose (HEC) as drug delivery vehicle for buccal delivery of propranolol hydrochloride as one of the method to enhance the bioavailability of proposed drug.

EXPERIMENTAL

Materials

Propranolol hydrochloride was obtained as a gift sample from Tablets (India) Ltd, Chennai. The polymers hydroxypropylmethylcellulose (HPMC-15 cps), sodium carboxymethylcellulose (Na CMC-15 cps), and hydroxyethylcellulose (HEC-15 cps) were procured from S.D.Fine Chemicals, Boisar, Gujrat. The dialysis membrane was purchased from Sigma, USA. All other chemicals in the study were of A.R.grade.

Methods

Preparation of buccal films

A series of buccal films containing 20 mg of propranolol hydrochloride (PHB) were prepared by solvent casting technique[14], where 5 mL of different polymeric solutions at various concentrations namely (4% and 6% HPMC, 4% and 6% Na CMC, 4% and 6% HEC) are mixed with glycerol (30% w/w of polymer solution) and were poured into a mould (2×2 cm^2 surface area) placed on a mercury substrate. The film was dried at 37±1° C for 24 hours. The dried films were carefully removed from the mould, checked for any imperfections and cut into a size of 1 cm^2, packed in aluminum foil and stored in a dessicator at room temperature.

Weight variation, thickness and folding endurance

The average weights of the formulated films were determined using electronic balance[15]. Thickness was measured using a screw gauge at different places and the average was calculated[16]. Folding endurance was measured manually for films of 2 cm^2 size[17]. The film was folded at the same place till it broke. The number of times, a film could be folded at the same place without breaking, gave the value of folding endurance.

***in vitro* bioadhesive strength**

The working of a double beam physical balance formed the basis of the bioadhesion test apparatus. The two pans of a physical balance were removed. The right pan was replaced with a lighter base and on the left side, a teflon ring was hanged with a copper wire. A teflon cylinder with 1.5 cm diameter, at 3 cm height, was hanged with a copper wire on the opposite side at this ring. The height of this total set up was adjusted to accommodate a glass container of 4.2 cm diameter and 4.2 cm height below it thus, leaving a head space of about 0.5 cm in between. A teflon block of 3.8 cm diameter of 2 cm height of 1.5 cm diameter on one of its face. This was kept inside the glass container, which was then placed below the left hand set up of the balance. The two sides were then balanced, so that the right hand side was exactly heavier than the left. The two sides at the balance were balanced with a 4 g weight on the right side. The hamster cheek pouch, excised and washed was tied tightly with the mucosal side upwards using a thread over the protrusion in the teflon block. The block was then lowered into the glass container, which was then filled with phosphate buffer pH 6.6 kept at 37±1° C, such that the buffer reaches the surface of mucosal membrane and keeps it moist. This was then kept below the left hand setup of the balance. The film was stuck with the little moisture, on to the cylinder hanging on the left hand side of the balance been raised with the 5 g weight on the right pan removed. This lowered the teflon cylinder along with the patch over the mucosal surface with a weight of 5 g. The balance was kept in this position for 3 min on the right pan, till the film separate from the mucosal surface. The excess weight on the pan is the total weight minus 5 g is the force required to separate the patch from the mucosa. This gave the bioadhesive strength of the film in grams[18].

Measurement of film swelling

The film swelling studies were conducted using two media namely, distilled water and simulated saliva solution[19, 20]. The batches with 6% w/v of polymers were selected for the study. Each film sample (1 cm^2) was weighed and placed in a preweighed stainless

steel wire mesh with sieve opening of approximately 800 µm. The mesh containing the film sample was then submerged into 15 mL medium contained in a plastic container (diameter 5 cm, height 2 cm). Increase in weight of the film was determined at preset time intervals until a constant weight was observed. Each measurement was repeated in triplicate. The degree of swelling was calculated using parameter $(W_t - W_0)/ W_0$, where W_t is the weight of film at time t, and W_0 is the weight of film at time zero.

Content uniformity

Buccal films of propranolol hydrochloride was dissolved in 10 mL of distilled water with vigorous shaking for 5 minutes and filtered through Whatman filter paper (No. 42). The drug content was then determined after suitable dilution with distilled water and the absorbance was measured spectrophotometrically at 290 nm against blank[15]. The experiments were carried out in triplicate and average values were reported.

***in vitro* release studies**

The *in vitro* release study was carried out employing dialysis method, where a dialysis membrane was tied to one end of open ended cylinder made up of glass, which acted as a donor compartment. This set up was placed over beaker containing 100 mL of distilled water, which acted as a receptor compartment. The temperature in the receptor compartment was maintained at 37±1° C and its contents were continuously stirred using a magnetic stirrer. 5 mL of samples were withdrawn from the receptor compartment at predetermined time intervals up to 12 hours. The quantity withdrawn was replaced with distilled water immediately to maintain the sink conditions. The collected samples were analysed spectrophotmetrically at 290 nm against a blank[15]. The experiment was carried out in triplicate and average values were reported.

