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Systemic Absorption of Propranolol Hydrochloride from Buccoadhesive Films

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The systemic absorption of propranolol hydrochloride (PHL) delivered through rabbit oral mucosa was studied. Drug-loaded buccoadhesive films of varying compositions with unidirectional drug release were applied to rabbit oral mucosa and inhibition of isoprenaline-induced tachycardia was achieved. *In vitro* drug release followed zero-order kinetics. The *ex vivo* mucoadhesivity tests using rabbit small intestinal mucosa on an in-house fabricated apparatus yielded correlation between film composition and mucoadhesivity. Selected batches of placebo films showing good bioadhesion and oral mucosal compatibility in human volunteers could form a basis of propronalol delivery through this route to avoid first pass metabolism.

The buccal mucosa provides direct entry of drug molecules into systemic circulation, thus avoiding hepatic first pass effect[1]. The ease of administration and ability to terminate drug delivery when required makes it a potentially attractive route for drug delivery[2]. The effectiveness of a mucoadhesive formulation is greatly determined by the nature of the polymer composites used[3]. Hence the present study was designed to study buccoadhesive films of PHL, which undergoes first pass effect, using combinations of sodium carboxy methyl cellulose (SCMC-low viscosity grade), carbopol (CP) 934 P and polycarbophil (PC) to improve mucoadhesion and to examine the usefulness of the device in suppressing isoprenaline-induced tachycardia in rabbits.

EXPERIMENTAL

PHL, CP, PC and SCMC were generously gifted by Sarabhai Chemicals (Vadodara), B.F. Goodrich Co. (USA), Lee Lab Inc. (USA) and CDH (Mumbai), respectively. Isoprenaline sulphate, phenobarbitone sodium (Burroughs Wellcome, Mumbai), heparin injection (Biological E. Ltd, Hyderabad) were obtained commercially. All other chemicals and reagents used were of analytical grade.

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Preparation of buccal films:

The composition of the films are given Table 1. PHL films were fabricated in two lots. In the first lot, the drug was dissolved in 100 ml of distilled water, containing the requsite quantity of the plasticizer, glycerol (10% w/v). To this solution, polymer(s) were added and stirred to form a solution. The solution was degassed and poured on levelled glass moulds (10x10x0.4 cm) and dried in an oven at 60° for 24 h. In the second lot 0.1 N sodium hydroxide was added slowly to the drug-polymer solution to adjust the pH to 6 and the volume was made up to 100 ml and poured as above. The dried patches were wrapped in aluminium foil and stored over fused calcium chloride in a desiccator at room temperature until further use.

Preparation of backing membrane:

Polymethyl methacrylate (PMMA-12.5% w/v) was dissolved in 100 ml of chloroform and to this dibutyl phthalate (15% w/w) was added as a plasticizer. The solution was poured on to glass moulds as described earlier and dried at room temperature (25°) for 24 h. A glass funnel, plugged loosely with cotton was inverted over the mould to control the rate of evaporation. The dried films were removed and stored as described above.

TABLE 1: FORMULATION VARIABLES OF THE VARIOUS BATCHES OF THE PATCHES PREPARED

Batch Code	Polymer combinations with respective amounts (g)	Casting pH	Glycerol concentration (% w/w of polymer)
S_1	SCMC (3)	6	10
S_2	SCMC (2.5) : CP (0.5)	4	20
S_3	SCMC (2.0) : CP (1.0)	4	20
S_4	SCMC (1.5) : CP (1.5)	4	30
S_5	SCMC (1.0) : CP (2.0)	4	30
S_6	SCMC (2.5) : CP (0.5)	6	20
S_7	SCMC (2.0) : CP (1.0)	6	20
S_8	SCMC (1.5) : CP (1.5)	6	30
P_1	SCMC (2.08) : PC (0.42)	4	20
P_2	SCMC (1.7) : PC (0.80)	4	20
P_3	SCMC (1.25) : PC (1.25)	4	30
P_4	SCMC (2.08) : PC (0.42)	6	20
P_5	SCMC (1.7) : PC (0.80)	6	20
P_6	SCMC (1.25) : PC (1.25)	6	30

SCMC - sodium carboxy methyl cellulose; CP-carbopol; PC-polycarbophil. The figures in parenthesis indicate the ratios in which the respective polymers were used.

