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Development of Buccoadhesive Systems of Pentazocine for Systemic Drug Delivery

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Abstract

Bucoadhesive patches of Pentazocine (PZ) for unidirectional drug delivery were prepared by casting carboxy methyl cellulose (CMC) with glycerol or propylene glycol and CMC-hydroxy ethyl cellulose (HEC) with glycerol. *In vitro* mucoadhesivity of the prepared patches were determined using a modified mucoadhesive bond strength apparatus using rabbit small intestine mucosa (SIM). Drug release kinetics was evaluated from composite patches, prepared by covering all but one side of the PZ patches with 3M backing material. Biocompatability / buccoadhesion time and *in vivo* permeation of placebo and PZ loaded patches were determined using a double blind cross over study in healthy human volunteers. Drug release from CMC-glycerol patches and pure HEC patches showed zero order kinetics with diffusional exponent (n) ranging between 0.79 to 1.046, while that from CMC-HEC and CMC-propylene glycol patches showed an apparent zero order release kinetics. The prepared patches were well tolerated by the human volunteers as they did not produce any side effects at the contact surface. The *in vitro* mucoadhesivity of CMC-propylene glycol patches were

significantly lower than CMC- glycerol based patches. The *in vivo* permeation of selected PZ patches delivered the drug well above the minimum buccal permeation rate, so as to attain effective blood concentration.

Key words: Buccoadhesive, In vitro mucoadhesion, Pentazocine, Buccal patches

Introduction

PZ, an opioid analgesic with mixed agonist-antagonist activity [1,2] and a plasma half-life of 2-3 hours in humans [3] undergoes extensive first pass metabolism. As a result, frequent drug administration is required to maintain its therapeutic efficacy. Thus the development of a non-parenteral dosage form that avoids the first pass metabolism should be a notable advantage for its analgesic therapy. Transdermal [4], rectal [5] and buccal [6] administration of PZ have been attempted earlier to improve the systemic bioavailability of PZ.

The buccal mucosa is collectively more permeable than the skin [7-9] and could be viewed as an alternative than the other systemic routes. Further, the buccal membrane with its large expanse of accessible smooth mucosal surface offers a convenient platform for prolonged drug delivery systems[10,11] and provides direct entry of drug molecules into systemic circulation, provided the device is designed for unidirectional (i.e., to the ora mucosal surface only) drug delivery, thus avoiding hepatic first pass metabolism. However, retention of such delivery systems at the oral mucosa for a period of 6 to 12 hours is affected adversely by salivary flow, ingestion of food and beverages, and movements of the oral mucosal structures. Resilient adhesive patches or adhesive controlled release tablets have a greater potential for sustained delivery than disintegrating tablets. In an earlier report [6] on buccoadhesive compacts of PZ, drug free peripheral and a backing layer of a mixture of magnesium state, Carbopol® 974P and HPMC K4M were used to restrict back-diffusion of the drug from the exposed surface of the compact. However, it is well known that both Carbopol® and HPMC swell in contact with aqueous fluids and thus over the period of retention of the device on the buccal mucosa, back diffusion of PZ from the core through the peripheral and backing

layers to the oral fluids is a distinct possibility. Therefore, this device is not likely to deliver PZ to the buccal mucosa only, rather drug delivery will be both to the mucosa as well as to the oral cavity. This defeats the very idea of circumventing the first pass metabolism of PZ by delivery directly to the buccal mucosa. Hence the present study was designed to study buccoadhesive films of PZ, using CMC alone and in combination with HEC to examine the usefulness of the device in sustaining unidirectional delivery of PZ across buccal mucosa in human volunteers.

Experimental

Materials

PZ, HEC (Natrosol® 250G) and 3Mfoam tape 1777were gifted generously by Ranbaxy Lab Ltd (India), Aqulon (HongKong) and 3M Pharmceuticals (Minnesota, USA), respectively. All other reagents used were of analytical grade. Albino rabbits (Central Animal House, Banaras Hindu University, India) of weight 2.45± 0.15 Kg were used.

Methods

Fabrication of bucoadhesive PZ patches

The plasticizers (glycerol / propylene glycol) at a concentration of 40% w/w with respect to the polymer(s) were added to distilled water under stirring and required quantities of the polymer(s) was added slowly untiil an uniform dispersion was obtained. The required amounts of PZ was dissolved in a minimum volume of methanol (Table 1) and added to the polymer dispersion and stirred for 12 hours. The resultant dispersion was degassed under vacuum and patches of desired thickness were prepared by casting the dispersion on glass substrates of dimensions 7.1x7.1x2.5 cm and drying in an oven at 50° C for 18-20 hours. The dried patches were removed, wrapped in aluminium foil and stored in airtight containers over fused calcium chloride in a desiccator at room temperature until further use. Placebo patches (without PZ) were prepared and stored as described.

Evaluation of the patches

Uniformities of weight, thickness and drug content

The thickness of the films were measured at 10different randomly selected spots using a screw gauge and for weight uniformity, patches of area (1.04 cm^2-discs) were punched out and 5 such patches from each batch were weighed individually. Drug content uniformity was determined by weighing 3 patches (1.04 cm^2) and dissolving in 100 ml of phosphate buffer pH 6.6. The resultant solution was filtered through G-2 glass filter and an aliquot of the filtrate was diluted suitably and analyzed for PZ content at 278 nm, spectrophotometrically (Shimadzu-1601, Japan).