Data treatment

Experimental results were fitted according to the following exponential equation[21].

$$M_t/M_\alpha = kt^n \quad \ldots(1)$$

Where M_t/M_α is the fractional solvent absorbed or drug released at time t. k denotes a constant incorporating properties of macromolecular polymeric system and n value is used for analysis of drug release mechanism of propranolol hydrochloride from buccal films as determined from log (M_t/M_α) vs log t plots. For example, n = 0.45 for case I or Fickian diffusion, which is characterized by a square root of time dependence in both; the

amount diffused and the penetrating diffusion front position; n = 0.89 for case II transport, which is completely governed by the rate of polymer relaxation, exhibits a linear time dependence in both; the amount diffused and penetrating swelling front position; n = 0.45 < n < 0.89 for anomalous behavior or non-Fickian transport, which exhibits whenever the rates of Fickian diffusion and polymer relaxation are comparable.

RESULTS AND DISCUSSION

In the present study, efforts were made to prepare buccal films of propranolol hydrochloride (PHB) using different polymers like HPMC, Na CMC and HEC. The drug delivery system was designed as a matrix and the release was controlled by using a polymeric rate controlling membrane. The composition and physicochemical evaluation of buccal films are shown in Table 1. The thickness of film varies between 0.18 mm to 0.22 mm and the weight of the film was between 160 to 190 mg. The thinnest being the formulation PHB-I (4% HPMC) and the thickest being the formulation PHB VI (6% HEC). Buccal films prepared with different plasticizers were transparent, dry and flexible. The folding endurance was measured manually, films were folded 250 times repeatedly and the films do not show any cracks. Maximum swelling was observed with formulation containing HPMC and Na CMC. It can be noted from the plots that the degree of swelling of Na CMC films was higher in distilled water than in simulated saliva solution. Conversely, HPMC films swelled at a greater extent in the simulated saliva solution (Fig. 2) than in distilled water (Fig. 1), but HEC film swelling was comparatively low to HPMC and Na CMC films.

These findings suggested that ionic strength and pH play an important role in affecting the swelling of HPMC, Na CMC, and HEC films. The swelling state of the polymer was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed is not very strong. The adhesion will increase with the degree of hydration until a point where overhydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. From the evaluation of the *in vitro* bioadhesion strength, it was observed that Na CMC films showed slightly higher bioadhesive strength values than HPMC films and HEC films. No significant difference was observed with 4% and 6% polymers in all the batches. Drug content in the formulations was uniform with a maximum variation of 0.25% as shown in Table 1. This indicates that the drug is dispersed uniformly throughout the film. The amount of drug entrapped in the matrix type of buccal films was found to be in the range of 80.31% to 90.09%. Among the six different formulations, the batch PHB – V showed a good extended release at the end of 12 hours with a maximum drug loading of 94.80%.

Table 1. Physico-chemical evaluations and in vitro release kinetics of buccal films containing propranolol hydrochloride

Formulation code	Weight variation (mg)	Thickness (mm)	Folding endurance	Bioadhesive strength (g)	Drug content (mg)	1st order plot		Koresmeyer and Peppas	
						k	r^2	n	r^2
PHB -I (4% HPMC)	180 ± 0.5	0.18 ± 0.01	>250	6.64 ± 0.06	16.62 ± 0.16	1.2305×10^{-3}	0.989	0.6058	0.995
PHB -II (6% HPMC)	190 ± 0.6	0.19 ± 0.02	>250	6.81 ± 0.04	17.34 ± 0.18	1.3882×10^{-3}	0.98	0.6111	0.994
PHB -III (4% Na CMC)	185 ± 0.3	0.19 ± 0.01	>250	8.72 ± 0.05	18.06 ± 0.14	1.3204×10^{-3}	0.979	0.6096	0.991
PHB -IV (6% Na CMC)	180 ± 0.4	0.20 ± 0.01	>250	8.96 ± 0.03	18.50 ± 0.15	1.3056×10^{-3}	0.997	0.6065	0.995
PHB -V (4% HEC)	190 ± 0.6	0.20 ± 0.02	>250	5.12 ± 0.03	18.96 ± 0.17	1.3874×10^{-3}	0.996	0.5989	0.991
PHB -VI (6% HEC)	190 ± 0.5	0.22 ± 0.02	>250	5.44 ± 0.03	18.23 ± 0.19	1.4879×10^{-3}	0.995	0.5892	0.99