Composite patches were prepared by sticking the impermeable membrane to one side of the buccal patch with Araldite®.

Evaluation of the patches:

The composite patches were used for evaluating the *in vitro* mucoadhesivity, *in vivo* mucoadhesion, *in vitro* release and pharmacodynamic efficacies. The thickness of the film was measured at 10 different randomly selected spots using a screw guage and for weight uniformity, the films of area 3.14 cm^2 were punched out and 6 such films, from each batch were weighed individually. Drug content uniformity was determined by weighing 3 patches (3.14 cm^2) and dissolving by homogenising with 40 ml of phosphate buffer pH 7.4 for 6 h. The volume was made up to 100 ml using the buffer and the resultant solution was filtered and analysed for PHL content at 290 nm (Shimadzu-1601, Japan). A modification of the ASTM test No-D 570-59 T was used for testing of moisture absorption/loss of patches (1.73 x 1.73 cm) and the MVT of the patches (2.2 cm^2) were determined using a modified ASTM Test No E-96-53T as described by Kanig and Goodman[4].

A modified USP tablet disintegrating tester[5] was used for determining the folding endurance of the patches. It consisted of a fixed and a movable jaw that could be moved up and down at the rate of 28 strokes per minute. The distance between the two jaws at their farthest and closest was 6 and 0.5 cm respectively. The patch (8 cm in length) was clamped between the two jaws in such a way that when the jaws were at their closest, the patch bent across its middle and when at their farthest, the patch was in a stretched condition. Thus, for every stroke of the movable jaw, the patch went through one cycle of bending and stretching. The folding endurance is expressed as the number of strokes required to either break or develop visible cracks on the patch. The test was conducted for 1 h equaling 1680 strokes.

The rate of swelling or water uptake properties of the prepared patches were evaluated using an in-house fabricated swelling rate apparatus. A USP dissolution basket was used to hold the patch (3.14 cm^2). The basket was placed in a petri-dish (8 cm diameter, 1.5 cm height) containing 70 ml of distilled water. The petri-dish with the basket was covered with a glass cover (dish of diameter 7.5 cm and internal height 7.5 cm) and placed on a platform, maintained at 37±1°. The weighed patch, placed in the pre-weighed USP dissolution basket, was immersed

in 70 ml of distilled water. The basket containing the device was removed at pre-determined time intervals, wiped with tissue paper and weighed. Care was taken to maintain a constant level of distilled water in the petri-dish. Swelling index (SI) was calculated using the following relationship, SI= (final wt of patch - initial wt of patch/ initial wt of patch) x 100. For surface pH determinations, the patches (3.14 cm^2) were allowed to swell in closed petri-dishes[6] at room temperature for half an hour in 0.1 ml of double distilled water (pH 6.0). The swollen device was removed and spread on a pH indicator paper to determine the surface pH. After 60 s the colour developed was compared with the standard colour scale.

In vitro mucoadhesivity:

The mucoadhesive bond strength of the prepared films was evaluated by using rabbit's small intestine mucosa (SIM). The evaluations were carried out using an earlier reported method[7]. In brief, the apparatus consisted of three parts: a tissue mount (5 cm height, 1.7 cm diameter) fixed on the centre of a round glass dish (7.5 cm height x 7 cm diameter), an acrylate film holder of diameter 1.5 cm and weighing 2.6 g and an acrylate pulley with a groove over which a nylon thread (thickness-0.38 mm, length-52 cm) was placed and tied to a small metallic pan. In an actual experiment PBS pH 7.4 was placed in the glass dish and stirred using a magnetic stirrer (100 rpm). One end of the nylon thread was tied to the film holder, the thread was then passed over the pulley groove and the pan was tied to the other end of the thread.