Batch Code	CMC (gm)	HEC (gm)	PZ
PA	1.0	-	180
PB	1.5	-	180
PC	2.0	-	180
PD	1.0	-	300
PE	1.5	-	300
PF	2.0	-	300
PG	2.0	-	500
PH	1.0	1.0	300
PI	0.5	1.5	300
PJ	1.5	0.5	300
PK	-	2.0	300
PG1	1.0	-	180
PG2	1.5	-	180
PG3	2.0	-	180
PG4	1.0	-	300
PG5	1.5	-	300
PG6	2.0	-	300

Tab. 1. Composition of oral Mucoadhesive Patches

Patches PA to PJ contains Glycerol at 40% w/w of polymer as plasticizer
Patches PG1 to PG6 contains Propylene glycol at 40% w/w as plasticizer
Patch PK does not contain any plasticizer.
Methanol 4,6 and 8 ml was used to dissolve PZ when used at 180, 300 and 500 mg respectively.

In vitro mucoadhesion test

A modified mucoadhesivity apparatus developed and validated by us[12] was used to study the mucoadhesive bond strength. The apparatus consisted of an aarylate mounting stage (5 cm height and 1.7 cm diameter) attached to the center of a dish (7.5 cm height and 7.5 cm diameter). The dish with tissue mount containing phosphate buffered saline (PBS) pH 6.6 was kept on a magnetic stirrer provided with temperature control. The buffer was agitated at 100rpm. An acrylate device holder of diameter 1.5 cm and weighing 2.6 gm was used. A nylon thread of thickness 0.38 mm and length 52 cm was placed over an acrylate pulley groove (7.5 cm diameter) in such a way that one end is tied to a pan and the other end to the device holder.

Over-night fasted albino rabbits (water ad-libitum) were sacrificed and the small intestine was carefully removed and rinsed with cold saline to remove any loose material. It was then cut into segments of 3 cm length and cut open longitudinally along the mesentry to expose the inner mucosal surface [13] and stored in cold saline (5-8° C) and used within 3 days [14].

The intestinal tissue (mucosal side out) was mounted securely with the help of silicone rubber band on the tissue mount platform within the dish containing PBS at 37±1°C. The level of PBS in the dish was maintained in such a way that it just touches the mucosal surface and every care was taken to prevent over hydration of the tissue. The patch (1.04 cm^2) was fixed on the device holder with cyanoacrylate adhesive. The patch was placed in contact with the mucosal surface and after a contact time of 2 minutes, standard weights in increments of 500 mg [15] were added on the pan after every 30 seconds. The weight at which detatchment took place was noted. This gave the mucoadhesive bond strength of the PZ patches in gm. After every half-an hour 100μl of PBS was added on the mucosal surface to prevent the drying of the mucosa. Gross observations indicated that dhesive failure occurred at the mucosa adhesive interface. Hence zero correction weights for the detachment was determined without the device and tissue and deducted from the

observed test weights. Experiment was carried out in triplicate (with fresh patch and mucosa) to ensure reproducibility.

Water Uptake and surface pH measurements

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 keep the patch (1.04 cm^2). The basket was placed in a petri dish (8 cm diameter and 1.5 cm height) containing 70 ml of phosphate buffer pH 6.6. The petri dish with the basket was covered with a glass dish (diameter 7 cm and internal height 7.5 cm) and placed on a platform, maintained at 37±1°C. The weighed patch, placed in the pre-weighed USP dissolution basket, was immersed in 70 ml of phosphate buffer pH 6.6. 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 the buffer in the petri-dish. The Swelling index (water uptake) was calculated using the relation [15-18].

Water uptake = $Sw_2 - Sw_1 / Sw_0$; where Sw_2 is the weight of swollen device and basket; Sw_1 is the weight of basket alone and Sw_0 is the initial weight of the device.

Equilibrium water uptake (EWU) was determined from the water uptake Vs time curve [19].

For surface pH determinations, the patches (1.04 cm^2) were allowed to swell in closed petri-dishes 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 1 minute the colour developed was compared with the standard colour scale.

In vitro release studies

The primary requirement of any buccoadhesive dosage form designed for systemic delivery requires unidirectional drug release throughout the study period [20-22]. The apparatus designed by us consisted of a device holder (3 cm diameter and 1.2 cm thickness), a central rod (5.6 cm long and 5mm diameter) and beaker cover (8 cm diameter and 2 mm thick). Both the device holder and beaker cover

were fixed with the central rod as shown in Fig 4. The dissolution medium (phosphate buffer pH 6.6) in the beaker was placed on a water bath thermostated at 37±1°C. To achieve unidirectional drug release. One surface of the patch (1.04 cm^2) was stuck on to 3M Pharmaceuticals foam tape and excess tape was trimmed to the circumference of the patch. The circumference of this composite patch was then covered firmly with foam tape so as to leave a projection of 1mm on the circumference of the drug-releasing surface and was stuck on to 2 cm diameter foam tape. The non-adhesive upper side of the 2-cm diameter foam tape was stuck on to the device holder with the help of 3M pharmaceutical grade transfer adhesive (PGTA). The foam tape acts as a backing layer and the covering on the circumference prevents lateral drug release, thus ensuring unidirectional drug release throughout the study period.

The polyacrylate cover of the device holder was placed on top of the dissolution beaker containing 100 ml of freshly boiled and cooled dissolution medium. This arrangement allowed for the immersion of the device holder in the dissolution medium. The dissolution medium was agitated at 250 rpm using a Teflon® coated magnetic bead (6x4 mm). 3-ml aliquots were withdrawn at pre-determined time intervals and replaced with an equal volume of the pre-warmed buffer. The samples were analyzed for PZ content at 278 nm, after appropriate dilutions.