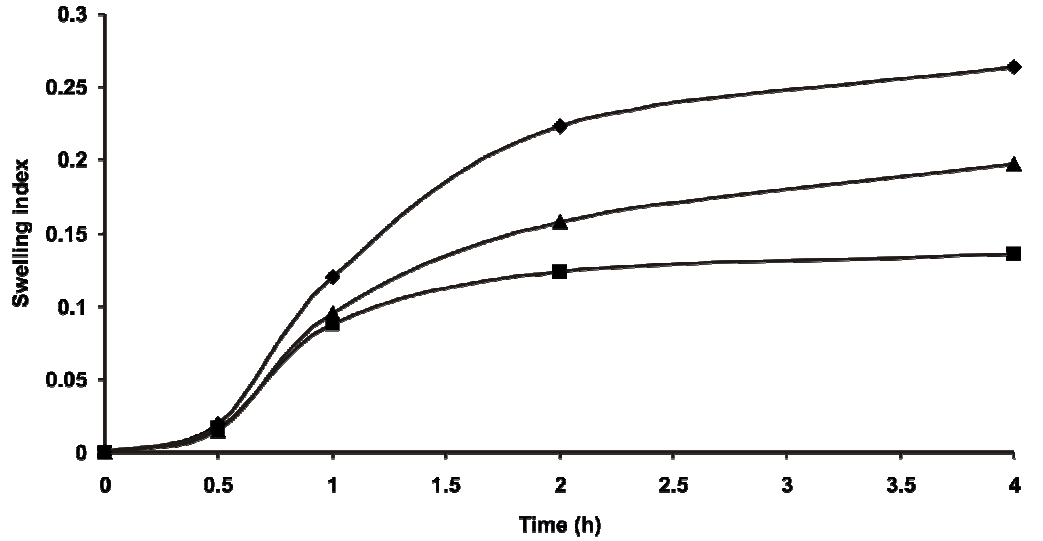

Fig. 1: Swelling index v/s time profiles of Na CMC (♦), HPMC (■), and HEC (▲) propranolol films in distilled water

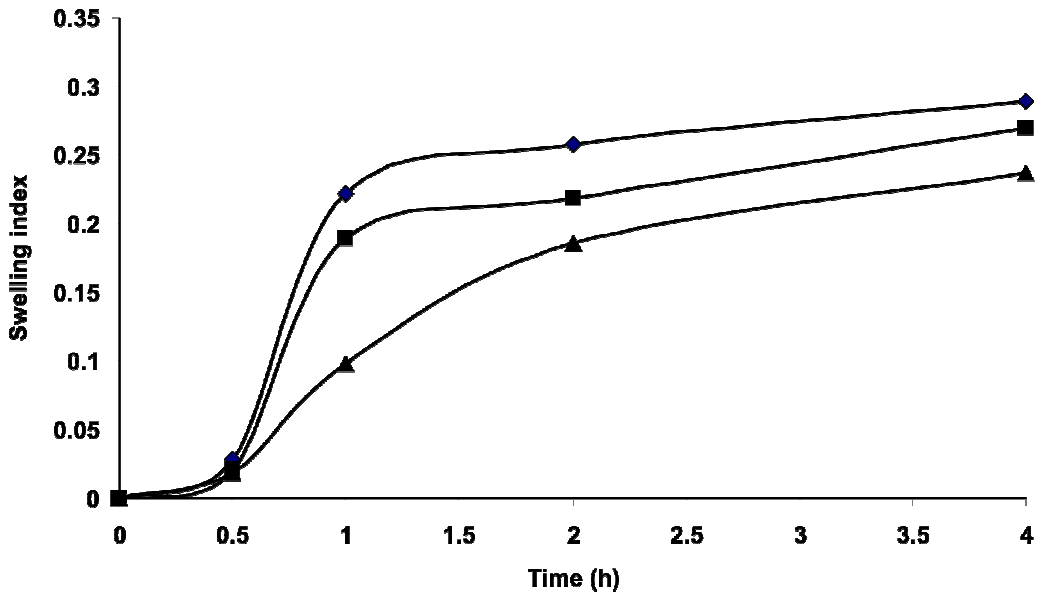

Fig. 2: Swelling index vs time profiles of HPMC (♦), Na CMC (■), and HEC (▲) propranolol films in simulated saliva solution