Preparation of mucosal tissue:

Overnight fasted (water *ad libitum*) rabbits were sacrificed and the small intestine carefully removed and rinsed with normal saline to remove any loose materials. The small intestine was cut into segments of 3 cm length and cut open longitudinally along the mesentery to expose the inner mucosal surface[8]. The small intestine was stored in cold (5-8°) normal saline and used within three days[9]. The tissue with the mucosal side facing upwards was mounted securely with the help of silicone rubber band on the tissue mount platform with the dish containing phosphate buffer saline (PBS) pH 7.4 maintained at 37±1°. The level of PBS in the dish was maintained in such a way that it just touches the mucosal surface. Care was taken to prevent over-hydration of the surface of the tissue. The excess moisture and any loose material on mucosal surface was removed with tissue paper. A patch of area 2.27 cm^2 was fixed on the device holder with cyanoacrylate adhesive. The patch was placed in contact with the mucosal surface and after contact times of 2, 5, 10 and 15 min, standard weights in increments of 500 mg were added on the pan after every 30 s. The weight at which detachment took place was noted. This gave the mucoadhesive bond strength of the patches in g. The experiment was carried out in triplicate (with fresh patch and mucosa) to ensure reproducibility.

In vivo mucoadhesion studies:

The compatability of placebo patches and the maximum time of bioadhesion were determined in healthy human volunteers, by a blind crossover study design. Five healthy human volunteers (age 26±3.45, 4 males and 1 female) participated in the study. The site of application/adhesion on the buccal mucosa was wiped with a cotton swab and a patch (1 cm^2 disc area) was pressed voluntarily on the buccal mucosa for 30 s. The volunteers were allowed to drink water from 30 min after fixing of the patch and were advised to perform their normal oral activities and not to disturb the patch by any means. The volunteers were asked to note the retention time of the device and opine about the acceptability of the patch. An index for irritation of mucosa, taste alteration and hindrance due to swelling were used to describe side effects of the patches. A score scale[10,11] was used to describe the biocompatability of the device.

In vitro evaluation:

The patches were evaluated for drug release using Keshary-Chien type glass diffusion cells. Cellophane sheets treated with 5% v/v of glycerol[12,13] were mounted between the donor and receptor compartments. The patch was placed on the cellophane sheet and the compartments clamped together. The cell was placed in a water bath maintained at 37±1°. The receptor compartment (25 ml capacity) was filled with phosphate buffer, pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. Ten millilitres samples were withdrawn at pre-determined time intervals and an equal volume of pre-warmed buffer was replaced. The samples were analyzed, after appropriate dilutions, for PHL content at 290 nm.

Pharmacodynamic evaluation:

The buccal delivery of PHL from selected batches of the fabricated patches was evaluated by measuring

the isoprenaline-induced tachycardia in rabbits. The study was designed after a slight modification of the method reported in literature[14-16]. Healthy albino rabbits of either sex (2.45±0.15 kg) were selected for the study and acclimatized to the laboratory environment for 1 w prior to the experiment. Overnight-fasted rabbits *(water ad libitum)* were anaesthetized by intraperitoneal administration of 35 mg/kg of phenobarbitone sodium in sterile normal saline. Anesthesia was maintained by hourly administration of 6 mg/kg of phenobarbitone sodium. ECG electrodes (stainless steel needles) were set subcutaneously (one each in right and left fore legs and right and left hind legs). Lead I or II was used for recording ECG on a student physiograph. The chart speed was kept at 5 mm/sec and heart rate was determined by counting 'R' waves of ECG. A catheter (scalp vein needle guage 24) was placed in the central or marginal ear vein. Heparinised saline (20 IU/ml) was filled in the catheter immediately after each injection to keep the catheter patent and to overcome its dead volume.

Pharmacodynamics of intravenously administered and buccal patches of PHL:

Normal heart rats of the rabbit was recorded before administration of isoprenaline. Two slow i.v infusions (for 30 s) of isoprenaline (0.25 µg/kg) were given at intervals of half an hour and heart rate was recorded for 30 s before and 2 min (4 x 30 s) after isoprenaline administration. PHL in sterile normal saline at a dose of 0.57 mg/kg was administered intravenously for 30 s through the catheter and flushed with 1 ml of heparinised saline. Isoprenaline (0.25 µg/kg) was administered at pre-determined time intervals for 5 h after PHL dosing. Heart rate (beats/min) was recorded as described after each isoprenaline administration. In case of the pharmacodynamic studies of the patches, the patch was stuck on the upper left oral mucosa after wiping the site with cotton swab. Isoprenaline (0.25 µg/kg) was administered and the heart rate was recorded as described. Care was taken to prevent the rabbit from disturbing the patch. All experiments were performed in triplicate.