In vivo studies

The biocompatability / *in vivo* buccoadhesion time of the placebo and PZ patches and the *in vivo* permeation of the PZ patches were determined in a double-blind cross over study in 6 and 4 male healthy human volunteers, respectively. The age of the volunteers who had participated in the *in vivo* buccoadhesion time studies ranged between 23 and 30 years (26.67±2.42) and their weights between 60 to 79 kg (70±6.96 kg), while volunteers in the permeation studies were aged between 25 and 31 years (27.17 ± 2.14 years) and their weights between 55 to 79 kg (68. ± 8.04 kg). Volunteers agreed to participate in the study after detailed explanation of the respective experimental protocols and written informed consent

was obtained from each volunteer. All subjects were in good health on the basis of medical history and complete physical examination.

The volunteers were given standard breakfast, lunch and dinner, prepared at the Institute's cafeteria at appropriate times, during the course of the experiment.

In vivo buccoadhesion time

After half an hour of the standard breakfast the composite patch (prepared as described earlier) was placed with slight mannual pressure for 1 minute on the buccal sulcus, opposite to the upper left or right canine tooth after wiping the site with cotton swab. During the experiment the volunteers were allowed to drink water after half an hour of administration of the patch. The volunteers were provided with standard lunch and dinner after 4 and 12 hours of administration of the patch, respectively. The subjects were allowed to perform their normal oral activities and instructed not to disturb the device by any means. They were trained to note the retention time of the patch and indicate the acceptability of the composite patch. Indices for pain, irritation of mucosa, taste alteration, hindrance due to swelling and redness and ulceration after removal of the device were used to describe the side effects of the patches. Fresh placebo composite patches was placed at each replicate point. A minimum period of 4 days was allowed between replicate applications. A score scale of 0, nil; slight : 1, moderate : 2 and severe : 3 was used to describe the biocompatability of the devices [23,24].

In vivo permeation study

Half an hour after a standard dinner, one composite patch (1.04 cm^2) was placed opposite to upper left or right canine buccal sulcus, before going to bed, after wiping the site with cotton swab. The composite patch was removed carefully immediately after awakening in the morning. Any swollen residue left at the site was removed with tissue paper. The residual PZ in the buccoadhesive patches after overnight placement in the volunteers was determined using a modified extractive spectrophotometric method reported by Le Brun et al [25]. The percentage of PZ absorbed was calculated from the amount remaining in the device after removing it completely from the site of application. The residual device was dissolved in 150 ml

of phosphate buffer pH 6.6 and filtered. An aliquot of the filtrate was alkalinized by adding 0.5 ml of 4N sodium hydroxide solution and then PZ was extracted with 5 ml of dichloromethane by shaking gently for 15 minutes. The organic layer was separated after centrifugation for 10 minutes at 4000 rpm. Anhydrous sodium sulphate was added to the separated dichloromethane portion and shaken for a minute. PZ content was determined at 282 nm using dichloromethane as a blank.

Results and Discussion

The composition of the various batches of PZ buccoadhesive patches are given in Table 1. The prepared PZ batches showed good uniformities in weight, thickness, drug content and surface pH (Table 2). The surface pH of the prepared patches ranged between 7 to 7.5, thus indicating that these patches are suitable for *in vivo* evaluation.

Batch Code	Thickness (mm)	Weight Uniformity ($gm/1.04cm^2$)	Drug content (mg)	Surface pH	In vitro mucoadhesivity (gm)
PA	0.18 ± 0.010	0.025± 0.002	2.9 ± 0.35	7	77.33 ± 24.38
PB	0.22 ± 0.025	0.037± 0.004	3.12 ± 0.31	7	98.0 ± 29.62
PC	0.32 ± 0.025	0.041 ± 0.170	2.74 ± 0.17	7	115.1 ± 3122
PD	0.20 ± 0.015	0.031 ± 0.001	5.29 ± 0.20	7.5	105.67 ± 18.77
PE	0.23 ± 0.024	0.036 ± 0.002	4.97 ± 0.38	7.5	120.33 ± 10.02
PF	0.35 ± 0.006	0.048 ± 0.002	4.57 ± 0.19	7.5	126.67 ± 15.28
PG	0.36 ± 0.006	0.047 ± 0.005	7.91 ± 0.32	7.5	174.33 ± 9.82
PH	0.39 ± 0.040	0.052 ± 0.009	4.96 ± 0.44	7.5	131.67 ± 18.56
PI	0.31 ± 0.050	0.043 ± 0.004	5.13 ± 0.89	7.5	54.67 ± 13.43
PJ	0.31 ± 0.015	0.045 ± 0.013	4.76 ± 0.13	7	161.0 ± 22.34
PK	0.32 ± 0.023	0.044 ± 0.003	5.5 ± 0.39	7.5	23.33 ± 5.13
PG1	0.19 ± 0.013	0.03 ± 0.003	2.88 ± 0.29	7	52.67 ± 10.60
PG2	0.22 ± 0.026	0.036 ± 0.004	2.93 ± 0.27	7	62.33 ± 9.61
PG3	0.35 ± 0.011	0.055 ± 0.006	3.1 ± 0.71	7	65.33 ± 6.00
PG4	0.22 ± 0.030	0.03 ± 0.003	5.23 ± 0.52	7	60.33 ± 6.51
PG5	0.24 ± 0.020	0.038 ± 0.002	5.49 ± 0.49	7	55.33 ±13.61
PG6	0.41 ± 0.068	0.056 ± 0.008	5.51 ± 1.02	7	70.33 ± 9.50

Tab. 2. Physico Chemical properties of the Prepared Patches

Release of PZ from and water uptake by CMC based patches

The release of PZ from the patches was studied with respect to plasticizer type, polymer concentration, drug loading and patch thickness.