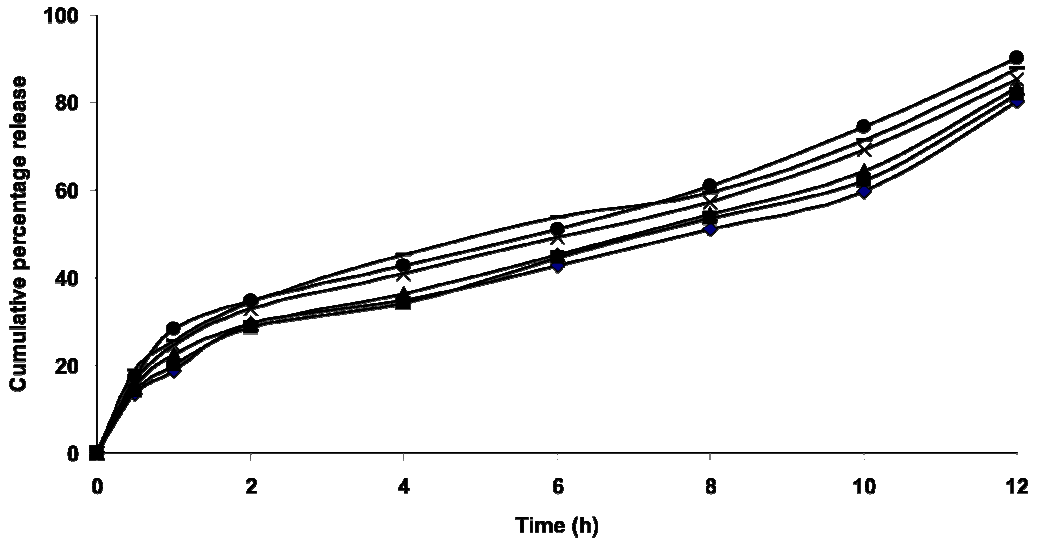

Fig. 3: Comparative *in vitro* release profiles of propranolol hydrochloride from buccal films PHB – I (♦), PHB – II (■), PHB – III (▲), PHB – IV (×), PHB – V (●) and PHB – VI (–)

Drug release from the prepared films varied with respect to the proportion of polymer as shown in Fig. 3. Increase in polymer concentration decreased the release of drug from the matrix. All the six formulations showed the required drug release through a semi-permeable membrane over an extended period for 12 hours. In Table 1, the values of k, r, and n values for all the batches are reported. Here all batches showed n values above 0.5; thus, indicating that the proposed release mechanism was found to be anomalous diffusion.

REFERENCES

1. M. J. Rathbone and J. Hadgraft, Int. J. Pharm., **74**, 924 (1991).
2. M. Gibaldi, Clin. Pharmacol., **3**, 49 (1985).
3. D. Harris and J. R. Robinson, J. Pharm. Sci., **81**, 1 (1992).
4. J. M. Schor, S. S. Davis, A. Nigalaye and S. Bolten, Drug Dev. Ind. Pharm., **9**, 1359 (1983).
5. M. Ishida, N. Nambu and T. Nagai, Chem. Pharm. Bull., **31**, 4561 (1983).
6. K. D. Bremecker, H. Streampel and G. Klein, J. Pharm. Sci., **73**, 548 (1984).
7. R. Anders and H. P. Merkle, Int. J. Pharm., **49**, 231 (1989).

8. J. H. Guo, Drug Dev. Ind. Pharm., **20**, 2809 (1994).

9. S. Burgalassi, L. Panichi, M. F. Saettone, J. Jacobson and M. R. Rassing, Int. J. Pharm., **133**, 1 (1996).

10. N. A. Peppas and P. A. Buri, J. Controll. Rel., **2**, 257 (1985).

11. Ahmed Mahmood, Memtaz and Hung-Seng Chng, J. Pharm. Pharmceut. Sci., **2**, 53 (1999).

12. E. Cid, F. Mella, L. Luchini, M. Carcama and J. Monasterio, Biopharm. Drug Dispos., **7**, 559 (1986).

13. T. Walle, E. C. Conradi, U. K. Walle, T. C. Fagan and T. E. Gaffney, Clin. Pharmacol. Ther., **24**, 668 (1978).

14. J. J. Scirra and R. N. Gidwani, J. Pharm Sci., **61**, 754 (1972).

15. S. Raghuranam, G. Velrajan, R. Ravi, B. Jeyabalan and Benito Johnson, Indian J. Pharm. Sci., **64(1)**, 32 (2002).

16. G. V. Pavankumar, V. Ramakrishna, G. J. William and A. Konde, Indian J. Pharm. Sci., **67(2)**, 160 (2005).

17. R. Khurana, A. Ahuja and R. K. Khar, Indian J. Pharm. Sci., **62**, 449 (2000).

18. A. Gupta, S. Garg and R. K. Khar, Indian Drugs, **30,** 152 (1993).

19. Kok Khiang Peh and Choy Fun Wong, J. Pharm. Pharmceut Sci., **2(2)**, 53 (1999).

20. B. Parodi, E. Russo, G. Cavilioi, S. Cafaggi and G. Bignaradi, Drug Dev. Ind. Pharm., **22(5)**, 445 (1996).

21. P. L. Ritger and N. A. Peppas, J. Controll. Rel., **5,** 37 (1987).

Accepted : 06.03.2008