RESULTS AND DISCUSSION

The formulation variables and the various physicochemical properties of the prepared patches are shown in Tables 1 and 2 respectively. The prepared patches were smooth in appearance, uniform in thickness, weight and drug content and showed no visible cracks or breaks, thus showing good folding endurance. The surface pH studies indicated that there was no change in the pH (of

TABLE 2: PHYSICO-CHEMICAL PROPERTIES OF THE PREPARED PATCHES

Batch code	MVT (75% rh) (g cm^2 h 10^{-4})		% moisture absorbed		Thickness (mmx10^{-2})	Weight (mg)	Drug content (mg)
	1 d	7 d	1 d	7 d			
S_1	5.9	16.6	7.2	24.9	22.40±0.55	68.0±2.82	2.086±0.109
S_2	7.7	20.5	9.4	20.4	20.25±0.50	64.8±0.84	2.276±0.081
S_3	5.9	10.5	6.4	18.6	20.25±0.50	62.8±4.66	2.222±0.080
S_4	4.9	99.4	9.4	16.1	22.44±0.52	66.0±3.53	2.342±0.076
S_5	4.7	10.5	6.3	11.5	19.25±0.50	64.0±1.83	2.226±0.081
S_6	6.9	12.1	8.1	21.5	20.50±0.56	65.33±3.61	2.148±0.104
S_7	4.2	12.8	7.9	19.2	19.50±1.04	68.4±0.89	2.219±0.059
S_8	6.5	24.8	6.5	13.3	19.16±0.75	66.8±3.11	2.205±0.068
P_1	7.8	34.1	5.7	10.6	21.00±0.23	68.0±4.90	2.400±0.079
P_2	8.9	14.9	6.2	10.3	20.42±0.33	65.20±3.11	2.059±0.095
P_3	6.8	20.1	6.8	10.9	19.28±0.51	64.24±2.84	2.230±0.019
P_4	5.7	20.8	7.9	13.7	19.44±0.27	64.20±4.32	2.316±0.014
P_5	4.9	10.5	8.9	17.6	20.48±0.49	64.87±3.02	2.175±0.014
P_6	6.5	17.3	8.1	16.5	21.22±1.02	62.21±0.94	2.201±0.014

All the batches showed an folding endurance > 1680

TABLE 3: SWELLING CHARACTERISTICS ON THE PREPARED PATCHES

Time (h)	Swelling Index*							
	S_1	S_2	S_3	S_4	S_5	P_1	P_2	P_3
0.5	39.52±3.59	61.71±1.33	11.43±4.62	8.42±2.12	15.43±2.71	18.32±0.92	9.43±1.82	8.42±0.31
1.0	33.37±3.80	71.26±3.51	23.58±3.84	18.70±4.21	33.00±2.44	36.28±0.81	17.26±2.46	15.56±0.27
1.5	22.34±1.78	45.71±8.70	22.48±0.55	17.43±3.02	38.23±2.52	36.42±2.34	16.41±1.42	18.42±0.12
2.0	16.62±3.14	28.08±1.24	19.64±1.52	17.86±1.20	44.19±2.38	38.63±2.42	15.25±1.05	20.36±0.24
3.0	14.62±0.74	22.39±0.95	22.67±3.74	20.88±0.24	31.19±2.44	29.53±1.32	14.54±2.30	18.61±1.49
4.0	9.57±4.2	16.30±3.02	18.62±0.37	28.41±2.21	33.25±2.54	41.08±1.24	13.31±1.08	15.38±2.98
5.0	6.17±0.81	15.03±2.41	21.71±1.52	26.94±0.16	35.02±2.68	42.84±2.32	12.71±2.02	11.92±2.14
6.0	4.89±0.40	11.44±4.16	19.08±3.42	27.41±1.42	37.50±2.94	46.48±1.42	13.41±2.51	8.45±2.22
7.0	4.03±0.14	9.31±2.21	23.85±3.74	29.28±2.82	36.46±2.27	47.83±2.22	12.65±3.14	6.42±0.84
8.0	3.43±0.16	7.68±2.06	22.62±1.52	30.81±2.12	33.76±2.02	58.41+-2.04	11.85±0.94	6.12±2.34