In general, almost identical PZ release from patches plasticized with either glycerol or propylene glycol was observed, though propylene glycol patches showed slightly higher release in the first three hours than glycerol containing PZ patches. Further, this was confirmed by the kinetic release constant (k) derived from the exponential equation $M_t / M_\infty = k\ t^n$; where M_t is the amount of drug released in time t; M_∞ is the overall amount released; k denotes the constant incorporating structural and geometric characteristics of the drug / polymer system and n is the diffusional exponent related to the mechanism of release [26-29], which showed higher k values for patches containing propylene glycol (PG4, PG5 and PG6) when compared to patches containing glycerol (PD, PE and PF) (Table 3).

Batch Code	k	n	Q Vs t	Q Vs $t^{1/2}$	MDT (hr)
PA	0.07 ± 0.01	1.04 ± 0.08	0.998	0.993	5.96 ± 0.97
PB	0.105 ± 0.02	0.85 ± 0.06	0.998	0.984	6.34 ± 0.71
PC	0.072 ± 0.001	0.89 ± 0.03	0.999	0.985	9.32 ± 1.1
PD	0.013 ± 0.02	0.94 ± 0.07	0.991	0.984	5.57 ± 0.49
PE	0.126 ± 0.02	0.78 ± 0.02	0.992	0.990	7.57 ± 0.61
PF	0.123 ± 0.03	0.79 ± 0.1	0.993	0.991	8.15 ± 0.94
PG	0.108 ± 0.017	0.69 ± 0.09	0.993	0.991	10.3 ± 1.49
PH	0.091 ± 0.01	0.76 ± 0.04	0.996	0.993	9.89 ± 1.38
PI	0.157 ± 0.007	0.67 ± 0.06	0.989	0.995	6.36 ± 0.99
PJ	0.098 ± 0.017	0.78 ± 0.02	0.995	0.990	8.6 ± 1.46
PK	0.131 ± 0.032	0.94 ± 0.12	0.997	0.986	4.22 ± 0.42
PG1	0.172 ± 0.005	0.67 ± 0.02	0.996	0.996	5.48 ± 0.05
PG2	0.156 ± 0.024	0.69 ± 0.05	0.997	0.988	5.93 ± 0.55
PG3	0.112 ± 0.013	0.81 ± 0.04	0.997	0.992	6.66 ± 0.004
PG4	0.168 ± 0.012	0.72 ± 0.02	0.997	0.995	4.88 ± 0.19
PG5	0.148 ± 0.008	0.66 ± 0.007	0.998	0.994	6.99 ± 0.67
PG6	0.113 ± 0.011	0.75 ± 0.004	0.995	0.933	7.76 ± 0.71

Tab. 3. Drug release kinetics and MDT of the prepared PZ patches

The effect of CMC concentration showed an inverse influence on PZ release from either propylene glycol or glycerol plasticized patches. Increased concentration of CMC / unit area of patch also caused an increase in the thickness of the patch. As expected, the increased thickness of the patch caused lower PZ release from CMC based patches. In drug loading studies, the thickness of the films obtained were approximately 190, 250 and 350μm for CMC patch prepared with glycerol. Drug release increased with increase in drug loading for identical lower thickness patches (approx. 190μm- PA, PD, PG1 and PG4), whereas patches of thickness 250μm (PB, PE, PG2 and PG5) or 350μm (PC, PF, PG3 and PG6) with different drug loadings showed insignificant increase in drug release. This was further confirmed by the mean dissolution time (MDT) values, calculated according to the equation MDT = $[n/n+1]\ k^{-1/n}$; where n and k denote the n and k terms in the earlier equation; which showed that the patches with lesser thickness (~ 190μm) with different drug loadings showed statistically significant higher MDT values ($p < 0.05$), while patches with higher thickness (~ 250 or 350μm) showed insignificant decrease in MDT values ($p > 0.05$) (Table 3).

The calculated n values (Table 3) showed that batches PA and PD (lower thickness) obeyed perfect zero order drug release while the other patches showed Case II (apparent zero order) release mechanism. Case II drug release characteristics was due to drug diffusion after polymer chain relaxation and erosion of polymer matrix, where as in zero order mechanism the drug is released mainly due to erosion of the polymer matrix [27,28,29]. Further Mockel and Lippold [30] have reported that apparent zero order kinetics prevails if $n > 0.66$. The calculated correlation co-efficient (r) values for Q Vs t were higher in all cases than Q vs $t^{1/2}$ (Table 3).

Water uptake properties of PZ patches based on CMC-glycerol showed higher equilibrium water uptake (EWU) [31] than CMC- propylene glycol patches (Fig 1A and B). This may be due to formation of stronger swollen gel in CMC-glycerol patches than CMC-propylene glycol patches. When the CMC concentration was

higher, water uptake properties for CMC-propylene glycol patches showed initial higher swelling followed by rapid decline in water uptake, whereas CMC-glycerol patches showed relatively slower water uptake followed by slower erosion of the swollen matrix.