*The values are represented as mean±S.D. and n=3. The swelling index was calculated by using the following formula SI = (Final wt. of patch-Initial wt of patch/initial wt of patch) x 100.

both the pH altered and unaltered batches). The percentage moisture absorbed and the rate of MVT increased with an increase in the period of exposure to the humidity conditions in all the cases. The patches containing higher proportions of SCMC absorbed more moisture than the other patches. The swelling index studies indicated that the rate of swelling was proportional to SCMC and inversely proportional to CP content of the patches (Table 3). *In vitro* studies indicated that the drug release from all the batches followed zero order kinetics. The drug release from the patches prepared from SCMC alone (Batch S_1) and in combinations with CP decreased in the order, $S_1 > S_2 > S_3 > S_4 > S_5$. The initial burst effect observed from batch S_1 may be attributed to the rapid hydration of SCMC, which is present in higher proportions. The progressive decrease in the amount of drug released and the rate, from batches S_2, S_3, S_4 and S_5 may be attributed to the increase in CP content and a consequent decrease in SCMC content. CP resins in general have an intricate network of cross-links, which makes possible the physical entrapment of drugs in the hydrogel domains that form when the polymer absorbs water and swells to form a gelatinous barrier around the device. As CP 934 P is highly cross-linked, it does not open up easily and higher drug concentrations are required to fill the large intestitial spaces between the swollen gel particles. Due to the rapid water uptake between the particles in the device and the resultant gelation and sealing of pores at the surface, the release of drug is limited. Swelling then continues slowly by diffusion through the growing gel layer, thus controlling the release rate of the drug.

An increase in the release rate of drug was observed from the pH altered patches, in comparison to the pH-unaltered patches, as evidenced from the amount of drug released from batches S_6,S_7 and S_8 (fig. 1). At pH 6, CP is present in the ionised state and as a result the polymeric network gets loosened comparatively, attributing for the higher drug release. Similarly, incorporation of PC retarded the drug release, evidenced from the drug release profiles of batches P_1, P_2 and P_3 (fig. 2). Drug release from the pH-altered batches was comparatively higher than pH unaltered batches. This is because, like CP, PC is also ionised at pH 6.

The mucoadhesivity of the prepared patches was determined for different contact times, using rabbit's SIM as model mucous membrane. When the contact time was 2 minutes, the batches S_1, S_2, S_3, S_4, S_5, P_1, P_2 and P_3 showed a mucoadhesivity of 44.7, 36.7, 30.2, 24, 21.16, 38.4, 24 and 20.2 g, respectively (Table 4). As the contact time was increased, a linear increase in the mucoadhesivity was observed. The studies further indicated that the time of mucoadhesion increased linearly with an increase in the concentration of CP/PC in the patches. The increase in the mucoadhesivity may be due to the formation of a strong gel that interpenetrates tightly into the mucin molecules. Pure SCMC patches alone showed good mucoadhesivity in the 2 min contact time, as compared to patches with SCMC, CP/PC combinations.

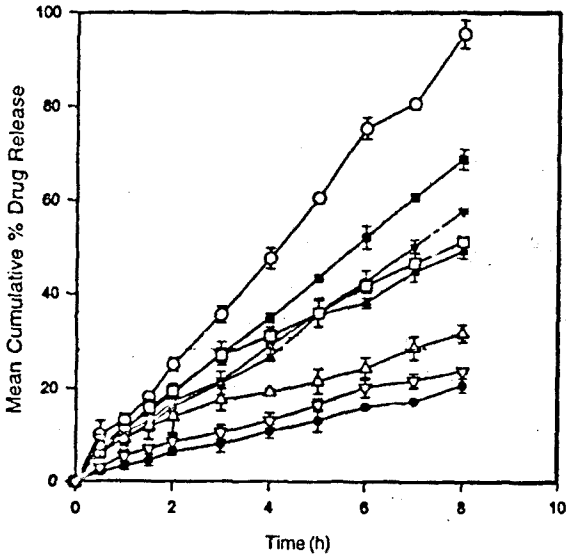

Fig. 1: *In vitro* release of PHL from pH altered and unaltered patches containing varying proportions of Carbopol

The *in vitro* release profiles of (-O-) S_1, (-□-) S_2, (-Δ-) S_3, (-∇-) S_4, (-o-) S_5, having pH4 and (-■-) S_6, (-▲-) S_7, (-▼-) S_8 having pH 6, conducted in phosphate buffer pH 7.4 are shown. The composition of these patches are shown in Table 1.