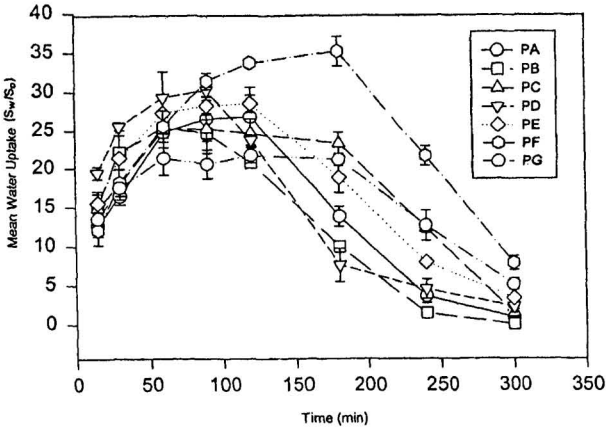


Fig. 1a. Water uptake of CMC based patches with Glycerol as plasticizer

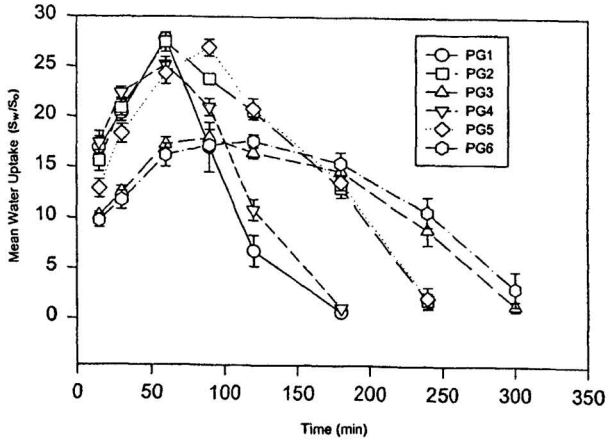


Fig. 1b. Water uptake of CMC based patches with Propylene glycol as plasticizer

Release of PZ from and water uptake by CMC-HEC based patches

Pure HEC patches without plasticizer showed higher PZ release than from HEC-CMC patches (Fig 2). Combination patches of HEC-CMC upto 1:1 proportion CMC patches showed an increase in drug release that was not statistically significant when compared with pure CMC based PZ patches ($p > 0.05$). This may be due to increase in the microviscosity of the swollen matrix up to 50% HEC in CMC patches as HEC has a tendency to increase the viscosity when mixed with an anionic polymer like CMC.

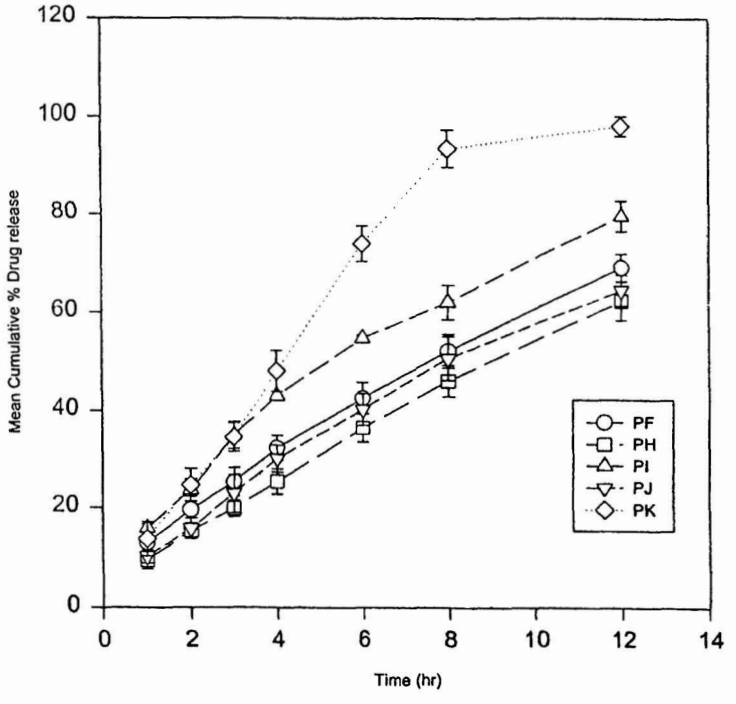


Fig. 2. Effect of CMC-HEC proportion on PZ release

Walker and Well [18] reported that greatest viscosity increase was found with combinations of sodium CMC and methyl cellulose (non-ionic). This was further

confirmed by the MDT values, which showed a statistically insignificant decrease in drug release up to 50% of HEC in CMC patches (batches PH and PJ- Table 3) when compared with pure CMC patches (PF) ($p > 0.05$). Patch with more than 50% of HEC in CMC (batch PI) released higher drug than batches PH, PJ and PG, but lower PZ release than batch PK.

A significant decrease in MDT values was observed for batch PI when compared with PZ patches based on CMC alone (Table 3).

The initial burst effect was statistically insignificant for PZ patches containing upto 50% HEC in CMC patches ($p > 0.05$); whereas significantly lower k values were obtained for pure CMC patches when compared with CMC-HEC (25:75) patches ($p<0.05$) (Table 3). The calculated n values were indicative of the fact that the drug release from HEC matrix alone (PK) was predominantly due to erosion of the swollen matrix (zero order) while that from CMC-HEC based patches was due to erosion and diffusion (apparent zero order). This was further confirmed by r values which was always higher for Q Vs t than for Q Vs $t^{1/2}$. Our results were in accordance with the results reported by Hussain et al [32] for chlorpheniramine maleate from HEC and CMC blended matrix.

The HEC-CMC combinations showed decreased water uptake than pure CMC patch (Fig 3). Increased concentration of HEC showed decreased EWU than pure CMC. A direct linear correlation was observed between HEC concentration in CMC patches and EWU. Thee results indicated that HEC dissolved in the swollen matrix resulting in the formation of loose hydrated matrix from which the drug was released at a relatively higher rate from CMC-HEC patches than the corresponding CMC based patches.

In vitro mucoadhesivity

Intestinal mucosa of pigs [33,34], guinea pigs [35], rats [36], rabbits [37], gastric mucosa of rabbits [38,39] and pigs [40-43] have been used. Furthermore, it is well established that pH plays an important role in bioadhesion and maximum adhesion is observed for pH 5 to 6 [44]. The pH of SIM ranges between 5 to 7, which is similar to the pH of buccal mucosa. Since there is no model tissue

earmarked for evaluation of buccoadhesive dosage forms, rabbit stomach mucosa and small intestinal mucosa were used in our studies because of regular availability of albino rabbits of uniform breed from the University's central animal house.

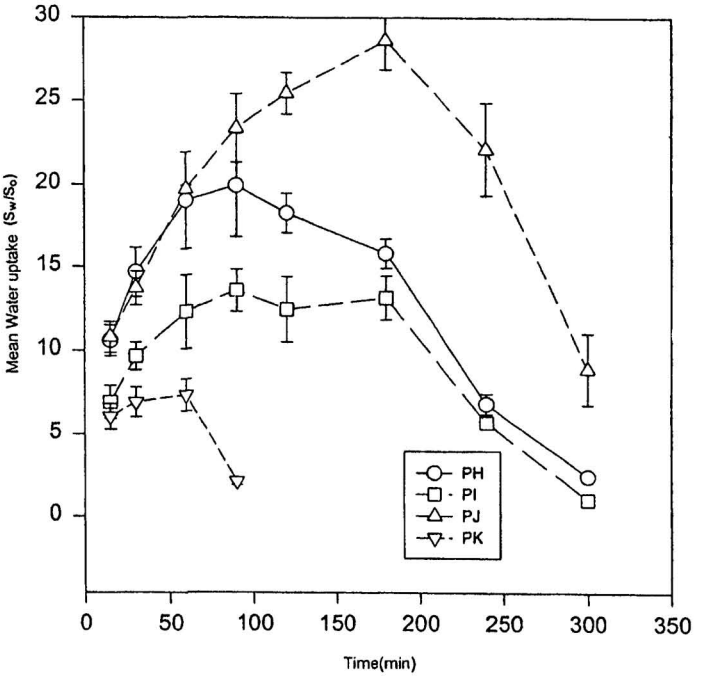
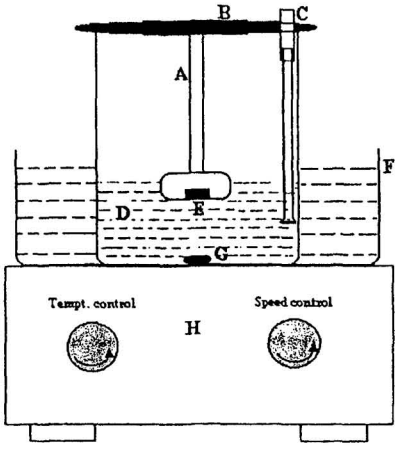


Fig. 3. Water uptake of CMC-HEC patches

A contact time (between the patch surface and the SIM tissue) of 2 minutes was found to give reproducible mucoadhesivity results for the patches. CMC-glycerol patches showed higher mucoadhesivity than CMC- PG based patches (Table 2). This could be attributed to the formation of a stronger swollen gel by CMC in presence of glycerol than propylene glycol. Rossi et al [45] reported that the strengthening of the sodium CMC – mucin interface was associated with rheological changes that occurred when the polymer is mixed with mucin. Higher

mucoadhesivity was observed with patches of 5mg/cm^2 of PZ than 3 mg/cm^2 patches. PZ, being a water insoluble drug helps in preventing overhydration and thereby formation of more strong gel with sufficient mucoadhesive bond than the low PZ loaded CMC patches. Increase in mucoadhesivity with an increase in thickness of the patch was also observed. Parodi et al [46] and Woolfson et al [47] reported similar observations.



A: Device holder
B: Polyacrylate cover
C: G-2 filter with rubber tubing
D: Phosphate buffer pH 6.6
E: Patch
F: Water bath
G: Magnetic bead
H: Magnetic stirrer

Fig. 4. Schematic illustration of *in vitro* dissolution test apparatus

Batches containing up to 50% of HEC in CMC patches showed statistically insignificant decrease in mucoadhesivity when compared to pure CMC based patches (Table 2). The reason could be due to an increase in the mucoadhesivity of the swollen matrix of CMC in the presence of HEC. The *in vitro* mucoadhesivity of CMC-HEC (25:75 and 0:100) patches showed a statistically significant difference when compared to other ratios of CMC-HEC ($p < 0.05$). Pure HEC patch (batch PK) showed the least mucoadhesivity when compared to patches of CMC or CMC-HEC. This could be due to the fact that HEC, being more water-soluble, forms relatively

more loose and swollen hydrogel while CMC or CMC-HEC patches form a relatively stronger, swollen rubbery matrix.

In vivo studies

On the basis of surface pH, *in vitro* release profiles, *in vitro* mucoadhesivity and water uptake properties, batches PF, PH and PG6 were selected for the *in vivo* studies in healthy human volunteers.

The patches were well accepted by the volunteers. Volunteers reported no to very slight bitter taste due to PZ around 6 hours after application of the patches (Table 4). Irritation and pain of mucosa and swelling hinderance were found to be well within tolerable limits [12]. There was no redness/ulceration of the mucosa upon removal of the device. In all cases, the device came off on its own from the contact buccal mucosa due to normal oral cavity movements. The buccoadhesion times of the drug loaded patches showed an insignificant difference when compared to the placebo patch (batch GE).