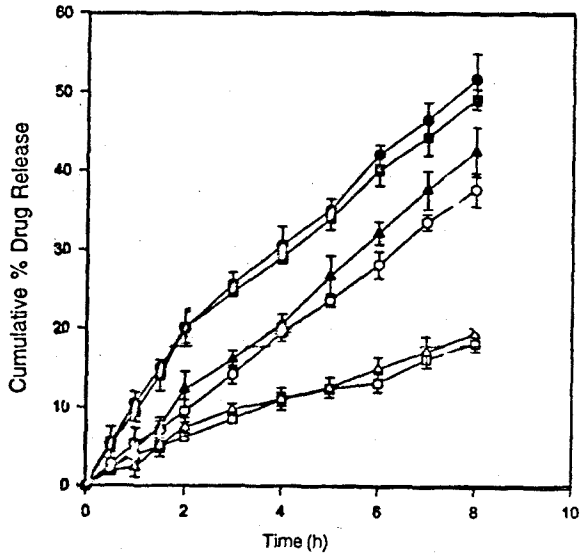

Fig. 2: *In vitro* release of PHL from pH altered and unaltered patches in phosphate buffer pH 7.4

The *in vitro* release profiles of (-O-) P_1, (-□-) P_2, (-Δ-) P_3, having pH 4 and (-o-) P_4, (-□-) P_5, (-▲-) P_6 having pH 6, conducted in phosphate buffer pH 7.4 are shown. The composition of these patches are shown in Table 1.

TABLE 4: *IN VITRO* MUCO ADHESIVITY TEST OF THE PREPARED PHL PATCHES

Contact time (min)	Mucoadhesivity* (g)							
	S_1	S_2	S_3	S_4	S_5	P_1	P_2	P_3
2	44.7±0.44	86.7±0.62	30.2±1.09	24.0±0.87	21.16±1.3	38.4±2.8	24.0±2.44	20.2±0.84
5	57.0±1.04	77.2±2.9	103.3±3.5	114.7±2.3	120.25±3.3	73.2±4.9	90.8±3.12	136.0±2.41
10	100±4.48	113.0±4.42	128.5±2.42	136.2±2.49	147.0±2.28	120.8±2.28	142.2±3.58	153.2±2.78
15	150.2±2.28	163.4±4.22	169.4±3.42	172.2±2.28	181.0±2.09	160.6±2.31	180.3±3.40	188.2±2.99

*The values are represented as mean±S.D. and n=3. The tests were carried out in rabbit intestinal mucosa. The batches S_1 to S_5 and P_1 to P_3 refers to the batches shown in Table 1.

Due to its hydrophilic nature, SCMC gets hydrated easily with less contact time and forms a sufficiently strong gel which entangles tightly with the mucin molecules.

The *in vivo* mucoadhesive studies showed that the patches were tolerated well by the volunteers. Slight hindrance due to swelling was reported by one volunteer (Table 5) in case of batches S_1, S_2, P_1 and P_4, due to the higher rate of swelling of the patches, as evidenced by the swelling index studies. Slight taste alteration was reported by one volunteer in case of patches S_1, S_2 and 2 volunteers in case of patches S_6 and P_4. The mean mucoadhesion time was less for pure SCMC patches and it seemed to increase linearly with increase in proportions of CP and PC in the patches.