Batch Code	In vivo buccoadhesion parameter scores (n = 6) (mean ± S.D.)						
	Irritation of mucosa	Swelling hinderance	Taste alteration	Pain of the mucosa	Redness after removal of device	Ulceration after removal of device	Buccoadhesion time (hr)
GE	0.24 ± 0.43	0.49 ± 0.47	0.48±0.38	0	0	0	7.71 ± 2.60
PF	0.03 ± 0.07	0.30 ± 0.37	0.63±0.22	0	0	0	7.90 ± 2.64
PH	0.33 ± 0.51	0.30 ± 0.45	0.56±0.27	0	0	0	7.34 ± 2.01
PG6	0	0	0.63±0.22	0	0	0	8.53 ± 1.68

Tab. 4. Bio-compatibility and oral mucoadhesion time of prepared placebo and PZ patches

Buccal absorption studies

The method adopted herein is an indirect methods of measuring the amount of PZ that is delivered via the buccal mucosa. Similar methods have been used by the Agarwal and Mishra [6], we had adopted this method since the study was a priliminary one and done on a small scale. The results of the buccal permeation of PZ through human buccal mucosa are summarized in Table 5. Night time

application was selected for buccal absorption studies due to to the relatively lesser movement of the oral mucosal tissues [7]. All the patches were retained on the applied buccal site until removed next morning. The patches could be removed without causing injury to the site of application and the backing layer was found to be intact in all the patches. No volunteer had reported bitter taste during the study period. This indicated that PZ was not released into the saliva and hence it could be safely assumed that PZ was absorbed only from the contact buccal mucosal site.

The percent PZ permeated (Table 5) among the batches studied did not show much difference. This was in agreement to the results of *in vitro* release studies, wherein almost identical PZ releases were obtained. The amount of PZ absorbed from the buccal patch / hour was calculated using the relationship: Total PZ absorbed / Patch retention time in the oral cavity.

Batch Code	Volunteers No.	Weight uniformity (gm/1.04 cm^2)	Thickness (mm)	Drug loading (mg)	RDC (mg)	Total drug permeated (mg)	Drug permeated /hr (mg/hr)	Time of removal (hr)	% drug permeated
PF	1	0.047	0.28	5.28	2.40	2.87	0.32	9.00	54.33
	2	0.051	0.32	5.70	2.97	2.73	0.34	8.00	47.87
	3	0.050	0.32	5.58	2.55	3.03	0.34	9.00	54.31
	4	0.052	0.33	5.81	2.88	2.95	0.35	8.50	50.91
	Mean± S.D.	0.05 ± 0.002	0.31 ± 0.02	5.79 ± 0.23	2.69 ± 0.26	2.91 ± 0.13	0.34 ± 0.01	8.63 ± 0.48	51.86 ± 3.11
PH	1	0.053	0.36	5.05	3.10	1.99	0.28	7.00	38.68
	2	0.050	0.34	4.77	2.57	2.20	0.28	8.00	46.06
	3	0.052	0.35	4.97	2.48	2.48	0.31	8.00	50.16
	4	0.054	0.36	5.15	2.62	2.52	0.32	8.00	49.11
	Mean± S.D.	0.052 ± 0.001	0.35 ± 0.01	4.99 ± 0.16	2.69 ± 0.27	2.29 ± 0.27	0.30 ± 0.02	7.75 ± 0.50	46.00 ± 5.18
PG6	1	0.058	0.42	6.09	3.41	2.67	0.38	7.00	43.90
	2	0.051	0.41	5.36	3.32	2.04	0.26	7.75	38.05
	3	0.052	0.41	5.37	2.93	2.44	0.33	7.50	45.36
	4	0.047	0.39	5.15	2.51	2.63	0.29	9.25	51.19
	Mean± S.D.	0.052 ± 0.005	0.41 ± 0.01	5.49 ± 0.41	3.04 ± 0.41	2.44 ± 0.29	0.31 ± 0.05	7.88 ± 0.97	44.63 ± 5.40

Tab. 5. In vivo permeation of PZ from CMC and CMC-HEC oral mucoadhesive patches in 4 healthy human volunteers

Conclusions

PZ needs a permeation rate of 77.62μg/hr to achieve minimum effective blood concentration [4]. The permeation rate was calculated using the formula $D= C_p \times V_d \times K_e$; where C_p is the effective plasma concentration; V_d is the volume of distribution and K_e is the rate of elimination. In the present study all the three batches delivered PZ well above the minimum blood concentration required to achieve effective PZ levels. Berkowitz et al [48] and Ehrnebo et al [49] have reported that mean peak plasma levels after oral (75 mg), intramuscular (45 mg) and intravenous (30 mg) administration were 0.14, 0.16 and 0.12 μg / ml, respectively in humans. Hence it is suggested that PZ delivered from the study patches was sufficient to achieve minimum effective blood levels without, or negligible, side effects when compared with the results reported by Berkowitz et al [48] and Ehrnebo et al [49]. Moreover the flexibility and integrity of the 3M® backing layer seems to be satisfactory towards use, comfort and unidirectional release of PZ.

In conclusion, PZ patches developed in the present study could form the basis of thrice-daily dosage regimen, as compared to 4 to 6 times administration of PZ injection at 30mg/injection.

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References

[1] Jaffe J H, Martin W R, In: The pharmacological basis of therapeutics, Gilman A G, Rall T W, Nies A, Tylor P (Ed), New York: Pergamon Press, 1990: 511.

[2] Wilson T D, In: Pentazocine in analytical profiles of drugs. Florey K (Ed), London: Academic Press Inc. 1984: 361.

[3] Reynolds J P, (Ed).: Martindale Extra Pharmacopoeia 30th edition. London: The Pharmaceutical Press, 1993: 635.

[4] Mandal S C, Bhattacharya M, Ghoshal S K. Drug Dev. Ind. Pharm. 1994; 20(11):1933.

[5] Reynolds J P, (Ed).: Martindale Extra Pharmacopoeia 30th edition. London: The Pharmaceutical Press, 1993:1092..
[6] Agarwal V, Mishra B. Drug Dev. Ind. Pharm. 1999; 25(6): 701.
[7] Robinson J R, Bologna W J. J. Controlled Rel. 1994; 29: 87.
[8] Rathbone M J, Drummond B K, Tucker I G. Adv. Drug Del. Rev. 1994; 13: 1.
[9] Harris D, Robinson J R. J. Pharm. Sci. 1992; 81: 1.
[10] Collins L M C, Dawes C. J. Dent. Res. 1987; 66:1300.
[11] Tucker, I. G. J. Pharm. Pharmacol. 1987; 39: 679.
[12] Sampathkumar D, Balasubramaniam J, Pandit J K.. Sci. Pharm. 2001; 69: 123.
[13] Mortazavi S A, Smart J D. Int. J. Pharm. 1995;116: 223.
[14] Dyik K., Graffner C. Acta Pharm. Nord. 1992; 4: 79.
[15] Balamurugan K, Pandit J K, Choudary P K, Balasubramaniam J. Ind. J. Pharm. Sci. 2001: 63(6): 473.
[16] Bottenberg P, Cleymaet R, DeMuynck C, Remon J P, Coomans D, Slop P. J. Pharm. Pharmacol. 1982; 44: 684.
[17] Kim I S, Kim S H, Cho C S. Arch. Pharm. Res. 1996; 19: 18.
[18] Balasubramaniam J, Thilekkumar M, Pandit J K, Kant S. Pharmazie 2001; 56(10): 793.
[19] Vyavahare N R, Kulkarni M G, Mashelkar R A. J. Membrane Sci. 1990; 54: 205.
[20] Deasy P B, Neill C T O. Pharm. Acta. Helv. 1989; 64: 231.
[21] Ishida M, Nambu N, Nagai T. Chem. Pharm. Bull. 1982; 30: 980.
[22] Taylan B, Capan Y, Guven O, Kes S, Hincal A A. J. Controlled Rel. 1996; 38: 11.
[23] Collins A E, Deasy P B. J. Pharm. Sci. 1990; 79: 116.
[24] Nakane S, Kakumoto M, Yukimatsu K, Chien Y W. Pharm. Dev. Technol. 1996; 1: 251.
[25] LeBrun P P H, Fox P L A, De Vries M E, Bodde H E. Int. J. Pharm. 1989; 49: 141.
[26] Peppas N A, Khare A R. Adv. Drug Del. Rev. 1993; 11: 1.
[27] Durrani M J, Andrews A, Whitaker R, Benner S C. Drug Dev. Ind. Pharm. 1994; 20: 2439.
[28] Ponchel G, Touchard F, Wouessidjewe D, Duchene D, Peppas N A. Int. J. Pharm. 1987; 38: 65.
[29] Chen W J, Hwang C C. Int. J. Pharm. 1992; 82: 61.
[30] Mockel J E, Lippold B C. Pharm. Res. 1993; 10: 1066.
[31] Technical Literature on Aqualon, Hong Kong.
[32] Hussain A S, Johnson R D, Shivanand P, Zoglia M A. Drug Dev. Ind. Pharm. 1994; 20: 2645.
[33] Smart J D, Kellaway I W, Worthington H T C. J. Pharm. Pharmacol. 1993; 36: 295.
[34] Schnurrer J, Lehr C M. Int. J. Pharm. 1996; 141: 251.
[35] Sam A P, Heuij J T M V, Tukker J J. Int. J. Pharm. 1992; 79: 97.

[36] Mortazavi S A, Smart J D. J. Controlled Rel. 1994; 31: 207.
[37] Cvetkovic N, Nesic M, Moracic V, Rosic M. Pharmazie 1997; 52: 536.
[38] Saettone M F, Giannaccini B, Torracca M T, Burgalassi S. Eur. Conf. of Biopharm. Pharmacokinetic Proc. 1987; Vol. I: 413.
[39] Saettone M F, Chetoni P, Torracca M T, Burgalassi S, Giannaccini B. Int. J. Pharm. 1989; 51: 203.
[40] Sanzgiri Y D, Topp E M, Benedetti L, Stella V J. Int. J. Pharm. 1994; 107: 91.
[41] Tobyn M J, Johnson J R, Dettmar P W. Eur. J. Pharm. Biopharm. 1995; 41: 235.
[42] Tobyn M J, Johnson J R, Dettmar P W. Eur. J. Pharm. Biopharm. 1996; 42: 56.
[43] Tobyn M J, Johnson J R, Dettmar P W. Eur. J. Pharm. Biopharm. 1996; 42: 331.
[44] Ch'ng H S, Park H, Kelly P, Robinson J R. J. Pharm. Sci. 1985; 74: 399.
[45] Rossi, S.; Bonferoni, M. C.; Ferrari, F.; Bertoni, M.; Caramella, C. (1996), Eur. J. Pharm. Sci. 4: 189.
[46] Parodi B, Russo E, Caviglioli G, Caffagi S, Bignardi G. Drug Dev. Ind. Pharm. 1996; 22: 445.
[47] Woolfson A D, McCafferty D F, McCarron P A, Price J H. J. Controlled Rel. 1995; 35: 49.
[48] Berkowitz B, Way E L. Clin. Pharm. Ther. 1969; 10: 681.
[49] Ehrenbo M, Boreus L O, Ionroth U. Clin. Pharmacol. Ther. 1980; 22: 888.

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