The prepared patches (S_1, S_6 and P_4) showed a gradual increase in percentage inhibition of heart rate to attain a delayed peak of inhibition, followed by a more gradual fall, thus maintaining the inhibition of the heart rate for longer periods suggesting good sustained release

TABLE 5: BIOCOMPATABILITY AND *IN VIVO* BUCCOADHESION PARAMETERS IN HUMAN VOLUNTEERS

Batch Code	*In vivo* Buccoadhesion Parameters Scores*				
	Irritation of the mucosa	Swelling hindrance	Taste alteration	Pain of the mucosa	Buccoadhesion time (h)
S_1	0	0.2±0.44	0.2±0.44	0	12.46±0.63
S_2	0	0.2±0.44	0.2±0.44	0	13.04±0.11
S_3	0	0	0	0	13.79±0.28
S_4	0	0	0	0	14.35±0.19
S_5	0	0	0	0	14.67±0.62
S_6	0.2±0.44	0	0	0	13.00±0.52
S_7	0	0	0.4±0.54	0.2±0.44	14.22±0.42
S_8	0	0	0	0	14.04±0.24
P_1	0	0.2±0.44	0	0	14.20±0.21
P_2	0	0	0	0	13.00±0.42
P_3	0	0	0.4±0.54	0	13.24±0.42
P_4	0	0.2±0.44	0	0.2±0.44	14.22±0.18
P_5	0.2±0.44	0	0	0.2±0.44	13.20±0.21
P_6	0	0	0	0	14.54±0.19

* The values are represented as mean±S.D. and n=5; S_1 to S_8 and P_1 to P_6 are the prepared placebo buccoadhesive patches, whose composition are given in Table 1.

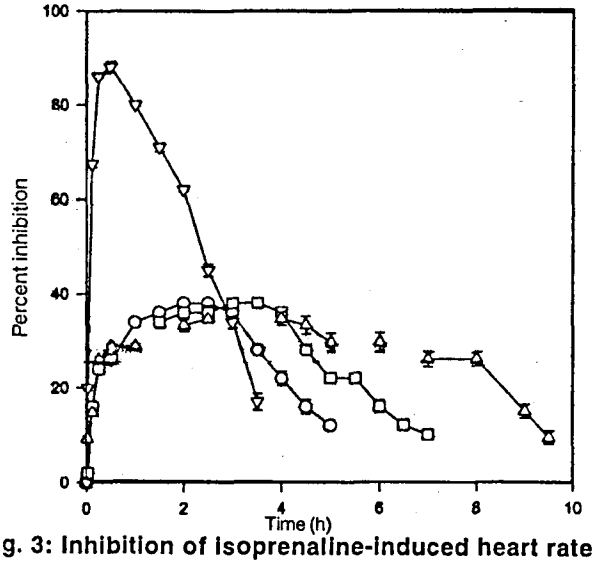

Fig. 3: Inhibition of isoprenaline-induced heart rate in Rabbits

Composition of polymers in the batches: (-O-) S_1, SCMC alone; (-□-) S_6-SCMC (2.5) : CP (0.5); (-Δ-) P_4-SCMC (2.08): PC (0.42), where SCMC, CP and PC indicate sodium carboxymethyl cellulose, Carbopol and Polycarbophil, respectively, (-∇-) i.v. indicates intravenously administered propranolol hydrochloride

property (fig. 3) Patch S_1 showed maximum inhibitory effect of 38% at around 3 h, a steady state for 1 h and decline in the inhibitory effect. The pharmacodynamic profile of S_6 was similar to S_1, excepting that the decline in the inhibitory effect was much more prolonged (upto 7 h) than S_1. The time to inhibit 25% of the heart rate for batches S_1, S_6, P_4 and i.v. dose were 4.13,4.96, 7.5 and 2.73 h, respectively, while the same formulations inhibited 30% of heart rate in 3.25, 2.88, 3.23 and 2.5 h respectively. $T_{50\%}$ and $T_{75\%}$ inhibition levels were achieved only by i.v. dose.

The placebo patches were generally tolerated well by the human volunteers who had participated in the study. Though, the number of volunteers used in the study was small, the results indicate the compatability of the patches, thereby suggesting that the selected polymers could form the basis of a mucoadhesive delivery system. The *in vitro* mucoadhesive studies indicated that the patches containing higher proportions of CP/PC showed better mucoadhesive properties and was found

to be proportional to the contact time. The prepared patches were successful in retarding PHL release *in vitro*. However, the pharmacodynamic evaluation in rabbits showed about 30% inhibition of isoprenaline induced tachycardia, probably due to low drug loading and some drug loss through the oral route. Nevertheless our studies indicate their prolonged effect *in vivo*. Further investigations on these lines are currently in progress.

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